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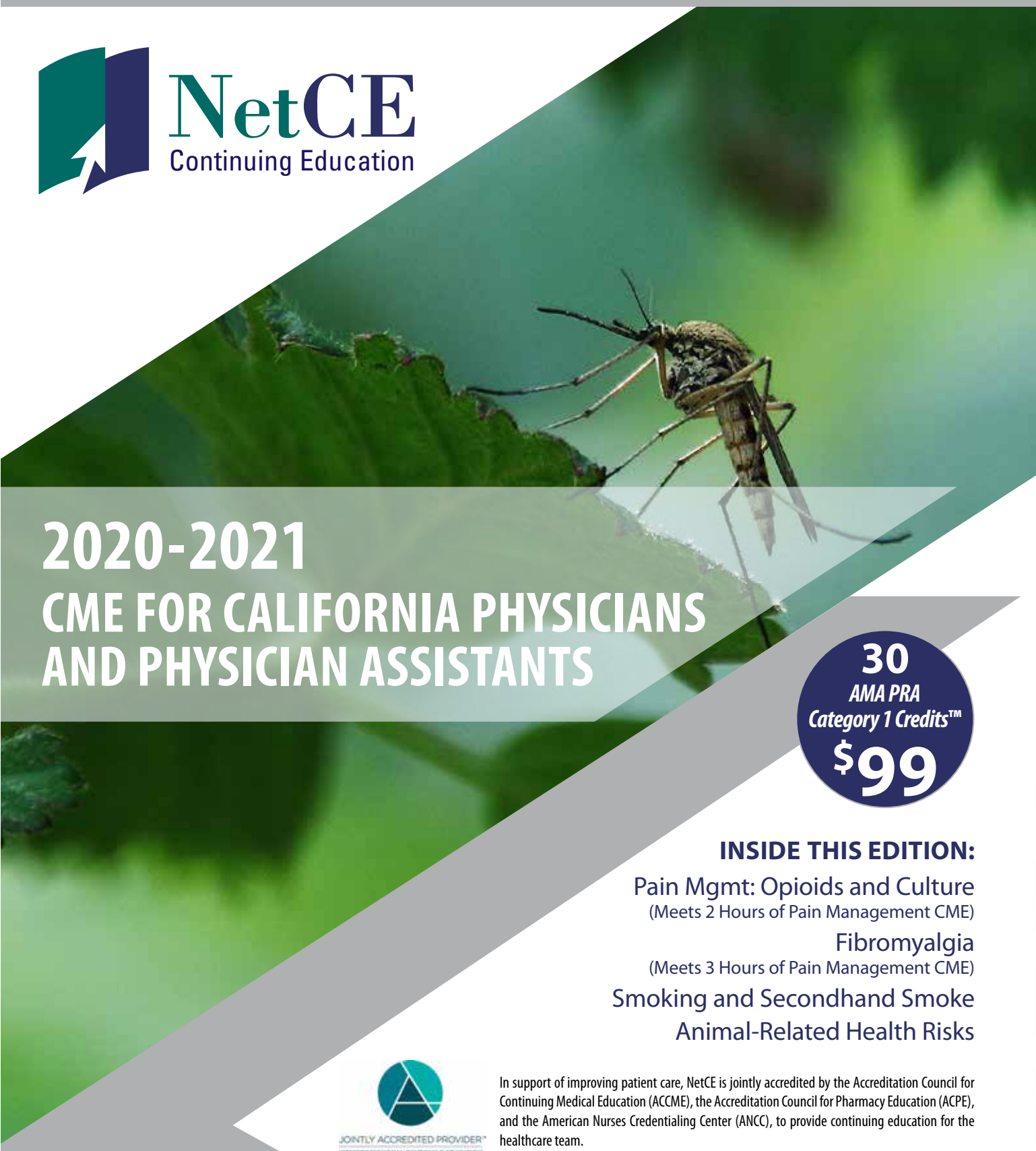

2020-2021
CME FOR CALIFORNIA PHYSICIANS AND PHYSICIAN ASSISTANTS

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Pain Mgmt: Opioids and Culture
(Meets 2 Hours of Pain Management CME)

Fibromyalgia
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Pain Management Pearls: Opioids and Culture

Special Approvals

This course is designed to meet requirements for opioid/controlled substance/pain management and cultural competency education. However, this course may not satisfy your jurisdiction's entire requirement.

For more information regarding your CME requirements, please go to: **www.NetCE.com/ce-requirements/physicians** (for MDs) or **www.NetCE.com/ce-requirements/physician-assistants** (for PAs).

In addition to receiving *AMA PRA Category 1 Credit*™, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 2 ABIM MOC Points, 2 ABA MOC Points, 2 ABP MOC Points, 2 ABO MOC Points.

Audience

This course is designed for physicians, nurses, and allied health professionals who may intervene to improve the treatment of pain in diverse patient populations.

Course Objective

The purpose of this course is to increase clinicians' knowledge and awareness of the appropriate prescription of opioids and the impact of culture on issues of pain and pain management in order to improve the provision of care and patients' quality of life.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss characteristics of appropriate and inappropriate opioid prescribing and contributory factors to both.
2. Outline the appropriate periodic review and monitoring of patients prescribed opioid analgesics.
3. Describe necessary components of patient/caregiver education for prescribed opioid analgesics, including guidance on the safe use and disposal of medications.
4. Analyze how culture, race and ethnicity influence how pain is defined, expressed, and experienced.

Faculty

Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to various law firms on matters related to substance abuse, is on the Board of

Directors of the Minneapolis-based International Institute of Anti-Aging Medicine, and is a member of several professional organizations.

Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families.

Previously acting as a faculty member at Capella University and Northcentral University, Dr. Yick Flanagan is currently a contributing faculty member at Walden University, School of Social Work, and a dissertation chair at Grand Canyon University, College of Doctoral Studies, working with Industrial Organizational Psychology doctoral students. She also serves as a consultant/subject matter expert for the New York City Board of Education and publishing companies for online curriculum development, developing practice MCAT questions in the area of psychology and sociology. Her research focus is on the area of culture and mental health in ethnic minority communities.

Faculty Disclosures

Contributing faculty, Mark Rose, BS, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

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Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 2 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

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Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

Pain affects all domains of life, and clinicians have few effective tools at their disposal to help these patients [1]. Opioids remain the strongest group of analgesic drugs available [2]. Millions of patients are safely and effectively maintained on relatively high-dose opioids for chronic, severe pain and require these medications to function. Public pressure and the mischaracterization of patients as "drug addicts" has increasingly deterred prescribers from treating patients with chronic pain successfully managed with opioids for years or decades rather than improving safety practices [3; 4]. However, opioids, like many medications, have serious risks and should not be treated like a cure-all [5]. This dichotomy has resulted in many patients for whom opioid analgesics are appropriate increasingly experiencing barriers to pain relief.

At greatest risk of unrelieved pain from stigma and bias are children, the elderly, racial and ethnic minorities, active duty or military veterans, and those with cancer, HIV, or sickle cell disease. Pain undertreatment in African American patients is especially widespread, from prevalent misperceptions that this group has higher pain tolerance and is more likely to abuse their opioid prescription [6]. As a result, prescribers, dispensers, and administrators would benefit from considering both the tenets of appropriate opioid prescribing and the impact of culture on experiences of pain and effective pain management.

OPIOID MANAGEMENT OF CHRONIC PAIN

All patients with pain have a level of risk that can only be roughly estimated initially and modified over time as more information is obtained. There are ten essential steps of opioid prescribing for chronic pain to help mitigate any potential problems [7]:

- Diagnosis with an appropriate differential
- Psychologic assessment, including risk of substance use disorders
- Informed consent
- Treatment agreement
- Pre- and post-treatment assessments of pain level and function
- Appropriate trial of opioid therapy with or without adjunctive medication
- Reassessment of patient levels of pain and functioning
- Regular assessment with the 5 A's (i.e., analgesia, activity, adverse effects, aberrant behaviors, and affect)

- Periodically review pain diagnosis and comorbid conditions, including substance use disorders
- Documentation

Despite limited evidence for reliability and accuracy, screening for opioid use is recommended by the American Society of Interventional Pain Physicians, as it will identify opioid abusers and reduce opioid abuse.

(https://painphysicianjournal.com/2012/july/2012;%2015;S67-S116.pdf. Last accessed July 27, 2020.)

Level of Evidence: Limited (Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.)

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [8]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications.

The treatment agreement also outlines joint prescriber and patient responsibilities. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug tests (UDTs). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

It is important to remember that treatment agreements are only one aspect of developing a safe opioid use plan. The evidence to support the use of such agreements to decrease the misuse of opioids is relatively weak, with little or no proof of improvements in adherence or patient care [9].

INITIATING A TRIAL OF OPIOID THERAPY

Opioid therapy should be presented as a trial for a pre-defined period (e.g., ≤30 days). As noted, the goals of treatment should be reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [8]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability. The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression.

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over extended-release/long-acting (ER/LA) opioid formulations. Taper opioid dose when no longer needed [10].

PERIODIC REVIEW AND MONITORING

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [8]. This can include input from family members and/or the state prescription drug monitoring program. Prescription drug monitoring programs are one of the most effective measures for reducing opioid analgesic diversion and abuse, but their efficacy is undermined by inconsistent use [9]. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. Decisions regarding the continuation, modification, or termination of opioid therapy for pain should be based on evaluation of the patient's progress and the absence of substantial risks or adverse events [8]. At every visit, chronic opioid response may be monitored according to the 5 A's [11]:

- Analgesia
- Activities of daily living
- Adverse effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

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Assessment During Ongoing Opioid Therapy

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [11]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Inability to concentrate or short attention span
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance
- Escalation of pain and/or pain medication dose
- Increasing number of medications prescribed to treat the side effects of opioids

Patients who display any of these signs or symptoms should be assessed for potential opioid misuse or use disorder/addiction. Persons in active addiction should be referred to an addiction and/or pain specialist.

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [8]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring database, and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses. A urine drug test should be performed prior to initiating opioid treatment.

Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations.

If substance abuse is active, in remission, or in the patient's history, one should consult an addiction specialist before starting opioids. In the setting of active substance abuse, opioids should not be prescribed until the patient is engaged in a treatment/recovery program or other arrangement are made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental exposure by children.

PATIENT AND CAREGIVER EDUCATION

Safe Use of Opioids

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unless prescribed [10]. A copy of this form may be accessed online at https://www.fda.gov/media/86281/download.

When prescribing opioids, clinicians should provide patients with the following information and instructions [10]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing
- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

Disposal of Opioids

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications. According to the Office of National Drug Control Policy, most medications that are no longer necessary or have expired should

be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [12]. The FDA recommends that most opioid medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [12]. Disposal by flushing down the toilet provides immediate and definitive elimination of safety hazards from intentional use or accidental exposure involving opioid products. All transdermal patch opioid products should be flushed down the toilet after folding in half by adhesive side against adhesive side [13]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so. Flushing unused medications has been the subject of controversy, with some state governments and boards recommending against the practice due to pollution concerns and effects on waterways and wildlife [14].

The American Medical Association recommends the following three steps to promote the safe storage and disposal of opioids [15]:

- Educate patients about the safe use of opioids, including not sharing prescriptions with others.
- Remind patients that medications should be stored out reach of children and in a safe place—preferably locked—to prevent other family members and visitors from taking them.
- Talk to patients about the most appropriate way to dispose of expired, unwanted, and unused medications. The preferred option is that unwanted or unused pills, liquids or other medications should be disposed of in a local "take-back" or mail-back program or medication drop box at a police station, pharmacy, or authorized collection site. Contact your state law enforcement agency or visit https://takebackday.dea.gov to determine if a program is available in your area.

CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [8].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [8]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [16].

MEDICAL RECORDS

Documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [8]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a joint discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [8].

Clinicians should provide physically dependent patients with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

THE IMPACT OF CULTURE ON PAIN AND PAIN MANAGEMENT

Patients' experiences of pain may be frustrating if they defy biomedical explanation, and the treatment of pain tends to be stigmatized [17]. When culture, race, and ethnicity are taken into consideration, the treatment of pain becomes even more complex. Practitioners should address how patients construct the meaning and experiences of pain rather than simply dealing with a set of medical procedures and routines [17].

Practitioners working with patients experiencing pain should be aware of the patient's cultural value and belief systems and how they impact their pain experience and also how their own cultural background and professional culture/system affects how they view pain. Furthermore, culture can influence access to and utilization of pain management services and medications and provider communication [22]. For the most part, practitioners are trained and socialized from a

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biomedical tradition [23]. Practitioners should reflect on their own experiences and the values and beliefs they attribute to pain [24]. Take a moment to consider the following self-reflective questions [24].

Pain Experiences in Childhood

- When you were a child, how did those who cared for you react when you were in pain?
- How did they expect you to behave when you had a minor injury?
- How did they encourage you to cope when you had severe pain?
- How did they encourage you to behave during an injection or procedure?
- When those who cared for you as a child were in pain, how did they react?
- What words did they use to describe the pain?
- How did they cope with their pain?
- Do you tend to follow their example?

Pain Experiences in Adulthood

- What painful experiences have you had as an adult (e.g., childbirth, fracture)?
- How did you express (or not express) your pain?
- Did the pain cause you fear? What were you afraid of?
- How did you cope with the pain?
- How did you want others to react while you were in pain?

Pain Experiences by Patients

- Have you ever felt uncomfortable with the way a patient was reacting (or not reacting) to pain?
- What did the patient do that concerned you?
- Why did you feel that way?
- Do you make value judgments about patients in pain who:
  - Behave more stoically or expressively than you would in a similar situation?
  - Ask for pain medication frequently or not often enough?
  - Choose treatments you do not believe are effective or with which you are unfamiliar?
  - Belong to a cultural group (e.g., ethnic, linguistic, religious, socioeconomic) different from your own?
- Do you tend to feel certain reactions to, descriptions of, or treatments for pain are "right" or "wrong?" What about these reactions makes them seem right or wrong?

FACTORS THAT CONTRIBUTE TO RACIAL AND ETHNIC DISPARITIES IN PAIN MANAGEMENT

It is clear that health disparities exist among racial and ethnic minority groups, and this is true for pain management services and medications. A large-scale national study in the United States found racial differences in the prescription of analgesics for patients with migraine, low back pain, and bone fractures [25]. Specifically, African Americans were less likely to be prescribed analgesics for their pain compared with their white counterparts. Racial minority patients are also more likely to experience longer wait times for medication compared with white patients [20].

Analysis of a national dataset found that African Americans were less likely to be prescribed opioids for back pain and abdominal pain compared with non-Hispanic white Americans [26]. The authors speculate that racial biases may influence prescribing behaviors. An examination of Medicaid patients who received epidural analgesia during vaginal childbirth also found statistically significant racial/ethnic differences [27]. In this study, 59.6% of the white patients received epidural analgesia, compared with 49.5% of African Americans, 48.2% of Asians, and 35.2% of Hispanics. Even after the researchers controlled for age, urban/rural residence, and the availability of anesthesiologists, race and ethnicity still predicted epidural analgesia prescribing trends [27].

In a meta-analysis of ethnicity and pain management researchers found that professionals under-rated ethnic minority patients' levels of pain and were less likely to indicate their pain scores on their charts compared with their white counterparts [28]. In addition, African American and Hispanic patients were less likely to have been given analgesics than white patients.

Studies have not definitively isolated the factors that contribute to these disparities. One of the challenges in understanding health disparities, and particularly pain management disparities, is the fact that racial and ethnic minority groups are heterogeneous [29; 30]. Recent immigrants from Japan, for example, are going to be very different from native-born Japanese who have resided in the United States for generations [29]. However, researchers have often combined these groups, as challenges in recruitment yield small sample sizes that make it difficult for statistical analyses to be meaningful. The literature has identified a variety of reasons for these disparities stemming from several factors [31].

Barriers Related to Western Biomedical Culture

Western biomedical culture emphasizes a clear dichotomy between the mind and the body as well as what is observable (objective) and what is not (subjective) [32]. Pain is not easily measured, making its assessment and treatment a challenge in Western medicine [32]. In addition, many healthcare professionals may not be adequately trained to

incorporate spirituality in the management and treatment of pain for patients who desire to incorporate a more holistic approach [33]. The Western American medical paradigm also leans toward cure rather than care [32]. Patients who present with symptoms that lead to a diagnosis for which there is a clear pathway of interventions and treatment are "favored." Because of the subjective nature of pain, healthcare professionals must often make clinical decisions in the face of a lack of absolute, clear physical evidence [34].

Societal and Institutional Barriers

Societal and institutional barriers include racism, discrimination, poverty, lack of health insurance, and deleterious environmental factors in communities [35]. For example, groups that have historically (or currently) been victims of institutional racism and discrimination are more likely to delay seeking help for pain [28]. Some studies indicate that African American men may experience higher levels of pain intensity in part due to their experiences with different forms of racial discrimination [20]. Even today, racial and ethnic minority patients are more likely to be placed in a negative valenced relationship [34]. In the context of pain management, healthcare providers are more likely to discount the pain due to the negative valenced relationship triggered by racism and discrimination [34].

It has been shown that physicians tend to have less involved communication and less participatory interactions with racial minority patients and low-income patients [32]. In addition, the stereotype that certain racial minority groups come from chaotic and disorganized families and environments increases the likelihood of healthcare professionals labeling them as "difficult." Just as healthcare professionals may have preconceived notions about patients, patients may have pre-existing assumptions about the provider. For example, one study of Native American patients found that the participants tended to feel that healthcare professionals were not interested in hearing about their pain experience and did not have confidence that they would be helped [36]. Thus, a cycle of myths and stereotypes continues.

One oft-cited study found that three-quarters of pharmacies located in areas of New York City with a high proportion of racial and ethnic minority residents did not stock adequate supplies of opioid analgesics [37]. Some pharmacists attributed the low supply to lower demand, but others cited factors related to racism and discrimination. In addition, pharmacies in areas with high concentrations of racial minorities are more concerned with burglaries, additional regulations, and penalties imposed by state and federal drug-enforcement agencies than pharmacies in predominantly white neighborhoods [37].

Healthcare Professional-Related Barriers

Healthcare professional barriers may include professionals' beliefs about appropriate pain management; lack of training and knowledge about the intersection of pain and culture, race, and ethnicity; lack of culturally sensitive assessment for pain; and expectations about racial and ethnic minority pain patients based on stereotypes [38]. Consequently, practitioners may underestimate and minimize racial minority patients' pain experiences. In a qualitative study, Native American individuals described their complaints of pain being dismissed, receiving inadequate care, and neglected aftercare [39].

Studies have also shown that the language and race/ethnicity of the healthcare professional influences pain management. For example, the ratings of pain tend to be comparable when the patient and healthcare provider speak the same language. When there is a native language, pain ratings tend to diverge. When literacy and language barriers are eliminated, assessment and treatment improves and racial and ethnic minority patients with pain fare better [40]. In addition, healthcare professionals' level of empathy appears to increase when the patient and healthcare professional share the same skin color or are of the same ethnic group [41; 42].

Patient-Related Barriers

Patient barriers to effective pain management include fear and anxiety about substance misuse and addiction, cultural values such as fatalism (i.e., pain is inevitable), and ideas about being a good patient [31]. Cultural values about pain coping, definitions, expression, and experience may also be patient-related barriers. For example, those with a fatalistic perspective of pain are often stoic. A qualitative study of Somali women found that the participants felt wailing or crying about one's pain was a sign of weakness [43]. Similarly, Hispanics and African Americans are more likely to embrace the importance of being stoic and are less likely to ask for pain medication [28]. Studies also show that Hispanic and African American patients with cancer tend to underreport their pain for fear of being labeled as complainers or of distracting the physicians treating their illness [44]. Some patients will not ask questions for fear that would be viewed as challenging an authority figure [45]. Some ethnic/racial minority patients disclose that they avoid pain medications because they overestimate the risk dependence [45; 46; 47].

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ALTERNATIVE REMEDIES

Practitioners should explore both traditional biomedical pain management interventions and non-traditional alternative remedies (as appropriate) when working with racial and ethnic minority patients. Complementary self-management approaches for pain can be generally classified as mind/body approaches or natural products [48]. Mind/body approaches include meditation, yoga, acupuncture, and breathing techniques. Natural products include herbs, vitamins, and topical ointments [48]. Some patients may be more receptive to traditional healing methods (e.g., herbal remedies, traditional healers) [36]. In focus groups, Native American participants reported using a range of alternative therapies for pain, including acupuncture, massage, chiropractic treatment, and guided imagery [39].

Alternative remedies for pain can be classified into five different areas, and many can be used as adjuncts to conventional therapies [49; 50]:

- Alternative medications: Nonpharmacologic substances, such as those associated with homeopathic medicine, traditional Chinese medicine, and Ayurveda medicine
- Mind-body interventions: Interventions that focus on using the mind to influence bodily symptoms, including biofeedback, meditation, music therapy, and guided imagery. Mind-body interventions help reduce pain and improve other comorbid conditions, such as depression.
- Biologically based interventions: Consumption of biologic products (e.g., herbs, vitamins, foods)
- Manipulation strategies: Adjustment of focused areas of the body (e.g., chiropractic measures, massage, acupuncture)
- Energy therapies: Balancing energy fields (e.g., electromagnetic therapy, reiki, qigong)

Some cultural groups subscribe to the hot/cold theory of disease, which argues that illnesses are the result of bodily imbalances and that foods and alternative medications are inherently "hot" or "cold." Pain is considered a "cold" disease, and some patients who adhere to traditional healing will take this into account when selecting and adhering to treatment approaches [51].

END-OF-LIFE CONSIDERATIONS

Palliative care is the noncurative care provided to terminally ill patients to relieve symptoms and improve quality of life [52]. The goal of palliative care is to not only meet patients' physical needs but also address their psychologic, social, religious/spiritual, and cultural needs [53]. Even across cultures, there appear to be common denominators for effective palliative care. In an analysis of studies on palliative care in various ethnic/racial minority groups, researchers found common cultural themes that cut across all groups in the area of palliative care [54]. These included:

- Pain management
- Support to achieve closure (i.e., resolve social and emotional concerns that are hindering well-being)
- Spiritual and religious care
- Support to family and friends
- Focus on the quality of life

One concept that has been helpful in pain management at the end of life is the idea of total pain. Total pain considers the contributions of physical noxious stimuli, affect/emotional discomfort, interpersonal conflicts, and nonacceptance of one's own dying [55]. A patient's cultural perspective can influence any of these factors and/or how they are conveyed. The most important consideration at the end of life is that the patient's wishes are followed, and this almost always includes a desire for a pain-free death, regardless of background and culture.

Customer Information/Answer Sheet/Evaluation insert located between pages 104–105.

COURSE TEST - #97280 PAIN MANAGEMENT PEARLS: OPIOIDS AND CULTURE

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 2 credit activity must be completed by July 31, 2023.

1. Which of the following is one of the ten essential steps of opioid prescribing for chronic pain that can help mitigate any potential problems?
- A) *Patient preference*
- B) *Trials of opioid monotherapy only*
- C) *Diagnosis with an appropriate differential*
- D) *A single assessment of substance abuse risk*

2. The goal(s) of opioid treatment should be
- A) *avoidance of all pain.*
- B) *avoidance of necessary medication use.*
- C) *reasonable improvements in pain, function, depression, and anxiety.*
- D) *Both B and C*

3. Which of the following is NOT one of the 5 A's of monitoring chronic opioid response?
- A) *Analgesia*
- B) *Acceptance*
- C) *Affect (i.e., patient mood)*
- D) *Aberrant drug-related behaviors*

4. When prescribing opioids, clinicians should provide patients with instructions to
- A) *immediately halt an opioid if the side effects are unacceptable.*
- B) *never break or chew/crush tablets or cut or tear patches prior to use.*
- C) *share opioids with friends and relatives that cannot afford their own prescriptions.*
- D) *take other central nervous system depressants to manage opioid side effects.*

5. What is the universal recommendation for the proper disposal of unused opioids?
- A) *They should be burned.*
- B) *They should be flushed down the toilet.*
- C) *They should be thrown in the garbage.*
- D) *There are no universal recommendations for the disposal of opioids.*

6. An opioid should be safely discontinued with
- A) *inadequate analgesia.*
- B) *resolution of the pain syndrome.*
- C) *significant aberrant medication use.*
- D) *All of the above*

7. Which of the following statements regarding pain disparities in ethnic minority patients is TRUE?
- A) *Professionals tend to under-rate ethnic minority patients' levels of pain.*
- B) *Ethnic minority patients are less likely to have been given analgesics than white patients.*
- C) *Professionals are less likely to indicate ethnic minority patients' pain scores on their charts.*
- D) *All of the above*

8. Which of the following is considered a societal/ institutional barrier to effective pain management in racial and ethnic minority groups?
- A) *Racism*
- B) *Fear of substance misuse*
- C) *The subjective nature of pain*
- D) *Lack of healthcare professionals' training regarding the intersection of pain and culture*

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9. All of the following are healthcare professional barriers to effective pain management in racial and ethnic minority groups, EXCEPT:

A) *Lack of culturally sensitive assessment for pain*
B) *Patients' beliefs about appropriate pain management*
C) *Expectations about racial and ethnic minority pain patients based on stereotypes*
D) *Lack of training and knowledge about the intersection of pain and culture, race, and ethnicity*

10. Which of the following is considered a mind/body approach to pain management?

A) *Yoga*
B) *Vitamins*
C) *Antidepressants*
D) *Electromagnetic therapy*

Be sure to transfer your answers to the Answer Sheet insert located between pages 104–105.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Fibromyalgia

Special Approvals

This course is designed to meet requirements for pain management education. However, this course may not satisfy your jurisdiction's entire requirement.

For more information regarding your CME requirements, please go to:
www.NetCE.com/ce-requirements/physicians (for MDs) or
www.NetCE.com/ce-requirements/physician-assistants (for PAs).

In addition to receiving *AMA PRA Category 1 Credit*™, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 3 ABIM MOC Points, 3 ABO MOC Points.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with fibromyalgia.

Course Objective

The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat fibromyalgia according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the diagnostic criteria established for fibromyalgia, and discuss potential difficulties in establishing a diagnosis.
2. Identify appropriate treatment modalities for patients with fibromyalgia and patient education and follow-up needs.

Faculty

Lori L. Alexander, MTPW, ELS, MWC, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the American Medical Writers Association (AMWA) Journal, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

Ronald Runciman, MD

Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Special Approvals

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INTRODUCTION

Fibromyalgia is a complex rheumatic disorder characterized by chronic widespread musculoskeletal pain and focal tenderness (tender points), often accompanied by fatigue, other somatic complaints, and disturbances of affect and cognition [1]. The definition of the syndrome has been expanded to include the presence of fatigue, stiffness, and nonrestorative sleep; however, individuals with fibromyalgia usually have a broad range of additional symptoms and comorbidities [1; 2; 3]. The onset of fibromyalgia is insidious, symptoms wax and wane in intensity, and the course is variable [3; 4].

Acceptance of fibromyalgia as a discrete clinical entity (not associated with an apparent organic disease) has been slow [3; 5; 6; 7; 8]. In fact, at one time, there was a 40% bias of a person with fibromyalgia being labeled "neurotic" [3]. Despite increasing support for the validity of the syndrome, consensus is lacking about its cause, diagnosis, and optimal treatment [6; 8; 9].

Fibromyalgia has a substantial negative effect on physical, psychologic, and social well-being, and the syndrome is associated with a significant burden in terms of both disability and healthcare costs. Fibromyalgia has been found to have a greater negative impact on quality of life than many other diseases, including osteoarthritis, chronic obstructive pulmonary disease, and permanent ostomies [9]. Activities of daily living and work within the home are often substantially limited. In a large survey of women 31 to 78 years of age, more than 25% had difficulty taking care of personal needs and bathing and more than 60% had difficulty doing light housework, going up/down one flight of stairs, walking one-half mile, or lifting/carrying 10 pounds [10]. The average survey respondent was assessed as having less functional ability than a typical woman in her 80s [10]. Approximately 20% to 50% of individuals with fibromyalgia are able to work few or no days; 36% are absent from work two or more days each month; 31% have lost employment; and 26% to 55% receive disability or Social Security payments [5].

The economic burden is also high. According to studies of large U.S. claims databases, the healthcare costs of fibromyalgia are two to three times higher (compared with controls) as a result of more visits to the physician's office or emergency department and a higher number of prescription medications [11; 12]. Healthcare utilization and costs are high in the year preceding as well as following the initial diagnosis of fibromyalgia [12].

EPIDEMIOLOGY

According to prevalence and population estimates, fibromyalgia affects approximately 5 million people in the United States [13]. Determining the true prevalence is difficult because of the problems associated with defining its diagnosis according to the available criteria [5; 13]. The prevalence is estimated to be 2% to 8% of the population and increases with age [14; 15].

As with autoimmune diseases, the prevalence of fibromyalgia is higher among women than men, although data are conflicting. A female-to-male ratio of 6:1 to 9:1 has been reported in some studies [5; 12; 16]. However, estimates that use newer, symptom-based diagnostic criteria show a female-to-male ratio of 2:1 [14; 15].

The prevalence of fibromyalgia is 5% to 6% among patients seen in family or general medicine practice settings and among 15% to 20% of patients seen by rheumatologists [8]. As such, the syndrome is among the 100 most common diagnoses made in the family medicine setting, as well as one of the most common diagnoses in office-based rheumatology practice [8; 17]. Fibromyalgia is usually diagnosed between the ages of 20 and 55 years, but the prevalence increases with age, peaking at 70 to 79 years of age (at approximately 7% for women and 1% for men) [5].

The prevalence of fibromyalgia according to race/ethnicity in older studies has been inconclusive, as studies have either included a predominantly white population or have not specified the race/ethnicity of the subjects [13]. In general, the prevalence is similar among racial and ethnic groups [18]. There is no evidence of a higher prevalence of fibromyalgia in industrialized countries and cultures. Among a cohort of 266 individuals with systemic lupus, black race had a negative association with fibromyalgia, and the prevalence has been low among Hispanic and Mexican individuals as well [19; 20].

PATHOGENESIS

Several etiologies for fibromyalgia have been postulated and explored; the syndrome has been thought to be an inflammatory condition, an autoimmune disease, an unexplained medical syndrome, or a psychiatric condition [3; 7; 8; 21; 22]. However, research has provided little or no evidence to support these bases, and the pathogenesis of the syndrome continues to be poorly understood [8; 9; 23].

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Pioneering sleep studies in the 1970s demonstrated that people with fibromyalgia had abnormal sleep physiology, suggesting a central pathology [24]. Since then, substantial evidence has supported a mechanism of central sensitization, or the amplification of pain in the spinal cord through spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses [4; 5; 6; 9]. Studies have also shown that, compared with healthy individuals, people with fibromyalgia experience pain differently and have physiologically lower pain thresholds [6]. Research has also indicated significant dysregulation of the hypothalamic-pituitary-adrenal axis is found in fibromyalgia [9]. In addition, there may be abnormalities of descending inhibitory pathways, neurotransmitters, or neurohumoral responses; low levels of serotonin and norepinephrine metabolites have been found in the cerebrospinal fluid of individuals with fibromyalgia [5; 6; 9].

Genetics is thought to be a factor in the susceptibility of fibromyalgia. Family clustering has been reported, and the risk for fibromyalgia is eight times higher for first-degree relatives of individuals with the syndrome [25]. Abnormalities in the serotonin transporter gene and the catecholamine-*O*-methyltransferase gene have been identified [5; 9; 26]. These abnormalities affect the metabolism or transport of serotonin and norepinephrine, which decrease the sensitivity of pain-processing systems through the descending central nervous system pain pathways [5].

POTENTIAL ENVIRONMENTAL RISK FACTORS

As with autoimmune diseases, several environmental risk factors have been thought to act as triggers for the development of fibromyalgia. Because research on the etiology of fibromyalgia is lacking, individuals' perceptions of triggers have been the source of some of the available information [27]. Perhaps as a result, data on the frequency of environmental triggers are conflicting, with some studies showing that half of all cases have a distinct physical or emotional trigger and other studies indicating that three-quarters of cases or more had no triggering event [9; 27; 28].

Psychiatric conditions have long been associated with fibromyalgia, and research suggests that such conditions may precede fibromyalgia and act as a trigger for the disease [6; 8]. In one study, when individuals were asked what they perceived to be a trigger for fibromyalgia, 73% attributed the development of the disease to emotional trauma or chronic stress; 24% noted emotional/physical abuse as an adult or child as a perceived trigger [27].

Injury/trauma and physical illness may also be triggers. Approximately one-third of individuals who attributed fibromyalgia to an environmental trigger noted physical injury (including those from a motor vehicle accident) as the perceived trigger [27]. Acute illness was perceived as a trigger in 27% of individuals in the same survey [27]. Viral infections have been associated with the development of fibromyalgia, and hepatitis C, Epstein-Barr virus, human immunodeficiency virus (HIV), parvovirus, and Lyme disease are thought to be viral triggers, but no causality has been established [6; 9; 28]. Other pain conditions, hyperprolactinemia, and autoimmune diseases have also been reported to be factors [9; 28].

ASSOCIATION WITH AUTOIMMUNE DISEASES

Several autoimmune diseases have been found in conjunction with fibromyalgia. In a retrospective study of 2,595 cases of fibromyalgia in a nationwide claims database, the likelihood of systemic lupus or rheumatoid arthritis was two to seven times greater than that for controls [29]. Other studies have confirmed an association between fibromyalgia and systemic lupus and rheumatoid arthritis, with reported rates of up to 65% and 57%, respectively [23]. High rates of Sjögren syndrome (up to 50%), and thyroiditis (up to 31%) have also been reported among individuals with fibromyalgia [3; 9; 30]. A small study has suggested that Hashimoto disease and/or subclinical hypothyroidism may be a predisposition to fibromyalgia; signs and symptoms of fibromyalgia were found in nearly one-third of individuals [30].

CLINICAL MANIFESTATIONS

Chronic, widespread musculoskeletal pain (on both sides of the body for at least three months) is the defining feature of fibromyalgia [1]. This pain is often associated with muscle tenderness (to palpation) adjacent to areas of tendon insertion [3; 31]. In addition, a constellation of other symptoms are common and vary across patients. Most patients complain of stiffness (especially in the morning), fatigue, sleep abnormalities, and difficulties of cognition, such as mental torpor, maintaining attention, and performing tasks that require rapid thought [1; 2; 3; 27; 31; 32; 33; 34].

The likelihood of depression is high among individuals with fibromyalgia [34]. Major depression has been identified in 20% to 62% of individuals with the syndrome [27; 28; 31; 34; 35]. Factors associated with major depression have included younger age, female gender, being unmarried, number of chronic conditions, and limitations in activities [34].

COMMON SYMPTOMS OF FIBROMYALGIA	
Symptom	**Reported Prevalence**
Stiffness	76% to 91%
Fatigue	24% to 90%
Sleep abnormalities	76%
Headaches	47% to 75%
Dry mouth	18% to 71%
Low back pain	67%
Paresthesias	44% to 67%
Restless legs syndrome	32% to 64%
Depression	20% to 62%
Irritable bowel syndrome	36% to 60%
Anxiety	30% to 56%
Raynaud phenomenon	9% to 53%
Muscle spasms	46%
Balance problems	45%
Cognitive dysfunction (impaired memory and/or concentration)	40%
Bloating	40%
Sinus problems	37%
Tooth disorders	32%
Jaw pain	29%
Bladder problems	26%
Source: [1; 3; 5; 22; 27; 28; 31; 32; 33; 34; 35]	*Table 1*

Cognitive dysfunction (often referred to as "fibrofog") affects approximately 40% of individuals [5]. The primary effect is on memory (working, episodic, and semantic), especially when tasks are complex and the individual's attention is divided [36]. Although memory impairment is not as common as many other symptoms, patients have considered them to be among the most troublesome, which is not surprising given that the impairment is equivalent to about 20 years of aging [27; 32; 36]. Attentional control/function is also commonly impaired in individuals with fibromyalgia [36; 37; 38]. Studies have indicated that cognitive dysfunction cannot be attributed solely to symptoms such as depression, anxiety, and sleep problems, but it does seem to be related to the level of pain [36; 37; 38].

DIAGNOSTIC EVALUATION

Fibromyalgia cannot be diagnosed on the basis of laboratory tests, imaging studies, or pathologic results. As a result, the diagnosis relies on a carefully taken history and comprehensive physical examination. The American Pain Society guideline recommends that the physical examination include a complete joint examination, manual muscle strength testing, and a neurologic examination [4]. The ACR established diagnostic criteria for fibromyalgia in 1990, but the classification system, designed for use in clinical research rather than clinical practice, has many limitations [1; 2; 3; 39].

The lack of objective testing has led to substantial delays in the diagnosis of fibromyalgia, with a diagnosis confirmed only after many visits to healthcare professionals, referrals, diagnostic tests, and several possible diagnoses [5]. Nearly half of individuals with the disease consulted three to six healthcare providers before the diagnosis was made, and 25% saw more than six providers before diagnosis [27]. Physicians also acknowledge diagnostic delay, noting that an accurate diagnosis of a chronic pain disorder (including fibromyalgia) often is not made until after two to three years and consultations with 8 to 13 healthcare professionals [5].

A self-administered questionnaire developed in 2010 may aid in detecting fibromyalgia. The tool, Fibromyalgia Rapid Screening Tool (FiRST), was developed by a group of rheumatologists and pain experts and consists of six questions that can be answered with a yes/no response [40]. A score of five

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INSTRUMENTS FOR ASSESSMENT OF FIBROMYALGIA-RELATED SYMPTOMS	
Symptom	**Assessment Tool**
Pain	Visual analog scale Brief Pain Inventory Short Form–McGill Pain Questionnaire Daily pain diary
Fatigue	Visual analog scale Multidimensional Assessment of Fatigue Instrument Multidimensional Fatigue Inventory Fatigue Severity Scale
Sleep	Visual analog scale Medical Outcomes Study Sleep Scale Pittsburgh Sleep Quality Index Sleep Assessment Questionnaire
Depression/anxiety	Beck Depression Inventory Patient Health Questionnaire Beck Anxiety Inventory Hospital Anxiety and Depression Scale
Quality of life/functional assessment	Fibromyalgia Impact Questionnaire Short Form–36 Health Survey
Source: [9; 22; 41]	Table 2

"yes" responses gave the highest rate of correct identification of fibromyalgia patients (87.9%), with a sensitivity of 90.5% and a specificity of 85.7% [40]. FiRST is meant to be used as an initial screening tool, with established diagnostic criteria used to subsequently confirm the diagnosis [40].

The current challenge in diagnosing fibromyalgia stems from many factors, including a wide range and variation in symptoms, a complex differential diagnosis, and difficulty with the established diagnostic criteria.

RANGE AND VARIATION IN SYMPTOMS

There is a wide range of symptoms and comorbidities associated with fibromyalgia, and they occur in a variety of combinations and differ in terms of severity. After the three primary manifestations (fatigue, stiffness, and sleep abnormalities), the most common symptoms are headaches (usually migraine), dry mouth, low back pain, and paresthesias (***Table 1***) [1; 3; 27; 31; 32; 33; 34]. In an online survey conducted by the National Fibromyalgia Association (NFA), 19 symptoms, affecting virtually all body systems, were noted by at least 25% of the respondents [27]. Nearly all individuals with fibromyalgia are polysymptomatic [27].

Most individuals with fibromyalgia describe pain as arising from muscles and joints and also have tender skin [3]. Pain is typically axial in distribution, and pain/stiffness usually occurs in the morning and evening [3]. Patients may note a feeling of swelling in the soft tissues, primarily around the joints, but there is no objective evidence of swelling [3; 28].

The American Pain Society recommends using self-reports as the primary source for pain assessment, focusing on such details as [4]:

- Type and quality of pain
- Source
- Location
- Duration
- Time course
- Pain affect
- Effects on quality of life

Several pain assessment tools may be useful in the setting of fibromyalgia (***Table 2***) [9; 22; 41].

Healthcare professionals should also ask about factors that may exacerbate musculoskeletal symptoms, as these symptoms are modulated in approximately 60% to 79% of individuals [1]. Emotional distress has been the most commonly reported exacerbating factor (83%), followed by changes in the weather (80%), sleeping problems (79%), and strenuous activity (70%) [27]. Many other factors are perceived to worsen symptoms, including fatigue, physical inactivity, mental stress, soft-tissue injuries, travel in a car or plane, and work-related conflict [3; 27].

Patient assessment must include evaluation of the severity of symptoms most often associated with fibromyalgia, as well as overall quality of life and functional assessment [4; 9; 22]. Most assessment tools used have been validated in other

COMORBIDITIES ASSOCIATED WITH FIBROMYALGIA		
Comorbidity	**Prevalence**	
	Lifetime	**Current**
Any gastrointestinal problem	72%	34%
Any psychiatric problem	68%	39%
Depression	68%	39%
Hypertension	49%	35%
Any genitourinary problem	48%	5%
Severe allergies	41%	21%
Any endocrine problem	40%	28%
Any lung problem	37%	19%
Source: [43]		*Table 3*

settings and are not fibromyalgia-specific. Healthcare professionals should ask patients about how their symptoms affect their ability to work, as physical limitations and cognitive dysfunction may result in an inability to maintain normal employment [3; 4]. A daily pain diary may also be useful in documenting how pain influences activities of daily living and quality of life [9].

In relating their history, individuals will often focus on the symptoms that are of most concern or that are most troublesome. According to the NFA survey, the most troublesome symptoms were (in descending order): morning stiffness, fatigue, nonrestorative sleep, pain, forgetfulness, poor concentration, difficulty falling asleep, muscle spasms, anxiety, and depression [27]. In another study, 100 individuals with fibromyalgia ranked symptoms slightly differently, but the top five symptoms were similar: pain or physical discomfort, joint pain/aching, fatigue or lack of energy, poor sleep, and cognitive dysfunction [32].

Because of the predominance of fibromyalgia among women, there are few data on the clinical profile for men with the syndrome. The available research points to differences in the clinical presentation according to gender. Women tend to report more symptoms, to describe more symptoms as major problems, and to report greater life interference from pain [8; 18; 42]. Men have noted significantly lower health perceptions and more physical limitations [42]. With regard to specific symptoms, fatigue and sleep disorders are more common among women, with some studies showing a threefold higher rate [8]. "Pain all over" is also more frequently reported by women than men [8]. The most powerful discriminator between women and men with fibromyalgia is the number of tender points [8].

Comorbidities

Given the broad range of symptoms and conditions found in association with fibromyalgia, it is difficult to differentiate true comorbidities from manifestations of the syndrome itself [43]. For example, irritable bowel syndrome and restless legs syndrome are traditionally thought of as comorbidities but may be part of the overall clinical syndrome [1; 8; 43]. This is true for many autoimmune diseases but particularly for fibromyalgia, which has been described as overlapping with virtually every other unexplained syndrome [7]. In a study in which current and lifetime comorbidities associated with fibromyalgia, rheumatoid arthritis, and systemic lupus were evaluated, fibromyalgia was associated with significantly higher rates of depression and psychiatric conditions, gastrointestinal problems, and severe allergies (***Table 3***) [43].

COMPLEX DIFFERENTIAL DIAGNOSIS

The multitude of symptoms and comorbidities associated with fibromyalgia add to the complexity of making a differential diagnosis. Many other conditions can mimic widespread pain, and these conditions must be considered in the differential diagnosis (***Table 4***). Although objective testing cannot confirm a diagnosis of fibromyalgia, it can play an important role in ruling out other possible diagnoses. A CBC, ESR, muscle enzymes, liver function studies, and thyroid function tests can help identify other conditions [4]. However, given the high rate of conditions that occur concurrently with fibromyalgia, clinicians must remember that finding another diagnosis does not automatically rule out a diagnosis of fibromyalgia [3]. Differentiating fibromyalgia from other rheumatic diseases and conditions involving widespread pain is especially difficult. Individuals who have widespread pain and fibromyalgia are typically more symptomatic, dysfunctional, and depressed than people who have widespread pain without fibromyalgia [3].

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DIFFERENTIAL DIAGNOSIS OF FIBROMYALGIA		
Diagnoses to Consider	**Shared Manifestations**	**Distinguishing Features**
Myofascial pain syndrome	Painful, tender areas in the muscles, commonly affecting the axial muscles	Pain arising from trigger points in individual muscles during examination
Chronic fatigue syndrome	Chronic pain and fatigue	Low-grade fever, enlargement of lymph glands, continuous subclinical inflammatory process, and acute onset of illness
Rheumatoid arthritis	Joint pain/stiffness	Involvement of hands and feet, positive rheumatoid factor (in 80% to 90% of cases), radiographic evidence of joint erosion
Systemic lupus erythematosus	Involvement of multiple systems, joint pain	Malar rash, positive antinuclear antibody test
Hypothyroidism	Profound fatigue, muscle weakness, mental slowing	Weight gain, hair loss, increased TSH level
Polymyalgia rheumatica	Pain/stiffness in sacrohumeral and pelvic girdle	Increased ESR (in 80% to 90% of cases), age older than 65 years, treatment with glucocorticoids resolves symptoms
Spondyloarthropathy	Pain in neck, mid-thoracic, anterior chest wall, or lumbar regions	Pain localized to specific spinal areas, radiographic evidence of sacroiliitis, or radiographic changes in vertebral bodies
Polyarticular osteoarthritis	Pain in multiple joints	Radiographic evidence of joint degeneration
Polymyositis or other myopathies	Muscle weakness	Proximal, symmetrical muscles affected, increased serum levels of muscle enzymes, abnormal findings on EMG testing and on evaluation of biopsy samples
Neuropathic pain syndromes	Tingling, numbness	Burning, shooting pain
EMG = electromyography; ESR = erythrocyte sedimentation rate; TSH = thyroid-stimulating hormone.		
Source: [3; 8; 28]		*Table 4*

DIFFICULTY WITH DIAGNOSTIC CRITERIA

The ACR designed the classification criteria for fibromyalgia for epidemiologic classification but noted that the criteria would also be useful for diagnosis [1]. However, the criteria are used by only about half of rheumatologists in routine practice and are seldom used in the primary care setting [3]. The classification system consists of two criteria: a history of widespread pain and pain in 11 of 18 tender point sites on digital palpation [1]. It has a sensitivity of 88%, a specificity of 81%, and an accuracy of 85%, but several important problems have been identified.

A primary problem with the criteria is the focus on the tender point evaluation, which has been difficult for clinicians, especially primary care providers, to perform correctly [2; 3]. Perhaps equally as problematic is that widespread pain as the only criterion for diagnosis does not seem sufficient, given the broad range of symptoms associated with the syndrome [3].

A third major problem is the lack of a severity scale, which means that an individual with fibromyalgia may not satisfy the diagnostic criteria for the syndrome if symptoms or pain at tender points improve [3]. As a result of these drawbacks, the diagnosis of fibromyalgia often has been symptom-based, and researchers have sought ways to modify the criteria or use alternative approaches [2; 3; 39].

In one study to assess alternative approaches, survey criteria consisting of a Regional Pain Scale score of at least 8 and a fatigue score of at least 6 was found to be concordant with the ACR criteria in 72% of cases [39]. Clinical diagnosis (the clinician's impression irrespective of the ACR criteria) was concordant with the ACR criteria in 75% of cases. The authors concluded that all diagnostic methods have utility [39]. In another study, an effort to modify the criteria to include the three most common symptoms—morning stiffness, sleep disturbances, and fatigue—yielded a sensitivity of 81%, a specificity of 61%, and an accuracy of 72% [3].

AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA FOR FIBROMYALGIA	
Criteria	
A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met: • WPI ≥7 and SSS score ≥5 or WPI 4–6 and SSS score ≥9. • Generalized pain is present, defined as pain in at least 4 of 5 regions (left upper, right upper, left lower, right lower, axial) • Symptoms have been generally present at a similar level for at least three months.	
Ascertainment	
WPI	Note the number areas in which the patient has had pain over the last week. In how many of the following areas has the patient had pain? Score will be between 0 and 19. • Shoulder girdle, left • Shoulder girdle, right • Upper arm, left • Upper arm, right • Lower arm, left • Lower arm, right • Hip (buttock, trochanter), left • Hip (buttock, trochanter), right • Upper leg, left • Upper leg, right • Lower leg, left • Lower leg, right • Jaw, left • Jaw, right • Chest • Abdomen • Upper back • Lower back • Neck
SSS score	For the symptoms of fatigue, waking unrefreshed, and cognitive dysfunction, indicate the level of severity over the past week using the following scale: 0 = No problem 1 = Slight or mild problems, generally mild or intermittent 2 = Moderate, considerable problems, often present and/or at a moderate level 3 = Severe: pervasive, continuous, life-disturbing problems Considering somatic symptoms[a] in general, indicate whether the patient has: 0 = No symptoms 1 = Few symptoms 2 = A moderate number of symptoms 3 = A great deal of symptoms The final score will be between 0 and 12.
[a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.	
Source: [221; 222]	*Table 5*

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To address the problems inherent in its classification system, the ACR published updated diagnostic criteria for fibromyalgia in 2016 [2]. The ACR used a symptom severity scale and the Regional Pain Scale (renamed the Widespread Pain Index) to construct a new case definition of fibromyalgia: a Widespread Pain Index (WPI) score of 7 or greater and a symptom severity score (SSS) of 5 or more OR a WPI score of 4–6 and a SSS of 9 or greater [2]. The WPI has been found to correlate well with findings of the tender point examination, eliminating the need for that examination [2]. The symptoms evaluated by the SSS are fatigue, cognitive dysfunction, and waking unrefreshed (***Table 5***) [2; 44]. In addition, the new criteria minimizes misclassification of regional pain disorders and eliminates the confusing recommendation regarding diagnostic exclusion [44]. Another advantage is that the criteria can demonstrate change in the individual's health status and allows for fibromyalgia to be seen as part of a continuum [2].

TREATMENT

As with all chronic illnesses, the goal of treatment in fibromyalgia is to reduce symptoms, improve function, and engage the patient's involvement in self-care [22]. Studies have shown that treatment is most effective when it includes the combination of patient education, nonpharmacotherapy approaches (including exercise), and selective pharmacotherapy for persistent symptoms or comorbidities [4; 8; 45; 46; 47; 48].

Treatment guidelines for fibromyalgia have been established by the American Pain Society and EULAR, and subsequent systematic reviews and meta-analyses have provided further findings to support both pharmacologic and nonpharmacologic treatment [4; 46; 49]. Familiarity of guidelines and recommended treatments, especially among primary care providers, is low, and adherence is suboptimal [5; 50]. For example, a substantial number of people with fibromyalgia take pain medications that lack evidence for effectiveness or that are less effective than alternative options [27; 50].

In addition, the practice guidelines for fibromyalgia have many limitations, the most important of which is that their evidence base predates the FDA approval of three drugs for the treatment of the condition. The treatment guidelines may also lack clinical utility because of the crucial need to customize treatment of fibromyalgia according to the unique combination of symptoms in an individual patient. A pooled analysis showed that pain reduction alone does not make people with fibromyalgia feel better; instead, improvements in fatigue, physical functioning, mood, and impact on daily living are important factors in feeling better [51]. These factors must therefore be considered when developing a treatment plan, and optimum treatment will depend on the level of various symptom involvement for the patient [5; 41]. Effective treatment of fibromyalgia may also necessitate guideline-based treatment for comorbidities (e.g., irritable bowel syndrome and restless legs syndrome) [41].

The approach most often used for initial management of fibromyalgia includes patient education and reassurance; an exercise program that combines stretching, aerobic conditioning, and strength training; and selective, low-dose monotherapy aimed at relieving symptoms that do not respond to nonpharmacologic measures.

NONPHARMACOLOGIC TREATMENT

Nonpharmacologic measures are important components of an effective fibromyalgia treatment plan. Strong evidence has been documented for exercise (aerobic and/or muscle-strength training), cognitive-behavioral therapy, and patient education, and the combination of the three components is recommended as the initial management approach [28; 45; 46; 48].

Patient Education

The goal of patient education is to effect a change in the patient's perception of his or her role in managing and coping with symptoms [28]. Patients benefit from an explanation of the disease and reassurance regarding symptoms and prognosis; other topics for discussion are treatment options, sleep hygiene, the importance of conditioning and exercise, and the role of pharmacotherapy for comorbidities such as mood and sleep disorders. There is good evidence that patient education is an essential component of effective treatment [4; 45; 46; 48]. Even a single multidisciplinary educational program was associated with significant improvements in pain, fatigue, morning tiredness, stiffness, anxiety, and depression [45]. Education in a variety of formats has been found to be useful, including lectures, written materials, group discussions, demonstrations, and web-based programs [45; 52]. Healthcare professionals should encourage their patients to take advantage of many reliable online educational resources.

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2015, more than 40 million Americans are foreign-born, 62 million Americans (21% of the population) speak a language other than English at home, and more than 25 million (8.5% of the population) report that they speak English less than "very well" [84]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [85].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [86]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [87; 88].

Exercise

Exercise not only helps to alleviate many fibromyalgia symptoms but also helps to reverse the effects of deconditioning and improve physical fitness [8; 47; 53; 54; 55; 56]. In a study of 207 women who were actively treated with medication for confirmed fibromyalgia, progressive walking, simple strength-training exercises, and stretching activities led to several improvements, including higher scores for functional status, reduced fatigue, better mental health, reduced depression, and greater self-efficacy [53]. The benefits of exercise are enhanced when combined with targeted self-management education [28; 53].

A meta-analysis showed that supervised aerobic exercise training has beneficial effects on physical capacity and symptoms related to fibromyalgia and that strength training may also have benefits on some fibromyalgia symptoms [54]. Another meta-analysis published in 2010 showed that aerobic exercise has a significant positive effect on a variety of disease-related symptoms, with reductions in pain, fatigue, depressed mood, and limitations of health-related quality of life, as well as improved physical fitness [56]. A 2013 Cochrane review found low-quality evidence that resistance training (moderate-to-high intensity) improves functioning, muscle strength, pain, and tenderness in women with fibromyalgia [57]. Other low-quality evidence suggests that aerobic exercise is superior to resistance training for improving pain, but resistance training is superior to flexibility exercise training in women with fibromyalgia for improvements in pain and multidimensional function. Moderate-to-high resistance training is safe for women with fibromyalgia [57].

Both the American Pain Society and EULAR recommend exercise programs as part of treatment for fibromyalgia [46; 58]. The American Pain Society recommends beginning with low levels of exercise and working gradually to a goal of moderately intense aerobic exercise at least two to three times per week [58]. However, fewer than one-third of NFA survey respondents said they engaged in aerobic exercise; more respondents said they participated in "gentle walking" (64%) and stretching (62%), and fewer noted use of physical therapy (24%) or strength training (18%) [27]. Aquatic physical therapy has also been recommended for relief of fibromyalgia-related stiffness [59].

A 2018 report provides evidence that a mind-body treatment approach, specifically a tai chi program, is of equal or greater benefit than standard care aerobic exercise alone [60]. In this blinded, prospective study, 226 adults with fibromyalgia (widespread pain index ≥7 and severity score ≥5) were randomly assigned either to supervised aerobic exercise (24 weeks, twice weekly) or to one of four classic Yang-style tai chi interventions (12 or 24 weeks, once or twice a week). Participants were followed for 52 weeks; the primary outcome was change in the fibromyalgia impact questionnaire scores at 24 weeks compared with baseline. The results showed that improvement in symptom scores was greater for subjects in each of the tai chi groups than for those receiving aerobic exercise. A clinically significant difference was only observed when comparing the highest-intensity tai chi program (twice weekly for 24 weeks) with aerobic exercise. Benefit with respect to secondary outcomes (assessment scores for anxiety, depression, coping strategies, functional limitations, sleep, and quality of life) also favored the tai chi interventions. At 52 weeks the combined tai chi groups continued to show more improvement in primary and most secondary outcomes than the aerobic exercise group.

EULAR notes that exercises should be tailored to the individual patient, and modifications should be made according to the severity of symptoms [46]. For example, a sedentary individual with moderate-to-severe fibromyalgia should begin with breathing, posture, and relaxation training, move to flexibility exercises, then to strength and balance exercise, and finally, to aerobic exercise [55].

Cognitive-Behavioral Therapy

The goal of cognitive-behavioral therapy is to move patients toward more adaptive beliefs about their ability to cope with symptoms, which in turn increases self-management [47]. Cognitive-behavioral therapy is designed to help individuals improve the way they think about fibromyalgia and cope with the overall effects of its symptoms [8]. It is most effective when it focuses on a specific outcome, especially one that is the subject of the patient's maladaptive thoughts and expectations [8; 47].

A systematic review of 23 studies showed that of 30 psychologic treatments for fibromyalgia, cognitive-behavioral therapy was associated with the greatest effect sizes, especially for short-term reduction in pain [61]. In addition to short-term and long-term reductions in pain, cognitive-behavioral therapy has been associated with reductions in sleep disturbances and depression and improvements in functional status [8; 46; 47; 58; 61]. Benefit is typically achieved in 10 to 20 sessions [28]. Despite recommendations for cognitive-behavioral therapy, it may be underutilized. According to the NFA survey, only 8% of respondents had used this strategy [27].

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Cognitive-behavioral therapy has been significantly beneficial in many individuals with psychiatric illnesses, such as depression and anxiety disorders, and so may be most useful for individuals with fibromyalgia who have these symptoms [47]. The individuals most likely to respond are probably those who have greater emotional distress, fewer coping skills, or less social support [28; 47].

Other Approaches

Relaxation techniques are often part of cognitive-behavioral therapy for fibromyalgia, and their effectiveness is generally accepted, even though direct evidence is lacking [47]. Relaxation/meditation was practiced by 47% of the NFA survey respondents [27]. Mindfulness-based stress reduction therapy has also been evaluated; however, only weak evidence exists for benefit in fibromyalgia [62].

The EULAR guidelines include a recommendation (level IIb) for heated pool treatment, with or without exercise, on the basis of studies showing improvement in pain and function [46]. A subsequent meta-analysis of 10 randomized controlled trials demonstrated moderate evidence that hydrotherapy has short-term beneficial effects on pain and health-related quality of life [63].

The lack of fully effective treatments has led patients—and sometimes their healthcare providers—to explore other options to help manage symptoms. Some of these options have no or weak evidence of effectiveness, and the approaches most commonly used by patients are often not recommended practices. For example, the three interventions used most often by the NFA survey respondents were resting (86%); distraction, such as reading or watching television (80%); and heat modalities, such as warm water or hot packs (74%) [27]. The issue is not that these methods are not helpful, rather that the use rates for these approaches are much higher than for many evidence-based recommended strategies [27].

Among the other approaches patients often try are complementary and alternative medicine; between 40% and 90% of individuals with fibromyalgia have tried at least one such method [27; 50; 64]. However, evidence indicates that most of these methods are ineffective. There is limited evidence to support spinal manipulation [65]. Evidence is also lacking on the effectiveness of herbal, nutritional, and dietary supplements (including St. John's wort, ginseng, valerian, melatonin, and botanical oil) for the symptomatic treatment of fibromyalgia [47; 65; 66]. Despite this, approximately 43% to 68% of people with fibromyalgia use such supplements, although they give low ratings for their effectiveness [27; 50]. Given the high rate of individuals with fibromyalgia who seek symptomatic relief from complementary and alternative methods, the American Pain Society guidelines recommend that clinicians ask their patients about their use of such practices and educate them about their effectiveness and possible negative interactions [4].

Methods with greater evidence of benefit include acupuncture and massage therapy. A 2013 Cochrane review found low-to-moderate level evidence that acupuncture (particularly electro-acupuncture) is effective for the treatment of fibromyalgia symptoms compared with no treatment or standard therapy [67]. Acupuncture in general may relieve pain and stiffness, and electro-acupuncture may improve overall well-being, fatigue, and sleep quality. A 2014 meta-analysis of nine randomized controlled trials found that massage therapy (for at least five weeks) has beneficial immediate effects on improving pain, anxiety, and depression in fibromyalgia patients [68]. However, no follow-up data are available to show long-term benefit. Long-term data are similarly unavailable for qigong, a somewhat popular Chinese medical exercise, but low-quality evidence exists for the short-term improvement of pain, quality of life, and sleep quality and very low-quality evidence exists for improvement of fatigue [69]. Increased psychologic well-being is often reported by qigong practitioners.

PHARMACOLOGIC TREATMENT

No single drug has been found to manage all fibromyalgia symptoms, and a combination approach is often used [27; 41]. Antidepressants were the first medications used to treat fibromyalgia; drugs in this class include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [26; 41]. In general, antidepressants reduce pain through a direct effect rather than an indirect effect mediated by an effect on depression [41]. Other drugs that have been shown to be effective include anticonvulsant drugs, some analgesics/muscle relaxants, and nonbenzodiazepines (***Table 6***) [5; 26; 28; 41; 49; 58; 70].

Antidepressants

Both the American Pain Society and EULAR found strong evidence (level I) for the use of a tricyclic antidepressant (amitriptyline) for the treatment of fibromyalgia [4; 46]. The American Pain Society recommends using amitriptyline for the initial treatment of fibromyalgia, whereas EULAR notes that any of a number of antidepressants should be "considered" [4; 46]. According to a 2009 meta-analysis, there is strong evidence for an association between treatment with antidepressant medications and reductions in pain, depression, fatigue, sleep disturbances, depressed mood, and a better health-related quality of life for people with fibromyalgia [75]. Treatment with an antidepressant does not completely eliminate pain, but tricyclic antidepressants have been found to be more effective for pain relief than either SSRIs or SNRIs [4; 75]. Amitriptyline was the fifth leading "ever used" drug in the NFA survey (reported by 55% of respondents), with 42% of those using the drug saying it was helpful [27]. In addition, use of prescription antidepressants was the third-highest ranked intervention overall in the survey [27].

PHARMACOLOGIC TREATMENTS USED IN FIBROMYALGIA			
Drug	**Dose**	**Common Adverse Events**	**Comments**
Antidepressants			
Amitriptyline	25–50 mg PO at bedtime	Nausea, vomiting, dry mouth, dizziness, drowsiness, headache	Recommended by American Pain Society and EULAR
Duloxetine	60 mg PO daily	Nausea, dry mouth, constipation, drowsiness, decreased appetite	Approved by FDA for fibromyalgia in 2008
Milnacipran	50–100 mg PO twice daily	Nausea, headache, constipation, dizziness, hot flush, dry mouth	Approved by FDA for fibromyalgia in 2009
Anticonvulsants			
Pregabalin	300–450 mg PO daily	Diarrhea, dizziness, blurred vision, dry mouth, vomiting	Approved by FDA for fibromyalgia in 2010
Gabapentin	1,200–2,400 mg PO daily	Viral infections (in children), dizziness, somnolence, ataxia	Limited data on effectiveness
Analgesics/Muscle Relaxants			
Cyclobenzaprine	10–30 mg PO at bedtime	Drowsiness, xerostomia, dizziness	Recommended by American Pain Society
NSAIDs	—	—	No evidence to support use, but may be of benefit in treating comorbidities
Glucocorticoids	—	—	No evidence to support use, but may be of benefit in treating comorbidities
Opioids			
Low-dose (tramadol)	200–300 mg PO daily	Hot flush, dizziness, headache, constipation, nausea	Recommended by American Pain Society and EULAR
Potent	—	—	Not recommended; should be used only if all other approaches have been exhausted
Sedative Hypnotics			
Zolpidem	5–10 mg PO at bedtime	Headache, somnolence, dizziness	Improves sleep; no effect on pain
Benzodiazepines and sedatives	—	—	Evidence of effectiveness is lacking

Source: [5; 26; 28; 41; 49; 58; 70; 71; 72; 73; 74] *Table 6*

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Two of the three drugs approved by the FDA are SNRIs: duloxetine and milnacipran [5]. Duloxetine was approved on the basis of two trials. In the first study, duloxetine led to a clinically significant treatment response (at least a 30% reduction in pain severity on the Brief Pain Inventory) in more than half of the study participants [76]. Two doses were evaluated: 60 mg once daily and 60 mg twice daily; both doses were associated with significantly higher response rates than that for the placebo group [76]. Duloxetine also significantly improved function and quality of life. Similar results were achieved with the same doses of the drug in the other study [77]. Neither study showed improvement in sleep; however, duloxetine did not interfere with sleep [41; 49; 76; 77]. The drug was also well tolerated, and nausea was the most common side effect. Given the similarity in response with the two doses of duloxetine, the approval is based on the once-daily dose. A 2014 Cochrane review indicated that there is a lack of efficacy data, but that 60–120 mg daily doses were associated with a greater improvement in mental symptoms than in somatic physical pain [78].

Two studies of milnacipran demonstrated the effectiveness of the drug in achieving a composite endpoint of improvement in scores for pain (30% improvement on a visual analog scale), patient global assessment ("very much" or "much" improved), and physical component of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (six points) [79; 80]. The studies also evaluated the effect of the drug on pain only (improvement in pain and patient global assessment but not SF-36). Two doses were used: 50 mg twice daily and 100 mg twice daily. In both studies, milnacipran was associated with significant improvements in pain, fatigue, patient global assessment, and physical function [79; 80]. Further follow-up has shown the efficacy to be maintained for 12 months [41]. The drug was well tolerated; the most common side effects were mild-to-moderate nausea and headache, both of which resolved with continued use of the medication [79; 80]. The FDA approved milnacipran at both doses.

A systematic review to compare the effectiveness of the three antidepressants demonstrated several differences [81]:

- Amitriptyline was superior to both duloxetine and milnacipran in reducing pain, sleep disturbances, fatigue, and limitations of health-related quality of life.
- Duloxetine was superior to milnacipran in reducing pain, sleep disturbances, and limitations of health-related quality of life.
- Milnacipran was superior to duloxetine in reducing fatigue.
- No differences in tolerability were found among the three drugs.

Anticonvulsants

The third FDA-approved drug for the treatment of fibromyalgia is pregabalin, an anticonvulsant agent. Several studies have shown pregabalin to significantly improve pain, patient global assessment, fatigue, and health-related quality of life, as well as sleep disturbances [41; 72; 82]. The effect of the drug has lasted for as long as six months [41]. The drug was well tolerated, with the common side effects being dizziness and sedation, which tended to resolve with time of treatment [41].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Scottish Intercollegiate Guidelines Network, pregabalin (titrated up to at least 300 mg daily) is recommended for the treatment of patients with fibromyalgia.

(https://www.sign.ac.uk/assets/sign136.pdf. Last accessed July 23, 2020.)

Level of Evidence: A (At least one high-quality meta-analysis, systematic review, or randomized controlled trial directly applicable to the target population)

Anticonvulsants have been evaluated in several trials, and the American Pain Society found level II evidence for this class of drug, whereas the later EULAR guidelines note level I evidence for pregabalin specifically [4; 46; 49]. Another anticonvulsant drug, gabapentin, has also demonstrated efficacy with respect to pain, patient global assessment, function, and sleep [41; 70; 72]. Gabapentin has not been approved by the FDA to treat fibromyalgia, and the drug is not specifically noted in treatment guidelines [4; 46]. Approximately one-third of the respondents in the NFA survey said they had "ever used" gabapentin, and 46% who had used it considered the drug helpful [27]. The side effect profile of gabapentin is similar to that of pregabalin, but the pharmacokinetic and pharmacodynamic profile is not as favorable [41]. An overview of systematic reviews of anticonvulsants showed that both drugs had a modest effect on pain reduction, and it was not possible to conclude if one drug was better than the other [72]. The long-term safety and efficacy of both drugs is also unknown, and many patients are expected to discontinue therapy due to a high incidence of adverse effects. The overview found no evidence of clinical benefit with any other anticonvulsant, including carbamazepine [72].

Analgesics

With a primary symptom of pain, fibromyalgia has often been treated with analgesics. According to the NFA survey, acetaminophen, ibuprofen, and naproxen were the top three ever-used medications (94%, 87%, and 66%, respectively) [27]. Slightly more than one-third to about one-half of the survey respondents said that these medications were helpful [27]. In another study, nearly 30% of 434 women with

fibromyalgia reported taking NSAIDs [50]. However, with no inflammatory mechanism, fibromyalgia is not expected to respond to NSAIDs, and there is no evidence to support the use of NSAIDs or glucocorticoids as a treatment modality [4; 46]. NSAIDs may be of benefit in relieving pain associated with comorbidities, such as osteoarthritis, rheumatoid arthritis, or systemic lupus, which may account for their high rate of use in the NFA survey [27; 41].

Strong evidence has also been documented for cyclobenzaprine, which has both muscle relaxant and tricyclic antidepressant properties [26; 58; 83]. A systematic review of five randomized controlled trials showed that individuals treated with cyclobenzaprine for fibromyalgia were three times as likely to report overall improvement and to note reductions in symptoms, especially sleep disturbances, than controls [83]. Among the NFA survey respondents, 64% had ever used cyclobenzaprine and 58% of these patients considered the drug to be helpful [27].

Neither the American Pain Society nor EULAR recommend the use of potent opioids for the treatment of fibromyalgia, noting that they should be used only if all other pharmacologic and nonpharmacologic options have been exhausted [4; 46]. The American Pain Society found moderate evidence (level II, III) and EULAR documented level I evidence for tramadol, a mild opioid [4; 46]. The drug is recommended in both guidelines and may be used alone or as an adjunctive measure [41; 46; 58]. The dose of tramadol should be increased slowly over time and should be tapered gradually when discontinued [4]. Caution should be used when prescribing tramadol because of the risk of dependence and abuse [46].

Sedative Hypnotics

Benzodiazepines and sedatives are not recommended for the treatment of fibromyalgia symptoms [28]. Zolpidem, a short-acting nonbenzodiazepine sedative, has been used to improve sleep in people with fibromyalgia, but because zolpidem does not relieve pain, it is useful only as an adjunct medication, and it has not been included in treatment guidelines for fibromyalgia [4; 41; 46]. Approximately 41% of the NFA survey respondents said they had ever used the drug, and 64% of these individuals considered it helpful [27]. In general, prescription sleep medication was the intervention that respondents considered the most effective of all interventions [27].

FOLLOW-UP

Individuals with fibromyalgia should be followed up routinely to assess response to treatment. Follow-up visits also offer an opportunity for healthcare professionals to encourage their patients to comply with pharmacologic and nonpharmacologic treatment. Reinforcement for the need to exercise is especially important, as 68% to 83% of people with fibromyalgia have been found to not engage in aerobic exercise [27; 55]. Rates of exercise among the general population are below optimum, and people with fibromyalgia need added encouragement because of many symptoms that may be perceived as barriers (e.g., fatigue, pain).

One approach to enhance adherence to an exercise program is to begin pharmacologic treatment targeting the most distressing or severe symptoms and then provide education about exercise as symptoms begin to improve [28; 55]. It is especially important to address sleep disturbances and fatigue. In contrast to recommendations for the general population, increasing lifestyle activity is not effective as exercise for individuals with fibromyalgia; instead, clinicians should encourage their patients with fibromyalgia to conserve their energy in daily life in order to have the ability to comply with prescribed exercises [55].

The authors of one review of nonpharmacologic treatment suggest that clinicians use the acronym ExPRESS to follow principles of nonpharmacologic pain management [47]:

- **Ex**: Exercise
- **P**: Psychiatric (i.e., addressing psychiatric comorbidities to help improve pain and disability)
- **R**: Regain function (helping patients pace activities to avoid doing too much on days they feel well)
- **E**: Education (referral to reliable resources)
- **S**: Sleep hygiene
- **S**: Stress management (such as cognitive-behavioral therapy and relaxation techniques)

PROGNOSIS

Fibromyalgia symptoms will persist in most individuals, but the majority still report that they feel better overall than at the time of diagnosis [8; 28]. Better outcomes have been associated with greater self-efficacy, help-seeking behavior, increased level of exercise, and pacing of activities [28].

Customer Information/Answer Sheet/Evaluation insert located between pages 104–105.

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COURSE TEST - #94300 FIBROMYALGIA

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 3 credit activity must be completed by July 31, 2023.

1. The prevalence of fibromyalgia in women is highest in what age-group?
A) *40 to 49 years of age*
B) *50 to 59 years of age*
C) *60 to 69 years of age*
D) *70 to 79 years of age*

2. For first-degree relatives of individuals with fibromyalgia, risk of developing the disease is
A) *double.*
B) *three times higher.*
C) *eight times higher.*
D) *100 times higher.*

3. Which of the following is most likely to be reported as an exacerbating factor for fibromyalgia symptoms?
A) *Sleeping problems*
B) *Emotional distress*
C) *Strenuous activity*
D) *Changes in the weather*

4. The three primary manifestations of fibromyalgia are
A) *stiffness, paresthesias, and anxiety.*
B) *stiffness, fatigue, and sleep abnormalities.*
C) *balance problems, headaches, and dry mouth.*
D) *depression, fatigue, and cognitive dysfunction.*

5. The American Pain Society recommends using what method/tool as the primary source for pain assessment in patients with fibromyalgia?
A) *Self-report*
B) *Visual analog scale*
C) *Brief Pain Inventory*
D) *Short Form–McGill Pain Questionnaire*

6. Which of the following features distinguishes hypothyroidism from fibromyalgia?
A) *Hair loss*
B) *Mental slowing*
C) *Profound fatigue*
D) *Muscle weakness*

7. According to a systematic review in which three antidepressants were evaluated for treatment of fibromyalgia, which of the following is TRUE?
A) *Duloxetine is better than amitriptyline in reducing pain.*
B) *Duloxetine is better than milnacipran in reducing fatigue.*
C) *Milnacipran is better tolerated than amitriptyline or duloxetine.*
D) *Amitriptyline is better than milnacipran in reducing sleep disturbances.*

8. Which of the following is TRUE regarding anticonvulsants for the treatment of fibromyalgia?
A) *The long-term safety and efficacy of pregabalin is unknown.*
B) *Pregabalin and gabapentin are both approved by the FDA for the treatment of fibromyalgia.*
C) *Gabapentin is associated with a higher rate of adverse events than pregabalin.*
D) *Pregabalin has improved pain and fatigue but not other fibromyalgia symptoms.*

Test questions continue on next page ➔

9. For individuals with fibromyalgia, cyclobenzaprine is most effective in reducing

A) *pain.*
B) *fatigue.*
C) *stiffness.*
D) *sleep disturbances.*

10. Which of the following is NOT a recommended nonpharmacologic approach to fibromyalgia?

A) *Bed rest*
B) *Exercise*
C) *Patient education*
D) *Cognitive-behavioral therapy*

Be sure to transfer your answers to the Answer Sheet insert located between pages 104–105.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

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Smoking and Secondhand Smoke

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board:
10 ABIM MOC Points, 10 ABP MOC Points, 10 ABO MOC Points.

Audience
This course is designed for physicians, nurses, and other healthcare professionals who may intervene to stop patients from smoking.

Course Objective
The purpose of this course is to provide physicians, nurses, behavioral health professionals, and other members of the interdisciplinary team with a formal educational opportunity that will address the impact of tobacco smoking and secondhand exposure in public health and disease as well as interventions to promote smoking cessation among their patients.

Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the history of tobacco and its impact on society.
2. Define the prevalence and economic impact of tobacco smoke exposure on public health.
3. Differentiate between available tobacco products.
4. Describe the neurophysiologic effects and addictive components of tobacco smoke.
5. Describe the anatomy and physiology of smoke inhalation, and outline key points in learning of behavior.
6. Define the psychologic and physiologic aspects of smoking dependence.
7. List the common health complications related to smoke exposure.
8. Identify the common comorbid conditions of tobacco users.
9. Describe the developmental complications related to prenatal exposure to smoke.
10. Define the effects of exposure to secondhand smoke for children and adults.
11. Identify the methods of detecting and measuring tobacco smoke exposure.
12. Define thirdhand smoke.
13. Outline the methods of tobacco cessation interventions, including necessary considerations for non-English-proficient patients.
14. Define the treatment modalities for tobacco addiction, including pharmacologic options.
15. Identify strategies to reduce exposure to tobacco smoke.

Faculty
Mark S. Gold, MD, DFASAM, DLFAPA, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. (A complete biography appears at the end of this course.)

Faculty Disclosure
Contributing faculty, Mark S. Gold, MD, DFASAM, DLFAPA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
John M. Leonard, MD

Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Designations of Credit
NetCE designates this enduring material for a maximum of 10 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 10 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Special Approvals
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INTRODUCTION

Tobacco smoke exposure is a major cause of the nation's most serious and preventable health problems. This course provides comprehensive clinical education on tobacco smoke in primary care and public health. It addresses core competencies as well as knowledge, assessment, and treatment-based competencies of healthcare providers. It covers the history of tobacco, epidemiology of tobacco use, tobacco smoke metabolism, dependence, treatment, and relapse. It also addresses complications associated with direct and indirect exposure to tobacco smoke, effects of prenatal exposure, methods of screening for exposure, and brief intervention training. This course includes a review of available screening tools, predisposing genetic factors, associated risk and protective factors, withdrawal symptoms and treatment, lab testing procedures, diagnostic tools, and age and gender issues.

DEFINITIONS

A clear understanding of tobacco use and smoking is dependent on a knowledge of the basic underlying concepts associated with addiction [1].

Tolerance: The need for greatly increased amounts of the substance to achieve intoxication (or the desired effect) or a markedly diminished effect with continued use of the same amount of the substance.

Withdrawal: Maladaptive behavioral change, with physiologic and cognitive concomitants, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing unpleasant withdrawal symptoms, the person is likely to take the substance to relieve or to avoid those symptoms, typically using the substance throughout the day, beginning soon after awakening.

Substance use disorder: A cluster of cognitive, behavioral, and physiologic symptoms indicating that the individual continues using the substance despite significant substance-related problems. There is also an underlying change in brain circuits that may persist beyond detoxification.

HISTORY OF TOBACCO USE AND RESTRICTION

Tobacco was the first export of the New World and was marketed in Europe as a remedy for stress, ulcers, headaches, asthma, and even rheumatism. Tobacco's botanical name, *Nicotiana tabacum*, is derived from Jean Nicot, a French ambassador to Portugal who, convinced of tobacco's medicinal value, sent the plant's seeds to the royal family in France [2].

Tobacco product use has been discouraged in the United States and abroad for centuries. In 1586 the first recorded tobacco prohibition was issued by Pope Sixtus V, who declared it a sin "for any priest to use tobacco before celebrating or administering communion." In 1604, King James I published *A Counterblaste to Tobacco*, describing smoking tobacco as, "a custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, [and] dangerous to the Lungs" [3]. Tobacco use and distribution saw further restrictions across the globe in the early 1600s. King James I levied heavy taxes on tobacco, the czar of Russia exiled tobacco users, and the Chinese executed persons caught selling tobacco [4].

However, in contrast to strict regulations found elsewhere in the world, tobacco was brought to the United States as a cash crop. The 1880s saw the invention of an automated cigarette-making machine, which paved the way for cigarettes to become the predominant form of tobacco with the start of World War I. The twentieth century also experienced the first major outcry against tobacco in the United States. Though medical concerns were suggested, the first tobacco prohibition movements in the United States were primarily driven by religious and moral motivations. Groups including religious leaders, the Women's Christian Temperance Union, and the Non-smokers Protective supported efforts for prohibition of tobacco. However, strong public resistance against alcohol prohibition also led to the repeal of tobacco restrictions, and by the 1930s these restrictions had all but vanished [5].

One of the lesser known consequences of World War II was that German smoking research and corresponding social change were not acknowledged by the rest of the world. In the 1930s and early 1940s, Germany conducted an aggressive anti-smoking campaign based on medical research from the 1920s and 1930s, which elucidated the carcinogenic effects of smoking. As part of the German movement aimed to preserve a racial "utopia" of pure, healthy Germans, they banned smoking in the workplace, imposed cigarette taxes, restricted advertising and farming, and implemented programs to eliminate smoking [6; 7].

Associations between smoking and cancer were not published in the United States until the 1950s and 1960s. The 1964 publication *Smoking and Health: Report of the Advisory Committee to the Surgeon General* led to immediate political notice of the tobacco issue and the advent of programs and policies to reduce smoking [8]. Anti-tobacco policies have included taxation on tobacco products, increased insurance premiums, warning labels, public health campaigns, and restrictions on tobacco sales to minors, smoking in public areas, and tobacco marketing. Prior to 1964 there were few if any laws regulating involuntary secondhand smoke (SHS) exposure. Studies revealing the detrimental effects of SHS to nonsmokers led to new anti-smoking legislation. As of June 2009, the General Services Administration (GSA) has established smoke-free environments for federal facilities.

Interior areas previously designated for smoking have been closed and smoking is prohibited in courtyards and within 25 feet of doorways and air intake ducts in outdoor spaces [9]. Further, nearly all 50 states have laws restricting smoking in places such as schools, public transportation, government buildings, elevators, and restaurants. In accordance with federal law, smoking is prohibited on buses, trains, and domestic airline flights. Such laws have decreased cigarette consumption by making smoking less socially acceptable and more inconvenient [5].

On June 22, 2009, President Barack Obama signed HR1256: The Family Smoking Prevention and Tobacco Control Act. This was enacted as a result of several findings made by Congress, specifically that almost all new users of tobacco products are younger than the minimum legal age to purchase such products. Under this law, the U.S. Food and Drug Administration (FDA) now has the authority to regulate tobacco products [10]. The FDA had previously attempted to assert jurisdiction under the Food, Drug, and Cosmetic Act in 1996 to regulate tobacco advertising, labeling, and purchasing restrictions (e.g., federal minimum age of 18 years and requiring retailers to check identification). However, the tobacco industry retaliated by suing the federal government, as there was no set legislation to give the FDA this authority. As a result, all FDA regulations were dropped [11]. Due to the 2009 law, the FDA can now establish a minimum age of sale of tobacco products, test and report on tobacco product ingredients/additives, prohibit cigarettes from containing any flavors other than tobacco or menthol, and apply the same restrictions on labeling and advertising of cigarettes to smokeless tobacco products. Of note, this law states that the FDA cannot ban existing products or require nicotine be eliminated from any product.

In 2017, the FDA unveiled a comprehensive plan on tobacco and nicotine regulation to reduce the number of preventable deaths caused by smoking and tobacco use. The two key areas of focus of this plan are reducing the nicotine levels in combustible cigarettes to render them minimally or nonaddictive and harnessing new forms of nicotine delivery that could allow currently addicted adult smokers to get access to nicotine without many of the risks associated with using combustible tobacco products. Similar to the 2009 policy, this plan will also explore the extent of tobacco flavoring in attracting youth and new smokers; menthol flavoring will be included in this plan. Of note, this policy only affects newly regulated tobacco products and will not affect any current requirements for cigarettes and smokeless tobacco. As of 2019, the plan was still in development and the FDA was continuing to seek public comment and expert opinion [472; 474].

PREVALENCE AND ECONOMIC IMPACT OF SMOKING

Approximately 480,000 Americans die each year as a result of active and/or passive smoking-related health consequences [12]. Despite the seemingly well-known and highly publicized health consequences of smoking, 13.9% of the U.S. population 18 years of age or older are current cigarette smokers [460]. Former U.S. Assistant Secretary for Health Howard Koh asserted that although evidence-based tools were successful in substantially reducing smoking prevalence between 1997 and 2004, efforts were not applied to their full potential nationwide, limiting the efficacy of anti-smoking campaigns [14]. Other experts have attributed declines in cigarette smoking to anti-smoking advertisements, stigma, smoking bans, and increased taxation [460]. Evidence-based tools remain valuable, indicated by slow, steady downward prevalence trends since 1997. However, they are only useful if they reach an audience. These tools seem not to be preventing the initiation of new smokers, despite the overall reductions in use [14; 15].

Nearly 1.8 million Americans initiated cigarette smoking in 2016, continuing a downward trend noted between 2002 and 2013 (ranging from 1.9 to 2.2 million); 40.6% of these were younger than 18 years of age [13]. About one-third of new smokers will ultimately die from a smoking-related illness [16]. Higher levels of education are correlated with a lower likelihood of having smoked cigarettes in the past month [13]. The number of first-time cigar users is slowly declining, from 2.8 million in 2011 to 2.4 million in 2016 [13]. In 2016, current use of any tobacco product was highest among American Indians/Alaska Natives (42.6%) followed by persons of two or more races (40.2%), whites (31.3%), blacks (27.8%), Hispanics (22%), and Asians (11.9%) [13].

Approximately 41,000 adult nonsmokers die each year from exposure to SHS, and this continues to be a significant environmental risk in the United States [19]. According to a 2009 study by Ellis and colleagues, the prevalence of smoking in New York City was lower than the national average (23.3% vs. 29.7%), but the proportion of nonsmoking adults with elevated cotinine levels was higher (56.7% vs. 44.9%), especially among Asians, even after close to two years after implementation of smoke-free workplace legislation [20]. They attribute this finding to the large amounts of people in such small proximity (26,000 people and 10,000 housing units per square mile vs. the national average of 80 people and 33 housing units per square mile) [20]. In a 2017 study, Perlman and colleagues reviewed cotinine levels in New York City nonsmokers, and found that 37.1% had elevated levels [17]. It is thought that this reduction is a result of smoke-free air policies enforced within the previous 10 to 15 years.

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The researchers also agreed that greater population density and pedestrian exposure continued to contribute to the high number of nonsmokers with elevated cotinine levels [17].

Tobacco use is one of the most expensive addictive behaviors in the United States. In 2015, an estimated 299.9 billion cigarette stick equivalents (based on the weight of 0.0325 ounces of tobacco per cigarette) were consumed in the United States, of which 262.7 billion were cigarettes; the rest were other combustible tobacco products [21]. This accounted for $93.9 billion in national expenditures on cigarettes alone in the 2017 fiscal year [23].

Smoking-related costs in the United States are staggering. The total annual public and private healthcare expenditures caused by smoking are estimated to be greater than $300 billion, including nearly $170 billion in direct medical costs and more than $156 billion in lost productivity related to premature death and exposure to SHS [12].

TOBACCO AND NICOTINE PRODUCTS

Cigarette smoking is on the decline in the United States, but use of other tobacco products is not [21]. In addition to a rise in use of smokeless tobacco, people across the United States (especially youth) are using e-cigarettes, cigars, cigarillos (small cigars), hookahs, kreteks, pipes, and bidis (or beedis) [18; 25]. Unfortunately, each of these products is just as dangerous (if not more so) as use of cigarettes. Cigarettes are defined by the U.S. Department of the Treasury as "any roll of tobacco wrapped in paper or in any substance not containing tobacco," while cigars are defined as "any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco" [26]. Cigars also differ from cigarettes in processing; they consist of filler, a binder, and a wrapper, all made of air-cured and fermented tobaccos [27]. Cigars show significant variability in physical and chemical characteristics, with total nicotine content ranging from 10.1 mg to 444 mg per cigar, length ranging from 68.0 mm to 213.5 mm, and diameter ranging from 8.0 mm to 20.5 mm [28]. Due to their size and makeup, smokers can spend up to an hour smoking a single cigar; therefore, its ensuing effects (e.g., rates of cancer, chronic obstructive pulmonary disease [COPD]) are more pronounced. Cigarillos, or "little cigars," are generally about half the size of a normal cigar, weighing 1.5 to 3 g on average [29]. Many types are made to look like cigarettes and are sold in packs of 20 with filter tips. Cigarillos are perceived as a less addictive, less harmful, and less expensive alternative to cigarette use [30; 31].

Due to increased federal taxation on cigarettes, cigarette tobacco, and small cigars, many consumers apparently switched to smoking products virtually identical to cigarettes or small cigars, but classified as large cigars, or from smoking roll-your-own tobacco to smoking pipe tobacco [22]. Subsequent to the 2009 tax increase and intensified FDA regulation, many companies simply relabeled cigarette rolling tobaccos as pipe tobaccos (not subject to increased taxation) [21]. Sales of "pipe tobacco" increased from 5.2 million pounds in 2009 to 43.7 million pounds in 2013 (a 740% change) while roll-your-own tobacco sales dropped from 21.3 million pounds to 3.8 million pounds [22]. Following a similar relabeling and marketing effort for small cigars, sales of large cigars jumped from 5.8 billion sticks in 2009 to more than 12.4 billion sticks in 2013, while small cigars decreased from 5.7 billion sticks to 0.7 billion sticks in the same years. In 2016, the FDA extended its limitations for tobacco products to include e-cigarettes, vaporizers, and other electronic nicotine delivery systems [458]. As a result, these products must include warnings and manufacturers must submit documentation to the FDA for review and limit sales to persons 18 years of age or older. The goals of these regulations are to increase public health awareness and, especially, reduce marketing and sales to adolescents, who are commonly targeted by providing tobacco flavors including apple, cherry, cream, grape, "jazz," strawberry, and wine. Before this ruling, there were no federal laws restricting sales of these types of products, but an alarming increase in unregulated tobacco products, especially among high school students, prompted the FDA to enforce regulations.

The rise of e-cigarettes in the past decade has introduced new variables in the prevention and treatment of nicotine addiction. Originally marketed as a smoking cessation tool, e-cigarettes are electronic products that typically deliver nicotine in the form of an aerosol [456]. Most e-cigarettes consist of a cartridge (which holds a liquid solution containing varying amounts of nicotine, flavorings, and other chemicals), a heating device (vaporizer), and a power source (usually a battery) [457]. In many e-cigarettes, puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge. The resulting aerosol or vapor is then inhaled (called "vaping") [457]. It is unclear if this delivery method decreases the risks seen with conventional tobacco smoking; however, it does introduce the risks of toxicity associated with consumption of the potent e-liquid.

In 2017, 2.8% of adults were current e-cigarette users. Adults 25 to 44 years of age have the highest rate of e-cigarette use (22.5%), followed by those 45 to 64 years of age (21.3%), 18 to 24 years of age (18.3%), and older than 65 (11%) [456]. Use is much higher among men (24.8%) than women (14.2%).

Adolescent use of e-cigarettes has skyrocketed from 1.5% in 2011 to 20.8% in 2018, making it the number one form of tobacco used among youth [459; 465]. In 2018, the FDA issued more than 1,300 warnings and fines to retailers who illegally sold e-cigarette products to minors [464].

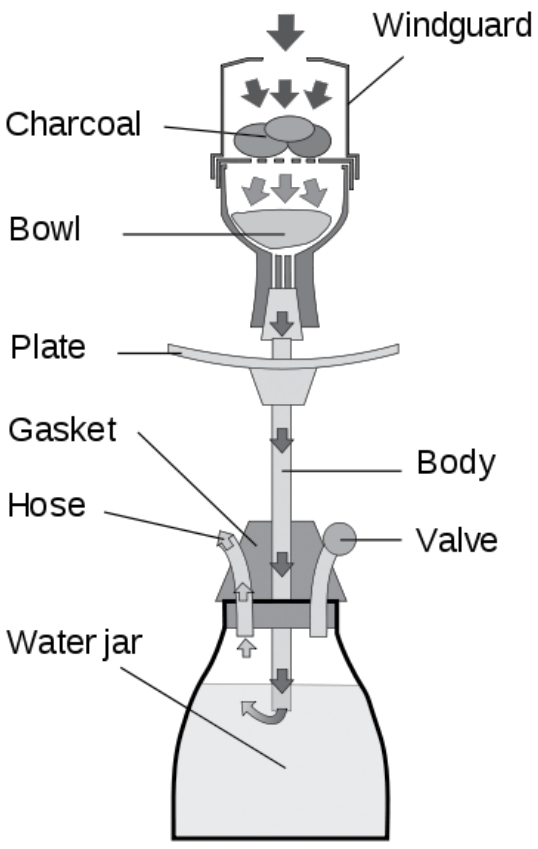
According to the Centers for Disease Control and Prevention (CDC), large cigar consumption increased 116% from 2000 to 2017, with cigar smoking being the third most common form of tobacco use among youth [32; 33]. However, it has been shown that adolescent (and likely adult) cigar use is significantly underestimated due to systematic misreporting on statewide surveys, which is mainly attributed to the language and definitions used in questions that assume knowledge of all types of cigars [34]. For example, it was found that more than half of Black & Mild (brand of cigars and cigarillos) users did not report any cigar/cigarillo use on a 2009 Virginia survey, largely because the usage of the terms "cigar" or "cigarillo" for this (and other similar products) is not common in the youth- or culture-specific lexicon.

Bidis consist of sun-dried tobacco, finely ground and rolled into a leaf of the *Diospyros melanoxylon* plant native to India. They contain concentrated tobacco, with an average 21.2 mg/g of nicotine compared with 16.3 mg/g of nicotine in filtered and 13.5 mg/g in unfiltered cigarettes, but have less total nicotine because they are shorter [35]. Nonetheless, an unfiltered bidi can release three to five times more tar and nicotine and contain more ammonia and carbon monoxide (CO) than a regular cigarette. Bidis look similar to small cigars or marijuana cigarettes and are available filtered or unfiltered in many flavors, including vanilla, chocolate, strawberry, cherry, and menthol [36]. Bidis are not commonly used in the United States, and sale and distribution is banned in some states (e.g., Illinois, Vermont, West Virginia). However, these products are available on the Internet [37].

Kreteks, or clove cigarettes, are composed of a mixture of tobacco (60% to 80%) and ground clove buds (20% to 40%), available with or without filters [38]. A popular, representative kretek brand contains less nicotine than popular cigarettes (7.39 mg), but smokers extract equal amounts of nicotine by altering smoking behavior [39]. For example, clove cigarettes can be smoked slower, using more puffs. Overall, smokers will do whatever is necessary to achieve plasma levels of nicotine comparable to their usual brand of cigarette.

A hookah is a type of waterpipe comprised of a head or bowl, plate, body, jar, hose, and mouthpiece (***Figure 1***). The body of the hookah fits down into the jar, which is partially filled with water, although any liquid (e.g., alcohol, juice) can be used. Tobacco is placed in the bowl at the head of the body and covered with a filter, such as perforated tin foil, and then burning embers or charcoal is placed above it (and sometimes covered by a cap). The hot air from the charcoal roasts the tobacco and the ensuing smoke is passed down into the liquid in the jar where it is partially filtered, diluted, and cooled. The smoke then bubbles up and passes through the hose and mouthpiece for inhalation. Repeated inhalation is required to keep the tobacco burning. The plate stores dead coals/embers. The types of tobacco used for hookah are *ajami* or *tumbak*, which is a pure, dark tobacco paste; "honeyed" or *tobamel* or *maassel*, containing 70% honey or molasses and featuring flavors (e.g., apple, mango, banana); or *jurak*, which may be sweetened or contain fruits or oils. It is commonplace to use 10–20 g at a time, and these tobaccos may be mixed with other drugs [40]. Smoking sessions last up to an hour or longer, and it has been reported that the nicotine content of the tobacco used for hookah is higher than that in cigarettes [41]. Thus, the smoker is exposed to a higher volume of smoke for longer periods (not to mention those in the vicinity). A report from the World Health Organization states that a hookah user may inhale as much smoke in one session as a cigarette smoker would after consuming at least 100 cigarettes [42]. Contrary to popular belief, waterpipe smoking is not safer or less addictive than cigarette

SCHEMATIC OF A WATERPIPE



Source: [46] *Figure 1*

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smoking [43]. The FDA began regulating the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of tobacco mixtures used for hookah in 2016 [24]. Hookah smoke contains higher concentrations of CO, nicotine, tar, heavy metals, and carcinogens, likely because of its method of use (i.e., tobacco mixtures heated by quick-burning charcoal or wood embers and inhalation through use of a plastic hose for an hour or longer) [44; 45]. It is also common to share a hookah, so users are also at risk of exposure to infections (e.g., herpes due to sharing of the mouthpiece) [46]. Hookah pipe smoking may be a gateway to cigarette smoking and other drug use. Although policies are in place to ban smoking in many public places, many times, hookah use is exempt because it is done in places which identify themselves as "tobacco bars," waterpipe smoking areas are set up outside, or the smoking is done in places where tobacco is sold.

TOBACCO-RELATED CONCEPTS

For many years, efforts to make cigarettes "safer" have been pursued as a compromise solution [48]. Filtering devices have been used to selectively reduce cigarette smoke constituents for almost 60 years [49]. Studies from the 1970s concluded that charcoal filters can remove up to 66% of ciliotoxic agents from mainstream smoke, and cellulose acetate filter tips can eliminate up to 75% of *N*-nitrosamines, which are known volatile carcinogenic compounds [50; 51]. However more recent studies have shown that neither type of filter is effective for reducing the free radical and reactive oxygen species content in the particulate or gas phase of cigarette smoke [52]. Additionally, remnant (i.e., post-filter) aqueous tar can cause the formation of DNA adducts, particularly the mutagenic 8-Oxo-2'-deoxyguanosine (8-oxo-dG).

The FTC performs tar, nicotine, and CO content measurements in all domestic cigarette varieties sold in the United States, which numbered almost 1,300 in 1998, the last year the report was conducted. The FTC defines tar as the particulates of cigarette smoke minus water and alkaloids, such as nicotine, detected using a method developed in 1966 [53]. In 2016, 99.7% of cigarettes sold in the United States had filters, and the FTC reported that 87.9% of the market share of cigarettes had less than 15 mg of tar, compared with only 2% in 1967 [53; 54]. Nevertheless, epidemiologic evidence does not indicate that modern cigarettes are any safer. Smokers participating in the Cancer Prevention Study II (CPS-II) from 1982 to 1988 manifested an almost sixfold increase in lung cancer death compared to Cancer Prevention Study I (CPS-I) participants during 1959 to 1965, even though filter tips were introduced in the 1950s and only the latter group benefited from their implementation [55]. Smoking pattern compensation and use of stronger tobacco strains may be at least partially responsible for this paradoxical trend.

Filter vents, usually shaped in rings of small perforations along the filter, allow air to mix with smoke, diluting the amount of tar, nicotine, and CO detected by the FTC method [53]. Interestingly, as many as 58% of smokers of cigarettes with tar less than approximately 7% (formerly labeled "ultralight") and 53% of smokers of cigarettes with tar levels of 8–14 mg of tar (formerly labeled "light") cover these vents to some extent [56; 57]. Blocking half of the vents of a 4.4 mg tar cigarette, as is done when smokers pinch the cigarette with their fingers or hold the cigarette in their lips, increases yields of tar by 60%, nicotine by 62%, and CO by 73% [58]. Poor reliability of the FTC method is further made evident in the work of Byrd and Robinson, who concluded that the "FTC yield cannot precisely predict nicotine uptake for an individual smoker" and "nicotine uptake by smokers is influenced by…many possible smoker-controlled parameters" [59]. Interestingly, this publication originates from the R.J. Reynolds Tobacco Company. Another contributing factor to the increase in mortality related to smoking may be the concentration of nitrate in tobacco leaves, one of the most important precursors for the endogenous formation of *N*-nitrosamines during smoke inhalation [60]. Cigarette nitrate content has increased from 0.5% in the 1950s to 1.2% to 1.5% in the late 1980s, possibly due to the increased use of chemical fertilizers and the introduction of plant ribs and stems into U.S. tobacco blends [61]. The carcinogenic potential of nitrosamines has been well documented.

All in all, efforts to reduce the health hazards of smoking leave much to desire, and in spite of filter tip implementation and reportedly lower tar values, cigarettes remain a serious health hazard, affecting smokers and those around them.

CIGARETTE SMOKE

Cigarette smoke is a complex mixture of more than 7,000 components, including nicotine, aromatic hydrocarbons, sterols and oxygenated isoprenoid compounds, aldehydes, nitriles, cyclic ethers, and sulfur compounds [62; 63; 134]. At least 70 of these components are known to cause cancer [134]. Firsthand smoke is defined as the smoke that the smoker inhales. Smoking tobacco products also generates environmental tobacco smoke, also known as SHS and passive smoke, which consists of both exhaled mainstream and sidestream smoke. These two forms of smoke differ in chemical composition and have different temperatures and oxygen levels during generation. The burning end of a cigarette produces sidestream smoke, which in turn is the main component of SHS. Some known toxins of the thousands of chemical constituents in tobacco smoke are also present in SHS, including benzene, cadmium, ethylbenzene, formaldehyde, hydrazine, lead, limonene, methylamine, methylene chloride, nicotine, pyridine, toluene, and radioactive polonium-210 [64; 65; 66]. One study identified indoor air pollution from SHS as 10 times greater than diesel car exhaust [67].

Many of the diseases once thought only to be caused by active smoking have now been authoritatively linked to environmental tobacco smoke [62; 68]. This finding is not surprising considering that many of the harmful components found in both firsthand smoke and SHS are more concentrated in SHS. Nicotine, tar, nitric oxide, and CO levels have been shown to be nearly twice as concentrated in SHS. Other harmful chemicals preferentially formed in SHS include carcinogenic aromatic amines (e.g., o-toluidine, 2-naphthylamine, and 4-aminobiphenyl) [62; 65; 69].

POTENTIALLY THERAPEUTIC COMPONENTS OF TOBACCO

According to Lans et al., the crushed leaves of *Nicotiana tabacum* are applied to wounds in Guatemala, and tobacco steam vapor is considered a cure-all in Latin America and the Caribbean. In addition to its most addictive component, nicotine, the tobacco plant contains many enzymes, flavonoids, and coumarins and malic, citric, and phenolic acids [70]. In a case-control study by Sandler et al., tobacco use and secondhand exposure (e.g., parents had smoked) reduced the risk of developing ulcerative colitis [71]. Plants of the genus *Nicotiana* have been manipulated in various experiments to express proteins that may be used medicinally. Indeed, transgenic tobacco plants have been used in the development of vaccines for measles, lymphoma, and diabetes [72; 73; 74].

ANATOMY AND PHYSIOLOGY OF SMOKE INHALATION

Administration of any drug via smoking is a highly efficient route, allowing rapid delivery to the brain. This act involves inhalation of a small volume of smoke (an average of about 35 ml for cigarettes) into the mouth from which it is drawn into the lungs [75]. The breathing pattern employed is different from normal tidal breathing in that a smoker's inhalation is deeper and more rapid, drawing the smoke in as a bolus at the beginning of inhalation [76]. However, this pattern varies greatly between smokers and during the course of consuming a single cigarette [77]. Uptake of smoke ingredients is determined by many factors, including chemical composition, smoker's inhalation behavior, lung morphology, and physiologic parameters such as tidal volume, vital capacity, rate of breathing, and rate of lung clearance [78]. Individual differences in size, metabolism, and genetics may also play a role. One hypothesis suggests that stimulation of nicotine-sensitive receptors in the upper airway by various elements of smoke governs the amount inhaled. Indeed, application of a topical anesthetic to the upper airway reduces the quantity of smoke inhaled [79].

Tobacco smoke consists of gaseous and particulate phases, with the particulate phase comprising about 8% of the total volume [76]. Particulate deposition depends on the size, shape, and hygroscopicity (ability to absorb water vapor) of the particles as well as the duration and depth of inhalation [77]. Smoke particles range from 0.1–1.0 mm in diameter as they exit a cigarette, doubling in size within half a second due to aggregation, cooling, and condensation [80]. Larger particles (1–5 mm) are likely to deposit in the trachea and bronchi, whereas smaller particles (0.01–1 mm) reach bronchioles, alveolar ducts, and alveoli. Irregularly shaped or fibrous particles tend to get trapped at branching points, although some of these particles can travel on to the alveoli [81]. Interestingly, smoking seems to result in a greater apical and central distribution of particles than normal tidal breathing. This finding may help to explain the pathogenesis of centrilobular emphysema [76].

Cigarettes deliver nicotine in a pulsatile manner, with plasma concentrations reaching their peak within 1.5 to 3 minutes of the commencement of smoking and gradually returning toward baseline within two to three hours [82]. Thus, nicotine levels rise and fall throughout the day with each cigarette smoked, declining to minimum amounts found in nonsmokers in the morning after the extended abstinence period of sleep. Such continuous flux in blood nicotine levels locks the user into an endless cycle of ups and downs and is thought to lead to the commonly held notion that smoking has a positive effect on mood. Considering smokers begin to experience withdrawal symptoms within hours of their last cigarette, and because these unpleasant effects are almost completely alleviated by smoking, this perception is hardly surprising. Daily repetition of this process links these perceived positive health benefits to the act of smoking in the smoker's mind and often results in the false identification of cigarettes as an effective form of self-medication [83].

LEARNING OF BEHAVIOR

What is it about smoking that makes it so addictive? On one hand, this form of drug delivery is very efficient; inhaled nicotine is absorbed through pulmonary rather than systemic circulation and can reach the brain within 10 to 20 seconds [84]. Once inside the central nervous system (CNS), nicotine stimulates release of dopamine from the nucleus accumbens, much like the use of cocaine and amphetamines, leading to the feeling of satisfaction and well-being. Given such rapid central reinforcement, it is not surprising that tobacco can become highly addictive. On the other hand, familial and social influences often play a crucial role in determining who might start smoking, quit, or become dependent [83]. For example, one study managed to train a small percentage of rhesus monkeys to smoke, but with such difficulty that it concluded that "environmental factors play the primary role in developing smoking behavior" [85].

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Experimenting with smoking usually occurs in the early teen years and is predominantly driven by psychosocial motives [83]. For a first-time user, lighting a cigarette is a symbolic expression of autonomy and independence; acquisition of the desired image is often a sufficient incentive for a novice smoker to tolerate the body's rejection of the first few cigarettes. Despite an admitted awareness of at least some of the deleterious effects of smoking, in 2018, 1 in 4 high school students and 1 in 14 middle school students admitted to using a tobacco product in the past 30 days [135]. Almost all people (90%) who will smoke as adults have started doing so by 18 years of age, and the earlier a person begins, the more likely they are to continue [135]. Within a year, adolescents inhale the same amount of nicotine per cigarette as adults, and they too experience the craving and withdrawal symptoms associated with nicotine addiction [83]. By 20 years of age, 80% of smokers regret ever having started.

The U.S. Preventive Services Task Force recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use in school-aged children and adolescents.

(http://annals.org/aim/fullarticle/1748857. Last accessed May 13, 2019.)

Level of Evidence: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Much research has been dedicated to uncovering reasons for the development of a smoking habit. Risk factors include [86]:

- Presence of a smoker in the household
- Single parent home and/or strained relationship with parent
- Comorbid psychiatric disorders
- Low level of expressed self-esteem and self-worth
- Poor academic performance
- In boys, high levels of aggression and rebelliousness
- In girls, preoccupation with weight and body image
- Increased adolescent perception of parental approval of smoking
- Affiliation with smoking peers
- Availability of cigarettes

In addition, twin studies revealed a significant genetic contribution to both smoking initiation and dependence [87; 88].

RITUALISM

In practice, many find the very act of smoking a cigarette ritualistic and calming. The process of "packing" cigarettes by tapping the box on the palm of a hand, removing a cigarette, lighting it, inhaling, and watching the smoke as it is exhaled all contribute to the perceived need to smoke. Some go so far as to claim that they "would not know what to do with their hands" if they were to stop smoking [83]. An investigation using denicotinized cigarettes illustrated that the sensorimotor experience of smoking makes a significant contribution to the perceived satisfaction [89].

MEDIA INFLUENCE

Mass media is another factor that contributes to the learning of smoking behavior. Historically, the tobacco industry recruited new smokers by associating its products with fun, excitement, sex, wealth, power, and a means of expressing rebellion and independence [90]. Such promotional efforts have proven to be especially effective on teenagers, a particularly lucrative market with a lifetime of cigarette consumption ahead of them [91]. Although at present tobacco companies can no longer directly advertise to teenagers, they retain the most potent form of marketing: movies. Smoking in film is a "more powerful force than overt advertising," perhaps because the audience is generally unaware of any sponsor involvement [92]. Philip Morris, one of the world's leading tobacco companies, stated in their 1989 marketing plan, "We believe that most of the strong, positive images for cigarettes and smoking are created by cinema and television" [90]. Although television is taking a more socially responsible stance on the subject of on-air tobacco use, movies continue to model smoking as a socially acceptable behavior, portraying it as a social behavior or a way to relieve tension [93; 94]. A study exploring the connection between a child's professed favorite movie star and that actor's on-screen smoking history revealed "a clear relation between on-screen use and the initiation of smoking in the adolescents who admire them" [95]. Tobacco use in movies, albeit falling through the 1970s and 1980s, increased significantly after 1990 [90]. Furthermore, despite declining tobacco use and increasing public understanding of the dangers of nicotine, smoking in movies returned to the levels observed in the 1950s, when it was nearly twice as prevalent in society as in 2002 [96]. A study analyzing the content of the top 25 grossing films each year from 1988 to 1997 found that 87% of movies depicted tobacco use, with an average of 5 occurrences per film. The vast majority of tobacco use was portrayed as experienced use (91.5%) and rarely did it represent a character's first use (0.3%) or a relapse from a previous quit attempt (0.5%). Despite the fact that R-rated movies contained most tobacco exposure and were more likely to feature a major character using tobacco, about 60% of the total coverage of smoking occurred in youth-rated films (G, PG, and PG-13). Negative reactions to tobacco use, including comments about health effects or gestures such as coughing, were depicted in only

5.9% of the occurrences. Unrealistic portrayal of cigarette smoking on the big screen may help to explain the somewhat surprising finding that children of nonsmoking parents are especially susceptible to the effects of movie smoking exposure [93]. Between 2002 and 2017, 6 out of every 10 movies rated PG-13 contained smoking or tobacco use, with historically high average of occurrences per film in 2016 (34 per film) and 2017 (29 per film), prompting many health groups to advocate for the requirement of an R rating (i.e., younger than 17 years of age require accompanying adult) for any films containing tobacco use. Researchers estimate that requiring a R rating would reduce the number of teen smokers by 18%, preventing up to 1 million deaths from smoking in the future [184]. Since May 2007, the Motion Picture Association of America (MPAA) has made smoking a factor in assigning ratings to films. The pervasiveness of tobacco use, context in which smoking appears, and whether or not the act is glamorized are all taken into account by film raters [97].

GENETICS

It has been suggested that high genetic vulnerability to cigarette smoking may explain why some people begin and continue to smoke despite associated risks [98]. Twin studies found significant heritability for persistence of smoking versus quitting. Heritability estimates for smoking persistence ranged from 27% to 70% and were greater for older than younger cohorts [99; 100; 101]. Madden et al. examined cross-cultural differences in the genetic risk of becoming a regular smoker and of persistence in smoking in men and women. They found strong genetic influences on smoking behavior, 46% for women and 57% for men, consistent across country and age group [102]. In a U.S. study, estimates of the genetic contribution to risk of becoming a smoker were 60% in men and 51% in women [103].

SMOKING DEPENDENCE

Of the numerous ingredients in tobacco smoke, nicotine is believed to be the primary cause of cigarette addiction [104]. Commercially available forms of nicotine-replacement therapy (NRT) increase cessation rates approximately 1.5- to 2-fold [105; 106; 107]. Yet, the fact that only a fraction of those who use such products succeed suggests that cigarette addiction depends on specific characteristics of cigarette smoking. It appears that the rapid delivery of nicotine via inhalation is a primary contributor to cigarette dependence [108]. Indeed, a district court judge found that major U.S. cigarette companies have designed their cigarettes to precisely control nicotine delivery levels and provide doses of nicotine sufficient to create and sustain addiction [109].

Active components of cigarette smoke affect many organ systems, but the effects on the CNS may be of most clinical importance due to its mediating role in dependence. Central effects of nicotine include electroencephalogram (EEG) desynchronization, with a shift toward higher frequency [110]. Studies have demonstrated that nicotine from cigarette smoke reduces global cerebral blood flow (gCBF), most markedly in the right hemisphere, and increases regional cerebral blood flow (rCBF) by more than 10% in the cerebellum, occipital cortex, and insula. Decreases in rCBF have been observed in such subcortical structures as the hippocampus, anterior cingulate, amygdala, and nucleus accumbens [111]. Positron emission tomography (PET) studies show that nasal nicotine administration increases cerebral glucose metabolism in the left inferior frontal gyrus, left posterior cingulate gyrus, left lateral occipitotemporal gyrus, left and right cuneus, and right thalamus, while it decreases glucose metabolism in the left insula and the right inferior occipital gyrus [112].

Further, the physiology of nicotine dependence has been characterized as biphasic; it stimulates the pleasure response in the brain and creates a relaxed state. As with cocaine, amphetamines, and morphine, addiction to nicotine is believed to result from increased release of dopamine in the nucleus accumbens. Nicotinic acetylcholine receptors are located throughout the CNS. Neurons located in the ventral tegmental area become more active with nicotine administration, leading to an increase in dopamine release into the nucleus accumbens [113]. Indeed, lesions to these pathways reduce rates of self-administered nicotine [114].

PSYCHOLOGIC DEPENDENCE

Many smokers believe that smoking increases concentration, treats stress, and gives pleasure. These beliefs are false. The light-headed feeling that may accompany the act of smoking gives the smoker a false sense of pleasure or release. However, smoking actually causes a decline in physical and cognitive functioning. Additionally, a study by Ota et al. showed that nurses in Japan indulged in smoking as a result of the psychologic demands of their jobs, and this psychologic job demand was positively correlated with their Tobacco Dependence Screener score. The nurses associated stressful tasks with dysphoria, insomnia, anxiety, and other symptoms similar to that of nicotine withdrawal. To alleviate these symptoms, the nurses would smoke and become increasingly psychologically dependent on nicotine with each demanding occupational event [115].

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HEALTH COMPLICATIONS RELATED TO SMOKING

PULMONARY COMPLICATIONS

Smoking severely compromises pulmonary function in a variety of ways, including causing infiltration of the airways with leukocytes. An imbalance among proteases, their endogenous inhibitors, and local cytokine secretion in the lung leads to airway inflammation and alveolar destruction. Smokers also experience more acute lower respiratory illnesses. Smoking has been implicated in the development of malignant and nonmalignant lung disease, including COPD, bronchitis, influenza, emphysema, pneumonia, and lung cancer. Smokers are also shown to be at increased risk of intraoperative pulmonary complications and a wide range of postoperative complications. For example, a study of postoperative care revealed smoking, being older than 65 years of age, and a history of chronic lung disease increased the risk of unplanned intensive care admittance [116].

Chronic Obstructive Pulmonary Disease

Smoking is the main cause of COPD, which encompasses both chronic bronchitis and emphysema. Between 20% and 30% of smokers (or about 1 in 4) will develop COPD, and risk is determined largely based on genetic susceptibility coupled with age at smoking initiation [117; 118]. It is very rare in nonsmokers; at least 80% of deaths from this disease can be attributed to cigarette smoking. The risk of death from COPD rises concurrently with the number of cigarettes smoked. If smokers with COPD quit smoking while they are still young, an improvement in lung function can be expected. However, such improvement is not possible in older people, although after cessation further deterioration will run parallel to that of nonsmokers.

The age at which one begins smoking is important. Wiencke and colleagues discovered that smoking as an adolescent causes permanent genetic changes in the lungs and forever increases the risk of lung cancer, even if the smoker subsequently stops [119]. A Canadian community health survey conducted between 2000 and 2001 found that the risks for heart disease, COPD, and rheumatoid arthritis were far higher among people who began smoking as teenagers than among their nonsmoking peers. For COPD alone, teen smokers were three times more likely to develop the condition later in life than nonsmokers. Similarly, a retrospective cohort study of adult smokers suggests that women are particularly at risk of COPD if they start to smoke before 16 years of age [120].

Influenza

Upper respiratory tract infections are common, and tobacco smoke is a proven risk factor for bacterial infection. The link between influenza and smoking has been demonstrated both for adult smokers and children exposed to smoke-filled environments. According to Arcavi and Benowitz, influenza risk is higher and infections are more severe (e.g., more cough, phlegm production, breathlessness, and wheezing) in smokers versus nonsmokers. Apparently, the antibody response is depressed in cigarette smokers. Nonsmokers should also avoid SHS exposure to decrease the risk of contracting influenza [121]. In a study of Israeli military men, presence and severity of influenza was stronger in smokers than in nonsmokers. Of all smokers, 68.5% contracted influenza compared with 47.2% of nonsmokers, and 50.6% of smokers required bed rest or lost workdays compared with 30.1% of nonsmokers [122]. A 2018 study of patients older than 65 years of age showed that smokers had a higher rate of hospitalization due to influenza (47.4%) compared with nonsmokers (42.1%). In addition, the effectiveness of the influenza vaccine in preventing hospitalization was 21% among current and ex-smokers and 39% in nonsmokers [376].

Pneumonia

Smoking is associated with a significant increase in the relative risk of pneumonia and pneumonia-related hospitalization [123; 124]. Pneumonia is not only more common among smokers, it is much more likely to be fatal. Longitudinal studies have identified an increase in the mortality rate from pneumonia in smokers associated with dose-response [125]. In general, cessation of smoking is not associated with a decrease in hospitalization for pneumonia; however, patients without COPD and a greater than 10-year history of not smoking are at a decreased risk [124]. A 2013 study found that children exposed to SHS were four times more likely to develop lower respiratory illnesses, including pneumonia [126]. Proposed explanations of the increased risk for infection in active, passive, and former smokers include increased bacterial adherence, decrease of lung and nasal clearance, and changes in the immune response.

CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease, defined as acute myocardial infarction (MI) and stroke, is strongly related to smoking and comprises 34% of smoking-related mortality; conversely, smoking yields 16% of cardiovascular-related mortality [62]. The relative risk of MI for smokers has been estimated at 2.88 for men and 3.85 for women, and the relative risk of stroke for smokers is estimated at 2.80. These estimates do not include the effects of passive smoking. Low-tar cigarettes and smokeless tobacco have similarly been shown to increase the risk of cardiovascular events among users in comparison to nonsmokers [127]. Cigarette smoking impacts all phases of atherosclerosis, from endothelial dysfunction to acute clinical events. Both active and passive cigarette smoke exposure predispose to cardiovas-

cular events. The exact toxic components of cigarette smoke and the mechanisms involved in smoking that are related to cardiovascular dysfunction are largely unknown, but smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol (LDL-C). Experimental and clinical data support the hypothesis that increased oxidative exposure may be a potential mechanism for initiating cardiovascular dysfunction. Research also suggests that small doses of toxic materials from tobacco smoke cause a nonlinear dose-response effect on cardiovascular function [128]. The risk for cardiovascular disease declines rapidly after smoking is ceased [129].

NEUROLOGIC COMPLICATIONS

Tobacco smoking is strongly related to atherosclerosis and chronic vascular disease. Atherothrombotic ischemic stroke, transient ischemic attack, and atherothrombotic origin symptomatic or asymptomatic peripheral arterial disease are all associated with a high risk of vascular death, MI, and stroke. Exposure to tobacco smoke is a noted risk factor of all these events. A positive association was found between cigarette smoking and subarachnoid hemorrhage (SAH), especially for aneurysmal SAH in women [130].

Evidence is emerging that suggests an association between the development of other neurologic diseases and smoking. A study by Riise et al. identified the risk of multiple sclerosis as higher among smokers than among those who never smoked [131].

Studies have shown that the amount of monoamine oxidase (MAO) is reduced by 30% to 40% in the brains of smokers, compared to nonsmokers or former smokers [132]. This reduction in brain MAO levels may result in an increase in levels of dopamine. It has been suggested that nicotine may have short-term protective actions against mechanisms that cause Alzheimer disease; however, the numerous toxins in cigarette smoke negate any benefit [133]. Though the risk for dementia is slightly higher in smokers, the relative risk for Alzheimer disease is unclear. A 2013 Alzheimer study using a mouse model found that smoking hastens disease onset, exacerbates amyloid pathology, and increases neuroinflammation and tau phosphorylation [133]. Further research is needed in order to better elucidate the risk.

CANCER

In the United States beginning in the early 1950s, a series of epidemiologic, biochemical, pathologic, and animal studies demonstrated a link between cigarette smoking and lung cancer. Tobacco smoking increases the risk of all histologic types of lung cancer. More than 80% to 90% of people who develop lung cancer are current or past smokers. However, not all smokers will develop lung cancer [134]. Cited reasons include the modification of lung cancer risk by previous respiratory disease. In comparison to nonsmokers, smokers are 23 times more likely to develop lung cancer if male and 13 times more likely if female. The risk of lung cancer increases directly with the number of cigarettes smoked and decreases when smoking is ceased. The most important parameter of smoking that affects lung cancer risk is the duration of smoking. Smoking low-tar cigarettes does not substantially reduce the risk of lung cancer [14].

Tobacco smoking is also causally linked to other types of cancer, including oral, oropharyngeal and nasal cavity, urinary tract, larynx, pancreas, esophageal, stomach, liver, cervix, colon, breast, endometrial, prostate, and leukemia. In most cases, the risk increases substantially with duration of smoking and amount of cigarettes/tobacco consumed. Similarly, alcohol in combination with tobacco greatly elevates the risk of many forms of cancer [14].

The U.S. Preventive Services Task Force recommends annual screening for lung cancer with low-dose computed tomography in adults 55 to 80 years of age who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

(http://annals.org/aim/fullarticle/1809422. Last accessed May 13, 2019.)

Level of Evidence: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

OSTEOPOROSIS

Smoking can lead to adverse long-term effects on bone health, rendering smokers prone to falls and fractures. Many smokers begin smoking during adolescence—a point in which bone mass is still being constructed; thus, smoking may hinder a person from reaching their maximum bone mass, leaving them fragile and prone to fractures with longer recuperation time [136]. Further, cigarette smoking has been shown to be a key risk factor for osteoporosis and unfortunately, menopausal women are at increased risk due to a loss of estrogen during this period of life. Giampietro and colleagues suggest that a genetic variation in interleukin 6 (IL6) and lipoprotein receptor-related protein 5 (LRP5) observed in smoking white women may confer risk for osteoporosis among smokers [137]. In a study of human-derived osteoblast-like cells and trabecular bone organ culture, Walker et al. demonstrated the presence of the α4 neuronal nicotinic acetylcholine receptor (nAChR) and found that nicotine modulates proliferation in a dose-dependent manner, upregulates c-fos transcription factor, and affects synthesis of osteopontin, a bone matrix protein [138].

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PROBLEMS WITH CONCEPTION AND EMBRYONIC HEALTH

Women who smoke prior to pregnancy are more likely to experience a delay in conception and have about 30% higher odds of infertility [139]. Further, men who smoke are at increased risk of erectile dysfunction due to decreased bioavailability of nitric oxide and damage to peripheral nerves, the vascular epithelium, and structure of corporal tissue. Smoking may also affect the quality and mobility of spermatozoa [140; 141]. Ramlau-Hansen et al. report a dose-dependent relationship between smoking and sperm concentration, testosterone, luteinizing hormone (LH), and the LH/free testosterone ratio [142].

Success of assisted reproduction therapy (ART) is reduced among smoking couples. In a meta-analysis, Waylen and colleagues found that smokers undergoing ART (e.g., in-vitro fertilization, intracytoplasmic sperm injection, gamete intrafallopian transfer, zygote intrafallopian transfer) had lower odds of live birth per cycle (i.e., birth of one or more infants that show signs of life). They also observed lower odds of clinical pregnancy per cycle (i.e., a sonographically visible gestational sac in the uterus) and higher odds of spontaneous miscarriage and ectopic pregnancy when compared to nonsmokers undergoing the same treatments [143]. A retrospective study published in 2018 found that smoking has a negative effect on endometrial thickness on the day of the embryo transfer, resulting in lower rates of implantation and pregnancy [466].

If conception is achieved (with or without ART), maternal smoking during pregnancy increases the risk for adverse conditions including low birth weight, spontaneous abortion, placenta previa, abruptio placentae, preterm premature rupture of the membrane (PPROM), and overall poor outcomes [144; 145].

The miscarriage rate among mothers who smoke may be as high as 33% [146; 147]. This may be due to an increased syncytial necrosis and increased thickness of syncytio/cytotrophoblast membrane, as smoking appears to induce dysfunction of villous and invasive trophoblasts early in pregnancy. Additionally, maternal levels of estriol, estradiol, human chorionic gonadotropin, and human placental lactogen are lower in smokers than in nonsmokers [148]. All of these are markers of prenatal health and well-being.

COMORBID CONDITIONS

ALCOHOL ABUSE

There is a strong comorbidity between alcohol consumption and tobacco use. Drinkers are more likely to smoke than nondrinkers, and smokers are more likely to drink than nonsmokers [149]. In fact, smokers are 30% more likely to consume alcohol and 10 times more likely to develop alcoholism than nonsmokers. Between 80% and 95% of all alcoholics also smoke cigarettes, and 70% are heavy smokers who consume more than one pack per day [150]. A study examining an association between alcohol and tobacco, using a combination of short-term (1-year) and long-term (15-year) follow-up intervals, found that past-year alcohol and tobacco use disorders were associated not only cross-sectionally, but also prospectively. These associations were present even after controlling for age, gender, and race. Year 1 tobacco dependence prospectively predicted diagnosis with an alcohol use disorder (AUD) at year 2, and a baseline diagnosis of AUD increased the likelihood of diagnosis with tobacco dependence 15 years later. Having been diagnosed with tobacco dependence at year 1 predicted AUD persistence, and vice versa. These findings demonstrate the complex association between tobacco dependence and AUDs [151]. Similarly, a study examining the natural course of AUDs from adolescence to early adulthood found that daily smoking predicted future AUD when adolescent AUD and other disorders were controlled. It is possible that chronic smoking may contribute to alcohol tolerance, increasing alcohol consumption and metabolism [152].

In the instance of nonsmokers, data from a study by Romberger and Grant suggests that patterns of alcohol abuse would be similar in workers exposed to SHS; however, the severity of the alcohol abuse may be less pronounced [153].

DRUG ABUSE

Smoking usually precedes illicit drug use. Among those who used both cigarettes and marijuana by the 12th grade, 65% smoked cigarettes before marijuana, and 98% of those who used both cigarettes and cocaine smoked cigarettes first. Apparently, the earlier a person uses tobacco, the more likely he or she will be to experiment with cocaine, heroin, and other drugs. More than half of those who start smoking before 15 years of age use an illegal drug in their lifetime, compared to only a quarter of those who do not start smoking until 17 years of age or later. Moreover, those who start smoking before 15 years of age are seven times more likely to use cocaine than those who never smoke. Also, heavy smokers are more likely to use marijuana or harder drugs. For example, young people who smoke more than 15 cigarettes a day are twice as likely to use an illicit drug and 16 times more likely to use cocaine than those who smoke less frequently. They are also 10 times more likely to use an illicit drug and 100 times more

likely to use cocaine than those who never smoked. Even heavy users of smokeless tobacco are more likely to experiment with drugs. High school students who used smokeless tobacco 20 to 30 days per month were four times more likely to concomitantly use marijuana than nonusers, and almost three times more likely to ever use cocaine [150].

PSYCHIATRIC DISORDERS

Many smokers report a link between smoking and anxiety. Researchers at the National Institute on Drug Abuse hypothesized that impaired respiration and the detrimental effects of nicotine on blood vessels to the brain elucidate why those exposed to smoking are at an increased risk of developing anxiety disorders [154; 467].

Smoking is shown to be highly comorbid with such psychiatric disorders as major depression, panic disorder, and schizophrenia. Cigarette smoke has other psychoactive properties apart from nicotinic receptor stimulation. For example, it inhibits MAO, which is the enzyme responsible for breaking down the biogenic amine neurotransmitters norepinephrine, serotonin, and dopamine in the brain [155; 156]. Not surprisingly, the association between smoking and major depression is well established [157; 158; 159]. Reports of severe major depressive episodes after smoking cessation are also common, with the onset of depressive symptoms ranging from two days to six weeks after the initial abstinence from smoking [160; 161]. In some cases, depression was alleviated with the use of NRT or antidepressants; in others, depressive symptoms went away after a relapse to smoking [160; 162]. In a trial of smoking cessation using fluoxetine (30 mg), 7% of participants with a previous history of major depressive disorder (MDD) were diagnosed with major depressive episodes after a 10-week treatment, suggesting that a subset of smokers may be particularly at risk for developing MDD after smoking cessation [163].

In addition to relieving depressive symptoms or major depressive episodes associated with nicotine withdrawal, antidepressants may aid in long-term smoking cessation by substituting for the antidepressant effects of nicotine that help maintain smoking. They may also have a specific effect on neural pathways (e.g., MAO inhibition) or receptors (e.g., nicotinic-cholinergic receptor blockade) that underlie nicotine addiction. A 2013 Cochrane review assessed the efficacy of antidepressant medications to aid long-term smoking cessation. The majority (75) of the 90 randomized trials included in the review were of bupropion and nortriptyline. The reviewers found high-quality evidence that bupropion significantly increased long-term smoking cessation when used as the sole pharmacotherapy, and moderate-quality evidence (limited by the small number of trials and participants) that nortriptyline also significantly increased long-term cessation. The drugs' effectiveness for long-term smoking cessation was independent of their antidepressant effects, with efficacy similar to NRT [156].

Smoking could also be a risk factor for panic disorder [164; 467]. A disproportionate number of persons with panic disorder smoke cigarettes compared to the general population [165]. Mild-to-moderate nicotine dependence was associated with an 11% lifetime prevalence of panic disorder, a rate approximately 2.5 times greater than in persons with no nicotine dependence. Pohl et al. found that female patients with panic disorder had significantly higher smoking prevalence at the onset of their illness than did control subjects (54% versus 35%) and that smoking prevalence for the female patients was also significantly higher than for the control subjects (40% versus 25%) [166]. Male smoking rates did not differ between patients and control subjects.

Although the cause of this comorbidity remains controversial, several explanations have been offered: smoking promotes panic by inducing respiratory abnormalities/lung disease; nicotine produces the physiologic effects characteristic of panic by releasing norepinephrine; cigarette smoking is a form of self-medication for panic disorder; and/or a shared vulnerability promotes both conditions [167]. One study examined the effect of smoking cessation on the reduction of panic symptoms by monitoring the post-cessation abstinence status of 185 smokers. Abstinence was biochemically verified at weeks 1 and 2 and month 1. The severity of panic-relevant symptoms was self-reported by the participants at month 1 and month 3, post-cessation. The 80 participants (43.2%) who remained abstinent for one month, relative to the 105 (56.8%) who did not, demonstrated significant reductions in self-reported panic symptoms [168].

Smoking is also more prevalent in persons with schizophrenia, although reasons for its pervasiveness remain debatable [169; 170; 171]. Investigators have suggested that nicotine might temper positive or negative symptoms, and cigarette smoking is used as self-medication (e.g., to treat cognitive impairment and anhedonia) [171; 172; 173; 174]. Nicotine may also attenuate the adverse effects of neuroleptics, perhaps by reducing elevated blood levels after use of antipsychotic medications [128; 175; 176]. Weiser et al. examined the prevalence of cigarette smoking in apparently healthy adolescents later hospitalized for schizophrenia. The number of cigarettes smoked was significantly associated with the risk for schizophrenia. Compared to nonsmokers, adolescents who smoked 1 to 9 cigarettes per day were 1.38 times as likely to be hospitalized later for schizophrenia, and adolescents who smoked 10 cigarettes per day or more were 2.28 times as likely; the latter difference was statistically significant. The authors concluded that the higher prevalence of smoking in future schizophrenia patients might indicate that impaired nicotinic neurotransmission is involved in the pathophysiology of schizophrenia [177]. Bupropion has been found to increase smoking abstinence rates in smokers with schizophrenia [178]. Additionally, a number of medications that target nicotinic acetylcholine receptors have been tested or are in development, but further research is necessary to determine their clinical utility in the treatment of schizophrenia [174].

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FETAL EXPOSURE

Maternal cigarette smoking before and during pregnancy adversely affects the health of both mother and fetus. However, analysis of data from the 2016 National Vital Statistics Systems (NVSS) indicated that 7.2% of pregnant women in the United States reported smoking during pregnancy [179]. In addition to the effects on fertility and embryonic health discussed, maternal smoking before conception increases the risk of sudden infant death syndrome (SIDS), and smoking at the time of conception increases the risk of infants being born with cleft lip, with or without cleft palate [14; 179; 180]. A 2010 study showed that as many as 8% of preterm deliveries, 7% of preterm-related deaths, 19% of term low-birth-weight deliveries, and 34% of SIDS cases in the United States were attributable to prenatal smoking [181]. Further, several studies indicate that the offspring of mothers who smoked during pregnancy are at elevated risk of developing nicotine dependence as adults [182; 183].

According to 2016 NVSS data, the prevalence of smoking during pregnancy was highest among women who were between 20 and 24 years of age (10.7%), followed by women 15 to 19 years of age (8.5%) and 25 to 29 years of age (8.2%). Among racial groups, the highest rates were found in non-Hispanic American Indian/Alaska Native women (16.7%%), followed by white (10.5%), black (6.0%), Native Hawaiian/Pacific Islander (4.5%), Hispanic (1.8%), and Asian (0.6%) women. Smoking rates were highest among those with a high school diploma or equivalent (12.2%), followed by those with less than 12 years of school completed (11.7%), and women with some college or an associate's degree (7.9%). Less than 1% of women with a bachelor's degree or higher reported smoking during pregnancy [179]. Rates of maternal smoking during pregnancy differ greatly between individual states, with West Virginia (25.1%) and Kentucky (18.4%) reporting the highest percentages, and the District of Columbia (2.6%) and California (1.6%) reporting the lowest. SHS exposure in infancy greatly increases the odds of respiratory tract infections, ear infections, and death from SIDS [14].

Ohida and colleagues performed cross-sectional surveys in Japanese obstetric clinics to investigate the effects of passive smoking on sleep disturbance during pregnancy [185]. Pregnant women exposed to passive smoking were likely to have insufficient sleep, difficulty initiating sleep, short sleep duration, loud snoring, or uncomfortable breathing. These experiences also occurred in pregnant women who were smokers.

Nicotine has a low molecular weight and high lipid solubility, allowing it to cross the placenta freely and accumulate in amniotic fluid. In animal models, nicotine could be identified in fetal tissues as early as five minutes following maternal injection [186; 187]. Because less than 5% of nicotine binds to human plasma proteins, the majority of the administered dose is available to equilibrate with fetal circulation [188]. Studies in humans showed that nicotine is readily transferred to the fetal compartment throughout pregnancy, with accumulation in placental tissue and amniotic fluid [189]. Apparently, a significant amount of nicotine is retained by the placenta and may later transfer to fetal and maternal circulation, thus prolonging the effect of nicotine on the fetus [188].

Acetylcholine causes dilation of blood vessels and maintains placental blood flow by the activation of endothelial muscarinic receptors. Nicotine blocks acetylcholine-facilitated amino-acid transport, depressing diffusion of amino acids and other nutrients from the trophoblast into placental circulation. Maternal smoking actually leads to trophoblast apoptosis and thickening of the trophoblast basement membrane [190; 191]. Further, CO from tobacco smoke crosses the placenta by passive diffusion, leading to increased carboxyhemoglobin in umbilical cord blood and placental hypoxia. The resultant hypoxia causes fetal growth retardation and alteration in the physiologic development of organs and tissues [192].

PHARMACOKINETICS AND DYNAMICS

Among pregnant smokers, maternal levels of cotinine correlate better with outcome measures such as birth weight than the number of cigarettes smoked per day [193]. Cotinine can accumulate in fetal compartments as early as 7 weeks' gestation in both active and passive smokers [194]. Of note, the half-life of nicotine is three to four times longer in newborns than in adults, whereas the half-life of cotinine is similar in newborns and adults. The prolonged elimination of nicotine, but not of cotinine, in the newborn compared with that in the adult may be a result of different newborn cytochrome P450 2A6 (CYP2A6) enzymatic substrate specificity, low CYP2A6 activity with another enzyme that is primarily responsible for cotinine metabolism, or differences in tissue distribution [195]. Also, pregnancy is well known for affecting metabolism of some drugs and may contribute to higher or lower clearances compared with the nonpregnant state [196]. Indeed, metabolic clearance of both nicotine and cotinine are substantially increased during pregnancy, resulting in a marked decrease in the half-life of cotinine. The mechanism for such increase in metabolic clearance is not known. It is possible that nicotine and cotinine clearances are accelerated by faster oxidation via CYP2A6 and faster glucuronide formation. Although nicotine and cotinine share the same metabolizing enzymes, their increased clearances may occur by different physiologic mechanisms. Nicotine is a rapidly cleared drug with a high affinity for CYP2A6, and the rate of clearance is primarily controlled by liver blood flow. Cotinine is a slowly metabolized chemical, with a low affinity for CYP2A6 relative to nicotine. The level of CYP2A6 in the liver, which is markedly elevated during pregnancy, primarily determines the rate of cotinine metabolism. A substantial increase in the percentage of nicotine and cotinine excreted as their glucuronide conjugates is also observed in pregnancy, but there is no increase in the percentage of

3'-hydroxycotinine excreted as a glucuronide. This suggests an acceleration of nicotine and cotinine metabolism via the *N*-glucuronidation pathway, but no effect on hydroxycotinine metabolism by the *O*-glucuronidation pathway. Also, the profile of nicotine and its metabolites in urine is altered during pregnancy. The excretion of nicotine is substantially decreased, and despite large differences in plasma cotinine concentration during smoking, there is no difference between the daily dose of nicotine absorbed from cigarette smoking during and after pregnancy [197].

NEUROLOGIC COMPLICATIONS

Fetal nicotine exposure can result in permanent abnormalities of the dopaminergic regulation of the brain [198]. These effects can occur even at low nicotine doses and lead to a greater nicotine dependence [182]. Unlike in mature organisms, where stimulation of a target cell elicits only a short-term response, receptor stimulation in the developing systems interacts with the genes controlling cell differentiation, permanently altering the cells' responsiveness. Nicotine exposure to the prenatal brain may also prematurely stimulate the shift from proliferation to differentiation; thus, nicotine may act as a cholinergic signal, mimicking trophic effects of acetylcholine. Because of the close regulatory association of cholinergic and catecholaminergic systems, adverse effects of nicotine involve multiple transmitter pathways and influence not only the immediate developmental events in the fetal brain but also the eventual programming of synaptic competence. Therefore, defects may appear after a prolonged period of apparent normality, leading to cognitive and learning defects that appear in childhood or adolescence. Similar modifications occur in peripheral autonomic pathways, leading to increased susceptibility to hypoxia-induced brain damage and perinatal mortality [199]. These changes are especially prominent in tissues rich in nicotinic cholinergic receptors, such as the brainstem [200].

Prenatal exposure to nicotine produces alterations in tegmental nuclei related to the following [201]:

- Cardiopulmonary integration (nucleus tractus solitarii, parabrachial complex)
- Regulation of arousal, attention, and rapid eye movement (REM) sleep (mesencephalic and pontine reticular formation)
- Somatic motor control (paramedian pontine and medullary reticular formation)
- Tongue and upper airway regulation (hypoglossal nucleus)

Autonomic deregulation could explain the inhibition of some homeostatic reflexes seen in infants exposed to tobacco smoke, including a deficiency in arousal responsiveness to hypoxia or hypercapnia [202]. Roy et al. evaluated cellular morphology and regional architecture in the juvenile and adolescent hippocampus and the somatosensory cortex in rats prenatally exposed to nicotine. They found a substantial decrease in cell size in the hippocampal CA3 region and dentate gyrus, with corresponding decrements in cell layer thickness and increments in cell packing density. Smaller, transient changes were seen in CA1. There was a reduction in the proportion of medium-sized pyramidal neurons in layer five of the somatosensory cortex and an increase in the proportion of smaller, nonpyramidal cells. All regions showed elevated numbers of glia. These data demonstrate that prenatal nicotine exposure compromises neuronal maturation, leading to long-lasting alterations in the structure of key brain regions involved in cognition, learning, and memory [203].

PULMONARY COMPLICATIONS

Fetal growth and duration of gestation are the major factors affecting lung development [204]. Intrauterine influences that retard fetal weight gain may irrecoverably restrict the growth of the airways, with consequences persisting throughout the individual's life span. Fetal exposure to nicotine is associated with several abnormalities in lung growth. In animal studies, nicotine has been shown to directly interact with nicotinic acetylcholine receptors in pulmonary vessels, altering connective tissue expression and producing vascular structural alterations [205]. Furthermore, maternal nicotine exposure results in larger alveolar volumes and suppresses alveolarization in the lungs of the offspring of rats, reducing the surface potentially available for gas exchange [206; 207]. Human smokers have a high rate of poor perfusion patterns, suggesting that smoking during pregnancy may compromise uteroplacental blood flow and contribute to poor fetal development [208; 209].

CARDIOVASCULAR COMPLICATIONS

Maternal smoking during pregnancy poses severe risks to the developing fetal heart. Nicotine alters cardiac cell differentiation to increase the cellular injury caused by hypoxia [210]. Prenatal nicotine exposure interferes with the ability of neonatal adrenal glands to secrete catecholamines in response to hypoxia [200]. Given that the neonatal heart lacks functional sympathetic innervation, there is virtually a complete dependence on circulating catecholamines secreted by the adrenal medulla to maintain heart rate response to hypoxia. Nicotine exposure reduces the number of cardiac ß-adrenergic receptors, magnifying functional consequences of impaired catecholamine release [211]. The resultant impaired cardiac function can lead to cardiovascular collapse, subsequent brain damage, and/or death during delivery [212; 213].

Adenosine diphosphate (ADP) is a major factor in determining electrical stability of myocytes, because the longer the action potential, the higher the likelihood of abnormal cardiac activity [214]. It is possible that a component in smoke temporarily disables electrical properties of ventricular myocytes, rendering the ventricular muscle more susceptible to developing arrhythmias [215].

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Fetuses exposed to smoke also manifest an increase in cardiac volume growth between 23 and 27 weeks' gestation [216; 217]. This could be attributed to either an exaggeration of normal cardiac growth patterns or a compensatory response to an increase in upper body growth at the time.

LOW BIRTH WEIGHT AND SMALL FOR GESTATIONAL AGE

Infants born to mothers who smoke weigh less than other infants (independent of maternal body mass index), and low birth weight (<2,500 grams) is a key predictor for infant mortality. Effects of maternal smoking during pregnancy on infant birth weight have been recognized since 1957; nevertheless, smoking remains the most hazardous factor affecting a newborn's weight, even at present [218; 219; 220]. Similar to earlier studies, Bernstein and colleagues report that maternal third-trimester cigarette smoking is one of the strongest predictors of low birth weight. This study is thought to be the first to accurately assess maternal smoking levels, and startlingly, they purport that there is an estimated 27 g reduction in birth weight per cigarette consumed each day during the third trimester, or roughly twice the amount previously shown [220]. Another study found that 11.5% of infants born to women smoking less than six cigarettes daily had low birth weight [221]. Taken together, these studies demonstrate that there is not a safe level of smoking during pregnancy [221; 222]. Additionally, Aagaard-Tillery et al. reported that tobacco-exposed infants were small for gestational age regardless of maternal body mass index or pregnancies complicated by diabetes or hypertension [223].

A study examining the effect of prenatal smoke on a fetus in midgestation identified greater early gestational upper-body growth with preferential growth of head dimensions, upper limb length, and abdominal circumference with smoke exposure. This was followed by decreases in biparietal dimensions of the head, abdominal diameter, and distal limb length. Data from the late gestation period revealed cranial dolichocephaly, proportionally longer upper limbs, and legs with relatively reduced tibias, indicating that smoke exposure altered the growth rate of individual body segments [216]. It is possible that during hypoxia, blood supply to the lower limbs and internal organs is reduced in order to preserve brain metabolism [224]. Retardation of limb growth by 32 weeks could be due to diminished oxygen availability for distribution to distal tissues. The tibia, being one of the last consumers in the fetal nutrient distribution food chain, is therefore regarded as a good marker of available oxygen resources [216].

MIDDLE EAR DISEASE

Passive smoke exposure is independently associated with an increased risk of otitis media [222; 225; 226]. Though the immediate complications of otitis media are significant, one must also consider the lasting complications including an increased prevalence of speech and language difficulties, attention disorders, and learning difficulty [226]. The mechanism by which cigarette smoke causes otitis media is currently unknown. Histologic changes in fetal alveolar and bronchial epithelium lend support to a contemporary theory that purports that fetal cigarette smoke exposure may interfere with the development of the middle ear and eustachian tube epithelium. An alternative theory proposes that passive smoke-related immune system depression allows for opportunistic middle ear infections [226].

CANCER

One of the potentially negative effects of smoking during pregnancy is exposure of the fetus to carcinogens [227; 228]. The potent tobacco-related carcinogen 4-aminobiphenyl has been shown to cross the human placenta and bind to fetal hemoglobin [229]. Two metabolites of the tobacco-specific transplacental carcinogen NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-Gluc), were detected in the urine from newborns of mothers who smoked cigarettes during pregnancy [144]. Studies relating childhood and in utero cigarette exposure to brain tumors and leukemia have been inconsistent in their findings [230]. A meta-analysis of the association between exposure to maternal tobacco smoke during pregnancy and cancer in childhood found a small increase in risk of all neoplasms (based on 12 studies) but not of specific neoplasms such as leukemia (based on 8 studies) and CNS tumors (based on 12 studies) [231].

OSTEOPOROSIS

Maternal smoking has been shown to modulate bone mineral acquisition for the fetus, which may lead to increased risk of osteoporosis later in life [232].

PSYCHIATRIC DISORDERS

Previous studies have reported an association between maternal smoking during pregnancy and behavioral problems such as hyperactivity and decreased attention span. The association with behavioral problems has been shown in investigations of hyperactive children and controls, sibling studies in which the mother smoked in one pregnancy but not in the other, and in neuropsychologic evaluations of children of smokers and nonsmokers using tests of sustained vigilance and attention [233; 234; 235; 236]. Naeye and Peters found that hemoglobin levels in neonates increased with the number of cigarettes smoked by the mother during pregnancy and that children who were more active or had shorter attention spans had significantly higher hemoglobin levels [235]. Further, early secondhand exposure to nicotine as a child via maternal smoking during pregnancy shows an association with offspring attention deficit hyperactivity disorder (ADHD) symptoms [237; 238]. Evidence also supports a statistical association between prenatal smoking and increased risk for antisocial outcomes in offspring. Maternal smoking during pregnancy has been shown to be associ-

ated with a significant increase in externalizing behavior (tendency to seek controversy, aggressive, hyperactive) but not internalizing behavior (withdrawn, depressed, anxious) problems [239]. Similarly, maternal smoking during pregnancy has been shown to have an adverse effect on the child's negativity [240]. In a sample of 99 children 2 years of age, maternal smoking was identified as a significant predictor of childhood negativity, independent of demographic factors, perinatal factors, maternal personality attributes, and the mother-child relationship. Behavior problems associated with in utero exposure to SHS seem to continue into childhood and young adolescence, demonstrated by increased risk for ADHD, conduct disorders, criminality, and substance abuse [241]. An 18-year epidemiologic study of 1,265 New Zealand children identified that maternal smoking during pregnancy contributed to risk of higher psychiatric symptom rates for conduct disorder(s), alcohol abuse, substance abuse, and depression [242; 243].

PASSIVE SMOKING EFFECTS ON CHILDREN

It is possible that SHS exposure during childhood may be potentially more hazardous to neurodevelopment than in utero exposure to maternal smoking. Young children have higher ventilation rates, meaning they receive higher levels of SHS for the same duration and level of external exposure [244]. Passive smoking is believed to increase the prevalence of sudden infant death syndrome (SIDS); exacerbate asthma symptoms; interfere with cognition and behavior; increase cancer risk; and cause respiratory tract illness [226; 245; 246]. Breastfed infants with a smoking or snuff-taking mother are exposed to nicotine in breast milk, with a mean intake of nicotine of 7 mcg/kg per day [247]. Older children experience decreased physical fitness and are susceptible to tobacco-related illnesses just as adult smokers are.

Aside from adverse health effects due to SHS exposure, parental smoking is also positively correlated to their offspring's smoking as adolescents and adults. Counseling parents on the adverse health effects of SHS on children has been shown to dramatically reduce their children's subsequent cigarette smoke exposure [6; 246]. Smokers should be encouraged to smoke outside their homes and minimize SHS exposure to their children [248]. However, studies have shown that, though smoking outdoors decreases SHS exposure, children of parents who smoke outdoors still have higher prevalence of ear infections and respiratory symptoms than children of nonsmokers [249].

The National Heart, Lung, and Blood Institute recommends promoting a smoke-free home environment for all children and reinforcing this message at every encounter, including urgent visits for respiratory problems.

(https://www.nhlbi.nih.gov/node/80308. Last accessed May 13, 2019.)

Level of Evidence: A (Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the Guidelines' target population)

NEUROLOGIC EFFECTS

Prenatal and perinatal exposure to SHS adversely affects neurobehavioral development. Evidence now supports the notion that tobacco-exposed infants are more excitable and hypertonic, require more handling, and show more stress and abstinence signs than infants not exposed to tobacco. Symptoms are particularly noteworthy in the CNS, gastrointestinal system, and visual areas [250]. The presumed neurobiologic effect of SHS is altered brain development resulting from fetal hypoxia, due to either nicotine acting to reduce blood flow to the fetus, or possibly CO, which produces higher levels of carboxyhemoglobin. Nicotine may also target specific neurotransmitter receptors in the fetal brain to discoordinate the events of cell replication, differentiation, and synaptic development in the brain. Nicotine is thought to disrupt brain development via cholinergic mechanisms. In rats, exposure to nicotine alone has been shown to result in a significant increase in acetylcholinesterase (AChE) activity in the brainstem and midbrain. A significant increase in ligand binding to nAChR has been observed in the brainstem and cortex following exposure to nicotine. This suggests that exposure to nicotine may impair neurobehavioral performance and affect the cholinergic pathways [251].

In another study, postnatal SHS reduced hindbrain (comprising the pons and medulla oblongata) DNA concentration, increased the protein-to-DNA ratio, and reduced the body weight of exposed rats. These data suggest that postnatal exposure to SHS affects the hindbrain, a region that undergoes significant postnatal growth, by reducing the total number of cells and by increasing cell size. The authors concluded that, despite preserved hindbrain weight, the effects of postnatal exposure to SHS might result in neurologic dysfunction [252]. This study provided clear biologic evidence for an alteration of brain development due to postnatal, but not prenatal, SHS exposure. Interestingly, although gross dysmorphology is demonstrable in the animal brain by SHS exposure to nicotine, brain structures are not grossly abnormal when examined later in adolescence or adulthood [203].

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However, longer-lasting changes in morphology are noted in the hippocampus and somatosensory cortex in the form of decreased cell size and elevated numbers of glia. In considering synaptic function, several neurochemical studies have identified multiple biochemical markers of cell injury that indicate prenatal nicotine exposure damages the developing brain [253; 254].

CARDIAC COMPLICATIONS

Nicotine exposure causes myocyte cell damage in newborns, reduced platelet activation, increased resting sympathetic nerve activity, and hypertension. In rats, exposure to SHS during the neonatal period resulted in abnormal vasoconstrictor and vasodilator responses and smooth muscle dysfunction [255]. Abnormalities of endothelial cell function were found in rabbits exposed to SHS for 3 to 10 weeks [256]. Exposure to SHS also appears to directly affect endothelial function in children by means of a dose-dependent decrease in the bioavailability of nitric oxide [257]. Exposure to SHS also caused left ventricular hypertrophy in rabbits [258]. SHS exposure in childhood reduces high-density lipoprotein levels [259]. In addition, adolescents exposed to their parents' smoke show depressed levels of high-density lipoprotein cholesterol (HDL-C), suggesting that SHS exposure may accelerate atherosclerotic change and place children at increased risk for the premature development of coronary artery disease [260; 261].

SIDS

SIDS occurs within the first year of life and is a significant cause of infant mortality, with an estimated 1,400 deaths in the United States annually [262]. SIDS is a diagnosis of exclusion, and etiology is presently unclear. Various risk factors have been suggested including prone sleeping position, sex, age, birth weight, parental cigarette smoking, maternal substance abuse, bed sharing, soft bedding, and overheating [262; 263]. Matturi et al. found evidence supporting an association between maternal smoking and SIDS. Specifically, CO from cigarette smoke forms carboxyhemoglobin, leading to brain hypoxia. This lack of oxygen inhibits normal brain development of the arcuate nucleus and normal brain function in the locus coeruleus and arcuate nucleus. These abnormalities could potentially affect control of the respiratory and cardiovascular systems, resulting in sudden unexplained infant death. Matturi et al. concluded that the most preventable risk factor for SIDS is maternal smoking during pregnancy [264]. Zhang et al. concluded that the association between maternal smoking and elevated SIDS risk is dose-dependent and significantly increased in infants who co-sleep with smoking mothers [265]. Another study that sampled pericardial fluid in SIDS cases found that 70% had elevated levels of cotinine [266].

PULMONARY COMPLICATIONS

Children with smoking parents demonstrate higher frequencies of common respiratory symptoms including cough, phlegm, asthma, breathlessness, and wheeze. Parental smoking inhibits lung growth and function during childhood [267; 268; 269; 270]. One study assessed the pulmonary function of 80 healthy infants soon after birth and found significantly reduced pulmonary function in infants whose mothers had higher urine cotinine concentrations [271]. Another study demonstrated an association between in utero nicotine exposure and variable DNA methylation in fetal lung and placental tissues, suggesting that this variation may have a role in the fetal origins of chronic diseases [272].

Cough/Wheeze

Both past and current SHS exposure has been shown by multiple studies to cause cough and wheeze in children. Joad et al. worked with guinea pigs to establish the mechanism by which air pollutants, particularly SHS, causes cough. Secondhand smoke modifies afferent sensory fibers (specifically C-fibers and rapidly activating receptors) in the lungs and airways, thereby activating a neurally controlled cough mechanism. The vagus nerve receives input from the afferent sensory fibers, which is modified by interneurons in the nucleus tractus solitarius (NTS). A few additional modifications of the efferent activity occur in the brain stem. Cough occurs when the efferent signal modifies input to the respiratory muscles involved in inspiration and expiration. Wheeze occurs with bronchoconstriction and mucus secretion, which can be caused by locally released neurokinins or parasympathetic fibers synapsing on airway ganglia [64].

Asthma

Asthma is a chronic inflammatory disease, often with an initial onset in childhood. An association has been established between exposure to passive tobacco smoke and pediatric asthma development, while a causal relationship has been shown between exacerbated pediatric asthma and environmental tobacco exposure [273; 274]. Cigarette smoke causes an "exaggerated bronchoconstrictor response" in asthmatics, leading to an increase in severity and frequency of acute asthma attacks as well as asthma-related hospitalizations [275]. Studies have shown a decreased respiratory drive and hypoxic ventilatory response in infants of smoking mothers [247]. Exposure to nicotine for the full gestation produced an increased risk of depressed hypoxic ventilatory response in rats [18]. Parents of asthmatic children should be strongly cautioned that smoke exposure is likely to dramatically worsen their child's asthma [276; 277].

DENTAL CARIES

Each year, several billion dollars are spent treating pediatric dental caries in the United States. Dental caries are an oral infectious disease caused by *Streptococcus mutans* colonization and subsequent lactic acid production leading to dental decay. In addition to poverty, passive smoking is a substantial risk factor for developing dental caries. The reason for an increased prevalence of dental caries in children of low socioeconomic status is unclear. However, as poor children are more likely to be exposed to SHS, it has been suggested that environmental tobacco smoke exposure may help explain the increased dental decay in this particular population. Environmental tobacco smoke is considered a causal factor for dental caries in primary but not in permanent teeth. Mechanisms for the role of cigarette smoke in the development of pediatric dental decay include nicotine promotion of bacterial growth; immunosuppression from environmental tobacco smoke; decreased levels of vitamin C leading to increased bacterial growth; passive smoking-related saliva reduction, which impairs the natural defense against bacteria-related acid production; and a general increase in inflammation [278].

VITAMIN DEFICIENCY

Vitamin C (ascorbic acid) deficiency is common among active smokers due to both increased metabolism and decreased dietary consumption [68]. Cigarette smoking-induced oxidant damage is caused by both the immune system's inflammatory response and free radicals in cigarette smoke. Vitamin C and other antioxidants play an important role in preventing oxidant-induced damage.

Studies have supported a dose-dependent inverse relationship between environmental tobacco smoke exposure and ascorbic acid and beta carotene concentrations [68; 279]. A 2011 study found that children with no SHS exposure had higher levels of vitamin A, C, and E, beta carotene, and folate (controlling for dietary and supplement intake) than children with either moderate or high SHS exposure [279]. A lower concentration of these key nutrients was associated with higher cotinine levels. Vitamin B6, B12, and D levels were not found to be significantly affected.

RESULTANT SYMPTOMS IN ADULTHOOD

The relationship between childhood passive smoke exposure and resultant health consequences in childhood has been firmly established. There is less known about the long-term respiratory effects of childhood passive smoke exposure. David et al. studied Chinese adults from the Singapore Chinese Health study who were exposed to cigarette smoke as children but never actively smoked, thereby eliminating active smoking as confounding bias often found in similar studies. They found an association, independent of adult SHS exposure, between childhood environmental tobacco smoke exposure and chronic dry cough and phlegm production. Other findings included a lack of an association between childhood SHS exposure and asthma or chronic bronchitis. Also, they found low-fiber predisposed patients to respiratory maladies [280]. One study found a 50% increase in adult-onset cancer for children whose fathers smoked, and the risk of hematopoietic cancer increased when both parents smoked [281].

Peppone et al. reported that never-smoking women who grew up with a smoking parent may have more difficulty becoming pregnant. Those exposed to SHS regularly in childhood and adulthood were 39% more likely to have suffered a miscarriage or stillbirth and 68% more likely to have trouble conceiving when trying for more than one year [282]. Further, among women exposed to environmental tobacco smoke in youth undergoing ART between 1994 and 1998, there was decrease in implantation rate and increased odds of spontaneous abortion [65].

In a study by Strohsnitter et al., early menopause was more likely to occur in never-smoking women exposed to maternal cigarette smoke. They attribute this association to smoke's effects on follicle production in utero [283].

PASSIVE SMOKING EFFECTS ON ADULTS

The International Agency for Research on Cancer (IARC) Working Group concluded that secondhand tobacco smoke is carcinogenic to humans [284]. Complications of exposure to SHS include adverse effects on the pulmonary, cardiovascular, and neurologic systems as well as increased risk for cancer and fibroblast changes.

OCCUPATIONAL EXPOSURE

Occupational exposure to SHS affects the health of countless employees worldwide. Workplace exposure is highly influenced by the type of smoking policy in the workplace. Airborne nicotine is present, often in excessive concentrations, in various job settings due to variable public smoking laws [285; 286]. Local and state regulation of smoking in public places was instituted in response to data published by the American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE). These standards assert that satisfactory indoor air quality cannot be maintained if smoking is allowed indoors, even with additional ventilation and air-cleaning devices [287]. Several studies have shown that smoke-free workplace policies decrease exposure of nonsmoking employees to SHS at work, while increasing rates of smoking cessation and decreasing the number of employees who smoke [14; 288; 289; 290; 291]. Policies that are less restrictive are associated with higher levels of sustained tobacco use among employees [290]. Policies that make indoor workplaces smoke-free result in improved worker health [290; 292]. For example, smoke-free polices in the hospitality industry have been shown to improve health among bar workers, who are often heavily exposed to SHS in the absence of such policies [184; 290; 293].

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Studies have shown that segregating smokers and nonsmokers within the same airspace reduces SHS exposure to nonsmokers but does not eradicate it. One such study, in smoking-segregated restaurants in Albuquerque, New Mexico, showed levels of nicotine in nonsmoking sections approximately equal to those found in smoking sections [294].

SHS remains an issue for those employed in some casinos, bowling alleys, restaurants, lounges, and bars [295]. These work environments can contain high concentrations of airborne nicotine in the air if there is a lenient smoking policy. One study found that male blue-collar workers are exposed to significantly more SHS than their counterparts in management/professional occupations [296]. Also, on average, blue-collar smokers smoke more heavily than white-collar smokers [296]. Interestingly, female blue-collar workers are far less likely to smoke than women in management/professional occupations [296]. However, women's SHS exposure is approximately equal regardless of occupation, and SHS exposure is lowest for female service industry workers.

In 1986, the National Academy of Sciences warned, "SHS (also called environmental tobacco smoke) is a hazardous substance and is the most frequent source of complaint about aircraft air quality. Because of the high concentration of SHS generated in the smoking zone, it cannot be compensated for by increased ventilation in that zone" [297]. The area, volume, and ventilation rate per smoker on an aircraft is the smallest of any workplace setting. However, essentially all airlines now prohibit smoking on their planes.

Overall, exposure to SHS in different microenvironments is based on the strength of the active source, the ventilation system, and the presence and effectiveness of air-cleaning devices. Personal SHS exposure is also affected by age, gender, and race. Constant exposure to SHS at workplaces leads to various complications to the exposed workers.

HEART DISEASE

SHS is estimated to cause 5% to 30% of premature deaths from heart disease each year in the United States among nonsmokers [14; 298]. A key difference between the effects of smoking on the risk of cancer compared with the risk of heart disease is that the effects on cancer develop slowly, whereas the effects of smoking on the cardiovascular system occur rapidly. Passive smoking has been shown to cause atherosclerosis in both animal and human models, increase platelet aggregation, and increase myocardial oxygen demand. Multiple epidemiologic studies have consistently found an increased relative risk of cardiac events in nonsmokers with regular SHS exposure [299; 300]. Investigators demonstrated through experimentation that 30 minutes of exposure to SHS compromised the endothelial function in coronary arteries of nonsmokers so that the endothelial response of nonsmokers was identical to that of routine smokers [301].

The CDC asserts that people at risk for heart disease should avoid SHS because it can increase one's risk of acute MI. A study was conducted to verify this assertion and concluded that smoking bans at public working places correlate with a reduced morbidity from heart disease [302]. Researchers have suggested that platelet activation, endothelial dysfunction, and broad inflammation may have some relevance [303]. Another theory states that even light exposure to smoke concomitantly restricts blood vessels and allows for blood clotting. This combination raises the risk for MI.

Atherosclerosis

Atherosclerosis, a chronic inflammatory atheromatous disease characterized by focal, noncircumferential, and (most often) proximal plaques, is a major underlying cause of cardiovascular disease, which continues to be the leading cause of death, accounting for 840,678 deaths in the United States in 2016 [304]. Monocytes play a key role in the pathogenesis of atherosclerosis. Monocytes migrate from the blood to the subendothelial space beneath injured endothelial cells, where they differentiate into macrophages. These subendothelial macrophages readily take up oxidized LDL, becoming "foam cells." Collections of "foam cells" are dubbed "fatty streaks" and may first appear in the aorta at 10 years of age. Fatty streaks are precursors to atherosclerotic plaques. Such plaques are advanced lesions characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells [63; 305]. Triggers of endothelial cell injury include hyperlipidemia; bacterial or viral infection; oxidative stress through abnormal regulation of reactive oxygen species, hypoxia, turbulent blood flow, and shear stress; and environmental irritants, such as tobacco smoke [306].

Yuan et al. exposed transgenic human apoB-100 mice to sidestream whole smoke (SSW) (a major component of SHS) in order to study the effects of SHS on atherosclerosis. The transgenic mice received SHS exposure comparable to SHS exposure a nonsmoker would receive from a typical smoking housemate. They found a decrease in plasma HDL-C levels; a decrease in the ratio between HDL-C and triglyceride; and a decrease in ratio between HDL-C and total cholesterol. Yuan et al. noted increased lipid accretion in the aorta, heart vessels, and hepatocytes corresponding to the noted blood lipid profile alterations. Furthermore, they found increased levels of monocyte chemoattractant protein-1 (MCP-1) in blood, heart tissue, and aortic tissue. Increased numbers of macrophages were noted in arterial walls. This finding was significant as MCP-1 is a chemokine that attracts monocytes to the damaged subendothelial cells in the process of plaque formation. Decreased adiponectin monomer levels were noted in the smoke-exposed mice [63]. Adiponectin is an adipocyte-specific plasma protein with potential anti-atherogenic properties. In vitro, adiponectin suppresses the endothelial inflammatory response, the proliferation of vascular smooth muscle cells, and the transition of macrophages to foam cells [307]. Finally, based on examination of

the cytokine profile, Yuan et al. determined that cigarette exposure caused a permanent pro-inflammatory state; the normal adaptive response (i.e., initial pro-inflammatory Th1 type cell-mediated response to a Th2 mediated immune response) did not occur [63].

Coronary Heart Disease

A strong association between active smoking and coronary heart disease has been well established, and one study found a 50% to 60% increase in risk for coronary heart disease development in passive smokers [308; 309]. Active and passive smoking are known to [310]:

- Increase the incidence and frequency to cardiac arrhythmias
- Decrease the oxygen-carrying capacity of blood
- Increase the incidence of coronary artery spasm
- Promote atherosclerosis, thereby increasing the risk of cardiovascular disease
- Increase the incidence and tendency for thrombosis

The relationship between SHS and coronary heart disease is supported by a study that shows exposure to SHS is associated with increased inflammatory markers, including higher white blood cell counts and levels of C-reactive protein, homocysteine, fibrinogen, and oxidized LDL-C [311]. The intensity of inflammation markers was proportional to the number of years of reported exposure to SHS. Furthermore, subjects with only occasional SHS exposure also experienced increased levels of inflammatory markers, showing that even low SHS exposure is a significant concern. Increased coronary risk is mechanistically mediated by increased platelet aggregation, reduced oxygen uptake and exercise capacity, accelerated lipid peroxidation, and endothelial damage by SHS [312; 313; 314]. Passive smoke causes arteriosclerosis by altering cholesterol concentrations or by accelerating lipid peroxidation via reductions in serum antioxidant defense [315].

Many elements of tobacco smoke, including CO, nicotine, and polycyclic aromatic hydrocarbons, contribute to the damaging effects on the cardiovascular system. Studies of the effects of tobacco smoke on platelet sensitivity suggest that nicotine is not the sole cause of increased aggregation. Burghuber et al. compared the sensitivity of platelets to the antiaggregatory action of exogenous prostacyclin (PGI2) in nonsmokers and smokers exposed to SHS for 20 minutes. No change was observed in the smoking subjects' platelet sensitivity to PGI2 after SHS exposure, but the smokers' platelets were significantly lower than that of the nonsmoking subjects' before SHS exposure. The nonsmoking subjects experienced significant changes in sensitivity to PGI2 with reported platelet sensitivities matching those of smokers after SHS exposure [316]. However, another study by Benowitz et al. showed that smokers and abstinent smokers with nicotine patches differed significantly in platelet activity despite similar nicotine levels [317]. Thus, nicotine is not the only component of tobacco smoke that mediates increased platelet aggregation.

A British regional heart study examined 4,729 men 40 to 59 years of age and found a 50% to 60% increase in coronary heart disease caused by exposure to SHS [309]. This study is significant because most studies on the relationship between SHS and coronary heart disease either show significant risk increases or only show modest risk increases. Whincup et al. used cotinine measurements to determine passive exposure to smoking. This study noted that although high cotinine levels were associated with an excessive risk of coronary heart disease, they showed little association with the risk of stroke. Whincup et al. offered an explanation for the underestimated association between serum cotinine and coronary heart disease, in that the association tends to decrease over long follow-up periods since assessment of exposure. Finally, this study suggested that risks associated with passive smoking are widespread among nonsmokers.

The American Heart Association's Council on Cardiopulmonary and Critical Care, the Scientific Committee on Tobacco and Health in the United Kingdom, and the California Environmental Protection Agency have all concluded that SHS increases the risk of heart disease [318; 319; 320].

STROKE

According to findings of the Health and Retirement Study, a national longitudinal study of U.S. adults 50 years of age and older and their spouses, never-smokers with spouses who were current smokers had a 42% increased risk of first stroke. Former smokers married to current smokers had a stroke risk similar to respondents who were current smokers [321].

LUNG DISEASE

Environmental tobacco smoke exposure is associated with respiratory symptoms, asthma, a slight impairment of lung function, and increased bronchial responsiveness [322]. A Swiss study on air pollution and lung diseases with a sample of 4,197 nonsmoking adults, showed that SHS was associated with increased risk of asthma, wheezing, bronchitis, and dyspnea [323]. Greater levels of cumulative exposure to tobacco smoke in the home and workplace are also associated with an increased risk of COPD [324]. It is estimated that a (hypothetical) elimination of SHS in home and work environments would decrease COPD diagnoses in the United States by 18% (or 11% and 7%, respectively).

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In a report by Schick and Glantz of unpublished in vivo research done by Philip Morris during the 1980s, inhaled sidestream smoke was found to be four times more toxic per gram of total particulate matter than mainstream smoke. They report that the gas/vapor phase of sidestream smoke is responsible for most of the sensory irritation and respiratory tract epithelium damage that occurs [325].

Asthma

SHS is an established trigger for the onset of asthma in children, and there is growing evidence that it is also a causal factor for asthma in adult nonsmokers [326]. Finland researchers found that subjects exposed to tobacco smoke in the workplace were twice as likely to develop asthma as those who were not exposed. Health effects for adult asthmatics include asthma attacks; increased sensitivity and reduced lung function; and irritation of the eyes, nose, and throat. Exposure to cigarette smoke for just one hour can cause 20% deterioration in short-term lung function of adults with asthma [327].

CANCER

Lung cancer holds the distinction as "the first disease linked definitively" to both active and passive smoking [299; 328; 329]. Zhong et al., based on epidemiologic studies, estimate a 30% risk of lung cancer in nonsmokers exposed to environmental tobacco smoke. Chinese women have one of the highest incidences of lung cancer in the world, yet active smoking does not appear to be a major risk factor for lung cancer in this population [328]. Smoking among Chinese women is relatively rare, and among those who do smoke, cigarette consumption is limited. However, smoking among Chinese men is especially common, so their spouses are exposed to considerable quantities of environmental tobacco smoke. Thus, nonsmoking Chinese women were an ideal population for a case-control study considering the effects of environmental tobacco smoke on lung cancer. Certain histologic types of lung cancer are more commonly associated with active smoking. The risk of developing squamous cell and small cell cancer is much higher than the risk of developing adenocarcinoma and large cell carcinoma [330; 331]. The study by Zhong et al. showed that passive smoking also favors the development of squamous cell and small cell lung cancers over adenocarcinoma and large cell carcinoma [328].

Zhong et al. conducted a meta-analysis study on the relationship between lung cancer and environmental tobacco smoke. They found a 48% increased risk of lung cancer in nonsmoking males exposed to environmental tobacco smoke in their homes, while nonsmoking males had a 29% increased risk of lung cancer if exposed to smoke at work. A 20% increased risk of lung cancer was noted in nonsmoking females exposed to smoke in their homes, while nonsmoking females had a 15% increased risk of lung cancer if exposed to smoke at work. Furthermore, environmental tobacco smoke-exposed nonsmoking women "showed statistically significant monotonic exposure-response relationships." Finally, Zhong et al. found that childhood environmental tobacco smoke exposure did not correspond to an increased risk of lung cancer in adulthood [66].

Genetics may play an influential role in the risk of developing lung cancer from SHS exposure. Polymorphisms in the gene glutathione S-transferase (GST) M1 show a greatly increased risk of developing lung cancer with SHS exposure. GSTM1 is believed to prevent tumorigenesis by detoxifying carcinogens in tobacco smoke. Lung cancer susceptibility has been associated with anomalies in several cytochrome P450 pathways and several GST enzymes that detoxify chemical carcinogens [332; 333; 334; 335; 336]. GST enzymes are considered phase II detoxification enzymes, which conjugate glutathione to carcinogens and reactive oxygen species to detoxify them. Two of the four polymorphic gene classes of GSTs, mu (μ) and theta (θ), have been linked to tobacco-associated cancers. The GSTM1 is a variant of the mu class, which contains a null allele that may be inactivated by a deletion of DNA coding sequences [336; 337]. Approximately 50% of the white populations of Europe and North America have homozygous null genotypes for the GSTM1 enzymatic activity [338]. Loss of GSTM1 enzymatic activity has been associated with increased risks of various cancers, including tobacco-associated lung cancer, head and neck cancer, larynx cancer, and bladder cancers. Bennett et al. found that SHS-exposed nonsmoking women with the null polymorphism represented 42% to 49% of the lung cancer cases [337]. Women with the homozygous null genotype have a greater risk of tobacco-associated cancer relative to men [339].

GSTTI is an isoenzyme of the theta class of GSTs, which is deactivated by a homozygous deletion in 11% to 18% of whites [338]. United deficiency of GSTT1 and GSTM1 produces a dramatically increased risk for lung cancer in U.S. populations [340]. Kawajri et al. found that a mutant variation in exon 7 of the cytochrome P450 1A1 (CYP1A1) enzyme was associated with higher rates of lung cancer in the Japanese subjects studied [341]. CYP1A1 is known to activate carcinogenic polycyclic aromatic hydrocarbons including the benzo(a)pyrene component of tobacco smoking [342]. Rebbeck et al. found a synergistic increase in lung cancer risk with both homozygous deletions of GSTM1 and the valine allele variant of exon 7 in CYP1A1 [338].

Large-scale genome-wide association studies have identified several novel lung cancer susceptibility genes, including those on chromosomes 5p15.33, 15q24-25.1, and 6p21 [343]. The 5p15.33 region is associated with risks specific to adenocarcinoma of the lung. The 15q25 region contains three nicotine acetylcholine receptor subunit genes. Their polymorphisms have been associated with nicotine dependence [343]. Associations of the 6p21 region have not been consistently replicated among studies [343; 344]. Other regions (e.g., 6q23-25, 13q31.3) have also been identified by genome-wide studies as being associated with risk of lung cancer, includ-

ing some studies specific to African Americans and to those who have never smoked. Further studies are necessary to assess individual susceptibility based on the combination of polymorphisms in multiple genes [343; 344; 345].

GLUCOSE INTOLERANCE/DIABETES

Houston and colleagues questioned whether active and passive smokers are more likely than nonsmokers to develop clinically-relevant glucose intolerance or diabetes. Of 4657 participants in the Coronary Artery Risk Development In Young Adults (CARDIA) study, 16.7% developed glucose intolerance at 15-year follow-up. Incidence of glucose intolerance was highest among smokers (21.8%), followed by never-smokers with passive smoke exposure (17.2%), then previous smokers (14.4%), and was lowest for never smokers with no passive smoke exposure (11.5%). The risk among current and never smokers remained after adjustment for sociodemographic, biologic, and behavioral factors, but risk in previous smokers was similar to that in never smokers without passive smoke exposure [346]. A meta-analysis conducted by Pan et al. found that both active and passive smoking are associated with significantly increased risks of type 2 diabetes. The risk was increased in individuals who had recently quit smoking, but decreased substantially as time from quitting increased. They also identified a dose-response relation for current smoking and risk of diabetes [347].

SKIN DISORDERS

Setty, Curhan, and Choi prospectively examined over a 14-year period (1991–2005) the relation between smoking status, duration, intensity, cessation, and exposure to SHS and incident psoriasis in 78,532 women from the Nurses' Health Study II. Prenatal and childhood exposure to passive smoke as well as current and past smoking and cumulative measures of smoking were associated with an increased risk of psoriasis. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers 20 years after cessation [348].

WOUND REPAIR

Passive smoking is known to interfere with normal tissue repair and remodeling, though the underlying pathology is not well understood. Passive smoking has been shown to obstruct wound healing by decreasing blood flow to the damaged tissue and hindering granulation tissue formation and function. Tissue repair and remodeling is heavily reliant upon fibroblasts, which migrate to the site of damage, proliferate, and secrete cytokines, growth factors, and extracellular matrix molecules. Wong et al. found that SSW smoke causes cytoskeletal changes in fibroblasts, which may account for decreased fibroblast migration. Furthermore, excess scarring in SHS-exposed individuals is likely due to a combination of prolonged cell survival (due to a cellular stress response invoked by SHS) and the aforementioned decreased cell migration [62].

AGE-RELATED MACULAR DEGENERATION

Khan and colleagues designed a case-control study to investigate a possible relation between smoking and risk of development of age-related macular degeneration (AMD) among whites. Although many risk factors are related to AMD (e.g., aging, hypertension, family history, obesity), they found a strong association between AMD and pack years of cigarette smoking, and the odds ratio increased with the amount smoked. Smoking impairs the functioning of the retinal pigment epithelium, causing buildup on the retina and subsequent damage to Bruch's membrane. Stopping smoking was associated with reduced odds of AMD and the risk in those who had not smoked for over 20 years was comparable to nonsmokers [349].

CERVICAL INTRAEPITHELIAL NEOPLASM (CIN)

Cervical intraepithelial neoplasm (CIN) is a precursor to cervical cancer, which is the fourth most common cause of cancer-related death in women worldwide [350]. Firmly established major risk factors for CIN include active smoking and human papillomavirus (HPV) infection. A 2006 case-control study of Taiwanese women established SHS as a major risk factor for CIN in addition to active smoking and HPV. The authors presented an indirect and a direct potential mechanism for the development of CIN following SHS exposure. CIN could be caused indirectly by immune suppression or directly by a polycyclic aromatic hydrocarbon-DNA adduct [69]. More recent studies continue to suggest an association between SHS and CIN, and while these studies continue to be conducted, few have provided conclusive results [468; 469].

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease is one of the most common liver diseases in the United States. Nonalcoholic fatty liver disease covers a broad range of diseases from steatosis to nonalcoholic steatohepatitis (NASH) and can have dramatically varied underlying pathology. NASH is a significant clinical concern due to potential disease progression resulting in cirrhosis and end-stage liver disease [351]. Yuan et al. employed a mouse model transgenic for human apoB100 to consider the effect of passive smoke on cholesterol and triglyceride levels. They found no significant change in cholesterol levels with passive smoke exposure but a marked increase in triglycerides in the liver. The increased lipid accretion in hepatocytes is consistent with lipid changes seen in nonalcoholic fatty liver disease [63].

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MEASURING SECONDHAND SMOKE EXPOSURE

Seventy percent to 80% of nicotine is initially metabolized to cotinine, primarily by CYP2A6 [195]. Cotinine is, for the most part, metabolized to 3'-trans-hydroxycotinine, mainly by the same CYP2A6 enzyme [352]. Both nicotine and cotinine undergo *N*-glucuronidation; however, 3'-hydroxycotinine undergoes *O*-glucuronidation [353]. Cotinine is also partly metabolized to 3'-trans-hydroxycotinine by CYP2A6 [352]. Cotinine has a half-life of 15 to 20 hours, and its serum concentrations are tenfold higher than nicotine; thus, cotinine is generally used as an index of nicotine exposure [354].

Cotinine can be measured in hair, nails, blood, saliva, or urine samples. Although other biomarkers for environmental tobacco smoke exposure exist, cotinine is currently the most sensitive and specific. Such objective quantification is especially important in studies concerning passive smoke exposure in children, as parental assessment of smoke exposure is frequently unreliable [65; 69; 277; 355; 356]. SHS exposure can also be assessed through CO breath analysis, measurement of certain carcinogens (e.g., NNAL can be found in urine, blood, and nails) or benzene, or measurement of respirable suspended particulates in the air [355].

Breath analysis has improved as an assessment tool. It utilizes the monitoring of volatile organic compounds, which are predominantly bloodborne and therefore enable monitoring of different processes in the body. One study utilizing a real-time breath analyzer identified the presence of volatile organic compounds (1,3-butadiene) after SHS exposure in the breath of nonsmokers [357]. While this method of smoking analysis is improving, studies using this tool still suffer issues of sampling and lack of normalization data. Results could be skewed by participants' varying degrees of exposure to other common sources of volatile organic compounds, for example, wood smoke and automobile exhaust [358].

Studies of genetic polymorphisms of genes that modulate cell growth and proliferation provide potentially helpful biomarkers associated with long-term exposure to carcinogens and eventual tumor formation. One such biomarker used to study lung cancer in SHS-exposed patients is the tumor suppressor gene *p53*. The *p53* gene encodes a multifactorial transcription factor that controls cellular response to DNA damage [359]. Husgafvel-Pursiainen et al. found a three- to fourfold increase in the risk of *p53* mutation in SHS-exposed patients who develop lung cancer, while in long-term heavy smokers, *p53* mutations are found in 50% of patients with lung tumors [360]. Furthermore, Husgafvel-Pursiainen et al. demonstrated that the majority of the *p53* mutations were G:C to A:T transitions. The CpG dinucleotide sites were mutational hotspots, accounting for 50% of the reported G:C to A:T substitutions within the *p53* gene. Endogenous deaminations of methylated cysteine residues or preferential carcinogen binding are proposed explanations for G:C to A:T substitutions within CpG islands. This evidence supports the role of *p53* as a biomarker for both passive and active tobacco-related carcinogenesis [360].

A combination of the measurement of body fluids for cotinine and hair for nicotine, with the questionnaire and interview-derived information, seems to be the optimal method for assessing SHS exposure. Empirical studies show general concordance of reported environmental or biologic measures of SHS exposure [361]. In addition, urinary cotinine is often used for evaluation of smoking-cessation program efficacy, monitoring of pregnancy/other at-risk groups, and assessment of occupational exposure [362].

THIRDHAND SMOKE

The term "thirdhand smoke," or "environmental tobacco smoke," has been and is often used synonymously with SHS, but it can be more accurately described as any airborne particulate matter originating from burning tobacco. It is comprised of both active mainstream smoke (tobacco smoke exhaled by active smokers) and sidestream smoke (smoke from the burning end of a cigarette) that is inhaled by nonsmokers, and evidence shows the possibility of harm for a significant period of time after the cigarette/tobacco product has been extinguished.

In a 2009 study by Winickoff et al., more than 80% of national survey respondents (regardless of smoking status) agreed that SHS was harmful to children, but only 43% of smokers and 65% of nonsmokers thought the same of thirdhand smoke (defined as "breathing air in a room today where people smoked yesterday") [363]. Thirdhand smoke, or any exposure to residual tobacco smoke contamination on surfaces or breathing air in a room where smoking previously occurred, can be dangerous. Unfortunately, not all smokers are cognizant of these harms. Many believe that confining smoking to one room in the home or smoking in the absence of children or even smoking outside with all household windows and doors closed is enough to protect their children. Tobacco smoke does not simply disappear after cigarettes are extinguished, and it (and other toxins) may linger even with what is perceived as adequate ventilation.

Hein and colleagues were likely the first to measure nicotine content of household dust. Nicotine has a high affinity for dust particles, and the amount of tobacco smoking that occurs in the home is highly correlated with concentration of nicotine in household dust [364]. According to a 2004 study by Matt et al., vapor components of tobacco smoke "are absorbed onto walls, furniture, clothes, toys, and other objects within 10 minutes to hours after tobacco smoke has been emitted. From there, they are re-emitted into the air over the course of hours to months" [365]. Similar to findings of a 2001 study of hair nicotine levels among children in New Zealand, whether household smokers smoked indoors in the presence of their child or attempted to limit their children's smoke exposure

by smoking outside or in the children's absence, the children were not protected from exposure to nicotine in the indoor air [366]. Further, skin-to-skin contact poses additional risk as nicotine was found on the index fingers of 92% of mothers in the sample [365].

Part of the reason behind the danger of thirdhand smoke may be the lead content of tobacco smoke. According to the Environmental Protection Agency, the tobacco leaves used to make cigarettes contain radioactive lead-210. Indeed, increased blood lead levels among youth is directly associated with household smoking and house dust [367]. Mainstream smoke contains at least 58 percutaneous penetration enhancers, which are used to enhance transdermal delivery of drugs. Of these, 69% are hydrophobic or strongly hydrophobic and can therefore readily permeate the skin and likely settle in percutaneous fat for continued exposure long after the cigarette has been extinguished [368]. Further, unpublished research from Philip Morris Co. shows that 4-(methylnitrosamino)-I-(3-pyridyl)-1-butanone (NNK) forms in sidestream smoke and increases up to 200% per hour during the first six hours after cigarettes are extinguished [369]. NNK has been shown to cause an exaggerated response in microglia (causing them to attack healthy brain cells) and overall neuroinflammation, which can lead to disorders such as multiple sclerosis [370].

Oie and colleagues report that low ventilation in homes can strengthen the effects of indoor pollutants. They found that odds of bronchial obstruction among children was higher in homes where they were exposed to environmental tobacco smoke as well as dampness, textile wallpaper, and plasticizer-containing surfaces [371].

The problem is not confined to homes. In a 2008 study by Matt and colleagues, it was found that cars of people who smoked in their vehicles contained elevated levels of nicotine in dust on surfaces and in the air when compared with cars of nonsmokers [372].

Haussmann et al. performed a study of fresh versus room-aged sidestream smoke to ascertain how the different types of smoke would affect rats. Their study revealed that the room-aged smoke had decreased concentrations of smoke components such as nicotine and total particulate matter. However, levels of CO remained equal to that of the fresh smoke. The rats manifested reserve cell hyperplasia in the nose and hyperplastic and metaplastic epithelial changes in the larynx; these effects were not as profound in those exposed to the room-aged smoke [373]. Rao and colleagues found that lung tissue from mice exposed to aged and diluted sidestream smoke exhibits increased angiogenesis associated with leukocyte rolling and adhesion. This phenomenon may lead to recruitment of inflammatory cells as observed in bronchitis or asthma [374]. These research studies confirm the unpublished research of Philip Morris Co. in the early 1990s, which revealed that aged sidestream smoke is more toxic to lab animals than fresh sidestream smoke [375].

INTERVENTIONS FOR SMOKING CESSATION

PRIMARY CARE INTERVENTION

Smoking cessation may be helpful in reducing firsthand and secondhand tobacco smoke exposure by eliminating the source: the smoker(s). Parents and caregivers of young children should receive cessation counseling and/or pharmacotherapy to quit smoking and eliminate the exposure of children to SHS. Parents should also be informed of the importance of a smoke-free environment for children and that it should be instituted before pregnancy. Pregnant women must learn that smoking will likely produce lasting adverse effects on their offspring. Furthermore, smoking parents should be aware that smoking is known to cause and exacerbate asthma, chronic serous otitis, otitis media, respiratory illness, and possibly childhood cancers. A healthcare provider is required to intervene if a child is suffering from one of these disorders. Healthcare providers are responsible for advising smoking parents about the harms of passive smoke as well as how to provide a smoke-free environment for their children [249]. There are many smoking cessation resources that may be provided to patients, including several "quitlines." These hotlines provide free telephone access to a smoking cessation counselor. The National Cancer Institute's quitline is 1-877-44U-QUIT (1-877-448-7848), and both English- and Spanish-speaking assistance is available. The website https://smokefree.gov also offers support, tools, and expert advice through their app, text messaging, and social media networks. Assistance for issues unique to different subgroups, such as veterans, women, adolescents, adults older than 60 years of age, and those who speak Spanish, are also available.

The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to adults who use tobacco.

(http://annals.org/aim/fullarticle/2443060. Last accessed May 13, 2019.)

Level of Evidence: A (There is high certainty that the net benefit is substantial.)

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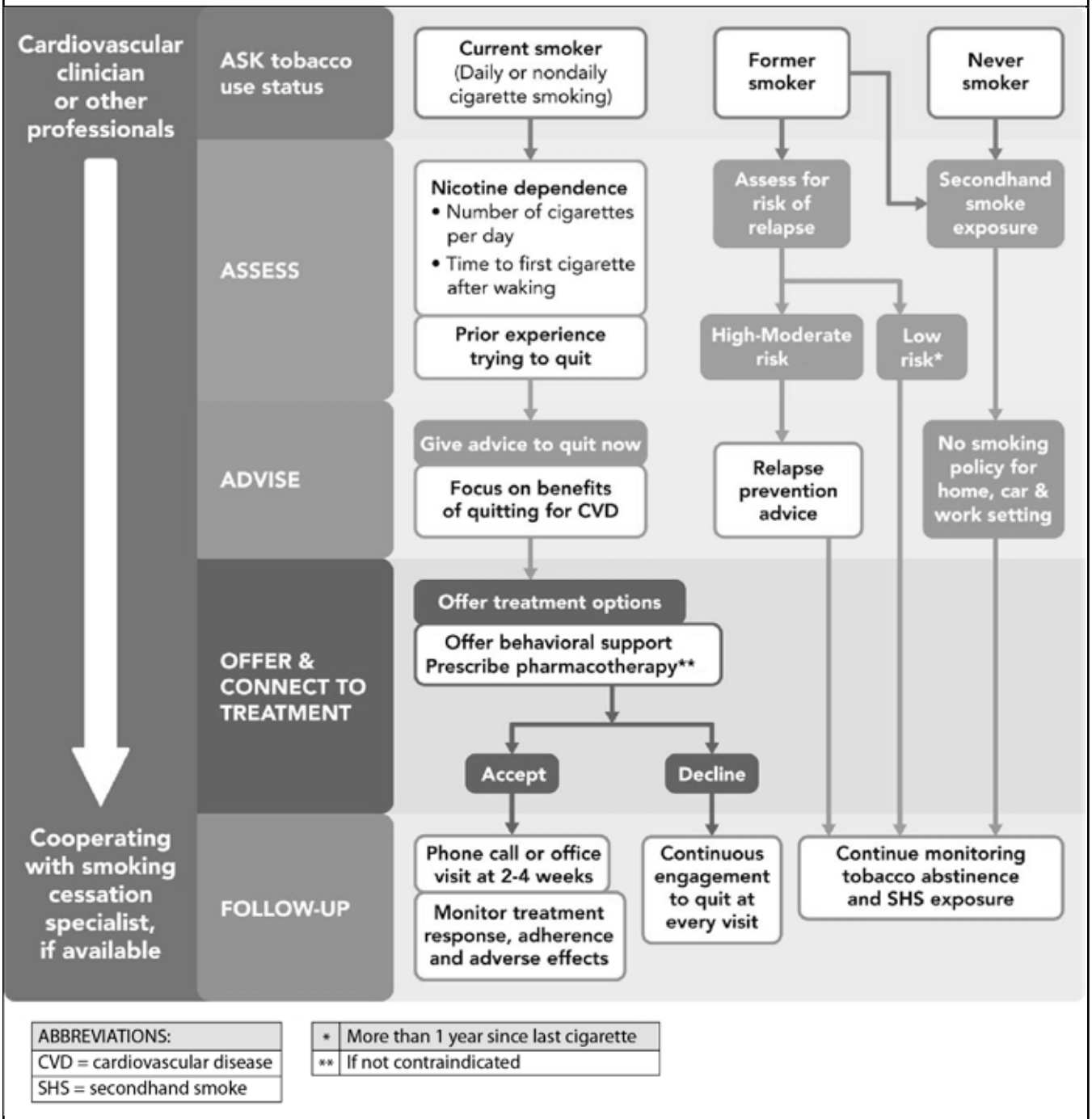
PATHWAY FOR TOBACCO CESSATION TREATMENT



Source: Modified with permission from Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018;72(25):3332-3365. *Figure 2*

Although nearly 70% of patients who smoke say they would like to quit, only 7.4% are able to do so without help [376; 377]. The advice of a physician alone can increase the smoking cessation rate to 10.2% [378]. It is important for physicians to add an inquiry about smoking to the questions routinely asked while a patient's vital signs are being taken (***Figure 2***). Further assessment using an abbreviated form of the Fagerström Test for Nicotine Dependence can provide information about whether a patient is addicted to or physically dependent on nicotine. The Fagerström test is a question and answer test that rates an individual's nicotine dependence on a scale of 0 to 10 [379].

After the diagnosis of nicotine dependence is made, the next step is to assess the patient's readiness to change. The five-stage model for readiness to change can be applied to addictive behaviors such as smoking. The stages are precontemplation, contemplation, preparation, action, and maintenance. In the precontemplation stage, a patient does not believe that smoking is a problem or refuses to consider smoking cessation. In the contemplation stage, the patient recognizes that smoking is a problem and is thinking about quitting. During the preparation stage, the patient makes specific plans to stop smoking, such as setting a quit date and determining how smoking cessation will be accomplished. In the action stage, the patient stops smoking. Finally, the maintenance stage is marked by the patient's continued abstinence from smoking. Relapse to smoking behavior is common. Patients often cycle through the stages of change several times before reaching stable abstinence [380].

Interventions can be classified into behavioral, pharmacologic, and alternative methods. Behavioral interventions include physician advice and individual, group, and telephone- or Internet-based counseling. Pharmacologic interventions include NRT, sustained-release bupropion, and varenicline. Alternative interventions include hypnosis, acupuncture, exercise, lobeline, anxiolytics, mecamylamine, and opioid agonists [381].

BRIEF INTERVENTION

Brief intervention training allows healthcare professionals to offer basic support, ensuring that all smokers who come into contact with these health professionals are able to receive help as appropriate. Brief intervention offers short-term professional input, self-help leaflets and videos, and complementary therapies. This type of information can be applicable for smokers at any level. Milch et al. compared the effects of two brief interventions against treatment as usual. The minimal intervention consisted of a smoking status vital sign stamp, which documents the patient's smoking status. The enhanced intervention consisted of a five-question form that assessed the patient's level of cessation readiness and provided cessation counseling prompts for clinicians. Medical record documentation of screening for smoking and cessation advice and self-reported patient smoking cessation rates were collected 8 to 10 months after implementation. Self-reported patient smoking cessation was higher in the enhanced intervention group (12%) compared with the minimal intervention (2%) and control (4%) groups. This demonstrated that even a short questionnaire that assessed readiness to quit and provided documentation of cessation advice improved rates of clinician cessation advice and patient smoking cessation compared with no intervention [382]. In a study by Smith and Burgess of patients admitted to the hospital with diagnoses of coronary artery disease, a minimal intervention (i.e., advice from physicians and nurses and two pamphlets) resulted in 35% of the group confirmed abstinent at 12 months [383].

According to the University of Michigan Health System, healthcare professionals should advise all tobacco users to seriously consider making a quit attempt using a clear and personalized message. Advice as brief as three minutes is effective.

(https://www.med.umich.edu/1info/FHP/practiceguides/smoking/smoking.pdf. Last accessed May 13, 2019.)

Strength of Recommendation/Level of Evidence: IA (Generally should be performed based on randomized controlled trials)

5 A's

The U.S. Public Health Service Clinical Practice Guideline was updated in 2018, but continues to recommend the 5 A's approach for intervening with the patient who smokes [384; 470]:

- Ask about smoking status
- Advise to quit
- Assess willingness to quit
- Assist by suggesting and encouraging the use of problem-solving methods for cessation
- Arrange for follow-up contacts and relapse prevention

Mullen et al. found that simple changes in question format, such as moving away from requiring "yes" or "no" answers and allowing responses such as "I used to smoke" or "I have cut down," increased smoking disclosure by 40% [385]. Every clinician should ask patients about tobacco use and advise them to quit. Abrupt smoking cessation with medical and psychologic assistance is more successful than tapering or "smoking less" [461].

Given the magnitude of tobacco use as a health risk, tobacco use status should be considered a vital sign requiring regular assessment [384; 386]. Nevertheless, studies continue to find that clinicians inconsistently practice assessment of tobacco use and advice to quit smoking [387]. The third step of the Five A's approach, after asking and advising, is to assess the patient's willingness to quit. For the patient who is unwilling to quit at this time, the clinician should help increase motivation by discussing the immediate and long-term risks of continued smoking, benefits of quitting, and the patient's perceived barriers to quitting. The clinician should try to make the discussion personally relevant to the patient and include risks and benefits in addition to those related to health [384]. For the patient willing to quit, the clinician should provide assistance, such as helping the patient choose a target quit date in the near future, suggesting appropriate pharmacotherapy, providing social support, advising the patient about the nature and time course of nicotine with-

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drawal, recommending behavioral and cognitive coping responses to use when the patient experiences urges to smoke, and perhaps making a referral to an intensive behavioral counseling program [384]. The last of the Five A's involves arranging follow-up contact. This strategy is also based on evidence that total contact time predicts treatment outcome [384]. Follow-up contact can take the form of additional office visits, telephone calls, text messages, or even written materials sent through the mail [462]. Such contact communicates the importance of the cessation attempt, provides social support, and offers the opportunity to intercede if problems have developed. Because the risk of relapse is greatest immediately after quitting, follow-up contact ideally should begin close to the target quit date [388].

MOTIVATIONAL INTERVIEWING

Introduced by Miller in 1983, motivational interviewing is a method of counseling designed to enhance patients' motivation to change by helping them explore and resolve their ambivalence about making the change [389]. It is a collaborative, non-confrontational, "guiding" approach. Motivational interviewing for tobacco cessation utilizes active listening to understand how the patient feels about his or her tobacco use in an effort to uncover any ambivalence [384]. The healthcare provider elicits the patient's own views regarding consequences of continuing to use tobacco and benefits of quitting and asks permission to share additional information on risks when necessary. Goals are developed collaboratively, based on the patient's current readiness to change. Originally developed as an intervention for alcohol abuse, it has shown promise as a successful strategy for smoking cessation. Lai et al. reviewed 28 studies and found that motivational interviewing yields a significant increase in quit rate, especially when conducted by primary care physicians or counselors for sessions lasting more than 20 minutes [390; 391]. Further, in a randomized, controlled trial, Ruger and colleagues reported that motivational interviewing for smoking cessation actually saves money, and prevents relapse, among low-income pregnant women with $628/quality-adjusted life-year saved versus usual care [392].

INTERVENTIONS FOR NON-ENGLISH-PROFICIENT INDIVIDUALS

Because communication with patients regarding cessation of smoking is a vital aspect of patient care, it is important that discussions and printed materials are provided in the language with which the individual is most comfortable. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party [393]. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes. The American Heart Association, the American Medical Association, and the American Academy of Family Physicians produce patient education references in several languages. Primary care providers may utilize these in their interactions with patients for whom English is a second language.

TREATING NICOTINE DEPENDENCE

Behavioral Modifications

Behavioral interventions are nonpharmacologic treatments delivered directly to individual smokers [388]. The main disadvantage of this approach is that relatively few smokers (about 5%) are interested in attending specific classes at any given time [394; 395]. Therefore, group sessions appear to be the most cost-effective approach to delivering smoking cessation interventions [396]. Although relatively few patients want to go to classes, physicians should still have a list of referral smoking cessation clinics in their area for those smokers who express an interest in attending them and for those who have failed to respond to other approaches. Simple text, app, and web-tailored cessation messages may also be an effective alternative for behavioral support, doubling the cessation rates. This concept has been incorporated into patient support programs provided by several manufacturers of smoking cessation products [394].

There are several behavioral interventions that have empirical support, such as multicomponent coping skills training (e.g., coping response therapy, problem-focused treatment, relapse prevention training, and cognitive-behavioral therapy). This training includes social support and didactic information about nicotine dependence, withdrawal symptoms, and situations that are risks for relapse (e.g., alcohol use, negative moods, or presence of other smokers) as well as training in the use of cognitive and behavioral responses to cope with urges to smoke that reduce the risk of relapse [397; 398]. Aversive therapy for smoking cessation, known as rapid smoking, involves smokers in a controlled clinical setting who deeply inhale on cigarettes at six-second intervals. Up to nine cigarettes would be smoked per treatment session to produce strong aversive reactions to cigarettes [399]. Aversive cigarette use greatly declined after the introduction of NRTs, and reviews have concluded that there is insufficient evidence to determine the efficacy of this method for smoking cessation [400; 401]. Another behavioral treatment, scheduled reduced smoking, involves three weeks of gradually reduced nicotine intake. In contrast with other

smoking cessation strategies involving reduction of smoking, the patient does not control when and where smoking will occur. Rather, an algorithm is used to determine when each cigarette is to be smoked based on the passage of time [402].

Pharmacotherapy

The first-line pharmacologic interventions for smoking cessation are NRT, bupropion, and varenicline [381; 403]. However, no pharmacotherapy has been approved for use among pregnant or nursing women. The five forms of NRT available are the patch, gum, lozenge, nasal spray, and inhaler. A Cochrane review found that all commercially available forms of NRT increased the quit rate by 50% to 70%, independent of the intensity of additional support provided to the individual. Although support is beneficial, it does not appear to be essential to the success of NRT [404].

All available pharmacotherapies are safe for non-pregnant or nursing adults. In a 2016 analysis, varenicline outcomes are found to be equal to NRT plus counseling, and varenicline is also associated with a reduced risk of relapse [463]. Bupropion has the added advantage of reducing smoking cessation-related hyperphagia and weight gain. It is also an antidepressant and can ameliorate withdrawal-associated anhedonia and depression.

The nicotine transdermal system, otherwise known as the patch, releases nicotine steadily during an extended period, with blood levels rising within the first 2 to 4 hours and then remaining relatively constant between 8 and 24 hours after application, depending on the product used [405]. A number of transdermal nicotine-replacement systems are available over the counter. Prescribing information inserts for all transdermal nicotine products indicate that they should be used as part of a cessation program; yet, many patients receive the patch without any physician advice or behavioral support [406]. Adverse reactions to transdermal nicotine-replacement systems seldom cause discontinuation of therapy. Thirty percent to 50% of patients experience mild skin irritation with the patch. In most patients, rotating patch application sites can alleviate this problem. Sleep disruption is usually resolved by removing the patch at bedtime [407]. Unfortunately, use of the patch without any behavioral support is not likely to be successful.

The U.S. Food and Drug Administration adopted labeling for the patch, allowing use beyond the standard duration of eight weeks. This decision was based in part on data showing that extended-duration (24-week) transdermal nicotine therapy reduced the risk for smoking lapses and increased the likelihood of recovery to abstinence compared to the standard 8-week duration of therapy [408; 409].

Nicotine chewing gum is a type of NRT that may aid in smoking cessation and/or quitting smokeless tobacco. Chewing allows nicotine to be delivered quickly into the bloodstream. Typically available in either 2- or 4-mg doses, nicotine chewing gum is expected to last one to two hours. Release of nicotine from the gum is proportional to the rate of chewing, a feature that allows for self-titration [410]. However, like the patch, nicotine gum is most successful as an adjunct to behavioral interventions. Indeed, Schneider et al. showed that merely dispensing nicotine gum resulted in a lower quit rate with active gum than with placebo treatment (8% nicotine gum, 13% placebo gum) [411].

The nicotine lozenge is similar to a hard candy. It slowly dissolves in the mouth (for 20 minutes or so) to release nicotine to the brain more quickly than the patch. Shiffman, Di Marino, and Pilliteri analyzed two trials of a 21-mg nicotine patch and 4-mg lozenge to assess the efficacy of each in heavy and dependent smokers. Both therapies were found to significantly increase six-month, continuous abstinence in heavy smokers (≥40 cigarettes per day) and the highly dependent (Fagerström score >7) [412].

A 2-mg sublingual nicotine tablet has shown efficacy in several studies and has been approved in Europe to manage nicotine withdrawal [413; 414; 415]. Interestingly, one study found that being married was strongly associated with smoking cessation while on this medication [416]. Sublingual tablets (2 mg) have similar pharmacokinetics to that of the 2-mg nicotine chewing gum [417]. One study of high-dependence smokers (those who smoked their first cigarette of the day within 30 minutes of waking) found that a 4-mg nicotine lozenge significantly reduced withdrawal symptoms and cravings over six weeks of treatment [418].

Nasal nicotine spray (NNS) was approved by the FDA in 1997. Available by prescription, each spray contains 0.5 mg of nicotine, and a dose is defined as one spray in each nostril. In clinical trials, subjects were allowed to take up to 5 doses/hour, with a maximum of 40 doses/day (40 mg of nicotine). The cessation rates in trials with NNS at 1 year ranged from 15% to 25% [419; 420; 421]. A meta-analysis of nicotine replacement suggested that NNS and the inhaler might have higher quit rates than the patch or gum [422]. Indeed, nicotine administered via nasal spray is considered to be the next fastest acting delivery method after smoking and requires 11 to 13 minutes for nicotine levels to reach peak plasma concentration [423].

The FDA also approved a nicotine inhalation system consisting of a mouthpiece and a nicotine-containing cartridge. Available with a prescription, each inhaler contains 10 mg of nicotine and 1 mg of menthol, of which 4 mg of nicotine can be extracted and 2 mg are systemically available. Shallow or deep puffing results in similar nicotine absorption. Nicotine is delivered mainly to the oral cavity, throat, and upper respiratory tract, with a minor fraction reaching the

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lungs. A single inhaler can be used for one 20-minute period of continuous puffing or periodic use of as many as 400 puffs per inhaler. With controlled puffing in laboratory testing, venous plasma nicotine concentrations from a single inhaler puffed 80 times for 20 minutes, averaged 8.1 mcg/L at 30 minutes. Lower concentrations of 6.4 to 6.9 mcg/L have been reported for self-administration under clinical conditions. The time to reach peak plasma concentrations varies but is always significantly longer than with cigarette delivery [424].

Quitting smoking can be a difficult process, even with use of NRT. When subjects were given denicotinized cigarettes along with IV saline or nicotine, the variable most responsible for craving satisfaction, psychologic reward, and craving reduction was the denicotinized cigarette [425]. When *ad libitum* smoking of preferred brands was also allowed, the combination of nicotine-less cigarette and bolus IV nicotine were the most effective in lowering craving, negative affect, and total amount smoked [89]. Sensations in the tongue, nose, back of mouth, throat, windpipe, and chest showed strong correlation between nicotine-less cigarettes and the usual brand smoked by the subjects, perhaps explaining the strong effects on smoking suppression observed [425]. Therefore, it is important to recognize that while NRT is a key part of cessation therapy, it does not address all aspects of smoking behavior. In addition, certain smoking cessation strategies, such as NRT, have been found to be less effective among women than men. Given that researchers have found that women are 31% less likely to quit smoking successfully, further studies on gender-specific smoking cessation strategies are warranted [471].

Bupropion is an atypical antidepressant that has both dopaminergic and adrenergic actions [426]. In 1998, the slow-release preparation of bupropion became available as a prescription item specifically for smoking cessation, with the trade name Zyban. This treatment could be appropriate for smokers who do not wish to use an NRT or for those whose treatment with NRT has failed. Unlike NRT, smokers begin bupropion treatment one week prior to cessation. The suggested dosage is 300 mg/day, and the duration of treatment is 7 to 12 weeks [427]. A double-blind, placebo-controlled trial randomized patients to placebo or sustained-released bupropion (50 mg twice a day, 150 mg once a day, or 150 mg twice a day) and treated them for six weeks. Smokers with active depression were excluded, though smokers with a history of depression were not. The cessation rates at the end of therapy were 10.5%, 13.7%, 18.3%, and 24.4%, respectively. Follow-up at one year suggested a continued benefit of bupropion therapy [428]. Data from a study of bupropion combined with transdermal nicotine showed high long-term quit rates with the combination therapy [429]. Discontinuation of treatment may be appropriate for individuals unable to achieve significant progress after seven weeks, as success after this point is unlikely [430].

Another effective non-nicotine therapy for smoking cessation is varenicline tartrate (Chantix), a partial agonist selective for nicotine acetylcholine receptor subtypes. Released in 2006, varenicline is available in monthly dose packs (0.5 mg and 1 mg tablets) and is approved for a 12-week course of treatment [403]. Patients able to quit smoking may continue the therapy for an additional 12 weeks for increased likelihood of long-term cessation; however, medication should be stopped and patients should be reassessed if the intervention has not led to smoking cessation [430; 431]. Clinical trials reveal that varenicline may be favorable to bupropion for abstinence (44% versus 30%); the medication has also been shown to help at least 20% of patients remain smoke-free for up to one year [432; 433]. Recognizing that cessation success rates increase when pharmacologic and behavioral therapies are combined, the manufacturer urges patients to combine use of varenicline with a behavioral support plan. Co-administration of varenicline and transdermal nicotine may exacerbate incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue. One study found varenicline alone to be more effective than other treatment options, while a meta-analysis study found that combination therapy (varenicline and NRT) was more effective than varenicline alone [434; 435]. Clearly, more clinical trials are necessary to further understand how varenicline compares to bupropion, NRT, and other therapies. Further, patients must be made aware that there are risks of serious neuropsychiatric symptoms with use of varenicline (e.g., suicidal ideation and behavior, worsening of pre-existing psychiatric illness or depressed mood, agitation, and overall changes in behavior) [430].

The two second-line drugs for smoking cessation are clonidine and nortriptyline [381]. Clonidine is an antihypertensive medication that is administered orally or transdermally. It appears to increase the smoking cessation rate by approximately 11%; however, clonidine is known to produce such side effects as dry mouth, dizziness, sedation, and orthostatic hypotension [430; 436]. Clonidine has not been approved by the FDA for smoking cessation but has been used with individuals who have failed NRT or bupropion [430]. Nortriptyline is a tricyclic antidepressant that has been used to assist smoking cessation, although this is an unlabeled use [430]. A 12% improvement in cessation over controls has been reported, but the limited number of trials, combined with the adverse side effects (e.g., dry mouth, weight gain, constipation, drowsiness, sexual problems), makes nortriptyline a second-line intervention [381].

Other drugs have also been used in smoking cessation. Silver acetate, which causes cigarettes to have a bad taste, has been used as a smoking cessation aid for many years. But, there appears to be little evidence for a specific effect of silver acetate in promoting quitting [437; 438]. The addition of mecamylamine, a ganglionic blocker classified as an antihypertensive agent, to transdermal nicotine replacement has been shown to improve the abstinence rate in smokers compared with use of the patch alone [439; 440].

Additional pharmacotherapy options are in the development phase. A nicotine vaccine and other partial agonists for the nicotine receptors are being evaluated [441]. Interference with the liver enzymes that metabolize nicotine is another approach being tested [442].

In addition, it was found that methoxsalen, a compound used to treat skin disorders, reduces the activity of CYP2A6, the enzyme that metabolizes nicotine. This allows for more nicotine, whether from a cigarette or nicotine replacement, to be present in the blood and to remain there longer, which should minimize smokers' craving to smoke. However, methoxsalen has not been proven safe for use in humans and must undergo more trials before it can be used in a smoking cessation program [443]. Tranylcypromine (a monoamine oxidase inhibitor used to treat depression) and tryptamine (substrate of MAO) are also being investigated for this purpose [444].

Withdrawal

Similar to all addictions, nicotine withdrawal elicits a number of clinical consequences. Desire to avoid withdrawal symptoms promotes smoking. Nicotine withdrawal may last for several weeks and include such symptoms as irritability, anxiety, depression, difficulty concentrating, weight gain, restlessness, and impatience [445]. Withdrawal effects can be elicited and observed in those exposed to secondhand smoke as well as in smokers. Intensity of these withdrawal symptoms may be related to the level of nicotine dependence. In 2017, there were an estimated 34 million adults that smoked cigarettes. Although the prevalence of cigarette smoking continues to decline, there is some evidence that this decline is a reflection of a migration to non-cigarette products, especially e-cigarettes [446; 456]

REDUCING TOBACCO SMOKE EXPOSURE

A dramatic increase in public awareness concerning the dangers of SHS has corresponded to social demand for smoking restrictions. Beginning in the 1990s, McMillen et al. found broad public support in the United States for smoking restrictions in many public places, including child care centers, hospitals, shopping malls, convenience stores, fast-food restaurants, and indoor sporting events [6]. An Irish study by Mulcahy et al. demonstrated dramatic reductions in SHS exposure following a national workplace smoking ban in Ireland. Thus, this study justified such bans given the known adverse effects of SHS, which include lung disease, heart disease, and asthma [356].

Workers suffering the detrimental effects of secondhand tobacco smoke have taken legal actions. For example, a group of 60,000 flight attendants filed a suit alleging that they had endured smoking-related illnesses from being exposed to high concentrations of environmental smoke in airplane cabins when smoking was still allowed on board [447]. Although the tobacco industry (Philip Morris, R.J. Reynolds, Brown and Williamson, the Ligett Group, and the Lorillard Group) made no admission of guilt, it established the Flight Attendant Medical Research Institute (FAMRI), a $300 million not-for-profit research institute, as a part of the settlement for flight attendants who suffered and died due to SHS exposure in air cabins. FAMRI's mission is "to sponsor scientific and medical research for the early detection and cure of diseases and medical conditions caused from exposure to tobacco smoke" [448].

Efforts to regulate tobacco products include the World Health Organization's Framework Convention on Tobacco Control (FCTC). Additionally, legislation has been passed to give the FDA regulatory authority over tobacco. The main reason for these proposals is to minimize death and disease caused by tobacco smoke by reducing the prevalence of its use and the toxicity of its products. Based on scientific studies and tobacco industry documents, it is believed that tobacco products could be made less toxic if their design, content, emissions, and manufacturing were better controlled [449].

Nationwide polls reveal broad public support for increased taxing of tobacco [450]. Since 2002, the average state cigarette tax has increased from 43.4 cents to $1.79 per pack [451; 453; 473]. In February 2009, President Obama signed a 61.66-cent federal cigarette tax increase into law, bringing the federal cigarette tax to $1.01. This increase resulted in an 8.3% decline in cigarette sales, one of the largest declines in years, and a continuing downward trend of cigarette sales [452; 453]. As of 2016, the CDC reported an average national retail price of $6.43 per pack of cigarettes [453]. Increasing the cost of tobacco not only decreases tobacco use by creating a larger economic barrier to smoking, it also motivates people to try to quit.

Effective behavioral and pharmacologic treatments exist and can work if they are affordable, widely available, and used properly in clinics and communities. Smoking cessation group programs have been found to be more effective than minimal treatment programs, although less intensive treatment approaches, when combined with high participation rates, can still influence larger groups. Tobacco policies have reduced cigarette consumption at work and worksite tobacco smoke exposure [454]. Innovative partnerships with public- and population-based organizations to reach smokers and reduce exposure to tobacco have been initiated. There is a high level of support for smoking restrictions in public places to protect nonsmokers from tobacco smoke [455; 473]. Due to the 2009 federal tax increase, several health benefits and cost savings are projected, including an increase in the number of children alive today who will not become smokers (1.2 million) and $51.9 billion in long-term healthcare savings from fewer adult and youth smokers over the lifetimes of the adults who quit and kids who never start [452; 473].

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Though the state and local governments and employers provide protection from tobacco smoke at work, private homes are not subject to such regulation. Educational strategies are needed to increase awareness of personal and childhood tobacco exposure both in and out of the home. As with the business microenvironment, air quality cannot be maintained if smoking is allowed indoors, even with additional ventilation and air-cleaning devices.

CONCLUSION

The purpose of this course was to increase awareness of the various implications of tobacco use and exposure and to provide examples of healthcare assessment and treatment. It should be noted that the health complications incorporated here are only part of an exhaustive list of issues linked to tobacco smoke—more findings are uncovered each day. Changes in policy (e.g., taxation, bans in federal and other public establishments, regulation by the FDA) may spur the public to take a second look before using tobacco products or exposing themselves and friends/family to its smoke. However, it is important to continue to combat tobacco use and exposure at the primary care level at every possible opportunity. Brief intervention methods are more helpful than many realize. Further, although cigarettes have historically been implicated for the majority of health problems, it is important to be cognizant of other tobacco products' health effects and the evolving trends of tobacco use.

FACULTY BIOGRAPHY

Mark S. Gold, MD, DFASAM, DLFAPA, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students.

He is an author and inventor who has published more than 1,000 peer-reviewed scientific articles, 20 text books, popular-general audience books, and physician practice guidelines. Dr. Gold was co-inventor of the use of clonidine in opioid withdrawal and the dopamine hypothesis for cocaine addiction and anhedonia. Both revolutionized how neuroscientists and physicians thought about drugs of abuse, addiction, and the brain. He pioneered the use of clonidine and lofexidine, which became the first non-opioid medication-assisted therapies. His first academic appointment was at Yale University School of Medicine in 1978. Working with Dr. Herb Kleber, he advanced his noradrenergic hyperactivity theory of opioid withdrawal and the use of clonidine and lofexidine to ameliorate these signs and symptoms. During this time, Dr. Gold and Dr. Kleber also worked on rapid detoxification with naloxone and induction on to naltrexone.

Dr. Gold has been awarded many state and national awards for research and service over his long career. He has been awarded major national awards for his neuroscience research including the annual Foundations Fund Prize for the most important research in Psychiatry, the DEA 30 Years of Service Pin (2014), the American Foundation for Addiction Research's Lifetime Achievement Award (2014), the McGovern Award for Lifetime Achievement (2015) for the most important contributions to the understanding and treatment of addiction, the National Leadership Award (NAATP) from addiction treatment providers for helping understand that addiction is a disease of the brain, the DARE Lifetime Achievement Award for volunteer and prevention efforts, the Silver Anvil from the PR Society of America for anti-drug prevention ads, the PRIDE and DARE awards for his career in research and prevention (2015), and the PATH Foundation's Lifetime Achievement Award (2016) as one of the "fathers" of addiction medicine and MAT presented to him by President Obama's White House Drug Czar Michael Botticelli. He was awarded Distinguished Alumni Awards at Yale University, the University of Florida, and Washington University and the Wall of Fame at the University of Florida College of Medicine. Gold was appointed by the University President to two terms as the University's overall Distinguished Professor, allowing him to mentor students and faculty from every college and institute. The University of Florida College of Medicine's White Coat Ceremony for new medical students is named in his honor.

Since his retirement as a full-time academic in 2014, Dr. Gold has continued his teaching, mentoring, research, and writing as an Adjunct Professor in the Department of Psychiatry at Washington University and an active member of the Clinical Council at the Washington University School of Medicine's Public Health Institute. He regularly lectures at medical schools and grand rounds around the country and at international and national scientific meetings on his career and on bench-to-bedside science in eating disorders, psychiatry, obesity, and addictions. He continues on the Faculty at the University of Florida College of Medicine, Department of Psychiatry as an Emeritus Distinguished Professor. He has traveled extensively to help many states develop prevention, education, and treatment approaches to the opioid crisis.

Customer Information/Answer Sheet/Evaluation insert located between pages 104–105.

COURSE TEST - #91783 SMOKING AND SECONDHAND SMOKE

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 10 credit activity must be completed by May 31, 2022.

1. Tobacco was originally marketed in Europe for many ailments, including
- A) *insomnia.*
- B) *dental pain.*
- C) *rheumatism.*
- D) *acute appendicitis.*

2. Which of the following statements about smoking prevalence is TRUE?
- A) *Current use of any tobacco product is highest among Hispanics.*
- B) *Approximately 1.8 million Americans initiated cigarette smoking in 2016.*
- C) *More than 20% of the U.S. population 18 years of age or older are current smokers.*
- D) *Higher levels of education are correlated with an increased likelihood of having smoked cigarettes in the past month.*

3. All of the following are TRUE about bidis, EXCEPT:
- A) *Bidis are filled with sun-dried tobacco.*
- B) *Bidis can be vanilla or cherry flavored.*
- C) *Bidis contain more ammonia than a regular cigarette.*
- D) *Bidis are rolled into air-cured and fermented tobacco wrappers.*

4. Kreteks, or clove cigarettes, are composed of approximately what percentage of tobacco?
- A) *20% to 40%*
- B) *40% to 60%*
- C) *60% to 80%*
- D) *All of the above*

5. Mainstream smoke is
- A) *smoke inhaled by the smoker.*
- B) *smoke exhaled by the smoker.*
- C) *the main component of secondhand smoke.*
- D) *smoke emitted by the burning end of a cigarette.*

6. After the commencement of smoking, nicotine from cigarette smoke reaches peak plasma concentrations in
- A) *20 to 30 seconds.*
- B) *1.5 to 3 minutes.*
- C) *20 to 30 minutes.*
- D) *one to three hours.*

7. Which of the following is NOT a risk factor for the development of a smoking habit?
- A) *Affiliation with smoking peers*
- B) *Comorbid psychiatric disorders*
- C) *Disinterest in body image in girls*
- D) *Presence of a smoker in the household*

8. Cigarette smoke affects many organ systems, but the one with the most clinical importance in developing dependence is the
- A) *skeletal system.*
- B) *circulatory system.*
- C) *respiratory system.*
- D) *central nervous system.*

9. Neurons located in the ventral tegmental area become more active with nicotine administration, leading to
- A) *an increase of hunger.*
- B) *a stimulation of dysphoria.*
- C) *an increase in dopamine release.*
- D) *a reduction in self-administered nicotine.*

10. What percentage of smokers develop COPD?
- A) *Less than 5%*
- B) *15% to 20%*
- C) *20% to 30%*
- D) *More than 35%*

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11. Cigarette smoking
- A) *decreases thrombosis.*
- B) *decreases inflammation.*
- C) *impacts endothelial function.*
- D) *decreases oxidation of low-density lipoprotein cholesterol.*

12. Smoking is highly comorbid with
- A) *schizophrenia.*
- B) *panic disorder.*
- C) *major depression.*
- D) *All of the above*

13. Fetal nicotine exposure
- A) *elicits only a short-term alteration in brain cells.*
- B) *stimulates an increase in arousal responsiveness to hypoxia.*
- C) *has no adverse effect on eventual programming of synaptic competence.*
- D) *results in permanent abnormalities of the dopaminergic regulation of the brain.*

14. Active and passive smoking are known to
- A) *decrease incidences of thrombosis.*
- B) *decrease occurrences of atherosclerosis.*
- C) *increase incidences of cardiac arrhythmias.*
- D) *promote the oxygen-carrying capacity of blood.*

15. Cotinine can be found in all of the following, EXCEPT:
- A) *Hair*
- B) *Urine*
- C) *Blood*
- D) *Breath*

16. The most sensitive biomarker used to confirm the extent of SHS exposure to nonsmokers is
- A) *cotinine.*
- B) *nicotine.*
- C) *benzine.*
- D) *albumin.*

17. "Thirdhand" smoke is
- A) *tobacco smoke contamination of dust.*
- B) *air in a room where smoking previously occurred.*
- C) *residual tobacco smoke contamination on surfaces.*
- D) *All of the above*

18. The Clinical Practice Guideline recommends the 5 A's approach for intervening with a patient who smokes. After the practitioner establishes that a patient smokes by asking about his or her smoking status, the second of the five steps is to
- A) *advise the patient to quit.*
- B) *arrange for follow-up contacts.*
- C) *assess the patient's willingness to quit.*
- D) *assist the patient to use problem-solving methods.*

19. Nicotine-replacement therapy is available in all of the following forms, EXCEPT:
- A) *Patches*
- B) *Shots and implants*
- C) *Nasal spray and inhalers*
- D) *Gum, lozenges, and sublingual tablets*

20. It is estimated that the 2009 tax increase on tobacco products will result in
- A) *no change in national smoking patterns.*
- B) *a decreased level of support for smoking restrictions.*
- C) *1.2 million children alive today never becoming smokers.*
- D) *$4 million in healthcare savings from fewer smoking-related strokes and myocardial infarctions.*

Be sure to transfer your answers to the Answer Sheet insert located between pages 104–105.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Animal-Related Health Risks

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board:
15 ABIM MOC Points, 15 ABP MOC Points, 15 ABO MOC Points.

Audience
This course is designed for physicians, nurses, and allied health staff involved in identifying, treating, and preventing zoonotic diseases, including West Nile virus, Lyme disease, and avian influenza.

Course Objective
The purpose of this course is to increase the awareness of zoonotic diseases and their management in both prevention and care. There are many potential diseases that can spread from animals to humans, and with basic precautions, most zoonoses are preventable or at least avoidable. The public has many misconceptions about what to do after a potential exposure to a zoonotic source, and healthcare professionals are often the first to help and answer questions.

Learning Objectives
Upon completion of this course, you should be able to:

1. Reflect on the history of zoonotic diseases.
2. Define the hosts and host characteristics associated with zoonotic diseases.
3. Compare the types of vectors and transmission of zoonotic diseases.
4. Discuss the classification of zoonotic diseases.
5. Identify the common pathogens involved in the spread of infection from animals to humans.
6. Discuss the clinical presentation, diagnosis, and treatment of Lyme disease.
7. Outline characteristics and treatment of other tick-borne zoonotic diseases, including tularemia, Rocky Mountain spotted fever (RMSF), and ehrlichiosis.
8. Discuss the clinical presentation, diagnosis, and treatment of West Nile virus infection.
9. Describe the characteristics and treatment of other viral zoonotic diseases, including avian influenza.
10. Discuss the background, clinical presentation, and prevention of bovine spongiform encephalitis (BSE) and its resulting disease in humans, variant Creutzfeldt-Jakob disease (vCJD).
11. Identify some of the common protozoal zoonotic diseases.
12. Describe the characteristics and treatment of anthrax infection.
13. Identify other common bacterial zoonotic diseases, including cholera.
14. Recall the characteristics of common parasitic zoonotic diseases and appropriate treatment.
15. Outline the role of an interpreter in treating non-English-proficient patients.

Faculty
Sharon Holt, DVM, MBA, ADN, graduated from Ohio University with a Bachelor's degree in fine art in 1977. She returned to Greater Hartford Community College and she earned an Associate degree in nursing in 1979. She later received a Master's in business administration in marketing management in 1983 from University of Hartford. She received her doctorate in veterinary medicine from Tufts University School of Veterinary Medicine in 1997. Dr. Holt has been working in wildlife medicine for 15 years and has lectured on the subject at the University of Massachusetts. Her nursing background includes acute care, emergency room, critical care, clinic settings, and case management for a non-profit visiting nurse association. She currently owns her own veterinary practice in Massachusetts and teaches veterinary science at Franklin County Technical High School, helping and mentoring the next generation of veterinarians.

Faculty Disclosure
Contributing faculty, Sharon Holt, DVM, MBA, ADN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner
John V. Jurica, MD, MPH

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Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 15 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

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INTRODUCTION

In this era of globalization and rapid world travel, diseases that were once localized to a country or region or that were uncommon in developed countries are now found in new or widespread areas. Examples include avian influenza, West Nile encephalitis, plague, "mad cow disease," rabies, and to a lesser extent, Lyme disease. These and many other diseases belong to a category known as zoonoses, or zoonotic diseases.

A zoonosis is an infection transmitted from a vertebrate animal to humans. The animal is the natural host and may simply be a carrier of the infectious agent without suffering any disease from the infection itself. This is the case in many diseases that are persistently difficult to control, such as infection with certain roundworms. The host may act only as the reservoir, with a vector being the actual source of the exposure and subsequent infection. Some diseases, such as Lyme disease, babesiosis, and Rocky Mountain spotted fever (RMSF), are transmitted to humans and other non-target hosts through insect (arthropod) vectors. The animal host may become ill from the infection, but the signs of illness can be quite different in human cases or the organism may target different organ systems when infecting other than the definitive host animal. The environment and degree of susceptibility will also determine whether transmission actually occurs after an exposure. Immunosuppressed individuals, the elderly, children, and pregnant women may have a greater susceptibility to illness caused by some zoonotic infections.

HISTORY

Several zoonoses have been known and documented as animal-to-human diseases from much earlier times. Rabies was known and written of many centuries ago, as were ringworm, tetanus, and plague (*Yersinia pestis*). For example, the bite of a "mad dog" was known to transmit rabies in the 1300s, though obviously the knowledge of the virus came much more recently [1]. The invention of the light microscope by Leeuwenhoek in the late 1600s allowed visualization of the agents of zoonoses for the first time. Bacteria and parasites could be seen, and the connection between a disease and its causative agent could be confirmed.

Tapeworms, liver flukes, and roundworms were readily seen with the early microscopes. Linnaeus began classification in the mid-1700s and was the first to describe many zoonotic parasites in an early edition of *Systema Naturae* [2]. The smaller parasites have been identified and described as the microscope's capability has advanced to recognize the role of microscopic agents in zoonotic diseases. Protozoa of zoonotic importance were not identified until the early 1900s, and smaller organisms are still being discovered today.

More refined microscopes and the use of stains allowed for the description of bacterial agents of disease in the 1870s. The ability to culture bacteria began in 1881, and most bacteria were quickly described in the next 20 years [3]. The ability to culture an organism allowed confirmation that the same agent present in a host animal could be the causative agent of a human disease. This is the basis of Koch's postulate: confirmation of the disease by isolating the proposed agent and then reproducing the disease by introducing the isolate into a host animal [4].

In 1934, the electron microscope allowed viruses to be visualized for the first time [5]. Most were known to exist from cellular changes seen with the light microscope, but once the viruses could be visually identified, they were quickly classified. If a carrier state exists or if only a small number of the host's population carry the disease, discovery of the etiology is more difficult. There may be an intermediate host or vector yet to be identified that is involved in the transmission.

It is interesting to note that various religions have historically had dietary restrictions that had the effect of curtailing the spread of foodborne zoonoses by limiting certain food products. For example, Jewish and Muslim religions banned the consumption of pork and other animals that rooted for food. Certain insect species that carry parasitic diseases can be accidentally ingested when the food animal roots in the ground. In some cases, the infected insect may be a part of the animal's regular diet.

Many processes and even whole industries have been developed as public health measures to deal with zoonoses. Pasteurization of milk, meat inspection, vaccinations, and insect control measures are examples of public health practices in the United States that are specifically aimed at preventing zoonotic diseases. Individual steps can be taken as well, such as boiling water that is of uncertain purity and cooking meat and fish properly. Improving the health of the public will require more education about food and safety issues if many of the dangerous zoonoses are to be avoided.

DEFINITIONS

HOST CHARACTERISTICS

A host is an animal (including humans) that can support an infective agent of a zoonotic disease. Many agents require more than one host to complete their lifecycle. The definitive host is an animal that supports an organism in the final reproduction phase of its lifecycle. Without the definitive host, normal reproduction of the organism will not occur. The secondary or intermediate host is needed in multiple lifecycle agents for some phase of their development. For example, the dog flea (*Ctenocephalides canis*) and the cat flea (*Ctenocephalides felis*) are the intermediate hosts for the dog tapeworm *Dipylidium caninum*. Ingestion of the flea, which carries the infective agent, leads to infection with the tapeworm.

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A dead-end or aberrant host is one in which the organism can survive, perhaps only briefly, but from which it cannot reproduce or transmit disease. Such is the case with eastern equine encephalomyelitis (EEE) and the horse. The virus cannot continue to spread from an infected horse because it will kill the animal before it has a chance to reproduce. The horse in this situation is a sentinel for EEE, because the incubation period is shorter in horses than in humans. Deaths in horses from the infection will be seen prior to documented human cases in the same area. Many horses are vaccinated against the disease in endemic areas, so the number of sentinels may be very small. Eastern encephalomyelitis (EE) in humans carries a high case fatality rate (33% to 70%), and the sentinel serves as an early warning that human cases may soon be presenting at emergency rooms in the same vicinity [6]. Transmission does not occur between horse and human, as both are aberrant hosts. Another animal must serve as the reservoir. In many cases, the zoonosis is seen only sporadically because the vector that transmits the disease is not present. In addition, the reservoir can vary in its carrier status from year to year.

An animal may be the natural host for the disease, and humans or other animals may be aberrant hosts. The actual signs and symptoms of the disease in the aberrant host may be a result of the organism's inability to support itself in the wrong animal host. The aberrant host may be significantly different anatomically or physiologically, making the agent unable to find a suitable site in which to exist. Digestive tracts vary tremendously between different mammalian, avian, and reptilian species. This can lead to a disease agent searching for a part in the aberrant host's body that is similar to the natural host. The aberrant host may not even have the same organ system that the agent requires to grow. This is the case in diseases that are manifested by migration of parasites throughout organs while they search for a target organ or system that is reasonably similar to that of the regular host. In some cases, the agent is in an environment so unlike what it is searching for that it will not produce a zoonosis. Humans are constantly exposed to many agents that do not affect us, such as heartworm.

Parasites have evolved through natural selection in ways that, under normal circumstances, will not render a healthy definitive host incapacitated. Natural selection eliminates parasites that kill their hosts before reproduction and transmission can be successfully achieved. Most have a symbiotic relationship and affect the animal in subtle ways, such as slower weight gain or a decrease in egg production. For an animal to actually appear unhealthy usually requires a fairly heavy infestation with parasites. Obviously, seriously infected animals or those sick from other causes would be more vulnerable to the effects of a heavy parasite load.

Like parasitic diseases, most bacterial and fungal infections tend not to impact the definitive host in such a severe manner as to be immediately noticeable. Some zoonotic bacteria are normal flora or commensals in one animal and pathogenic in another species. *Pasteurella* spp. in a cat's mouth are considered normal flora but can be a difficult-to-treat zoonosis when transferred to a human via a bite wound. *Escherichia coli* contamination of meat is another example of normal flora from an animal making the consumer ill.

Viruses produce more variability in the degree of illness seen in the hosts. Reproduction of a virus occurs at the cellular level in the host, with either a cell's RNA or DNA. There are groups of RNA viruses that are transmitted through arthropod vectors, but most require some type of direct contact, such as a bite wound. Not being independent organisms, these viruses require direct transmission or a vector that can transmit effectively while maintaining the viability of the virus. Most are sensitive to temperature fluctuations and other environmental factors.

VECTORS

An insect that allows multiplication or growth of an agent while it is in the host is a biologic vector, as with the earlier example of the flea. Ticks and mosquitoes are biologic vectors for many zoonoses. Some of the more serious zoonoses transmitted by arthropods are Lyme disease, RMSF, Q fever, malaria, plague, and West Nile encephalitis. Insects can also transmit less serious diseases, such as tapeworms and some species of trematodes (parasitic flatworms).

Mechanical vectors can be something as simple as shoes carrying disease from work to home. Airborne sources or fomites can transmit diseases such as tuberculosis from animal to human or from human to animal. Meat or other animal-derived consumer products can carry zoonotic agents. For example, pork products are likely sources of trichinosis.

TRANSMISSION

Transmission of zoonoses can be either direct or indirect. A disease that is directly transmitted from an animal to humans usually requires close or intimate contact. As examples, direct transmission occurs when the act of touching a ringworm lesion on a cat directly results in infection, or when rabies is transmitted from the bite of a rabid animal. Indirect transmission occurs with the presence of a vector between animal and human. Insects, inanimate objects, or animal food products can all be sources of indirect transmission of a zoonosis. Some insects can transmit an infectious agent in their bite, as in the case of ticks and mosquitoes. Flies, such as the housefly, can carry many pathogenic organisms in their mouth parts and on their feet. They can spread a zoonosis by contaminating open wounds or other breaks in the skin of the host. Many arthropods, such as the horse fly (*Tabanus* spp.), bite and spread disease in the same manner.

There are associated risk factors that determine transmission rate. As noted, immunocompromised individuals, the elderly, and the very young may be at greater risk, depending on the zoonosis. Pregnant women are at risk for zoonoses that can cross placental barriers or potentially cause spontaneous abortion.

The time of year affects the shedding rates of some parasites. Many viruses and bacteria have temperature preferences that affect the time of year that they are most frequently seen. Some parasites reproduce at intervals that coincide with their definitive host's reproduction cycle. In this way, they increase their numbers when more hosts are potentially less able to combat the organism with natural immune capabilities. The environment will also affect the transmission rate of some organisms. Sunlight, pH, air quality, humidity, and temperature are classic variables used to determine the degree of transmission rate for a zoonosis and the agent's survivability in the environment.

State public health departments have surveillance plans for the more serious zoonotic diseases [7]. National public health concerns are also under the surveillance of the Centers for Disease Control and Prevention (CDC) and other organizations [7]. Global surveillance is monitored by several international concerns, including the World Health Organization (WHO) [7]. Depending on the degree of risk of a particular disease and how serious a threat it is, a report of a zoonosis will be considered an epidemic when a predetermined number has been exceeded. In animals, this is called an epizootic. If the disease occurs worldwide, it is referred to as a pandemic (panzootic). Even when a zoonosis is only an individual exposure without associated serious risks, the state public health department may be interested in being informed of the incidence, if only for monitoring purposes.

MORBIDITY, PREVALENCE, AND MORTALITY

Morbidity refers to individuals who become ill in the susceptible population in any outbreak. The susceptible population might be an isolated village or an entire country, depending on the disease and its transmission characteristics. The mortality rate is the number of individuals in the susceptible population who die of the illness over a specific period of time. The prevalence rate is the number of individuals out of the potential population who are ill at any one time or specified period of time. The case fatality rate is simply the fraction of known affected individuals who die, expressed as a percentage; for example, a zoonotic outbreak of 50 confirmed cases with 5 deaths would have a case fatality rate of 10%. This percentage gives a sense of the severity of the zoonosis, especially when the number of actual cases may be low. For example, Ebola carries a high case fatality rate, 80% to 90% in some regions, and rabies is nearly 100% fatal when untreated anywhere it occurs [8; 9].

CLASSIFICATION AND REPORTING

The scope and multitude of zoonotic diseases are too great for a single course to cover. There are a tremendous number of zoonoses that are not seen commonly in the United States but that are of major importance in other countries. These will not be addressed in detail, but healthcare professionals should have an idea of the basic concepts of the zoonoses and the agents that cause them. This knowledge can help serve the patient who has a recent travel history outside the United States and presents with a mysterious illness. If the illness is unexplained, a zoonotic disease may be considered when taking the history. Contacting an appropriate agency for assistance may be indicated. The CDC can provide information about specific diseases in different countries if a local resource, such as the Public Health Office, is not able to help. The United States Department of Agriculture (USDA) can also assist in identifying specific zoonoses prevalent in different countries and can caution travelers about what types of things to avoid in terms of food and animal products while traveling. In addition, the USDA carefully monitors agricultural products brought into the country.

There are many ways of categorizing common zoonoses. In this course, zoonoses will be categorized by causative agent initially, and some important specific zoonoses will be discussed in detail. Parasites are responsible for many zoonotic diseases, so the type of illness manifested can be similar for different species of parasite [10]. Bacterial agents are also a common etiology, as are viruses [10]. Although it is commonly overlooked, humans can transmit diseases to animals as well. For example, tuberculosis has been passed to elephants in zoos and primates in research facilities.

Some zoonoses are reportable by law for either animal or human cases. Typhus and tuberculosis are prime examples [11]. A classification system for zoonotic disease cases has been developed, with a rank of 1 to 5, with subclassifications that should be utilized when determining if a case report or notification is necessary (***Table 1***). This classification system has been agreed upon internationally and drafted by the American Public Health Association (APHA), which derived it from guidelines written by the WHO [12]. International animal zoonoses with serious risk are reportable to the Office International des Epizooties (OIE) [12]. Generally, if in doubt, there is no harm in reporting, because the case report could be helpful at some later date.

AGENTS

Parasites

Parasites that can cause disease directly in the host (not just transmission of a zoonosis) are represented in five different phyla: the pentastomida, nematodes, trematodes, cestodes, and protozoa (***Table 2***) [10].

The pentastomida are very primitive, worm-like parasites that primarily infect the lungs of reptiles. Human infection is by the larval stage. The spleen, liver, and/or lungs may be infected, but fortunately, the disease is self-limiting and usually not significant. While no fatalities have been reported, because any parasite is a foreign protein, a hypersensitivity reaction is a possible outcome with any of the parasitic zoonoses.

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CLASSIFICATION SYSTEM FOR REPORTING ZOONOTIC CASES			
Class	**Reporting Requirement**	**Subclass**	**Types of Diseases/Conditions**
1	Case report is universally required by International Health Regulations (IHR) or as a Disease Under Surveillance by the World Health Organization (WHO).	1A	Diseases subject to IHR or those that are internationally important and are quarantinable (e.g., plague, yellow fever)
		1B	Diseases under surveillance by the WHO (e.g., some forms of typhus)
2	Case report is regularly required whenever disease occurs.	2A	Notification to local health officials by expedient means (i.e., telephone report). Quick reporting could make a difference in preventing additional cases. Botulism or other clostridial infections fall into this category.
			Notification by most practical means, as with trichinosis
3	Selectively reportable in recognized endemic areas. These are diseases that are not an issue in some locales and at the same time are significant problems in other areas.	3A	Where it is reportable, treat the disease as a 2A (e.g., Lyme disease in some areas)
			Where it is reportable, treat as with 2B (e.g., Rocky Mountain spotted fever)
4	Obligatory report of epidemics. No case report is required, but make a prompt telephone report of unknown outbreaks or other diseases of public health importance.	NA	Food poisoning
5	Official report is not ordinarily justifiable. Those diseases are not as easily transmitted and/or are sporadic in occurrence. Outbreaks do not have control measures and are of low risk, but epidemiological interest exists.	NA	Common cold

Source: [12] *Table 1*

Nematodes are commonly referred to as roundworms, with hookworm being a common example. There are many zoonotic forms of nematode infections. One example is trichinosis, which will be discussed in detail later in this course. In general, most nematode zoonoses are transmitted through ingestion of the egg stage of the organism [10]. When in the feces, the eggs will hatch into the infective larval stage after 24 hours in most species. Occasionally, the larval phase of the parasite will penetrate the skin, usually through the sole of the foot because an individual has walked barefoot where larval forms of the nematode are present. This form of infection is referred to as cutaneous larval migrans. It is one of the better reasons not to walk barefoot in a city park, an unfamiliar backyard, or a veterinarian's office.

Trematodes, commonly called flukes or flatworms, are usually transmitted via ingestion [10]. As with the nematodes, some species can penetrate the skin and migrate to various organs. Most hatch in the gastrointestinal tract and migrate to other areas of the body to cause infection, unless they penetrate the skin. The liver and lungs are the most commonly affected tissues in a human host by the adult form of the agent.

Cestodes or tapeworms are primarily gastrointestinal parasites, but one type (*Taenia* spp.) can encyst in organs and cause severe disease, with occasional associated fatalities in humans [14]. These parasites reproduce by shedding segments (proglottids), so some species can autoinfect the host via the fecal-oral route. Some transmit by biologic vectors that are ingested by other hosts.

Protozoa are well documented as gastrointestinal parasites and can cause serious levels of disease [10]. Being the smallest of the parasites, they can inhabit a number of different locations in a host, including red blood cells (e.g., malaria) and the mucosal cells of the intestines. Another example is *Giardia*, which inhabit the brush border of intestinal epithelial cells. They produce diarrhea, which can be mild to severe depending on the agent causing the disease, the parasite burden present, and the underlying state of health of the host. Most protozoa spread via the fecal-oral route. Unlike the larger intestinal parasites, which are identified using routine direct stool sampling techniques where the eggs are "floated" up out of the fecal material for identification, protozoa can be difficult to detect because of their very small size.

PARASITIC ZOONOSES	
Agent	**Disease in Humans**
Nematodes	
Ancylostoma braziliense	Cutaneous larva migrans
Ancylostoma caninum	Cutaneous larva migrans
Anisakis marina	Anisakiasis
Baylisascaris procyonis	Visceral larva migrans
Bunostomum phlebotomum	Cutaneous larva migrans
Capillaria aerophila	Capillariasis
Capillaria hepatica	Capillariasis
Haemonchus contortus	Trichostrongyliasis
Ostertagia spp.	Trichostrongyliasis
Toxocara canis	Visceral larva migrans
Toxocara cati	Visceral larva migrans
Trichinella spiralis	Trichinosis
Uncinaria stenocephala	Cutaneous larva migrans
Trematodes	
Echinostoma ilocanum	Echinostomiasis
Fasciola gigantica	Fascioliasis
Fasciola hepatica	Fascioliasis
Fasciolopsis buski	Fasciolopsiasis
Paragonimus westermani	Paragonimiasis
Schistosoma japonicum	Schistosomiasis
Schistosoma mansoni	Schistosomiasis
Cestodes	
Diphyllobothrium latum	Fish tapeworm
Diphyllobothrium spp.	Sparganosis
Dipylidium caninum	Dog tapeworm
Echinococcus granulosus	Hydatidosis
Echinococcus multilocularis	Hydatidosis
Taenia saginata	Beef tapeworm
Taenia solium	Pork tapeworm
Protozoa	
Babesia bovis	Piroplasmosis/Babesiosis
Babesia microti	Piroplasmosis/Babesiosis
Balantidium coli	Balantidiasis
Cryptosporidium parvum	Cryptosporidiosis
Entamoeba histolytica	Amebiasis
Giardia lamblia (intestinalis)	Giardiasis
Leishmania mexicana	American leishmaniasis
Plasmodium spp.	Malaria
Sarcocystis hominis (bovihominis)	Sarcocystosis
Toxoplasma gondii	Toxoplasmosis
Source: Compiled by Author	*Table 2*

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BACTERIAL ZOONOSES	
Agent	**Disease in Humans**
Gram-Negative Bacteria	
Aeromonas hydrophila	Vibriosis
Bartonella henselae	Cat scratch fever
Brucella abortus	Brucellosis
Brucella canis	Brucellosis
Brucella melitensis	Brucellosis
Brucella suis	Brucellosis
Campylobacter jejuni	Campylobacter enteritis
Escherichia coli	Colibacillosis
Francisella tularensis	Tularemia
Pasteurella haemolytica	Pasteurellosis
Pasteurella multocida	Pasteurellosis
Salmonella arizonae	Arizona infection
Salmonella spp.	Salmonellosis
Shigella spp.	Shigellosis
Vibrio spp.	Vibriosis/cholera
Yersinia enterocolitica	Yersiniosis
Yersinia pestis	Plague
Yersinia pseudotuberculosis	Yersiniosis
Gram-Positive Bacteria	
Bacillus anthracis	Anthrax
Clostridium spp.	Clostridial histotoxic infection
Clostridium botulinum	Botulism
Clostridium tetani	Tetanus
Erysipelothrix rhusiopathiae	Erysipeloid
Listeria monocytogenes	Listeriosis
Mycobacterium spp.	Tuberculosis
Mycobacterium leprae	Hansen disease (leprosy)
Staphylococcus aureus	Staphylococcosis/food poisoning
Streptococcus spp.	Streptococcosis
Spirochetes	
Borrelia spp.	Lyme disease
Borrelia spp.	Endemic relapsing fever
Leptospira spp.	Leptospirosis
Rickettsiales	
Chlamydia psittaci	Psittacosis
Coxiella burnetii	Q fever
Ehrlichia chaffeensis	Ehrlichiosis
Ehrlichia ewingii	Ehrlichiosis
Rickettsia rickettsii	Rocky Mountain spotted fever (RMSF)
Rickettsia typhi	Murine typhus
Source: Compiled by Author	*Table 3*

VIRAL ZOONOSES	
Agent	**Disease in Humans**
DNA Virus	
Herpes viruses B and T	Simian herpes
RNA Viruses	
Arthropod-borne (Arboviruses) Group A Group B	Encephalomyelitis (EE) St. Louis encephalitis Yellow fever
Coronaviruses (novel type)	SARS, MERS, COVID-19
Chikungunya virus	Chikungunya fever
Ebola virus	Ebola disease
Hepatitis A virus	Hepatitis infection
Influenza virus	Influenza infection Avian influenza
Lymphocytic choriomeningitis virus	Lymphocytic choriomeningitis
Marburg virus	Marburg disease
Rabies virus	Rabies
Source: Compiled by Author	*Table 4*

Bacteria

The range of zoonotic diseases from bacteria is wider than that from parasites, although the total number of agents is less. Cholera, tularemia, shigellosis, salmonellosis, plague, and cat scratch fever are examples of gram-negative bacteria that can cause serious zoonotic diseases (***Table 3***). Gram-positive bacterial zoonoses include botulism, anthrax, Hansen disease (leprosy), and listeriosis. Diseases caused by spirochetes (specific types of gram-negative bacteria) include Lyme disease and leptospirosis. Some of the rickettsial diseases (gram-negative) are Rocky Mountain spotted fever, Q fever, and psittacosis.

Bacteria can be transmitted via all of the routes discussed, and more than one avenue of transmission may occur with the same agent. For example, tularemia can be transmitted by a bite wound from an infected cat or rabbit or from an arthropod source [15]. Tuberculosis is primarily transmitted by inhalation but can also be transmitted by the ingestion of raw milk [15].

Most bacterial zoonoses are treatable with appropriate antibiotics, antitoxin where applicable (e.g., tetanus), and supportive care [15]. However, recognition of the disease in a timely fashion is critical for a positive outcome in some bacterial zoonoses that can be fatal if not treated promptly.

Viruses

There are many viruses that may be transmitted from animals to humans (***Table 4***). Viral transmission can be through direct contact, bites, arthropods, airborne inhalants, and other vectors. Treatment and prevention are specific to each disease. Some, such as rabies, have vaccines available, but most must be managed by careful preventive measures and universal precautions rather than pre- or postexposure treatments.

Zoonotic DNA viruses of concern include herpes simian B and T virus. Simian B virus causes simian herpes in humans, which carries a 70% to 85% case fatality rate [16]. A bite wound from an infected monkey or contamination of broken skin with saliva is usually required for transmission; however, it is now known that infection can also occur though contamination of the mucous membranes or eyes [16]. Fortunately, people generally do not have direct contact with the species of monkeys that are carriers of herpes B unless they work in zoos or research facilities that house them.

Most zoonotic viruses are RNA viruses. Rabies, Ebola, yellow fever, and the hemorrhagic fevers are examples of RNA viruses with serious zoonotic potential. Other viral zoonoses are fairly common and include West Nile encephalopathy, avian influenza, and the hantavirus syndromes. These will be discussed in detail later in this course.

TICKBORNE DISEASES

Tickborne zoonoses include Lyme disease, Rocky Mountain spotted fever (RMSF), tularemia, and babesiosis. These diseases are of significant medical interest.

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LYME DISEASE

Lyme disease was first described as a zoonotic disease in 1975, although the rash common to this illness was originally documented in Sweden in 1909 [1]. After being reported as an arthritic process in a cluster of children in and around Lyme, Connecticut, it has become the most commonly reported vector-borne disease in the United States [17]. In 2018, state health departments reported 33,666 confirmed or probable cases of Lyme disease to the CDC [18]. The geographic distribution of high incidence areas has expanded over the past decade as the number of counties with an incidence of 10 or more confirmed cases per 100,000 persons increased from 324 in 2008 to 415 in 2018. The disease is concentrated heavily in the Northeast, middle Atlantic, and upper Midwest. Pennsylvania has had the greatest number of cases in recent years.

The primary agent of Lyme disease is the spirochetal organism *Borrelia burgdorferi*; however, in the United States, there are at least one other bacteria (*Borrelia mayonii*), two other known genospecies, and as many as 40 disease-causing subspecies of *Borrelia* [19; 20; 235]. The host reservoir, in most instances, appears to be the white-footed mouse (*Peromyscus leucopus*) [21]. White-footed mice are small and reddish brown in color with a tail that is usually shorter than their body length [22]. They do not commonly come into human habitation sites, preferring stone walls, fields, brush piles, and even old birds' nests as places in which to live. They are not likely to carry the agent or vector into a home as they tend to avoid such habitats.

The primary Lyme disease vectors are the ticks *Ixodes scapularis* or *Ixodes dammini* in the eastern United States and *Ixodes pacificus* in the West [18]. Other *Ixodes* spp. ticks, also known as deer ticks, can carry the organism in some of the less disease-prevalent areas [23; 24].

The vector has an interesting two-host lifecycle requiring both the white-footed mouse and the white tail deer (*Odocoileus virginianus*). The tick spends the first two years on the mouse host, and then it spends its third and final year on the deer, which is the definitive host. The spirochete *B. burgdorferi* does not reproduce well in the deer, only in the mouse. Disease rates are much higher in areas where both the white-footed mouse and high deer populations coexist. Research has shown it takes the nymph stage of the tick 72 hours and the adult 96 hours to transmit the disease to humans [17]. Finding a tick on a body can be difficult, considering a nymph, when fully engorged, is the size of a poppy seed, and more than 15 adults could fit on a dime. In addition, the saliva of the tick contains a local anesthetic agent, so the bite is not usually felt [17]. Fortunately, ticks in the smaller larval phase do not transmit disease. The larva has not yet fed on the reservoir and therefore cannot contain the spirochete.

As noted, Lyme disease is the leading arthropod zoonosis reported in the United States [18]. Although there is a year-round occurrence of Lyme disease, the ticks are most active in the spring and fall, when the ambient daytime temperature is in the 50s and the ticks have reached the maturation stage and must seek their final host. New cases cluster around the months after the spring and fall tick activity periods. Ticks climb up grasses and low shrubs and wait for deer to brush past or stop to browse. They will drop onto any animal that comes close enough to touch the vegetation where they are waiting. Ticks in the nymph stage tend to crawl on the lower grasses, as they are coming from ground dwelling mice. Adult ticks have more commonly dropped off a deer or an aberrant host. The adults are more adept at moving greater distances and can climb higher in the vegetation. Adult ticks will remain on the deer until engorged and will drop off when ready to lay their eggs. It is important to remove engorged adult ticks without rupturing or smashing the body, as this could release thousands of eggs.

Lyme disease has an extremely variable expression between species [25]. The hosts of *B. burgdorferi* can be asymptomatic or carriers. No outward signs of disease have been reported in mice or deer, but because they are wild animals, there may be unrecorded signs. Among domestic animals, the dog is the most commonly affected; however, no rash is seen in dogs, even with experimentally inoculated animals.

Diagnosis

Humans can have varied and severe reactions to Lyme disease; most organ systems have the potential to be affected. *B. burgdorferi* has an affinity for cartilage cells and the transitional cells of the urinary bladder.

The first signs of Lyme disease are usually flu-like symptoms and joint pain. In an elderly person, pre-existing arthritis may complicate early diagnosis. Three distinct stages have been described in patients with untreated infections [25]. Stage 1 (early localized stage) occurs 3 to 30 days after the tick bite and is associated with the appearance of the characteristic "bull's-eye" skin lesion of erythema migrans. Various sources estimate that approximately 70% to 80% of the documented infections will have the characteristic expanding rash [18]. This initial stage may show the nonspecific clinical signs of malaise, headache, arthralgia, fever, myalgia, and regional lymphadenopathy. If they never see a rash, many patients will not consider Lyme disease as the source of their symptoms.

Stage 2 (early disseminated stage) develops through hematogenous spread and is evident after days to weeks post-tick bite [18; 26]. Possible manifestations include subtle encephalitis with headache and cognitive difficulty, stiff neck, cranial neuropathy (with facial palsy being a common finding), cerebellar ataxia, motor and sensory radiculoneuritis, myelitis, and visual disturbances. This stage is associated with acute neuroborreliosis in a significant number of cases [18; 26]. Most patients with neuroborreliosis are affected by meningitis, facial nerve palsy, and/or radiculitis, with only a limited number having parenchymal spinal cord or brain involvement [238].

Stage 3 (late disseminated stage) is the chronic phase, which may appear months to years after the initial infection [18]. Various names for this stage have been proposed and are currently used, including post-Lyme syndrome, post-Lyme disease syndrome, post-treatment chronic Lyme disease, or chronic Lyme disease [238]. One of the most common findings in this stage is oligoarthritis, with the knee being the most frequently affected joint, although other joints can become inflamed [18; 26]. Pain is usually out of proportion to the swelling [18]. Musculoskeletal pain, spinal radiculopathy with paresthesias, encephalopathy, and the symptom complex of fibromyalgia or chronic fatigue syndrome may be present. This stage is associated with chronic borreliosis; consequently, cardiac arrhythmias, respiratory compromise, and spread to the entire nervous system are liable to occur. It is suspected that fibromyalgia may be a long-term sequela to chronic Lyme disease. If untreated, chronic expression results in potentially crippling arthritic changes as well as organ system involvement. The organism can establish itself in the bladder wall and reoccur with another exposure or stress from another illness [23].

Concurrent infection with other tickborne diseases occurs in approximately 4% of Lyme-positive patients [27]. The combination of Lyme disease and either *Ehrlichia chaffeensis*, or an as yet undefined *Ehrlichia* or babesiosis can cause overwhelming illness for some individuals. Those concurrently infected will have the additional discomfort of dealing with changes in their circulatory system, as erythrocytes or leukocytes are infected and cannot deal with the demands of mounting an immune response to Lyme disease. *Ehrlichia* infections usually produce a high fever in the initial infection period [28]. The rare patients who go on to develop acute respiratory distress syndrome have a high correlation of concurrent infection with *Ehrlichia* [29].

Many of the symptoms of Lyme disease are caused by the body's immune system. Because the spirochete infects the cartilage cells intracellularly, the neutrophils concentrate in the region, resulting in a pain similar to the pain of rheumatoid arthritis. Damage to the cartilage cell and subsequent pain is caused by neutrophils attacking both infected and healthy cells. The amount of discomfort and joint destruction varies among patients depending upon their individual immune response.

Clinical suspicion from history, signs, and symptoms is paramount in the diagnosis of Lyme disease [18]. Patients can present with a variety of clinical findings, and not all classic signs or symptoms are present in those with active Lyme disease. If patients have a rash and recognize it as visceral migrans, it may be too early for other symptoms to be noted or for testing to yield positive results. Additionally, early but inadequate antibiotic treatment may prevent full antibody development in patients who are still clinically ill [30]. Varying severity and expression can make Lyme disease difficult to diagnose in some patients. The criteria as set by the CDC do not always fit the signs, symptoms, and test results. This can be very frustrating for patients as well as medical professionals. A few good diagnostic procedures are available, although they require diligent interpretation.

Laboratory Tests

The CDC recommends sampling blood with a two-step process [18]. The first test should include an enzyme-linked immunosorbent assay (ELISA) or, rarely, an indirect immunofluorescence assay (IFA); however, false positives occur with cross reactions to other spirochetes, such as syphilis, mononucleosis, some autoimmune diseases, and oral cavity flora. If the first step is positive or indeterminate, the second step should be performed. The second step, the Western blot test, identifies antibodies for the different spirochetes [18]. Serologic assays for immunoglobulin G (IgG) and M (IgM) are frequently used blot tests. In any serologic testing, a comparison test repeated after an interval of a few weeks should be performed. Antibody levels should be monitored over this period of time to determine if the disease is worsening or improving as determined by the immune system's reaction. The CDC recommends that ELISA or IFA should always be performed before immunoblot testing in order to decrease the likelihood of false positive results [18].

It is important to caution patients that exposure based on serology does not necessarily mean active disease. Many individuals have titers deemed positive without evidence of Lyme disease, and individuals may have evidence of disease without positive titers. The levels of IgG in the serum can remain high for many years [18].

The most definitive diagnosis is made with a combination of positive ELISA and specific Western blot results [18; 23]. Western blot serology is both more sensitive and more specific than ELISA. It is prudent to check the laboratory standards for what is deemed positive, as there is variability between individual testing laboratories. It is highly recommended that the laboratory report and specify the bands. Many will just list the test as positive, equivocal, or negative.

The specific antibodies of importance appear as bands on the Western blot assay. The antibody bands are individual molecular weights of specific antibodies against *B. burgdorferi* antigens that give specific evidence of exposure to the agent. In reporting the bands, the designation kDa stands for kilo Daltons of molecular weight and Osp refers to the outer surface protein of the organism. The bands that are most specific to Lyme disease are 23-25 kDa (Osp C), 31kDa (Osp A), 34 kDa (Osp B), 39 kDa, 41 kDa and 83-93 kDa [31]. IgG and IgM Western blot assays have the same antibody band specificity. Ideally, both should be performed at the same time. IgM can be positive as early as one week after exposure, and the positive response can last for the first six to eight weeks. IgG takes longer to respond and has some varying levels of response.

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The CDC requires that two of three bands (i.e., 23, 39, 41 kDa) on the IgM or five of ten bands (i.e., 18, 21, 28, 30, 39, 41, 45, 58, 66, 93 kDa) on the IgG be present to positively diagnose Lyme disease [18; 32; 33; 34]. This can be an insurance issue for some patients. If the national standard criteria are not met in the testing procedure, some insurance companies may deny payment. In some cases, the IgM test will be slightly more reactive, and this will meet the CDC criteria. In cases that seem to be Lyme disease but for which standard testing is not yielding a positive answer, the IgM Western blot can be a very helpful tool.

The Lyme Urine Antigen Test (LUAT) was once used widely as a diagnostic tool and is still used by some laboratories [26]. However, because of unreliability and inconsistencies, the U.S. Food and Drug Administration (FDA) has advised against the use of this test for the diagnosis of Lyme disease. In addition, they recommend that polymerase chain reaction (PCR) analysis on inappropriate tissues, such as blood or urine, not be accepted as diagnostic, and that Western blot tests only be interpreted according to validated criteria [33]. Like the CDC, the FDA advises initial testing be done by ELISA or IFA and specimens that are positive or equivocal be followed up with a standardized Western blot assay [33]. As of 2017, CDC recommends and has validated only this two-step process for Lyme disease testing [18].

As noted, PCR technology is also available for testing. Appropriate sources most likely to contain the agent are serum, cerebrospinal fluid (CSF), and synovial fluid. The result is positive in approximately 30% of patients with active Lyme disease [34]. Disadvantages of PCR testing include the likelihood of false-negative results due to a sparsity of spirochetes in infected tissues. Inexperience with PCR also can yield false-positive results when care is not taken to prevent contamination and when incorrect primers are used to prepare the specimen. PCR may be useful in confirming persistent or recurrent disease, because a positive result is highly specific for exposure to *B. burgdorferi*. However, the test has not been standardized and is not currently used in routine testing [34]. In general, all of these tests can be negative or inconclusive, and the patient can still have Lyme disease as documented with electron microscopy, but this is not a practical test due to cost and time issues. At this time, there are no good imaging procedures to help in the diagnosis of Lyme disease, and there are certainly no definitive test procedures that warrant withholding or denying treatment [26]. Treatment is usually indicated even if all, or almost all, routine diagnostic procedures are negative when there is a strong clinical suspicion of Lyme disease based on history and physical findings.

Treatment

Prompt and complete treatment of early Lyme disease with antibiotics is important to prevent the development of chronic Lyme disease and/or chronic neuroborreliosis and their troublesome sequelae. The International Lyme and Associated Diseases Society (ILADS) suggests that Lyme disease should be treated with doxycycline as the antibiotic of choice for prophylaxis following an *Ixodes* tick bite with known feeding, irrespective of the amount of tick engorgement or the local tick population infection rate [35]. Where doxycycline is contraindicated, antibiotics known to be effective for treating Lyme disease, such as amoxicillin, azithromycin, or cefuroxime, may be substituted. The recommended adult dose and prophylactic regimen is 100–200 mg doxycycline twice daily for 20 days [35].

According to the International Lyme and Associated Diseases Society, clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline twice daily for 20 days. Other treatment options may be appropriate on an individualized basis.

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Strength of Recommendation/Level of Evidence: Recommendation, very low-quality evidence

According to ILADS guidelines, the treatment of erythema migrans rash in adults is a four- to six-week regimen with recommended first-line antibiotics, including amoxicillin 1,500–2,000 mg daily in divided doses, cefuroxime 500 mg twice daily, or doxycycline 100 mg twice daily [35]. Studies in Europe have shown that a minimum of 21 days of azithromycin 250–500 mg daily is equally or more effective than these three agents and may be considered, particularly for patients that place a high value on minimizing the number of days taking antibiotics. The recommended pediatric regimen is also four- to six-weeks of treatment of amoxicillin 50 mg/kg/day in three divided doses (maximum daily dose: 1,500 mg), cefuroxime 20–30 mg/kg/day in two divided doses (maximum daily dose: 1,000 mg), and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily (maximum daily dose: 500 mg) [35]. Doxycycline is an additional option for children 8 years of age and older at 4 mg/kg/day in two divided doses (maximum daily dose: 200 mg). Higher daily doses of the individual agents may be appropriate in adolescents [35]. Patients should be instructed regarding the importance of completing the entire course of antibiotics; if a dose is missed, the course should be continued at the next regularly scheduled time and the missed dose taken at the end. Studies have found no evidence that treatment regimens of longer duration than those recommended result in better outcomes for patients whose rash is resolved, but they do increase the chance for antibiotic-related adverse events [35].

Patients who have not fully recovered (i.e., erythema migrans rash still visible) at the end of initial treatment but who show a strong-to-moderate response should be continued on the same agent; a dosage increase of the same antibiotic or switch to another first-line agent (or tetracycline) is recommended for a moderate response [35]. Patients with minimal or absent response should be prescribed two first-line agents. Injectable penicillin G benzathine or intravenous ceftriaxone may be considered for these patients and also for those with disease progression or recurrence [35]. This aggressive treatment is required if neurologic symptoms are present in either the acute or chronic stages or if quality of life impairments are significant or rapidly progressive.

Treatment of neuroborreliosis and chronic Lyme disease has been addressed by the American Academy of Neurology in a guideline reaffirmed in 2014. Three major recommendations are made [238]:

- Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for central nervous system Lyme disease with or without parenchymal involvement (Level B recommendation).
- Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for central nervous system Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives, but supporting data are lacking.
- Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

Doxycycline (suggested dosage: 200 mg daily for 14 days) is the only recommended oral regimen for neuroborreliosis, as it has shown a response rate of 98.6% that of parenteral penicillin or ceftriaxone in an aggregation of data from eight studies [238]. Symptomatic treatment is recommended if therapy fails to resolve arthritis and if PCR results from synovial fluid or tissue are negative [239]. Treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, or disease modifying anti-rheumatic drugs, such as hydroxychloroquine; referral to a rheumatologist is also recommended.

Patients with Lyme disease can frequently be frustrated with the long-term nature of the treatment and will need support, especially to maintain the antibiotic regimens. The long-term effects can also be very discouraging for the unfortunate patients who eventually develop the syndrome, which mimics fibromyalgia or chronic fatigue syndrome. Fortunately, it appears that early treatment, and in most cases even late treatment, can prevent or eliminate these sequelae [18; 23].

Prevention

As with any disease, prevention is the best solution. Educating people about how the disease is transmitted and its early signs will help reduce the overall incidence and lessen the severity in those who receive early treatment. The following advice should be given to patients, family, and friends.

If walking where ticks might be present, wear clothing that provides protection from tick exposure. Bare legs should not be exposed and socks should be pulled up over pant legs. Ticks are not able to get through clothing to exposed skin, but they can climb up socks and reach exposed skin if the pant legs are not inside the socks. Long-sleeve tops and having long hair under control will help as well. Clothing should be removed and washed on arrival home. A thorough tick check should be completed, especially in body creases such as the groin and the axilla (armpit) [18]. Many people have been fooled into thinking ticks were freckles and have not removed them before they became engorged. It is most important that embedded ticks be removed promptly. If the capitulum, or head, is broken off, it may cause a local reaction. *Borrelia* is actually in the body of the tick, so transmission likelihood will decrease the faster the body is removed. It takes at least 24 to 36 hours of contact by the tick for the disease to be transmitted.

Though the organism is shed in the urine of mammals, no transmission has been documented to have occurred from urine exposure. Pregnant women should be especially alert when in areas known to have ticks, as there appears to be placental transmission of Lyme disease [18]. Some question this, despite evidence that some infants have positive titers after maternal antibodies should have disappeared. For now, erring on the side of caution would seem prudent. Lyme disease, unlike its close relative syphilis, has not been shown to be a sexually transmitted infection.

Dogs and cats can bring ticks into the house. Usually, once on an animal, the tick will remain and not drop off unless the animal has been treated with repellents. Most products to repel ticks will prevent them from ever getting into the house, as they will not remain on the dog or cat long enough to get indoors. Some products are designed to kill the tick if it does succeed in embedding [18].

Public health strategies have included methods to curtail deer populations. This is one way to lower the incidence of Lyme disease in local human inhabitants, because without the definitive host for the tick, the tick population will decrease. It will take a few years after the reduction of the deer population to see a drop in the number of human cases. This is because the newer generation of ticks on the mice will remain at a higher level. In fact, ticks may seem more numerous for the first two to three years after lowering the deer population because of the lack of the correct definitive host.

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Insecticides, such as permethrin, and insect repellents, especially n, n-diethyl-m toluamide (DEET) in a concentration of at least 20% to 30%, can be very useful if used properly. Permethrin kills ticks on contact and can be used in a backyard, around a house, or on clothing. DEET is a well-known repellent that can be applied to clothing or exposed skin [18; 36]. Some have suggested placing pesticide applicators at deer feeding stations to kill ticks on the deer that come to feed. Of course, controlling the mouse population will also help to reduce the number of cases.

Finally, it is important to know how to properly remove ticks. Petroleum jelly, mineral oil, heat, nail polish, or other materials should not be applied to the tick or immediate area. Embedded ticks are best removed with fine-tipped tweezers. The tick should be grasped as close to the body as possible and removed with a gentle steady pull. Even if all of the mouth parts are not removed, the threat of Lyme disease is very unlikely because B. burgdorferi is usually located in only the midgut and salivary glands of the tick. The area where the tick was located can be washed and cleansed with an antiseptic [18].

Vaccination

The FDA approved the first vaccine for human use, LYMErix, in 1998 [23]. However, in 2002 the manufacturer announced that they were discontinuing production of the vaccine, citing low demand; it is no longer commercially available [23]. When available, the results of trials showed a 50% vaccine efficacy in the first year after vaccinations were given as two injections approximately two months apart. The effectiveness of the vaccine increased to 75% in the second year, after a single booster; however, those who were previously vaccinated are no longer protected [37]. Investigation has been conducted to develop a new human vaccine [26; 37].

TULAREMIA

Tularemia is primarily a disease of rural populations, although occasional urban cases have occurred. The infective organism, *Francisella tularensis*, is a gram-negative intracellular coccobacillus with very marked pathogenic infectivity [38; 39]. Humans can become infected by ingestion of or contact with contaminated water, food (e.g., rabbit meat), or soil; handling infected animal tissues; the bites of infective mammals, such as cats; or the bite of infective ticks, biting flies, or mosquitoes. Person-to-person transmission does not occur [38; 39].

Tularemia occurs naturally in a wide variety of animals, including mice, rabbits, squirrels, water rats, and voles, which acquire the disease by bites from mosquitoes, flies, and ticks. Animals can also become infected by contact with contaminated soils. Rabbits are the most commonly infected animals in the United States. The disease is endemic throughout much of North America and Europe, with the south central and western states being the most involved in the United States [40; 41]. In Europe, most tularemia cases are reported in the northern and central regions, especially Scandinavia and the former Soviet Union.

Classification

There are several classification systems for clinical tularemia. One such system categorizes tularemia as either ulceroglandular (occurring in the majority of patients) or typhoidal [42]. Ulceroglandular disease is characterized by lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 centimeter, or both. Typhoidal tularemia describes systemic manifestation of the disease without skin or mucous membrane lesions [38; 42]. In addition to these two types, pneumonic tularemia, caused by inhalation and primarily manifesting as pleuropneumonic disease, also occurs [38; 42]. Pneumonic tularemia is often considered a type of typhoidal tularemia.

Typhoidal Tularemia

As noted, typhoidal tularemia is an acute, nonspecific febrile illness and is not associated with prominent lymphadenopathy or skin lesions [38]. This type of tularemia is caused by inhalation or ingestion of bacilli and may involve significant gastrointestinal symptoms. It is believed that this type would be most prevalent during an act of bioterrorism [39; 42].

The incubation period is usually 3 to 5 days (range: 1 to 21 days), although aerosol exposures have been shown to result in incapacitation in the first day [38; 42]. Symptoms may include fever with chills, headache, myalgia, sore throat, anorexia, nausea, vomiting, diarrhea, abdominal pain, and cough [42]. Patients may develop tularemia sepsis and/or pneumonia, which can be fatal. This syndrome manifests with hypotension, respiratory distress syndrome, renal failure, disseminated intravascular coagulation, and shock [42].

Pneumonic tularemia results from inhalation of infected aerosols or spread of existing, untreated disease. Hemorrhagic inflammation of the airways is an early sign [38]. Radiologic studies show pleuritis with adhesions and effusions and peribronchial infiltrates; hilar lymphadenopathy is also common [38; 42]. These signs, however, are not always present. Patients may develop acute respiratory distress syndrome and require mechanical ventilation [42].

Ulceroglandular Tularemia

Ulceroglandular tularemia occurs in 70% to 80% of cases [41]. It is generally caused by an arthropod bite or by handling the carcass of an infected small mammal, such as a wild rabbit; transmission has also been reported from ingestion of or contact with contaminated water, exposure to contaminated mud or animal bites, and exposure to aerosolized water droplets or dust from contaminated soil or grains [38; 41; 42; 43; 44]. A local papule develops at the inoculation site, with progression to a pustule and ulceration within a few days. The ulcer may be covered by an eschar [38; 41]. Lymphadenopathy may also

occur [41]. The nodes are usually tender and may become fluctuant, rupture, or persist for months to years [41]. In most cases, there is a single ulcer with raised borders. Other symptoms include fever, chills, headache, and cough [41].

Ulceroglandular tularemia is characterized by the presence of a small, ulcerated papule at the site of a tick bite or other contaminated break in the skin, followed by tender regional adenopathy and fever. A variation of this syndrome is oropharyngeal tularemia, presenting with subacute to chronic exudative pharyngitis/tonsillitis, cervical adenopathy, low-grade fever, and malaise (easily confused with infectious mononucleosis). Oropharyngeal tularemia likely arises from direct transmission via the hands or by droplet nuclei or dust arising from handling the carcass or dressing out meat from an infected animal [41; 42]. Finally, there is a well-described oculoglandular form of tularemia, whereby inadvertent direct inoculation of the eye, as from touching the face or eyebrow after handling a dead wild animal results in a unilateral conjunctivitis and preauricular adenopathy [38; 41].

Diagnosis

Diagnosis of tularemia requires a high index of suspicion, as the disease often presents with nonspecific symptoms [41]. A history of tick bite or exposure to wild game (e.g., rabbit, deer) provides a clue. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings, or pharyngeal exudates. Because the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis [41].

There are several biologic variants (biovars) or subspecies of *F. tularensis*. Type A is considered to be more virulent, while the European biovar, *F. tularensis* var. *palaearctic*, typically causes a milder form of the disease [38]. Both types can be identified with direct fluorescent antibody (dFA) analysis, which gives a presumptive diagnosis of tularemia. Direct examination with gram stain may not be helpful because *F. tularensis* is a weakly staining pleomorphic gram-negative coccobacillus that may be difficult to identify. *F. tularensis* can be grown in appropriate cultures, but may not be identifiable for 48 hours. Antibody or other serologic tests and/or culture are necessary for confirmation of the diagnosis. The antibody detection assays include ELISA, tube, and microagglutination, but significant antibodies may not appear until 10 to 14 days after the onset of the illness [38]. A positive dFA test on a culture can confirm the diagnosis.

It should be reinforced that significant personal safety precautions be taken when handling tissues or other samples possibly containing *F. tularensis*, as it is among the top 10 most common causes of laboratory-associated infections in the United States [45].

Treatment and Prevention

All forms of tularemia may be treated with streptomycin or gentamicin [38; 41]. Gentamicin may be more readily available and easier to administer [41]. Also, because streptomycin has been associated with ototoxicity in fetuses, gentamicin is the drug of choice for pregnant women [46]. Doxycycline or ciprofloxacin are also acceptable alternatives [38].

When using aminoglycosides parenterally, the dosage must be calibrated to the patient's renal function (as estimated by the creatinine clearance), taking into account the expected reduction in renal function associated with aging. The adults, the starting dosage of streptomycin is 1–2 g administered intramuscularly (IM) every 12 hours for 7 to 14 days [46]. In very sick patients, streptomycin may be given initially at 15 mg/kg IM every 12 hours, then adjusted downward once there is clinical improvement. This is also the common pediatric dose [46]. The usual adult starting dose for gentamicin is 3–5 mg/kg/day IV or IM once a day (or in three divided doses), to achieve a peak serum level of at least 5 mcg/ml and a trough level <2 mg/kg. This is continued for 7 to 14 days [46].

Doxycycline is a good alternative for patients who are not seriously ill; the dosage is 100 mg IV or orally twice daily at 12 hour intervals for 14 to 21 days; however, relapses are reported to occur more often than with aminoglycoside therapy. Unfortunately, fully virulent streptomycin-resistant organisms have been described. In these cases, ciprofloxacin may be used at a dose of 400 mg IV twice a day (may switch to 500 mg orally twice a day when indicated), although ciprofloxacin use for tularemia treatment is not FDA approved [46].

As with all tickborne diseases, prevention begins with wearing appropriate clothing while in areas where ticks may be present. Also, contact with animals that might harbor the disease should be avoided. If working with domestic animals, be aware of tick infestations and wear protective clothing if contact with possibly infected animals is necessary [41]. The use of tick repellents, such as DEET or the newer plant-derived agents, applied to the clothing or lightly on the skin can be helpful. Wearing light-colored clothing so that ticks can be spotted more easily and tucking pant legs into socks is also recommended. Ticks should be removed as soon as possible after being discovered on the body. Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as F. tularensis can be shed from such lesions for one month or longer.

No licensed vaccine is available for protection against tularemia; however, a live vaccine strain (LVS) may be given to at-risk laboratory personnel as an investigational new drug (IND) [47]. This vaccine is not commonly available in the United States [240]. An attenuated vaccine was used in the former Soviet Union to immunize tens of millions of people, and was subsequently sold to the U.S. military in 1956. Testing of the vaccine in military personnel proved it to be safe

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and reasonably effective; however, the scarification technique (similar to small pox inoculation) used to administer the vaccine is inconvenient and highly variable.

ROCKY MOUNTAIN SPOTTED FEVER

RMSF is the most common rickettsial disease in the United States. The incidence of RMSF and other rickettsial infections has increased over the past two decades, from 495 reported cases of spotted fever rickettsiosis in 2000, to more than 6,000 cases in 2017 [48]. The case fatality rate for rickettsial infection has declined since the 1940s, when tetracycline antibiotics cane into use. Using surveillance data, the CDC estimates that the current case fatality rate for all spotted fever rickettsioses is roughly 0.5%, somewhat higher for RMSF [48].

RMSF is caused by the organism *Rickettsia rickettsii* and is found throughout most of the Western hemisphere and in all states except Maine, Hawaii, and Alaska. The disease is most prevalent from April to September in the coastal Atlantic states but may occur year round in the warmer and southern states. This seasonality varies in different regions according to the climate and tick vectors involved [48].

The wood tick, *Dermacentor andersoni*, is the principal vector in the western regions of the United States, while the dog tick, *Dermacentor variabilis*, is more prevalent in the eastern and southern states. The incidence of RMSF is highest (8 cases per million) in adults 55 to 64 years of age; the incidence in children 5 to 9 years of age is 4 cases per million [48]. Human-to-human transmission is not documented and does not appear to occur [40; 48; 49].

Clinical Presentation and Diagnosis

The classical presentation of RMSF includes the sudden onset of headache, fever, chills, and an erythremic exanthem that appears within the first few days after the symptoms. The lesions are first present on the palms, soles, wrists, forearms, and ankles. The rash then appears on the buttocks, axilla, trunk, face, and neck. The lesions are initially pink and macular and blanch with pressure but later become maculopapular and petechial [48]. Occasionally, the lesions coalesce and become regions of ecchymosis and ulceration.

Symptoms usually appear within 2 to 14 days after the tick bite and can also include malaise, myalgia, nausea, and vomiting [48]. In rare cases, severe respiratory distress, circulatory failure, and neurologic complications may occur; this is especially true for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The tick bite is remembered by 50% to 70% of patients who develop a tickborne disease [40]. As with the other tick-disseminated zoonoses, this is a helpful clue in establishing a diagnosis. Other information, such as exposure to high grass and tick-infested areas, contact with dogs, similar illnesses in family members or pets, or history of recent travel to areas of high incidence also can help establish a diagnosis [48]. If a rash is present, a skin biopsy and PCR or immunohistochemical staining for *Rickettsia* can be used. These tests have good sensitivity (70%) when applied to tissue specimens collected during the acute phase of illness and before antibiotic treatment has been started [48].

IFA with *R. rickettsii* antigen is the gold-standard serologic test for diagnosis of RMSF. The test is performed on two paired serum samples. The first sample should preferably be taken in the first week of symptoms; the second sample should be taken two to four weeks later. In most cases, the first IgG titer is low or negative, and the second typically shows a fourfold increase in IgG antibody levels. IgM antibodies usually rise at the same time as IgG (i.e., near the end of the first week of illness), but they are less specific than IgG antibodies and more likely to result in a false positive. Both IgM and IgG levels can remain elevated for months or longer after RMSF has resolved, and they can be detected in up to 10% of currently healthy people who were previously exposed to *R. rickettsii* or a similar organism. For these reasons, clinicians requesting IgM serologic titers should also request a concurrent IgG titer [48].

Treatment and Prevention

The treatment of RMSF should begin immediately when the disease is suspected and not be delayed until a firm diagnosis is made during the convalescent period. The recommended first-line treatment is doxycycline. The recommended dosage for adults is 100 mg every 12 hours. The recommended dosage for children who weigh less than 45 kg is 2.2 mg/kg body weight, twice daily [48]. Treatment is most effective at preventing death if doxycycline is started in the first five days of symptoms. If the patient is treated within the first five days of infection, fever generally subsides within 24 to 72 hours. The minimum duration of therapy is five to seven days, though doxycycline should be continued until the patient has been afebrile for at least three days. Severely ill patients may require longer periods of treatment before fever resolves [48].

Doxycycline to treat suspected RMSF in children is standard practice recommended by both the CDC and the American Academy of Pediatrics Committee on Infectious Diseases. For patients with life-threatening allergies to doxycycline and in some pregnant patients for whom the clinical course of RMSF appears mild, chloramphenicol may be considered as an alternative antibiotic. Oral formulations of chloramphenicol are not available in the United States, and use of this drug carries the potential for other adverse risks (e.g., aplastic anemia, grey baby syndrome, increased fatality risk) [46; 48]. The standard treatment duration is 7 to 14 days [48]. The use of fluoroquinolones is not recommended at this time because their benefit has not been documented [40; 48; 49]. The preventive measures are the same as for the other tickborne diseases.

EHRLICHIOSIS

Ehrlichiosis is an emerging tickborne disease caused by *Ehrlichia* spp., gram-negative rickettsial organisms that infect human leukocytes. Ehrlichiosis was first recognized in the United States in the 1980s and became a reportable disease in 1999 [28]. The number of reported cases of ehrlichiosis has increased steadily, from 200 cases in 2000 to 1,799 cases in 2018 [28].

Most human disease is the result of infection with *E. chaffeensis*, but infection with *E. ewingii* was designated a separately reportable disease in 2008 [28]. In 2009, four cases of ehrlichiosis were attributed to a newly discovered *Ehrlichia* species closely related to *E. muris*, a species not found in the United States previously [53]. This section will focus mainly on *E. chaffeensis* infection, also referred to as human monocytotropic (or monocytic) ehrlichiosis.

Humans become infected through the bite of infected ticks; the lone star tick (*Amblyomma americanum*) is the primary vector for *E. chaffeensis*, and the white tail deer is the most common reservoir [28; 54]. Cases are predominantly reported in the summer (June and July) in the southeast and south-central United States, which generally corresponds with areas in which lone star ticks exist [28]. The states with the highest concentration of all reported cases are Missouri, Arkansas, and Oklahoma [28].

Clinical Presentation and Diagnosis

The clinical presentation of ehrlichiosis is very similar to that of RMSF, though the incidence of rash is less common. After an incubation period of one to two weeks, a patient with ehrlichiosis will typically present with acute onset of fever and one or more of the following symptoms or signs [28]:

- Headache
- Myalgia
- Malaise
- Anemia
- Leukopenia
- Thrombocytopenia
- Elevated hepatic transaminases

Nausea, vomiting, and diarrhea also occur in some patients. A non-pruritic skin rash may also develop (in 60% of children, but less than 30% of adults), with appearance ranging from maculopapular to petechial [28]. In some patients, the rash may resemble that often seen with RMSF, making careful differential diagnosis vital.

Diagnosis is generally made based on clinical presentation and clinical evidence and confirmed by IFA, PCR, or isolation of *E. chaffeensis* in cell culture. IFA using *E. chaffeensis* antigen, performed on paired serum samples, is the gold-standard serologic diagnostic test [28]. Any tests completed in the first week should be repeated after two to four weeks, as antibodies may not be present in sufficient quantities to be detected in the first week.

The CDC recommends that healthcare providers consider Heartland virus testing in patients who develop fever, leukopenia, and thrombocytopenia who have tested negative for *Ehrlichia*. Heartland virus was first isolated in Northwestern Missouri in 2009; six additional cases were identified during 2012–2013. The virus likely is transmitted through the Lone Star tick or other arthropods [55].

Treatment and Prevention

Doxycycline is the first-line treatment for adults and children of all ages and should be initiated immediately if ehrlichiosis is suspected [28]. The recommended regimen is 100 mg twice daily for adults or 2.2 mg/kg twice daily for children weighing less than 45.4 kg [28]. For patients with severe diseases or who are hospitalized, intravenous administration is preferred. Treatment should continue for at least three days after the fever subsides and until evidence of clinical improvement, usually at least five to seven days [28]. Prevention should focus on measures established for all tickborne diseases.

BABESIOSIS

Babesiosis is the only tickborne zoonosis in the United States caused by a protozoan, *Babesia microti*. Two other *Babesia* species, *B. bovis* and *B. divergens*, can be zoonotic as well but are less commonly identified [52]. Babesiosis is most prevalent in the United States in the Northeast and upper Midwest and usually peaks during the warm months [52]. *B. microti* is transmitted by the *Ixodes scapularis* (blacklegged deer tick). Rodents are the primary reservoir for human cases [52].

Historically, the description of the early recognition of babesiosis parallels Lyme disease. The first case was documented on Nantucket Island, Massachusetts, in 1969 in an elderly woman whose case was described as a "malaria-like" illness. *B. microti* was identified, and the island's hospital began regularly treating cases shortly after identification and diagnosis of the first case [51].

Clinical Presentation and Diagnosis

Many cases of babesiosis remain subclinical. In fact, some young patients may be asymptomatic carriers for years. Those individuals who become ill may experience influenza-like symptoms, with fever, headache, malaise, myalgia, and hemolytic anemia and hemoglobinuria of varying severity. These symptoms usually occur within one week; jaundice and renal failure may follow [40; 52]. Risk factors for severe disease include asplenia, advanced age, and immunodeficiency states. As noted, the clinical presentation may resemble malaria. The disease can be fatal in patients who have a prior history of splenectomy [52]. Animals other than humans with babesiosis have a very similar course.

Diagnosis of human babesiosis requires a high index of suspicion because the clinical manifestations are nonspecific. Examination of a blood smear from a suspected individual with infection will reveal the characteristic red blood cell parasite inclusions that resemble a Maltese cross. Fluorescent

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antibody serology and PCR amplification are available for diagnosis when the evaluation of the smear is not conclusive [52].

Treatment and Prevention

All cases of active babesiosis require treatment with a combination of either atovaquone plus azithromycin or clindamycin plus quinine (for severely ill patients) [52]. The suggested doses for adults include 750 mg of atovaquone two times per day for 7 to 10 days plus an initial oral dose of 500–1,000 mg azithromycin (decreasing to 250–1,000 mg/day as appropriate). An alternative is clindamycin 600 mg orally three times per day or 300–600 mg IV four times per day plus quinine 650 mg orally three times per day [36; 40; 163].

In severely ill patients with high titers of parasitemia (greater than 10%), significant hemolysis, or renal, hepatic, or pulmonary compromise, a partial or complete red blood cell exchange transfusion may be lifesaving. Patients in hemolytic crisis should be treated for shock, with particular consideration for maintaining renal function to counteract the potential damage from hemoglobinuria. The medical regimen is aimed at preventing anemia from becoming severe [40; 49].

Individuals who have previously undergone splenectomy should exercise extreme caution in *Ixodes* tick territory. A thorough tick check should be done after being in the woods. Insect repellent will provide deterrent but should not be relied upon for complete protection against any arthropod vector. Rodent control measures can help reduce the reservoir numbers around the home and yard [52].

VIRAL ZOONOTIC DISEASES

Several human viral diseases can be contracted from animals, some by means of an intermediate arthropod vector important to the life cycle of the virus, others by direct contact or inhalation of aerosols released by the animal or generated from the contaminated environment. Well-described mosquito-borne viral zoonoses include West Nile and similar forms of viral encephalitis, Zika virus (ZIKV) disease, and Dengue. Rabies is unique in its association with the bite of an infected wild of domestic mammal. Avian and swine influenza, hantavirus, and novel coronavirus infections have more complex modes of transmission involving direct (touch) contact and/or inhalation of infectious aerosols created by handling the host animal, processing a food product, or cleaning the immediate environment. Bovine spongiform encephalopathy ("mad cow disease") will be included in this section because the infective organism, a prion, is closer to a virus than the other zoonotic organisms.

WEST NILE VIRUS

The West Nile district of Uganda was the site of the first documented human case of West Nile virus in 1937. The virus was later identified in a serious outbreak of meningoencephalitis in Israel in the late 1950s. The first human cases in the United States occurred in the New York City area in 1999, where seven deaths were reported [56]. It has since been documented throughout the entire continental United States. A total of 47 states and the District of Columbia reported West Nile virus infections in people, birds, or mosquitoes in 2019 [58]. Overall, 917 human cases of West Nile virus disease have been reported to the CDC, of which 607 (66%) were classified as neuroinvasive disease (e.g., meningitis, encephalitis, flaccid paralysis) [58]. Hawaii, Alaska, Puerto Rico, and the Virgin Islands have been free of the disease; however, the disease has spread throughout the contiguous United States and Canada. In Canada, Ontario and Quebec have experienced the most cases [36; 57]. The states with the greatest number of cases in the United States in 2019 were California (214), Arizona (174), Colorado (121), Nevada (44), and New Mexico (40) [58]. Most cases occur between June and September, but as the disease has spread into the warmer southern and southwestern states, year-round exposures have become more frequent [36; 57].

The West Nile virus is a single-stranded RNA flavivirus, similar in many respects to the virus that causes St. Louis encephalitis. Kunjin virus, present in Australia, is closely related to West Nile virus [59]. The virus is primarily transmitted by the *Culex* spp. mosquito, although it has been isolated from several other species. The *Culex* is an overwintering mosquito, meaning that adults can survive throughout the winter. The virus has also been documented to live throughout the winter while in the mosquito. Because a blood-feeding arthropod is the vector, the virus is called an arbovirus [60].

West Nile virus is transmitted from the primary reservoir, birds, to a vertebrate host after being maintained in a bird-mosquito-bird cycle. More than 160 species of birds have been documented to harbor the virus. Passerine birds have been noted to be the most commonly affected type of birds [56]. This group includes perching species such as songbirds and sparrows. The passerine group, crows, and many other common birds in the United States and around the world are evidently capable of being the amplifying host, in which the West Nile virus can replicate and markedly increase in number. It is also possible that other animals can harbor and amplify the organism. In a somewhat alarming finding, investigators confirmed that farmed alligators in Florida were capable of serving as an amplifying reservoir for West Nile virus. Humans and domestic animals that become infected with the organism are aberrant hosts, and the viremia is usually brief and low-grade [56; 61; 62; 63].

Clinical Presentation

Most (70% to 80%) human West Nile virus infections are subclinical and unapparent. Approximately 20% of those who contract the virus experience a mild febrile illness called West Nile fever [36; 64]. Only about 1 out of 150, or less than 1%, of those infected will develop severe neurologic effects [36]. Among patients with neuroinvasive disease, the case fatality rate is approximately 10% [58]. Although the full

spectrum of West Nile fever cases in the United States has not been determined, there are degrees of clinical involvement that can be noted [64; 65].

The mild infection of West Nile fever appears after an incubation period of about 2 to 14 days and lasts for 2 to 6 days [36]. It is described as a febrile illness of sudden onset accompanied by malaise, anorexia, nausea, vomiting, headache, and myalgia. Some patients complain of eye pain and upper respiratory symptoms, and there may be a rash or lymphadenopathy [36]. Interestingly, the macular, papular, or morbilliform erythematous rash and lymphadenopathy seen in earlier outbreaks of the disease were not common in the more recent cases [56].

More severe infections have occurred in older patients and those with coexisting morbidities. The rate of severe neurologic disease was 10 times higher for patients 50 to 59 years of age and 43 times higher for those older than 80 years of age. This indicates that advanced age is the most significant factor involved in the development of severe disease [64]. In recent outbreaks, encephalitis was more common than meningitis. Hospitalized patients demonstrated significant fever, weakness, gastrointestinal symptoms, and cognitive changes. Several experienced muscle weakness and a flaccid paralysis with the more common neurologic findings being ataxia and extrapyramidal signs, myelitis, optic neuritis, seizures, polyradiculitis, and cranial nerve abnormalities. The constellation of findings is similar to other viral encephalitides and cannot be distinguished from them clinically [36].

The clinical signs of West Nile meningitis can include nuchal rigidity, Kernig or Brudzinski sign, and photophobia or phonophobia. A fever of 38 degrees C or more, or hypothermia of 35 degrees C or less, help to make the diagnosis. West Nile encephalitis can present with lethargy, an altered level of consciousness, or a personality change lasting more than 24 hours. There may also be focal neurologic deficits, seizures, and all of the usual findings seen with a viral encephalopathy [56; 65].

The acute flaccid paralysis seen with West Nile virus infections usually presents as a limb weakness that progresses markedly over a 48-hour period. There is an absence of pain, but paresthesia, areflexia or hyporeflexia, and asymmetry are commonly seen. About one-half of the patients hospitalized with severe disease in the United States experience a significant degree of weakness, and approximately 10% of the New York patients had acute flaccid paralysis, including several patients who developed a paralysis that resembled Guillain-Barré syndrome without the usual nerve conduction findings [66].

There is still no firm data regarding the long-term effects of West Nile virus infections. In the New York outbreak in 2000, over one-half of those hospitalized had not returned to their functional level by discharge, and only one-third were fully ambulatory. The most persistent long-term symptoms included fatigue, memory loss, difficulty walking, weakness, and depression [56; 64; 65; 66].

Diagnosis

A high index of suspicion based on symptoms, time of year, history, and the presence of other known cases is paramount in diagnosing West Nile fever. Other arboviral diseases, such as St. Louis encephalitis, Kunjin virus, or other diseases caused by flaviviruses can have a similar initial presentation [36; 57]. Fortunately, there is a specific neutralizing antibody to West Nile virus that can be used in serologic tests to help make the diagnosis. A fourfold rise in titer between acute and convalescent samples, determined by plaque-reduction neutralization assay, is confirmatory. A useful serologic test on serum or CSF is the assay for IgM using the antibody-capture ELISA procedure [36; 57]. The finding of IgM in the CSF is a very good indication of meningoencephalitis if found within eight days of the onset of symptoms [36; 56; 67]. Some IFA tests have also been suggested as being helpful in the diagnosis.

Peripheral blood samples are usually not helpful because the leukocyte count is often normal, although it can be elevated in some cases [67]. There can be a lymphocytopenia or even anemia. The CSF will frequently have an increase in cell count, with a predominance of lymphocytes and increased protein. CSF glucose is usually normal [67].

Imaging studies may be helpful after the development of meningoencephalitis to exclude other etiologies [67]. Computed tomography (CT) scans usually do not show evidence of acute disease, but about one-third of the magnetic resonance imaging (MRI) studies revealed changes in the leptomeninges or periventricular areas. MRI studies have also shown lesions in the basal ganglia and thalamus [56].

Culture of the organism is difficult, but an unambiguous diagnosis of West Nile fever can be made by virus isolation in cell culture, or in suckling mice by IFA analysis. In fatal encephalitis cases, the West Nile virus can be readily detected by immunohistochemistry or molecular amplification methods. Brain tissues at autopsy can be stained to show the viral antigens as well as the neuronal necrosis and microglial infiltrates caused by the disease.

Treatment and Prevention

The treatment of West Nile virus infections is supportive, with hospitalization of any patient who appears to have meningitis or encephalitis. Intravenous fluids and respiratory assistance are often required, and the prevention of secondary infections should be considered. Patients with severe neurologic findings will need a great deal of supportive care [36].

Interferon alpha-2b, IgG, and ribavirin in high doses have shown some activity against the virus in vitro, but there has been no confirming evidence of their usefulness in patients. Other possible medications being tested are steroids, antiseizure drugs, and antiosmotic agents [64; 66; 67].

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The most prudent means of protection against West Nile virus is to avoid mosquito bites by wearing long-sleeved shirts and pants and being aware of the usual biting times of early morning and evening. This is often not practical, so using the proper insect repellent is the next best means of protection [36]. The CDC recommends that consumers use repellent products that have been registered by the Environmental Protection Agency (EPA). These products include DEET, with a concentration of 20% to 30%, picaridin (KBR 3023), oil of lemon eucalyptus or para-menthane-3,8-diol (PMD), and IR3535 applied to the clothing and skin [68]. Compounds containing permethrin may also be used and are highly effective in repelling and killing ticks, mosquitoes, and other arthropods but should only be applied to clothing, netting, and gear and not to the skin [68]. Permethrin retains effectiveness on clothing even after laundering.

A vaccine for humans is not available at this time; however, the National Institutes of Health sponsored a trial of an inactivated vaccine developed by scientists at the Oregon National Primate Research Center in Portland [69]. The phase I trial including 50 adults was completed December 2016, and as of April 2017, no results have been published [241]. In mice, the vaccine protected against a lethal dose of West Nile virus, successfully eliciting neutralizing antibody responses and CD8+ T cells, which attack infected cells [69].

ZIKA VIRUS

ZIKV is the latest in a series of related human arboviral pathogens that has migrated out of Africa and Asia into the Americas over the past two decades [251; 252]. Like yellow fever, dengue, and chikungunya viruses, the vector for ZIKV is the *Aedes* mosquito, and epidemics within susceptible population groups are sustained by a mosquito-human-mosquito transmission cycle.

In the 2015–2017 outbreak within the United States, cases of ZIKV disease were primarily reported in returning travelers and in women having unprotected sex with men infected while traveling to regions with ongoing mosquito transmission. A total of 43,092 cases were reported between 2015 and 2018 in the United States and U.S. territories [256]. The potential for a localized or regional outbreak of ZIKV disease in the United States is significant given the level of travel exposure, opportunities for ZIKV migration, and the prevalence of *A. aegypti* mosquitoes along the southern and southeastern rim of the country [257].

In epidemic settings and endemic areas, ZIKV infection is primarily vector-borne, transmitted by the bite of an infected *Aedes* mosquito. In addition, other modes of transmission are now known to be important in human ZIKV disease. These include sexual transmission from an infected male to female and male partners; transplacental transmission from mother to fetus during pregnancy, leading to congenital ZIKV disease; and perinatal transmission from a viremic mother to her newborn infant [258; 259]. There is theoretical concern that blood transfusion and tissue/organ transplantation could also serve as vehicles of transmission. Therefore, the FDA has recommended universal screening of donated whole blood and components for ZIKV in the United States and its territories [260].

All reported cases of sexual transmission have involved vaginal or anal sex with men shortly before, during, or shortly after a symptomatic illness consistent with ZIKV disease [261]. It is not known whether infected men who never develop symptoms can transmit ZIKV to their sex partners. For now, the CDC recommends that men who have been diagnosed with ZIKV consider using condoms or abstaining from sex for six months following infection [261]. Sexual transmission of ZIKV from infected women to their sex partners has not been reported. The consistent and correct use of latex condoms is known to reduce substantially the risk of acquiring sexually transmitted infections, including those caused by viruses.

In the course of acute infection during pregnancy, ZIKV can be transmitted across the placenta to the developing fetus. Evidence for intrauterine fetal infection includes demonstration of ZIKV in the placenta and products of conception following spontaneous abortion, identification of ZIKV RNA in amniotic fluid by RT-PCR, and virologic and serologic studies of infants born with microcephaly. The true incidence and natural history of this phenomenon, including the importance of such factors as gestational age, level and duration of viremia, and immune enhancement by pre-existing heterologous anti-flavivirus antibodies, is currently unknown [262].

Two cases of intrapartum transmission of ZIKV from a newly infected, viremic mother to her newborn infant have been reported [263]. One infant was considered to be asymptomatic; the other child developed a rash and transient thrombocytopenia. Although ZIKV has been identified in breast milk, there have been no reports of transmission through breastfeeding.

Clinical Presentation and Diagnosis

In epidemic settings, the majority of primary ZIKV infections are asymptomatic, and those who do become ill usually experience a self-limited, mild febrile illness with rash, conjunctivitis, myalgia, and arthralgia lasting three to six days. The incubation period for ZIKV is not well defined; it is considered to be similar to that of other mosquito-borne flaviviruses—usually less than one week and in the range of 3 to 10 days.

During the period from September 2015 through February 2016, 72 of 88 women enrolled in a study tested positive for acute ZIKV infection by RT-PCR on blood, urine, or both. All women had rash, as this was an inclusion criterion; the prevailing pattern was a descending macular or maculopapular exanthem accompanied by pruritus in 94% of patients. Arthralgia was reported in 65% of ZIKV-positive women, conjunctival injection was seen in 58%, and lymphadenopa-

thy (generalized or regional) was present in 41%. Fever was documented in only one-third of patients and, when present, was low-grade and of short duration. Nausea and vomiting were reported in 21%, and respiratory findings were evident in 7% [264].

From these observations there emerges a distinctive, though nonspecific, clinical ZIKV syndrome: an acute onset descending maculopapular rash (often with pruritus), conjunctival injection, arthralgia, myalgia, and transient low-grade fever. Lymphadenopathy may be present, but respiratory symptoms and signs are conspicuously uncommon. ZIKV disease should be considered in patients with any combination of these symptoms who have traveled to areas with ongoing transmission in the two weeks preceding onset of illness. Rare manifestations of acute ZIKV infection, based on isolated case reports, include meningoencephalitis, myelitis, thrombocytopenic purpura, and ocular complications [263; 265; 266].

Because dengue and chikungunya viruses have the same vector of transmission and share a similar geographic distribution and clinical profile with ZIKV, patients with suspected ZIKV disease should be evaluated and managed for these possibilities as well. Other considerations in the differential diagnosis include malaria, rubella, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsiosis, and group A streptococcal infections [267].

The possibility of ZIKV disease should be considered in the patient with a compatible clinical syndrome (e.g., febrile rash illness with arthralgia and conjunctivitis) and epidemiologic risk factors, such as residence in or travel to an area of active ZIKV transmission within the previous two weeks, or sexual contact with a person known or suspected of recent ZIKV infection. Laboratory confirmation relies on molecular detection of the viral genome (via RT-PCR) in blood or body fluids and serologic assay for acute-phase ZIKV-specific IgM antibody.

The FDA has issued an emergency use authorization for two diagnostic tools for ZIKV: the Triplex Real-Time RT-PCR assay and the Zika MAC-ELISA for anti-ZIKV IgM [255]. These have been distributed to qualified laboratories that are certified to perform high-complexity tests in the United States. Clinicians should contact local and state health departments to facilitate diagnostic testing. The CDC provides updated guidance for the selection and timing of ZIKV diagnostic testing at https://www.cdc.gov/zika/hc-providers/testing-for-zika-virus.html.

Treatment and Prevention

There is no effective antiviral therapy for ZIKV infection; treatment is supportive and directed toward relief of symptoms. When the diagnosis is uncertain and dengue, or coinfection with dengue, is a possibility, the patient should be managed expectantly for each. In consideration of dengue, aspirin and NSAIDs should be avoided and the patient should be monitored for signs of progression to hemorrhagic fever or shock [254]. In managing ZIKV disease, patient education and secondary prevention are important, especially in regard to sexual transmission and risk reduction in pregnancy. All pregnant women with molecular or serologic evidence of recent ZIKV infection should be evaluated and managed (monitored) for adverse pregnancy outcomes.

Pregnant women who report symptoms or signs consistent with acute ZIKV disease and who have traveled to or who live in areas with active ZIKV transmission or who have had potential sexual exposure (i.e., sexual contact without barrier/condom method with a person who lives in or has traveled to an area with ZIKV) should be tested for ZIKV infection. Serum and urine RT-PCR tests are recommended for those seeking care less than two weeks after onset of symptoms [253]. A positive RT-PCR result confirms the diagnosis of recent maternal ZIKV infection. Patients with a negative RT-PCR test result should receive ZIKV IgM and dengue virus IgM antibody testing. Symptomatic pregnant women who seek care 2 to 12 weeks after symptom onset should first receive ZIKV and dengue virus antibody testing. If the ZIKV antibody test is positive or equivocal, reflex RT-PCR should be automatically performed on the serum sample to determine whether ZIKV RNA is present.

DENGUE FEVER

Dengue fever is caused by one of four similar flaviviruses (dengue viruses 1 through 4) that are transmitted via mosquito in tropical and subtropical regions [135; 162]. The WHO estimates that there may be 390 million dengue infections worldwide each year, of which 97 million have clinically significant symptoms, including 500,000 cases of dengue hemorrhagic fever and more than 12,500 deaths, mainly among children [135]. Although dengue is relatively rare in the United States, it is endemic in many parts of the world, including Africa, the Eastern Mediterranean, Southeast Asia, the Americas, and the Western Pacific, with the Americas, Asia, and the Western Pacific being the most severely affected.

The incidence of dengue has been increasing rapidly in the last several decades, particularly since 1981 [135; 162]. The disease is both appearing in new areas and increasing in numbers of infections per year. Almost all cases of dengue fever in the continental United States have been acquired through travel to endemic regions [162]. However, there have been limited local outbreaks in Texas, Florida, and Hawaii. More importantly, dengue is endemic to Puerto Rico, the U.S. Virgin Islands, Guam, and Samoa, and citizens in these regions are at increased risk for infection [135; 162]. Although the geographic distribution of dengue is similar to that seen with malaria, it is more common in urban and more populated areas rather than more rural areas [135]. Infection rates for travelers to endemic regions range from 2.9% to 8% [163].

The principle vector for dengue is the mosquito *Aedes aegypti*, a species that originated in Africa but is now commonly found in most tropical and subtropical areas [164].

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The *Aedes albopictus* mosquito, which is native to Asia, has also been implicated in the spread of dengue. World travel of the mosquitoes in cargo is a likely culprit [164]. Direct person-to-person transmission has not been documented, but there have been cases linked to dengue-infected blood, organs, or other tissues from blood transfusions; solid organ or bone marrow transplants; needlestick injuries; and mucous membrane contact with dengue-infected blood [163].

Clinical Presentation

The first signs and symptoms of dengue infection typically develop within 4 to 7 days of the infectious mosquito bite and last for 3 to 10 days [162]. The characteristic presentation of classic dengue fever includes a high fever (up to 105 degrees F), severe headache, retro-orbital pain, severe joint and muscle pain, nausea and vomiting, rash, hemorrhagic manifestation, and/or leukopenia [163; 165]. The characteristic rash is macular or maculopapular and generalized and usually develops as the fever subsides. An estimated 50% of patients may remain asymptomatic, while about 1% of patients will develop dengue hemorrhagic fever [163].

The most clinically relevant sign of dengue hemorrhagic fever is vascular leakage, with all of the following criteria necessary for diagnosis: fever or recent history of fever, any hemorrhagic manifestation, thrombocytopenia (i.e., platelet count $<100{,}000/mm^3$), and evidence of increased vascular permeability [163]. In a few patients, most commonly children experiencing their second dengue infection, dengue shock syndrome will develop [165]. Dengue shock syndrome is characterized by the presence of all of the criteria for dengue hemorrhagic fever with the addition of hypotension, narrow pulse pressure (≤20 mm Hg), or shock [163].

Diagnosis

Clinicians should obtain a complete personal and travel history for all patients suspected of having dengue fever or hemorrhagic fever [166]. Cases can be laboratory confirmed with the use of RT-PCR, anti-dengue IgM or IgG antibody titer, or immunofluorescence or immunohistochemical analysis of autopsy tissue [162]. In conjunction with a thorough history indicating recent febrile illness and travel to an endemic area, a positive test suggests probable infection. However, it is important to note that a positive antibody test will only indicate that the patient has ever been infected; it does not necessarily confirm recent illness. Furthermore, there is some cross-reactivity with other flaviviruses, including West Nile virus and yellow fever [163].

Treatment and Prevention

There are no approved treatments available for dengue, although a vaccine was approved for endemic areas (i.e., American Samoa, Guam, Puerto Rico, and the U.S. Virgin Islands) in 2019 [132; 135; 163; 236]. Supportive care, in the form of bed rest and adequate fluids to maintain hydration, is recommended [135; 163]. In more severe cases, maintaining the patient's circulatory volume will be key. Antipyretics may be necessary to reduce fever, and the CDC recommends the use of acetaminophen [163]. Narcotics may be used to treat severe pain. Aspirin (and other salicylates) and NSAIDs should be avoided due to the risk of hemorrhage and, in children, Reye syndrome [163].

As with many zoonotic diseases, the best treatment for dengue fever is prevention. This includes vaccination (if indicated) and all measures necessary to prevent being bitten by an *Aedes* mosquito, such as bed nets, use of DEET-containing insect repellants, and wearing long-sleeved shirts and long pants [135; 163; 165]. Travelers should be advised to choose accommodations with air conditioning and window and door screens [163]. Because mosquitoes breed in standing water, eliminating these habitats (e.g., earthenware jars, metal drums, concrete cisterns used for domestic water storage, discarded plastic food containers, used automobile tires) in urban or residential areas has become a priority [135].

RABIES

Rabies is caused by the rabies virus, an RNA rhabdovirus belonging to the genus *Lyssavirus*, which under electron microscopy has a distinctive "bullet" shape [70]. Its genome and the various types of viral antigens particular to individual types of animals in given regions have been elucidated.

The disease, in animals and humans, has been known since ancient times. The name dates to about 3000 B.C.E. and means "to do violence" in Sanskrit. Detailed investigation of rabies began in the latter part of the 19th century, and Louis Pasteur discovered a vaccine for rabies in 1885. The development of a vaccine for animals, particularly the widespread vaccination of dogs and cats in the United States begun in the 1940s and the oral vaccination program for raccoons begun in the 2000s, has markedly decreased the number of human cases in the United States in the past century [71]. Additionally, effective human rabies immune globulin and human rabies vaccines have been developed. However, many thousands of human cases still occur worldwide each year, with 34 documented cases in the United States between 2003 and 2014 (10 of which were contracted outside of the United States and its territories) [74; 77]. At the present time, approximately 5,000 animal rabies cases are reported to the CDC each year, of which more than 90% are in wildlife. The most commonly identified rabies hosts in the United States are bats, raccoons, skunks, and foxes.

The number of human fatalities associated with rabies in the United States has decreased from 100 or more each year in the early 1900s to just one or two per year today. From 1960 to 2018, a total of 125 human rabies cases were reported in the United States, about 25% of which resulted from dog bites sustained during international travel [71]. Of infections acquired in this country, 70% were attributed to bats. Deaths are primarily due to failure to seek medical assistance, usually because the individual is unaware of exposure, as is common with bat bites. In addition to animal bites, cases have also been documented from corneal and organ transplants [71;

73]. It is estimated that about 55,000 people worldwide die from the disease every year, mostly in developing countries where preventive measures are not adequate [77].

Rabies is present in essentially every country in the world and in every state in the United States, except for Hawaii. During 2017, 49 states and Puerto Rico reported 4,454 animal cases and 2 human cases [71]. Historically, human deaths have occurred in all regions where animal cases are present. In the United States, domestic animals accounted for 9% of all rabid animals reported in 2017 [71]. All mammals can contract rabies, but interestingly, birds do not get or carry the disease. Of the common wild animals in the United States, raccoons are the most infected in the East; skunks are the most infected animals in the Midwest and California; foxes and coyotes are most afflicted in Texas, the Southwest, and Alaska; and mongoose are most affected in Puerto Rico [74].

Rabies is the infectious disease with the highest known case-fatality rate in the world [75; 76]. It is an acute, progressive encephalitis that almost always leads to the death of the patient if they do not begin to receive the vaccine series soon after exposure. The disease occurs when the virus enters the body, most commonly by the bite from an infected animal. Infection can also occur from contact with contaminated animal body parts, saliva, or other body fluids, especially when it involves penetration through mucous membranes or broken skin [70]. Fortunately, case reports have shown this type of transmission is much less likely to happen. There does not appear to be human-to-human transmission of rabies, except via infected transplanted tissues or organs [72; 73]. After entering the body, the virus particles pass via the peripheral nervous system to lodge and replicate in the central nervous system. The rabies virus becomes distributed throughout the brain and is also disseminated to the salivary glands and other organs.

The incubation period is usually about two weeks but can be as long as several months. Shorter incubation periods appear to be associated with inoculations closer to the head [76]. If untreated, rabies is almost 100% fatal [8; 70]. The only existing treatment for non-vaccinated humans is injection with rabies immune globulin and rabies vaccine within days after exposure; therefore, timely diagnosis of the disease is extremely important.

Clinical Presentation and Diagnosis

The clinical presentation often begins with a feeling of fatigue, malaise, and possible paresthesias near the site of inoculation. Most patients have a low-grade fever, but some remain afebrile in the early stages prior to developing a fever over the next few days. Nausea and vomiting can be present as well as lethargy and anorexia. The signs and symptoms of a central nervous system disease and encephalitis usually follow rapidly. Diplopia or other visual defects, unsteady gait, cranial nerve palsies, cognitive changes, photophobia, phonophobia, restlessness, and limb weakness are common findings. The neurologic condition of the patient rapidly declines, with increasing confusion, disorientation, tremors, twitching or myoclonic muscle movements, seizures, and increased pain sensations. Some patients develop laryngospasm when attempting to drink. Many patients eventually have pulmonary problems, leading to poor ventilation and respiratory failure. Autonomic system collapse and coma ensue, with death following regardless of supportive measures [70; 76].

There are descriptions of two possible forms of disease presentation. One is called the paralytic form, whereby an ascending paralysis similar to Guillain-Barré syndrome predominates. The other, which is more common, is the encephalitic or "furious" form described above [75; 76; 78].

It is imperative to make the diagnosis of a rabies-prone exposure during the period prior to the development of symptoms. A delay in diagnosis and treatment can mean almost certain death for the patient [76]. Therefore, a history of suspicious animal bite or contact with a victim of the disease, especially the saliva of a victim, must lead to the performance of diagnostic tests.

Several tests are necessary to diagnose rabies in humans; no single test is sufficient [70]. Fortunately, there are several very good diagnostic procedures that can be performed fairly quickly on serum, saliva, CSF, or skin biopsies taken from the nuchal region of the neck. Antibody analysis can be performed on serum or CSF, and skin biopsy samples can be examined for rabies antigen in the cutaneous nerves at the base of the hair follicles [70]. Other laboratory tests include electron microscopy, virus culture, and immunohistochemistry. Laboratory analysis also allows for the determination of the type of animal involved and, in many cases, the locality from which the infection originated. There are many public health and other designated facilities available to perform these procedures. Neuroimaging procedures, including CT scans and MRIs, are usually normal initially but show signs of cerebral edema and other features of encephalitis as the disease progresses.

If possible, the suspected animal should be tested for rabies antigen. Tests on animals may require samples of their brain tissue [70]. Because of its high sensitivity and specificity, the direct fluorescent antibody (DFA) test is considered the gold-standard diagnostic method for rabies determination in animals in the United States [70]. The presence of Negri bodies, characteristic intracytoplasmic inclusion nodules within neurons, is confirmatory evidence of the disease. The rapid determination of whether an animal is rabid can save a potential victim from psychologic trauma and an expensive treatment regimen [70].

Treatment and Prevention

Any wound from an animal should be intensively cleaned with soap and water. Antiviral compounds (e.g., povidone iodine) should be used if available; thorough wound cleansing has been shown to markedly decrease the risk of bacterial infection [242]. As discussed, postexposure treatment can

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prevent the disease if given early and prior to the onset of symptoms.

In non-immunized individuals, treatment consists of the use of immune globulins and vaccine [242]. A human rabies immunoglobulin (HRIG) is available in the United States and most other developed countries. Historically, equine rabies immunoglobulin (ERIG) was used and regimens included a series of painful and sometimes dangerous injections. The currently available ERIG is highly purified and is considered "quite safe" by the WHO [79]. A skin test should always be performed before using ERIG. The safer HRIG is expensive, but requires only an intragluteal injection, usually with a dose of 20 IU/kg [79]. The WHO advises that HRIG, like ERIG, also be administered in the vicinity of the bite wound [79].

In addition, rabies vaccine must also be started. According to the CDC Advisory Committee on Immunization Practices (ACIP), the vaccine should be injected IM at a site distant from the HRIG injection site, possibly the deltoid. The ACIP recommends giving four doses of human diploid cell vaccine or purified chick embryo cell vaccine, 1.0 mL (at days 0, 3, 7, and 14) for immunocompetent individuals and the usual five-dose regimen for immunocompromised individuals [80; 242].

When symptoms appear, diligent supportive measures are required, including induced coma for patients with involuntary muscle movements and severe pain [76; 82]. Additional treatment regimens have included IV ribavirin and other antiviral agents under investigative drug protocols; however, there are very few reports of recovery [76; 81]. The experimental Milwaukee protocol is associated with significantly longer survival than conventional treatments for symptomatic rabies, but has been tested on an exceedingly small number of patients and "excellent and adaptive medical intensive care and careful avoidance of mistakes and complications of intensive care may prove to be essential to positive outcomes" with this treatment regimen [82]. The probability of treatment failure, even with this protocol, is extremely high [76].

Individuals who had been previously adequately vaccinated for rabies are treated differently. The ACIP suggests that these patients receive rabies vaccine IM as soon as practical with a second injection three days later [83; 242]. The recommended site is the deltoid muscle. They do not advise giving HRIG to previously immunized patients [72; 81; 242].

In the United States, every state has some type of requirement that household dogs and cats be vaccinated for rabies. Although the vaccine is commercially available, almost all vaccinations of domestic animals are performed by veterinarians. Some states or municipalities also impose quarantines of varying periods to help reduce the possible spread of rabies [84].

The CDC and the WHO suggest that individuals who might have a higher risk of coming in contact with a rabid animal be vaccinated. This pre-exposure prophylaxis includes occupations such as veterinarians, laboratory workers, animal control officers, and animal handlers. The recommended vaccine is a cell culture vaccine (CCV) [85]. It is also recommended that the production and use of nerve-cell vaccines cease.

The WHO suggests that an intradermal administration of CCV 0.1 mL be used in three doses at day 0, 7, and then between 21 and 28 days or, alternately, intramuscular administration of 0.5 to 1 mL, depending on the type of vaccine, on the same three-day schedule [85]. However, rabies vaccine adsorbed is no longer available in the United States and therefore intradermal administration is no longer recommended [83]. Intramuscular vaccinations should be administered in the deltoid area of the arm for adults and the anterolateral area of the thigh for children younger than 2 years of age; the vaccine should not be administered in the gluteal area. Serologic analyses should be performed every six months for those at high risk and every two years for those at lower risk; a booster injection is not recommended unless rabies-virus neutralizing antibody titers fall below 0.5 IU/mL [85]. Booster injections are not recommended for individuals travelling to high-risk areas if they have previously completed pre-exposure or post-exposure prophylaxis.

AVIAN INFLUENZA

The influenza viruses that are carried by birds, both domesticated and wild, rarely have infected humans. This is partly due to the fact that avian influenza (AI) viruses attach to receptors found on bird cells but not found on human cells. Human viruses prefer the receptors found in the human respiratory tract. Pigs have receptors used by avian, swine, and human influenza viruses and have traditionally been the link between avian and human influenza viruses. Because pigs acquire all three types of viruses, reassortment/antigenic shift of the hemagglutinin and neuraminidase proteins occurs in the pig host, which then transmits the new strain to humans or other pigs [86; 87].

However, there now exists evidence that avian influenza can spread directly to humans [87]. In 2004, areas of Asia experienced large-scale outbreaks of avian influenza, specifically the H5N1 virus, in poultry. The virus went on to infect humans, with a high mortality rate. The number of countries, people, and animals affected by the virus reached unprecedented levels. In 2006, the CDC summarized the H5N1 outbreak. Wild birds and poultry had been infected in Asia, parts of Europe, the Middle East, and Africa. Human infections continued to be reported in China, Egypt, Indonesia, Azerbaijan, Cambodia, and Djibouti. There were some probable human-to-human transmissions of H5N1, but these were rare. As of June 2016, the WHO reported 850 human cases of H5N1, with a fatality rate of approximately 53%

[88]. In January 2014, the first case of a human infection with H5N1 in the Americas was reported in Canada; the patient, who died, had recently travelled to Beijing, China [243]. Both the CDC and the WHO have reported that there is a strong threat of a future pandemic of avian influenza and that preparedness is vital [90; 91; 92]. In August 2012, the Indonesian Ministry of Health announced another H5N1 death of a man infected either from birds he kept in his home or from exposure to H5N1 near his home, which is about 50 meters from a poultry slaughterhouse. This brings the total of confirmed cases of H5N1 in Indonesia to 191 with 159 deaths, a fatality rate of 83% [93].

Although influenza A viruses can infect all birds, domestic poultry flocks are more vulnerable to infections that can reach epidemic proportions. Generally, domesticated fowl transmit the virus in saliva, nasal secretions, and feces. However, it is thought that the fecal-oral route is the common way the virus is spread among flocks. Wild birds rarely become sick but are a source of infection through their droppings because they carry the virus in their intestines. Free-roaming domestic fowl are at more risk from wild bird droppings than housed flocks. Both food and water supplies can be contaminated by droppings or sharing with wild birds. At first it was thought that wild birds spread the virus from farm to farm, but further study indicated that people and equipment probably spread the virus to domesticated flocks [94; 95].

AI viruses are classified as low pathogenic and high pathogenic based on their genetic sequence and the resulting illness in birds. Low pathogenic AI has been detected in wild birds, mostly ducks, geese, and gulls, since 1975 [94; 96]. Low pathogenic AI virus causes only ruffled feathers and a reduction in egg production. Fortunately, most AI viruses are low pathogenic; however, in six to nine months, they can mutate to high pathogenic. High pathogenic AI viruses, first noted in 1878 in Italy, are highly contagious, spread rapidly, and are almost 100% fatal. Fowl can die the same day that they first exhibit symptoms [96; 97; 98].

Whenever an AI virus infects a human directly, there is much concern. Humans rarely have any immunity to AI viruses. Medical resources around the world quickly mobilize when there is a case of AI that skips reassortment in swine and directly infects a human. Fowl within a 2-mile (3-kilometer) radius of the source bird/flock are killed in order to contain the virus. An AI virus in humans usually produces upper respiratory disease and conjunctivitis. The infected humans and their contacts are watched closely for secondary transmission. For a pandemic to follow, these factors are needed:

- Humans do not have immunity to the virus
- Direct transmission from bird to human
- Sustainable transmission from human to human
- Movement of infected/contagious individuals to other geographic locations

Once a new pandemic influenza virus emerges, it generally circulates for many years [94; 97]. Researchers at the University of Wisconsin, Madison, have been combining H5N1 with a seasonal flu strain (H3N2). As a result, they have found such reassortment flu viruses are highly pathogenic; 22 were more pathogenic for mice than the original H5N1, and 3 caused extremely severe disease [99].

Avian Influenza Viruses

The hemagglutinin antigens that historically have caused human influenza are H1, H2, and H3. Although all known hemagglutinin subtypes occur in birds, H5, H7, and H9 have been implicated more in recent outbreaks. Various combinations with the neuraminidase antigens occur. All of these AI viruses are type A, as B and C do not infect birds. Some of the cases focused on in the past two decades have included the following [90; 100; 101]:

- H5N1 – Hong Kong, 1997, first documented human infection-18 hospitalized, 6 deaths, 1.5 million chickens culled
- H9N2 – Hong Kong, 1999, 2 mild cases in children, several in mainland China
- H7N2 – Virginia, 2002, 4.7 million chickens and turkeys culled
- H7N7 – Netherlands, 2003, 80 poultry workers, 3 family members infected (79 eye infections, 6 influenza-like), 1 veterinarian death due to acute respiratory distress syndrome and complications
- H5N1 – Hong Kong/China, 2003, 2 ill, 1 death
- H9N2 – Hong Kong, 2003, 1 case confirmed in a child
- H5N1 – Asia, 2004–2005 (H5N1 had been found in Asian chickens April, 2003), 112 confirmed cases, 57 deaths; too widespread to cull all fowl
- H7N3 – British Columbia, 2004
- H5N2 – Taiwan, 2004, low pathogenic, no human illness
- H7N2 – Delaware, 2004, no human illness
- H5N2 – Texas, 2004, no human illness
- H5N1 – Russia/Romania/Turkey/Azerbaijan, 2006, some human illness, unknown deaths
- H5 Outbreaks – 21 U.S. states and Canada, 2014–2015, highly pathogenic, found in backyard and commercial flocks and wild birds, no human illness
- H7N8 – Indiana, 2016, highly and low pathogenic virus detected in nine commercial turkey flocks, all culled, no human illness
- H7N9 – China, 2013–2017 (ongoing), contact with poultry at farms and live markets, 1,347 laboratory-confirmed human infections (as of April 2017)

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Fortunately, although in some of these outbreaks bird-to-human transmission did occur, human-to-human transmission has been extremely rare. Limited transmission possibly did occur between humans in the Netherlands, but no sustainable transmission occurred, so an epidemic or pandemic did not follow. There were 14 cases and 12 deaths (11 children) from H5N1 virus in Vietnam. The viruses isolated from those who expired in Vietnam were mostly resistant to amantadine and rimantadine. Studies are continuing as to the effectiveness of oseltamivir and zanamivir against H5N1 viruses. There is some evidence that H5N1 is sensitive to oseltamivir; however, some evidence of resistance to oseltamivir has been reported in highly pathogenic avian influenza H5N1 viruses isolated from human cases [94; 95; 97; 101; 102; 103]. Most of the H5N1 outbreaks were controlled by veterinarian officials or spontaneously died out. However, H1N1 continues to fulminate in poultry in Egypt [104].

Avian Influenza and Humans

Most cases of AI in humans have resulted from contact with infected poultry or contaminated surfaces. It is also possible for the virus to become aerosolized and then land on exposed surfaces of the mouth, nose, or eyes. Aerosolized virus could also be inhaled directly into the lungs. Eating poultry products has not been associated with the development of AI. Influenza viruses are destroyed by adequate heat.

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit poultry to be imported from countries in which there were confirmed human cases of AI, such as China's ban of U.S. chicken in 2015. However, the risk of AI spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or chilled. All documented transmission to date has been from live birds [101; 105].

Humans have no immunity to AI viruses, so illness tends to be severe and the fatality rate is high. Prevention is difficult because the viruses tend to be highly contagious. Because of the mobile nature of people and efficient, rapid transport, any virus can spread quickly around the world. The current manufacturing process of influenza vaccine requires several months. The elements are all in place for a pandemic.

In August 2007, a team of scientists at the National Institute of Allergy and Infectious Diseases reported that it had developed a way to generate vaccines and therapeutic antibodies that could target constantly mutating influenza viruses, such as H5N1. The team focused on mutations that enable H5N1 hemagglutinin protein to better recognize and enter human cells and those mutations that will elicit antibodies. This information will enable researchers to consider how to design potential vaccines that will protect people from future emerging AI virus mutants, possibly helping to contain a pandemic in its early stages [106].

In order to understand how influenza viruses mutate, researchers have been working to synthesize the hemagglutinin responsible for the 1918 influenza ("Spanish flu") pandemic. The success of this endeavor was reported in 2004, and scientists have since discovered how subtle alterations enabled the virus to move from birds to people [107].

The H5N2 avian influenza virus continues to be monitored around the world by scientists. It is highly virulent but has not been transmitted person-to-person yet [92; 108]. In 2015, H5N2 avian influenza virus (along with H5N8 and H5N1) were found in more than 200 bird samples, indicating the likelihood that 40 million farm and backyard birds have been infected in 20 states [245].

Clinical Presentation and Diagnosis

As noted, humans have no immunity to avian influenza A viruses, so illness tends to be severe and the fatality rate is high. The symptom complex can range from the typical influenza findings of fever, headache, myalgia, sore throat, and cough to severe respiratory distress. Many humans develop conjunctivitis, which can be the initial complaint. This usually includes red, itching, and tearing eyes with associated photophobia and purulent discharge. The severe form progresses to pneumonia, which can be fulminant and followed by multiorgan failure and death. Although the very young and very old are most at risk for the viral pneumonia, fatalities have occurred among previously healthy adults [89].

Laboratory testing is required to diagnose avian viral disease; it cannot be determined by clinical signs and symptoms alone [89]. Diagnosis is initially based on the history from a patient with the symptoms of influenza who has had contact with birds, poultry, or an endemic area. A complaint of eye irritation, which on examination appears to be conjunctivitis, is another clue to the presence of the disease. The available laboratory tests include viral culture and reverse transcriptase PCR (RT-PCR). These can be performed on samples of eye exudate, tears, or throat swabs. Analyses are most useful if obtained within four days of the onset of symptoms, and eye swabs are more likely to be positive than throat culture [109].

Treatment and Prevention

As in other viral diseases, supportive treatment is a mainstay in avian viral infections. Over the past few years, several regimens have been attempted in the treatment of avian viral disease. The antiviral medications amantadine, rimantadine, oseltamivir, and zanamivir have been used in cases of human influenza in the United States. However, amantadine and rimantadine were shown to be ineffective against the H5N1 strain of avian influenza in humans during the outbreaks in Asia in 2004 and 2005 [110]. The CDC and the WHO recommend oseltamivir, peramivir, or zanamivir for treatment and prevention of human infection with avian influenza A viruses; however, as noted, some evidence of resistance to oseltamivir has been reported in viruses isolated from some human cases [89]. The suggested adult dose for the treatment

of influenza is 75 mg twice per day, starting within two days of symptoms and continuing for five days. Results are best if the drug is started within two days after contact with an infected individual or fowl. For prophylaxis, the dose is also 75 mg twice a day, but taken for 10 days [46].

A major step to limiting disease and transmission among domesticated fowl is to destroy all diseased birds and their flock mates. Because the virus appears to be carried by people and machines, possibly on shoes and tires to surrounding areas, the recommendation is that all fowl in a 2-mile (3-kilometer) radius of the diseased flock be culled. Obviously, no shipping of live poultry from the infected areas should occur.

During the outbreaks of avian influenza in poultry in Asia during 2003–2004, people were not restricted from traveling to outbreak areas because of the limited transmission to humans. However, the following recommendations were sent to embassies and Americans living abroad [111]:

- Practice frequent and careful handwashing with soap and water or with a hand cleanser if soap and water are unavailable.
- Avoid bird markets and poultry yards where avian influenza is most likely to be transmitted.
- All poultry and eggs should be cooked well, as influenza virus is destroyed by heat.
- Protect pets by keeping them inside to avoid exposure to birds that may be sick, refraining from feeding them raw meat or poultry, and avoiding all contact with stray cats or dogs.
- Masks and other personal protective equipment in public areas are not recommended.
- Travelers should be immunized with the current influenza vaccine against human influenza strains before traveling and should be reminded that winter (flu season) occurs in the Southern Hemisphere when the Northern Hemisphere is experiencing summer.

The CDC has also developed guidelines for airline personnel dealing with a suspected case of avian influenza on board an international flight originating in an area in which avian influenza has been reported [112]:

- As much as possible, airline staffs are to keep the sick person separated from close contact with others.
- A surgical or procedural mask should be provided to limit the amount of droplets coughed into the air. If the passenger cannot wear the mask, anyone assisting him/her should be masked.
- The passenger should be taught cough etiquette if it is not being practiced.
- Disposable gloves are to be worn for any contact with body fluids, and hands are to be washed well when gloves are removed.
- The captain is to report the illness to the nearest U.S. Quarantine Station if the aircraft is coming to the United States. The Quarantine Station will coordinate appropriate medical assistance when the plane lands and will notify the appropriate CDC staff.

Influenza viruses are destroyed by adequate heat. Because the pathogen is found in poultry, all individuals should be reminded to cook poultry, including eggs, thoroughly. Chicken should be cooked until the internal temperature reaches 180 degrees F. All utensils and surfaces that have come in contact with raw poultry should be washed well with soap and water immediately following use. A separate cutting board should be used to cut raw poultry. In order to retard bacterial or viral replication, all poultry products should be defrosted in the refrigerator, not at room temperature.

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit imported poultry from countries in which there were confirmed human cases of avian influenza. However, the risk of avian influenza spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or well chilled. All documented transmission to date has been from live birds [105].

Vaccine Development

As with the development of all vaccines, the first step is to isolate the organism. In the case of AI, various research centers and companies around the world are working to make a vaccine. The first step is to isolate the virus (e.g., the H5N1 influenza A virus in 2004). Next, the virus is dismantled so the most virulent elements can be excluded. Then the virus is reassembled without those virulent elements, and attempts are made to produce it [105]. As noted, the virus has been isolated and the virulent elements have been identified to allow vaccine development to proceed. In 2006, a new recombinant H5N1 virus became available for distribution to companies interested in pandemic vaccine development [114]. In 2007, GlaxoSmithKline received a contract from the U.S. Department of Health and Human Services to manufacture 22.5 million doses of AI vaccine in addition to the 5 million doses ordered in 2006 [115]. Research to find novel media or methods (rather than using eggs) is ongoing [116].

In April 2007, the FDA approved the first human vaccine for the AI virus H5N1 [117]. This vaccine is intended for individuals 18 to 64 years of age who could be at an increased risk of exposure to the H5N1 influenza virus. The vaccine is not available commercially, but rather has been purchased by the federal government to be distributed if necessary. The vaccine consists of two 90-mcg IM doses given 28 days apart. There is thimerosal, a preservative, in this vaccine [46; 117]. Because this vaccine has been approved by the FDA and found to be safe and effective, it is no longer considered

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experimental. Therefore, it can be used during a pandemic without the time-consuming protocol and signed informed consent necessary for an experimental drug or vaccine [117]. Data from trials being conducted on ACAM-FLU-A show that the vaccine generates a robust antibody response against H5N1 avian influenza [118].

SWINE INFLUENZA

As discussed, pigs represent an important link in the interspecies transmission of influenza and in the creation of new virus types. In addition, swine influenza has the potential to cause significant disease in humans, although it is difficult to predict the potential impact of swine influenza in humans. Because most individuals, with the possible exception of those with regular contact with pigs, do not have immunity to these viruses, the potential for pandemic exists.

Swine influenza is usually caused by the H1N1 subtype, but other swine influenza A viruses do occur, including H1N2, H3N1, and H3N2 [119]. Although swine flu viruses do not typically infect humans, sporadic human infections have occurred. When this occurs, these viruses are called "variant viruses" and are denoted by adding the letter "v" to the virus subtype designation. Human infections with H1N1v, H3N2v, and H1N2v viruses have been detected in the United States [119; 120]. Pigs may become infected with more than one virus subtype simultaneously; in these cases, genes from the viruses may mix and create a new "reassortment" virus [121]. The main swine influenza viruses circulating in U.S. pigs in the past decade include triple reassortant (tr) H1N1, trH3N2, and trH1N2 [119; 120].

Among pigs, swine influenza is a highly contagious acute respiratory disease. In many countries, including the United States, swine populations are routinely vaccinated against the prevalent subtypes. Vaccination of pigs, while not sufficient to produce sterilizing immunity, can reduce the levels of virus shed by the animals and reduce the potential for human exposure and infection [121].

In 2009, an outbreak of H1N1 influenza A (hereafter referred to as 2009 H1N1), popularly referred to as the "swine flu," occurred. Tests showed this virus was similar to influenza viruses normally occurring in pigs in North America. However, with more extensive testing scientists learned that there were two genes present that typically occur in pigs in Europe and Asia. In addition, there were also avian and human genes. A quadruple reassortment virus was the result [122].

It should be noted that the so-called Spanish Influenza of 1918–1919 was also an H1N1 virus. The hemagglutinin gene in 2009 H1N1 influenza apparently descended from the avian-origin 1918 pandemic influenza virus. The 2009 H1N1 virus is not a new subtype, but many humans had no pre-existing antibody to it (especially those younger than 65 years of age) and widespread transmission resulted. This led to the first pandemic since 1968. The virus quickly spread worldwide, and on June 11, 2009, the WHO declared it a worldwide pandemic. In the United States the virus was first detected in humans in April 2009. By September more than 99% of the circulating viruses were 2009 H1N1. It remained the predominant circulating virus for the entire 2009–2010 influenza season [122; 123]. On June 23, 2010, the public health emergency for 2009 H1N1 expired in the United States, and the WHO declared the pandemic over on August 10, 2010 [124].

Data from past pandemics show that influenza activity occurs in waves. A second wave of 2009 H1N1 occurred in the fall of 2010 and peaked in the first three weeks of October [125]. Experts believe that 2009 H1N1 will continue to circulate for some time, perhaps as a typical winter flu. As noted, it was included in the formulation of the 2016–2017 vaccine [131].

Transmission

Like all flu viruses, 2009 H1N1 is mainly spread among people by coughing, sneezing, talking, and occasionally via fomites. It is not spread by food or by eating pork or pork products. There have been no cases acquired from influenza-contaminated drinking water. Chlorine treatment of drinking water has been shown to inactivate the highly pathogenic H5N1 virus, and H1N1 would be similarly affected. A documented case of influenza from any water exposure (drinking or recreational) has not occurred.

Pets, such as dogs, cats, and ferrets, can be infected with H1N1 from close contact with a sick human. All available information indicates that H1N1-infected dogs, cats, and ferrets do not transmit the illness to humans. So far, there is no H1N1 vaccine for animals. Most recover with supportive care [122].

When a swine influenza virus does become a source of widespread human illness, the transmission patterns change. Instead of being mainly limited to swine contact, the virus will spread by human-to-human contact. According to the CDC, available data indicate that the 2009 H1N1 virus is transmitted in ways similar to other influenza viruses, primarily large-particle respiratory droplet transmission [126]. Because humans have little to no immunity to influenza viruses of swine origin, transmission may be common.

H1N1 survives on surfaces, including kitchen counters, door knobs, desk tops, and other fomites, for two to eight hours. Individuals can pick up the virus when they touch contaminated objects and unconsciously then touch their eyes, mouth, or nose. Thus it is vital for people to learn to keep their hands away from their mouths, eyes, and nose and to frequently wash their hands well with soap and water or use an alcohol-based hand sanitizer. An alcohol-based product, bleach solution, or hot, soapy water can be used to clean surfaces [127]. One positive result of the H1N1 pandemic, as indicated in a study conducted in Hong Kong, is that people are washing their hands more frequently and wearing face masks when having influenza-like illness or when in public areas [128].

A major transmission concern with 2009 H1N1 was regarding newborns whose mothers had the virus. The CDC and State Health Departments strongly recommended the 2009 H1N1 vaccine for this population because of demonstrated risks to both infants and pregnant women. However, many disregarded the recommendation. It was then decided that infant and mother should be separated until the mother had been on antivirals for at least 48 hours, was afebrile for 24 hours without antipyretics, and could control her cough and respiratory secretions. Before visiting the infant, the mother was instructed to clean her hands well with soap and water or an alcohol-based hand sanitizer, wear a face mask, and observe respiratory/cough etiquette. If her gown had been contaminated with byproducts of coughing or sneezing, she was instructed to change to a fresh gown. Following these guidelines, the mother was then permitted to hold, feed, and care for the infant [125].

Prevention

Like seasonal influenza, vaccination is the most important preventive measure. Other common sense preventive steps (e.g., appropriate cough cover, correct disposal of used tissues, adequate rest, good fluid intake, staying home when ill) should be practiced.

Vaccine

The CDC identified five groups who were given first priority 2009 H1N1 vaccination [129]:

- Pregnant women
- Persons who live with or provide care for infants younger than 6 months of age
- Healthcare and emergency medical services personnel
- Children and young adults 6 months to 24 years of age
- Persons 25 to 64 years of age at higher risk for influenza-related complications

These patients were vaccinated as soon as the vaccine was available. As with seasonal influenza vaccine, it is also important to note that two doses of the vaccine are necessary for previously unvaccinated children younger than 9 years of age, as they typically have had limited exposure to influenza viruses and are not immunologically primed [129; 131]. For the 2016–2017 flu season, the ACIP recommended that children 6 months through 8 years of age not previously immunized be given two doses at least four weeks apart [131]. At least one study has shown that a single injection is adequate when vaccinating pregnant women [131].

Symptoms and Diagnosis

Similar to seasonal flu, H1N1 symptoms include chills, fever, myalgia, fatigue, headache, cough, sore throat, and rhinitis. But unlike seasonal flu, there may be vomiting and diarrhea in some people. Others may have respiratory symptoms without fever [122; 127].

Unless it becomes a pandemic, swine influenza infection in humans generally goes undistinguished from typical human influenza as a result of the overlapping flu seasons and the relatively mild clinical presentation. The disease is diagnosed by analysis of a sputum sample collected in the first four to five days of illness, when an individual is most likely to be shedding the virus [119]. A new test for 2009 H1N1 was authorized by the FDA in June 2010 to be used on upper or lower respiratory secretions. The CDC Influenza 2009 A (H1N1) pdm Real-Time RT-PCR panel (IVD) replaces the test authorized in April 2009 [133].

In the case of the 2009 H1N1 virus, the CDC recommended that clinicians test persons for the virus if they had an acute febrile respiratory illness or sepsis-like syndrome [126]. Patients who require hospitalization or who are at high risk for severe disease should be tested and treated first.

It was believed that persons at greater risk for complications of seasonal influenza would also be at greater risk for complications associated with 2009 H1N1 flu. This included [126]:

- Pregnant women
- Children younger than 5 years of age
- Persons 65 years of age or older
- Adults and children who have chronic illnesses
- Adults and children who have immunosuppression
- Children and adolescents who are receiving long-term aspirin therapy

However, as the epidemic progressed it became apparent that those younger than 65 years of age were at great risk (***Table 5***) [125].

Treatment

While most swine influenza cases were sufficiently mild to resolve spontaneously, antiviral medications were used if treatment was indicated. The specifically recommended agents were determined based on clinical and epidemiologic assessment of the virus. For example, in the case of the 2009 H1N1 outbreak in North America, the virus's susceptibility profile indicated that the preferred antivirals would be oseltamivir or zanamivir (or peramivir in case of severe illness requiring hospitalization) [119; 121].

During the 2009 H1N1 pandemic, the CDC recommended antiviral treatment for all persons with suspected or confirmed influenza requiring hospitalization [123]. In addition, early empiric treatment with oseltamivir or zanamivir was considered for persons with suspected or confirmed influenza who were at higher risk for complications, including [123]:

- Children younger than 2 years of age
- Persons 65 years of age or older
- Pregnant women and women up to two weeks postpartum (including following pregnancy loss)
- Persons of any age with certain chronic medical or immunosuppressive conditions

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DISTRIBUTION OF 2009 H1N1 AND SEASONAL INFLUENZA BY AGE GROUP				
Influenza Type	**0 to 17 Years**	**18 to 64 Years**	**0 to 64 Years**	**65 Years and Older**
Cases				
2009 H1N1	33%	57%	90%	10%
Seasonal	--	--	<10%	90%
Hospitalizations				
2009 H1N1	32%	58%	90%	10%
Seasonal	--	--	40%	60%
Deaths				
2009 H1N1	10%	77%	87%	13%
Seasonal	--	--	10%	90%
Source: [125; 134]				*Table 5*

- Persons younger than 19 years of age who are receiving long-term aspirin therapy

The recommended treatment for adult and adolescent patients is either 75 mg oseltamivir twice per day for five days, 10 mg (two 5-mg inhalations) of zanamivir twice daily for five days, or a single 600 mg IV infusion of peramivir over 15 to 30 minutes [46; 119; 123]. Children 7 years of age and older may be treated with the adult dose of zanamivir. However, calculating oseltamivir doses for children is more complicated and has been the source of medical errors [136]. It is important to note that while healthcare providers in the United States generally write prescriptions for liquid medications in milliliters, oseltamivir is dosed in milligrams [136]. For children younger than 1 year of age, the oseltamivir dose is based on age. Infants younger than 3 months of age should be given 12 mg twice daily; infants 3 to 5 months of age should receive a dose of 20 mg twice daily [46]. Infants 6 to 11 months of age should receive a dose of 25 mg twice per day. For children between 1 and 12 years of age, dosage is based on weight [46; 123]:

- <15 kg (<33 lbs): 30 mg twice daily
- >15 kg to 23 kg (>34 lbs to 51 lbs): 45 mg twice daily
- >23 kg to 40 kg (>51 lbs to 88 lbs): 60 mg twice daily
- >40 kg (>88 lbs): 75 mg twice daily

Treatment should continue for five days in most cases, but longer treatment should be considered for patients that remain ill after five days [46; 123]. Pregnancy is not considered a contraindication to the use of oseltamivir or zanamivir.

As of December 2012, 2009 H1N1 was susceptible to both oseltamivir and zanamivir, with a few exceptions. Those resistant to oseltamivir have been sensitive to zanamivir. Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified, but the public health impact has been limited [137]. As of October 2012, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide [137].

Investigational Drugs

A study at Utah State University examined the use of oseltamivir combined with T-705 (favipiravir), an antiviral in late-stage development, on mice. This combination was effective against H1N1, N3N2, and H5N1 influenzas. The study indicated that two antivirals may be a better strategy for treatment of humans with influenza [138].

Because there were no FDA-approved intravenous drugs to treat influenza at the time of the 2009 pandemic, a new investigational antiviral drug, peramivir (approved 2014), was used with patients hospitalized with H1N1 under an Influenza Emergency Use Authorization (EUA) and special permission [139]. Peramivir acts by inhibiting the neuraminidase enzyme that affects the release of viral particles, which results in less virus in the body. The EUA permitted the use of the IV drug only for those hospitalized with a severe suspected or laboratory-confirmed case of 2009 H1N1 who were not responding to inhaled or oral antiviral therapy or for whom the approved antivirals were not acceptable [139]. It was not to be used for seasonal or uncomplicated flu. A creatinine clearance test was required before administration to assure that the patient did not have renal insufficiency. Peramivir is contraindicated for any patients with allergies to zanamivir, oseltamivir, or any component in peramivir. Children, birth through 17 years of age, are not permitted to receive peramivir; because safety and efficacy in this population has not been established, this use is investigational [140].

Peramivir is available in a 200 mg/20 mL single-use vial, which is stored at 59 to 86 degrees F (15 to 30 degrees C). After dilution, it should be given immediately or refrigerated and administered within 24 hours. Some patients on peramivir experienced diarrhea, nausea/vomiting, or neutropenia. Less common side effects included nervousness/agitation, hypertension, headache, depression, dizziness, cystitis, anorexia, hematuria, hyperbilirubinemia, hyperglycemia, somnolence, insomnia, electrocardiogram abnormalities, and nightmares [140].

HANTAVIRUS SYNDROMES

In 1993, there was a series of mysterious deaths due to pulmonary failure in healthy young adults in the four corners region of the American Southwest [141; 142]. Considerable research into the problem resulted in the identification of a virus, harbored in local mice, as the cause of the illness. The virus identified was an RNA *Hantavirus*, a group related to the *Bunyaviridae* family that causes hemorrhagic fever with renal syndrome (HFRS) in Asia and hantavirus pulmonary syndrome (HPS) in the Americas.

Although many thought that HPS was a new entity, the local Navajo inhabitants described a similar disease that they had known about for many years. Between 1993 and January 2017, 728 cases were reported in the United States, with a 36% fatality rate [141; 142]. HPS has been documented in 35 states, with 96% occurring in states west of the Mississippi river and more than half of the confirmed cases reported outside the Four Corners area. In 2017, an outbreak of HPS was linked to home-based rat-breeding facilities in Wisconsin and Illinois; infected rats may have also been distributed or received in Colorado, Delaware, Georgia, Idaho, Iowa, Minnesota, Missouri, New Jersey, Pennsylvania, South Carolina, Tennessee, and Utah [237]. There have also been reported cases in Central and South America [142; 143].

The main host for HPS is the deer mouse (*Peromyscus maniculatus*), but other mice and rodents have been found to carry the organism. There have been other documented hantavirus infections in the United States, with some having specific rodent carriers. The Bayou virus caused disease in Louisiana, and the New York-1 virus was isolated after producing illness in a patient in the Northeast. The causative agent for the 1993 outbreak and subsequent HPS cases has become known as the Sin Nombre virus. In the United States and Canada, the Sin Nombre hantavirus is responsible for the majority of cases of HPS [142].

HPS virus particles are shed by the rodents in their saliva, urine, and feces. They do not seem to have any signs of illness while carrying the virus. Although the disease can be contracted by the bite from a rodent or by contamination of foodstuffs, the most common means of spread is from aerosols. The dried excrement of the animals is easily swept or blown into the air, where it is inhaled into the lungs [142; 144]. Most patients who contract the disease remember cleaning rodent excrement or dead mice from an enclosed area in or around their home. Human-to-human spread does not occur [142; 143; 144].

Clinical Presentation and Diagnosis

The incubation time from contact with the virus until the onset of symptoms is thought to be about one to five weeks. Almost everyone who develops the disease will have fatigue, fever greater than 38.3 degrees C, and myalgia, usually in the large muscles of the back, thighs, and shoulders. There is usually hypotension, tachypnea, and tachycardia. About one-half of patients experience nausea and vomiting, headache, dizziness, and abdominal pain [142; 144]. After 4 to 10 days, the late symptoms of HPS appear with the onset of coughing, shortness of breath, increasing pulmonary distress, and pulmonary edema [142]. HPS appears to resemble acute respiratory distress syndrome in patients with advanced disease. In some patients, renal impairment may also develop, but this is more common in illness caused by hantaviruses other than the Sin Nombre virus.

Chest x-ray shows bilateral interstitial edema, which becomes progressively worse and develops into alveolar edema as the patient deteriorates. Differentiation from acute respiratory distress syndrome can usually be made based on clinical findings; however, good laboratory tests are also available. Laboratory diagnosis can be made by the detection of hantavirus-specific IgM or rising titers of hantavirus-specific IgG. PCR analysis of clinical specimens is also useful. In addition, blood samples can be analyzed for hantavirus antigen by immunochemistry. Patients with HPS often have a left-shifted increase in neutrophils, which helps to differentiate the early symptoms from other viral infections [142; 143; 144].

Treatment and Prevention

No treatment has proven to be useful for HPS, with the exception of supportive care. Ribavirin, which has helped in some hantavirus infections in Europe, has not proven to be of use in patients with HPS [130; 144]. In most cases, admission to an intensive care unit is necessary, and oxygen is required as the patient becomes hypoxic. Broad-spectrum antibiotics are suggested to help combat secondary bacterial infections. Analgesics and antipyretics provide comfort, but fluids should be carefully monitored due to possible capillary leakage [130; 144]. Mechanical ventilation and cardiopulmonary support should be available in the event of a sudden onset of pulmonary failure.

As noted, even with treatment, about 36% of patients have died from the disease [142]. This makes prevention an important factor in decreasing the morbidity and mortality associated with HPS. Educating the public in the proper handling of rodents and their excrement is the primary method of prevention. Avoiding contact with rodents is an obvious rule, but this is not always possible. Using latex or other protective gloves is suggested if contact with a dead rodent or its excrement is necessary. Because aerosolizing of the excretory products is documented to cause the disease, it is advised to "wet down" dead rodents or any areas where rodents have been present before attempting to clean the region. An enclosed area should be left open to air out before entry, if possible [142; 144].

Attempt to rodent-proof the home and outbuildings by sealing off the possible points of entry and removing foodstuffs from kitchen counters and tables, especially at night. Garbage cans and other refuse containers should have tight lids.

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Trapping rodents or using traps and baits to decrease their numbers has been shown to reduce the number of cases in a local area [142; 144]. The virus is inactivated by alcohol and chlorine preparations, which can be used as disinfectants in indoor and outdoor areas. Complete drenching with a 10% bleach solution is recommended [142]. Sunlight can also kill the virus. The use of respirators is only suggested for workers in regions of high rodent population or where the disease is known to be present but is a sensible precaution when working in enclosed areas with limited ventilation [142; 144].

LYMPHOCYTIC CHORIOMENINGITIS (LCM)

Lymphocytic choriomeningitis (LCM) has the house mouse (*Mus musculus* Linnaeus) as its reservoir species. The disease is primarily a mild one, though probably underdiagnosed in individuals with normal immune systems [145]. Transmission is through contaminated food ingestion, aerosols, and bites from infected rodents. The house mouse is a very common rodent throughout the world and is sold in many places as a pet. LCM virus can also be spread by hamsters and guinea pigs if they have contact with infected mice. The CDC has maintained contact with retail stores, and some have stopped selling these rodents during periods of outbreaks [146]. This is not an uncommon disease. The prevalence of LCMV antibodies in urban human populations is 2% to 5%, and its distribution is worldwide.

Clinical Presentation and Diagnosis

Rodents infected with LCM virus show little sign of illness. Serologic testing of the rodents has not been very reliable, and the animals can shed virus for the duration of their lives without appearing to be ill [146]. In humans, LCM is characterized by a flu-like illness lasting only a few days. A few cases will relapse afterward, and these rare cases may develop meningeal inflammation signs, beginning with nuchal rigidity, headache, fever, malaise, and muscular pain. A limited number of cases progress to meningoencephalitis with paralysis and coma. Most will recover, although severe cases may have a protracted recovery time [146; 147]. If a pregnant woman contracts the disease in the first or second trimester, there can be serious consequences for the fetus. Case fatalities are rare, except in immunocompromised patients. LCM can be isolated from the blood of febrile patients or from CSF in patients with meningitis; however, laboratory diagnosis in a patient suspected of having LCM is usually made by CSF PCR or by serologic studies (IgM and IgG antibody titers) on acute and convalescent serum.

Treatment and Prevention

Treatment of LCM is based on symptom management. Prevention of the disease involves care in cleaning and disinfecting cages and regions of wild mouse activity. Pregnant women should avoid handling possibly infected rodents. Wholesale and retail merchants should be aware of outbreaks and keep groups of rodents isolated from each other to prevent cross contamination [146].

BOVINE SPONGIFORM ENCEPHALITIS (BSE)

Bovine spongiform encephalitis (BSE), commonly known as mad cow disease, has received a considerable amount of attention in the medical and lay press since the first reported outbreaks in 1986 [148]. The human disease is called variant Creutzfeldt-Jakob disease (vCJD) and is different from the naturally occurring Creutzfeldt-Jakob disease (CJD) seen mostly in older patients; both are degenerative, progressive, and fatal brain disorders with no known cure [148]. While CJD occurs spontaneously, vCJD has only been seen where there was a connection to ingestion of diseased animal tissue. As of February 2020, there were a total of 231 cases of vCJD reported throughout the world [148]. Most cases were in the United Kingdom (178) and France (28); however, cases have been reported by many countries, including Spain (5), the United States (4), Ireland (4), the Netherlands (3), Italy (3), Portugal (2), Canada (2), Japan (1), Saudi Arabia (1), and Taiwan (1) [148]. Several cases of the disease being diagnosed in the United States and other countries (excluding France) occurred in individuals who had contracted the disease in the United Kingdom [148]. There have been three possible bloodborne transmissions of vCJD through a transfusion, but there has never been a documented case of human-to-human transmission [148].

In 1986, BSE was first identified in cattle in England, and in 1989, it was officially listed as a zoonosis. By 1996, the disease seemed to jump the species barrier to humans, presenting as a new variant of CJD [148; 149]. This new strain was linked to BSE, possibly through eating meat from BSE-infected cattle. BSE and vCJD are together called transmissible spongiform encephalopathies (TSEs) because they reduce the brain to the same spongy appearance, with gaps appearing within the tissue. TSEs present in sheep as scrapie, in cows as BSE, and in humans as vCJD.

By the end of 2004, millions of cattle throughout the world, but predominately in the United Kingdom, had been slaughtered as part of a plan to control the disease [149; 150]. Some researchers believe the disease has peaked already (during 2006–2008), while others point to the disease's long incubation period and suggest that thousands may be affected in the future. The number of new cases does appear to be decreasing annually [151].

Understanding the history of BSE and vCJD makes this complex zoonosis much easier to put into perspective. While sheep, cows, and humans were part of the outbreak in the 1990s and 2000s, heightened awareness as a result of this outbreak led to the knowledge that deer, elk, mink, and cats have related diseases as well [152]. Other species can be experimentally infected, but they do not appear to propagate the illness [152].

Part of the difficulty in making the connection between the species during the initial investigative stages was the lack of identification of a causative agent. Depending on the source, the agents are either prions, virions, or not named

at all and merely referred to as TSEs. Most authorities now use the term prions, an acronym for proteinaceous infectious particles. Closely related to viruses, but not a virus, they have no DNA or RNA. Prions make their way into the brain and incorporate themselves into brain cells as proteinase-resistant fibrils. In cows, only the brain has measurable amounts of these fibrils. In sheep, the fibrils can be isolated from a number of different locations, including placental tissue.

In the final stage of the disease, brain tissue becomes sponge-like and the cows become "mad" or "maniacal" before dying. In sheep, advanced disease makes the animals scratch and bite at themselves until they scrape off their coats and excoriate their skin. The brain lesions found in scrapie are identical to that in BSE [152].

The initial recorded BSE outbreak in the 1980s coincided with changes in rendering sheep and an increase in the sheep population in the United Kingdom. The outbreak began after the winters of 1981 and 1982, when cattle were fed with meat and bone meal products contaminated by rendered brain parts from sheep infected with scrapie [152]. A ban on using ruminant rendered products in animal feeds was enacted in 1988 in the United Kingdom and was followed by most developed countries. The initial 1997 feed bans in the United States and Canada have since been replaced with enhanced feed bans in 2009 and 2007, respectively, to eliminate high-risk animal byproducts from all animal feeds, pet foods, and fertilizers, rather than from cattle feed alone [148]. These enhanced bans were implemented to mitigate the recognized limitations of the original bans [148].

The slaughter of possibly infected animals became mandated following the first death attributed to vCJD. It was determined that because of the possibility that the disease could be transmitted to humans in the same way as to animals, ruminant byproducts that might include the brain should be banned to prevent the possibility of transmission. A large number of products in the United Kingdom used ruminant byproducts, leading to public panic. Articles such as lipstick, which might have used rendered material, became objects of concern. This may have been warranted, but the slow release of information contributed to the public uneasiness. It was not until November 1998 that the European ban was lifted on beef from the United Kingdom. In cows, only brain tissue appears capable of transmitting disease [149; 153].

No direct transmission has been documented between cows; however, vertical (placental) transmission has been reported [154]. Sheep pass the disease vertically, and it has been theorized that transmission through ingestion of placental tissue from infected animals that give birth in the field is possible.

Kuru, another human disease characterized by a spongy appearance and gaps in the brain, is also contracted through ingestion of animal products infected with TSEs. The brain lesions in vCJD and kuru are identical to those seen in sheep with scrapie. As in vCJD, kuru causes the death of brain cells, with such symptoms as unsteadiness, insomnia, memory loss, and dementia. The Fore people of Papua New Guinea practiced ritualistic consumption of the brains of their deceased relatives as a sign of respect, thus propagating the disease [153]. Variant CJD is not transmitted like kuru. Proof that it is transmitted through ingestion of infected brains is quite difficult due to the long and somewhat unknown length of time from infection to first signs of disease. Injecting neuronal tissue from cows infected with BSE into mice will induce disease, as will brain tissue from infected sheep injected into monkeys. However, it is not possible to draw conclusions about human transmission from this research [155].

In 2007, a new neurologic disorder originating in pigs was reported in a group of slaughterhouse workers processing severed heads [156]. This new condition, referred to as progressive inflammatory neuropathy or immune polyradiculoneuropathy, is believed to be caused by inhalation of brain tissue that is aerosolized by the use of compressed air guns to harvest the organ. The condition is characterized by an enlarged spinal root, pain, weakness, fatigue, and numbness or tingling in the extremities [156; 157]. The condition is not believed to be infectious or foodborne, although investigations are ongoing. At this time, it is not believed to be directly related to spongiform encephalitis.

Clinical Presentation and Diagnosis

It is difficult to document the disease agent when it is non-antigenic, as the body does not mount any immune response, making tests such as standard antibody titers useless. Diagnosis of vCJD therefore tends to be based on signs and symptoms with confirmation by examining brain tissue.

This makes the differentiation of vCJD from other progressive, neurodegenerative processes difficult, especially in older patients. The diagnosis is also hampered by the very long incubation period of vCJD, which can be many years between contact with the organism and the development of symptoms [158]. Usual symptoms can include progressive dementia, myoclonus, visual changes, cerebellar dysfunction, pyramidal or extrapyramidal signs, and akinetic mutism. Pain is experienced by about one-half of the patients [159].

When the more common causes are eliminated and a spongiform encephalopathy is suspected, there are several ways to distinguish between "classic" CJD and vCJD. The most obvious is age; classic CJD causes death at a mean age of 68 years following a rapid course with a duration of illness of only four to five months [148]. Variant CJD is a disease of young people, with death at a mean age of 28 years following a more prolonged course, usually over a year. Classic CJD presents with early neurologic signs and dementia, but patients with vCJD often have early behavioral or psychiatric symptoms and painful dysesthesias, with delayed neurologic findings [158].

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MRI has been used successfully to diagnose vCJD. An unusual appearance of the thalamus or a specific increase in intensity in the posterior portion of the thalamus, the pulvinar region, has been found in neurologically confirmed cases of vCJD [158]. This finding, called "the pulvinar sign" has not been observed in classic CJD [159].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Radiology notes diffusion-weighted imaging can help identify and characterize Creutzfeldt-Jakob disease.

(https://acsearch.acr.org/docs/69477/ Narrative. Last accessed April 17, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

As noted, the firm diagnosis of vCJD is made with either a brain biopsy during life or examining pathology material at autopsy; however, Western blot analysis of lymph node specimens has shown the presence of prion material in patients with the disease. Florid plaques have been described in brain sections of patients with vCJD but not in those with classic CJD. The vacuolation (spongiform change) has been seen in many portions of examined brains, with most disease found in the occipital cortex and cerebellum [149; 160].

Prevention and Treatment

There is no treatment for this disease in any species mentioned. This makes prevention and radical public health measures essential to control BSE, vCJD, and scrapie. All are reportable diseases. Compulsory slaughter has been practiced to eradicate herds with BSE-positive cattle; this was obviously done at huge costs to the public, farmer, and government. The United States has a scrapie eradication program to eliminate scrapie from the sheep herds in the country. The United States and other countries have barred blood donations from people who have lived in the United Kingdom or continental Europe for a cumulative three months or more between the years 1980 to 1996 as a precautionary measure against the spread of vCJD [246].

The best way to protect ourselves and educate patients is to have the correct information and to practice safe consumption. Due to the nature of the prion proteinase resistance and probably its small size, the agent is not destroyed with ultraviolet light, freezing or thawing, boiling for 30 minutes, or formaldehyde. In other words, there is no way to safely cook the agent out of a brain or render a tissue absolutely free of the agent. In 2006, the European Union ban on British beef was lifted due to enhanced BSE testing and control measures (e.g., the banning of feeding cow proteins, including brains, to other cows) [160]. Travelers to the United Kingdom, Ireland, or certain other European countries (France, Greece, and Poland) should be advised that if they are concerned about contracting vCJD, avoiding beef products altogether is the only certain option, but that eating whole muscle meat, rather than ground meat or foods made with brains, carries an "exceedingly low risk" of infection [160; 247]. Aside from the European countries listed above, the risk posed by BSE in other European countries is similar to that from U.S. beef. The risk status of Canadian beef is an estimated 18 to 48 times higher than that of U.S. beef and is considered to have similar risk as United Kingdom beef. Cow milk and milk products from all countries are believed to be safe [160].

Because there is no cure or vaccine for the TSEs, treatment is generally confined to supportive measures and symptomatic therapies. It has been suggested that phenothiazines may inhibit prion production, but this has not been confirmed in a series of studies [161]. Anticonvulsants are used to manage seizures and violent outbursts [158]. Experimental therapies include the antimalarial quinacrine and the antipsychotic chlorpromazine to prevent abnormal prion protein conversion. One patient has been treated with pentosan polysulphate and had no evidence of disease progression for 23 months [158]. The agent inhibits prion protein production, replication, and cell toxicity associated with vCJD. Unfortunately, the treatment must be initiated soon after infection to prevent disease onset, which, outside of experiments, is likely impractical.

PROTOZOAL ZOONOTIC DISEASES

The common zoonotic diseases caused by protozoa include toxoplasmosis, giardiasis, babesiosis, cryptosporidiosis, malaria and balantidiasis. Toxoplasmosis and giardiasis are seen fairly often in North America.

TOXOPLASMOSIS

The agent of toxoplasmosis is *Toxoplasma gondii* (phylum Apicomplexa). *T. gondii* is one of the most widely disseminated parasites known in the world [167]. It has a two-host lifecycle, present in both predator and prey. The intermediate hosts are humans, swine, goats, sheep, dogs, rodents, cattle, and cats. Cats are the definitive host but can be intermediate hosts as well. All members of the cat family can carry the organism, but domestic cats are clearly the source of zoonosis in most people, resulting from fecal-oral transmission [15; 167; 168]. Studies of cat populations show 16% to 80% of cats in the United States have been infected; the estimated worldwide prevalence in domestic cats is 30% to 40% [169].

Cats become infected with toxoplasmosis when they ingest tissue infected with the bradyzoite phase of *T. gondii*, which is encysted in the muscle tissue of their prey. When shedding oocysts, a cat can excrete up to 20 million organisms per day. The cyst opens in the gastrointestinal tract, and the bradyzoites are released to enter the enteroepithelial cells in

the cat's small intestine. They then shed eggs (oocysts) sporadically into the feces for 7 to 21 days after ingestion [167]. Antibody titers in the cat will not start to rise until after the first round of shedding has stopped. Immunity will last in the cat unless major re-exposure occurs or if high-dose steroid therapy is initiated. Some authorities believe that direct transmission from cats to humans is uncommon and that the organisms are more likely transmitted from contaminated soils or undercooked foods [170]. Kittens, rather than adult cats, have been identified as a cause of direct transmission to humans [167]. It has been reported that 8% of beef, 20% of pork, and 20% of lamb is infected with toxoplasma [170]. In the United States, an estimated 11% of the population 6 years of age and older has been infected with toxoplasma and are chronic, asymptomatic carriers of the parasite; some places in the world have shown infection rates as high as 95% [167].

When an intermediate host becomes infected or consumes meat with encysted toxoplasma, the bradyzoites enter the enteroepithelial cells of the host but do not remain there, as in the definitive host. In the intermediate host, they penetrate the lymphatics of the gastrointestinal tract and from there disseminate throughout other tissues, including the placenta and fetal tissue. Congenital toxoplasmosis is seen in children of mothers who may not realize that they are carrying the organism. In general, the infection must occur during the pregnancy for the disease to be transmitted to the fetus [167; 170; 171].

Immunocompromised individuals, especially acquired immunodeficiency syndrome (AIDS) patients, can suffer severe complications and should be advised to consult their healthcare providers to determine whether they have been infected with toxoplasma [167; 169; 170]. It is important to note that immunocompromised individuals have the same rate of infection regardless of whether they are cat owners or not [170]. Contaminated meat or contact with soil contaminated with cat feces is a more common transmission method than poor handling of a litter box. Nevertheless, the CDC advises pregnant women to avoid changing cat litter [167].

Clinical Presentation and Diagnosis

The clinical manifestations of infection in humans are similar to the flu or mononucleosis. As noted, the concern is greatest for pregnant women and HIV-positive individuals. In the first trimester of pregnancy, spontaneous abortions, retinochoroiditis, hydrocephalus, microencephaly, and psychomotor retardation of the fetus are the most common sequelae to exposure [167; 171]. In an immunocompromised host, toxoplasmosis can be life-threatening. These individuals are more prone to a disseminating version that can lead to hemorrhagic lesions in the brain. Myocarditis, hepatitis, meningoencephalitis, chorioretinitis, and internal organ involvement have also been reported [171].

Diagnosis of toxoplasmosis is usually made with serologic testing. Indirect IFAs of IgG and IgM are positive within a few days after infection [167]. Imaging studies and PCR analysis of CSF are useful in immunocompromised patients with signs of encephalitis or focal mass lesions within the brain. In such patients, a brain biopsy may be considered for definitive diagnosis and to exclude other diagnostic possibilities (e.g., brain abscess, lymphoma, metastatic carcinoma). In many cases, the history of the consumption of undercooked or raw meat aids in making the diagnosis [170].

Treatment and Prevention

Treatment is rarely necessary in people with normal immune systems as most recover without treatment. Suspected cases in persons who are ill may be treated with the combination of pyrimethamine and sulfadiazine, plus folinic acid (leucovorin) for a period of three to four weeks. Clindamycin may be substituted for sulfadiazine in patients sensitive to sulfa drugs [167]. For encephalitis, the treatment is continued for four to six weeks. Patients with HIV/AIDS who are toxoplasma-seropositive and who have CD4 counts <100 cells/mcL should receive prophylaxis against toxoplasmosis. This can be accomplished with trimethoprim/sulfamethoxazole (TMP-SMX) double-strength daily dose or alternately, TMP-SMX double-strength three times weekly [172]. The recommended therapy for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin [173].

It is very important to educate immunocompromised individuals and pregnant women in prevention techniques. All meat should be thoroughly cooked. Not coming in contact with cat feces or contaminated soil is very important, as is handwashing after gardening or yard work. If there is a sandbox in the backyard, it should be covered. If possible, limit a household cat's ability to consume rodents, which would best be accomplished by keeping the cat indoors, and only feed commercial pet food [167]. Oocysts hatch about 24 hours after being shed in the feces and are not infective before hatching. If the litter box is changed daily, exposure risk will be reduced. Encourage others in the household to participate in the cat's care, and ask them to change the litter box to protect the family members who are at risk. If the at-risk person must change the box, gloves, dust mask (to prevent swallowing or inhaling oocysts), and diligent emptying of the box daily are recommended. If you are working with a woman in early prenatal screening who owns a cat or who comes in contact with them, recommend having a titer if exposure must be documented and explain the importance of handwashing after handling cats or raw meat. Because of the potential seriousness of this zoonosis for certain populations, research is being conducted on a vaccine. At this time, there is no approved vaccine available [167].

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EVIDENCE-BASED PRACTICE RECOMMENDATION

In order to prevent *Toxoplasma gondii* infection, the American Academy of Pediatrics recommends that pregnant women avoid contact with material/soil potentially contaminated with cat feces, especially handling of cat litters or gardening.

(https://pediatrics.aappublications.org/content/pediatrics/early/2017/01/26/peds.2016-3860.full.pdf. Last accessed April 17, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

GIARDIASIS

Giardiasis is one of the most common diarrheal diseases in the world, and nearly 33% of people in developing countries have had giardiasis [174]. The causative organism, *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*), is found in food, soil, water, and surfaces that have been contaminated with feces. It is now the most commonly identified parasite in the United States [174]. The symptoms of giardiasis usually appear about a week or two after the *Giardia* cysts are ingested. Very few organisms are required for infection, with only about 10 cysts causing an infection rate of 100% [174].

The cysts produce trophozoites, which colonize the upper portion of the small bowel. They generally cause a significant non-bloody diarrhea in the human or animal victim, which can then be transmitted by the fecal-oral route. Contaminated water is the most common source of infection, but venereal transmission has also been reported [174].

Morbidity is moderate and primarily involves gastrointestinal symptoms. Mortality from giardiasis is unlikely, unless associated with extreme dehydration [15; 175].

Clinical Presentation and Diagnosis

The majority of patients present with an insidious onset of diarrhea. This usually consists of frequent loose stools that do not contain blood or mucus. Watery diarrhea and malodorous soft or greasy stools can be interspersed with episodes of constipation. The gastrointestinal symptoms are often exacerbated by eating and may be associated with mid abdominal pain and cramping. Nausea, gastroesophageal reflux, malaise, fatigue, lactose intolerance, and weight loss are common. Adult patients with long-term disease may develop malabsorption syndrome, while children can demonstrate the findings of failure to thrive [174; 176].

Physical examination is usually normal, with the exception of possible abdominal tenderness upon palpation. In extreme cases, there may be dehydration and wasting. Laboratory studies should include stool examination with at least three samples taken at two-day intervals [174; 177]. Because antibiotics, laxatives, or barium may mask the presence of the organism in the stool, the samples may need to be obtained after a 5- to 10-day hiatus. There are ELISA and IFA tests available for stool samples that have excellent sensitivity and specificity [177]. Cultures are useful primarily to detect other causes of diarrhea, because *Giardia* is not easily grown from stool samples. The most useful serum study is IgM analysis, but only for the determination of acute versus chronic infections [177]. Endoscopy, with duodenal aspiration or biopsy, may also be used to obtain a diagnosis.

Treatment and Prevention

For many years, the first-line treatment in the United States has been metronidazole [178; 179]. The usual adult dose is 500 mg orally twice daily for five to seven days [46]. Tinidazole is a newer drug, approved in the United States, that can be administered in a single oral dose of 2 grams, taken with food. For children older than 3 years of age, the recommended dose is 50 mg/kg [46]. For women in the first trimester of pregnancy, for whom metronidazole and tinidazole are contraindicated, paromomycin 25–35 mg/kg/day in three divided doses should be used for 5 to 10 days [46]. Quinacrine is commonly used outside of the United States. Other antibiotics and antiparasitic agents, such as nitazoxanide, have also been used to effectively treat the disease [46; 174]. Some authorities feel that asymptomatic cases of diagnosed giardiasis infection, especially in children, should be left untreated. However, if untreated, an individual can shed the organisms for weeks to months. In rare cases, hospitalization is required for fluid and nutritional replacement, but most cases will resolve with minimal treatment.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The World Gastroenterology Organisation asserts that nitazoxanide is an effective antiprotozoal in the treatment of diarrhea caused by *Giardia intestinalis*.

(https://www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english. Last accessed April 17, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

Prevention includes the avoidance of potentially contaminated water and foodstuffs. Drinking water from a stream, shallow well, or other unfiltered source can lead to ingestion of the cysts. The cysts can live for extended periods of time in an outdoor environment. However, they are inactivated by chlorine and can be eliminated from a water source by filters of less than 1 micron (e.g., National Safety Foundation [NSF] Standard 53 or NSF Standard 58 for cyst and oocyst reduction) [174].

Giardiasis cannot be transmitted by blood products, but any possible fecal contact can be a source of infection, which includes accidentally swallowing water in a recreational pool or pond. Peeling or washing fruits and vegetables in clean water is also recommended [15; 174]. When traveling to countries with an unsafe water supply, only drink water that has been boiled for more than one minute or bottled water labeled as reverse osmosis treated, distilled, filtered through an absolute 1 micron or smaller filter, or "1 micron absolute" [174; 180]. Additionally, ice should not be used [174].

MALARIA

Malaria is a mosquito-borne parasite most common in sub-Saharan Africa. However, the disease is also apparent in Southeast Asia, the Middle East, Latin America, and areas of Europe [181]. It is mainly found in tropical and subtropical areas that allow for the growth and survival of the *Anopheles* mosquito and the malarial parasites. Because temperatures colder than 68 degrees F will halt the parasites' life cycles, transmission is seasonal in some areas [181]. In equatorial countries, malaria transmission is continual and more intense; these are considered malaria-endemic or malaria-stable countries [182].

Approximately 50% of the world's population is at risk for malaria and each year about 212 million people contract and become ill due to the disease [181; 182]. In 2018, an estimated 405,000 people died of malaria-related illness, most of them young children in sub-Saharan Africa [182]. Although malaria has been considered eradicated in the United States since the 1950s, about 1,500 to 2,000 cases of the disease are diagnosed and treated each year [184]. The CDC has also reported a total of 63 local outbreaks in the United States since 1953, all of which originated from a person who contracted the disease in a malaria-endemic country. Because the vector for malaria transmission (*Anopheles* mosquito) is present in the United States, there is a risk that the disease will be reintroduced.

The four protozoan species known to cause malaria in humans, *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, are transmitted from person to person via infected mosquitoes. The most common are the *P. falciparum* and *P. vivax* species; *P. falciparum* also results in the most significant morbidity and mortality [181]. Although, as noted, the female *Anopheles* mosquito is the natural vector for malaria, in rare cases, direct transmission from mother to child, blood transfusion, organ transplant, or shared needles has been documented. Between 1963 and 2015, there were 97 reported cases of transfusion-transmitted malaria in the United States [184]. In areas of high transmission, it is children who are at risk of severe malaria and death, whereas in areas of low or unstable transmission, all age groups are at risk [185]. Pregnant women also have higher susceptibility to *P. falciparum* malaria, which increases infant mortality [184].

Clinical Presentation and Diagnosis

Prompt and accurate diagnosis of malaria is a cornerstone of the treatment process. Identification not only of the presence of the disease but also of the causative agent is necessary in order to implement appropriate and effective treatment. This can be difficult, as the initial signs and symptoms of malaria are nonspecific and may be confused for other systemic viral infections. After infection, there is typically a 7- to 30-day incubation period, or longer if antiviral medications have been taken prophylactically. The classically described malaria attack (cold, hot, and sweating stages) is rarely observed [186]. More often, the first symptoms are a combination of headache, weakness, fatigue, abdominal discomfort, and/or muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting, and/or worsening malaise [185; 186]. Possible signs include elevated temperature, enlarged spleen, and perspiration. If the disease is limited to this stage, it is considered uncomplicated, and treatment is often successful. Relapse of malaria can occur after two to four symptom-free years in persons infected with *P. vivax* and *P. ovale* species [184].

If the disease is caused by the *P. falciparum* species, it can progress to severe malaria. Severe malaria is complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Advanced severe malaria can result in [186]:

- Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
- Severe anemia
- Hemoglobinuria
- Pulmonary edema or acute respiratory distress syndrome, which may occur even after the parasite counts have decreased in response to treatment
- Abnormalities in blood coagulation and thrombocytopenia
- Cardiovascular collapse and shock

Other conditions that should raise concern in malarial patients are acute kidney failure, hyperparasitemia, metabolic acidosis, and hypoglycemia [186]. In patients for whom the malaria infection reaches the severe stage, the mortality rate is 15% to 20% [185].

In addition to the clinical diagnosis, there are three main tests used in the parasitologic confirmation of the diagnosis of malaria: light microscopy, rapid diagnostic tests, and PCR. Light microscopy remains the standard test for detection of malarial parasites [113]. The test is conducted by staining a blood smear, usually with the Giemsa stain, and examining the specimen by microscope. There are also several rapid tests available that utilize antigen detection. These tests provide results quickly (within 2 to 15 minutes), but their use is restricted by limited accuracy and higher costs [113]. When they are used, it is usually as an adjunct to microscopy or as

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TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA			
***Plasmodium* species**	**Drug**	**Dosing**	**Comments**
P. falciparum or "species not identified" in areas **without** chloroquine-resistant strains	Chloroquine	Initial oral dose: 600 mg base (1,000 mg salt), followed with 300 mg base (500 mg salt) at 6, 24, and 48 hours Maximum dose: 1,500 mg base (2,500 mg salt)	Use adult dosing in pregnancy. Adjust pediatric dosing by patient weight; do not exceed recommended adult dosing. Consider atovaquone-proguanil (preferred) or mefloquine if quinine is unavailable. Quinine and atovaquone-proguanil are recommended for use in children 8 years of age and younger.
	Hydroxychloroquine (2nd-line alternative)	Initial oral dose: 620 mg base (800 mg salt), given immediately, followed with 310 mg base (400 mg salt) at 6, 24, and 48 hours Maximum dose: 1,550 mg base (2,000 mg salt)	
P. falciparum or "species not identified" in areas **with** chloroquine-resistant strains	Atovaquone/ proguanil	1 g/400 mg as a single dose, once daily for three days	These are fixed dose combination medicines that may be used for nonpregnant adult and pediatric patients. Both have been found to be very effective.
	Artemether/ lumefantrine	Patients 25 to <35 kg: Three tablets at hour 0 and hour 8 on the first day, then three tablets twice daily on days 2 and 3 Patients >35 kg: Four tablets at hour 0 and hour 8 on the first day, then four tablets twice daily on days 2 and 3	
	Quinine sulfate plus doxycycline, tetracycline, or clindamycin	648 mg every eight hours for three to seven days	Quinine sulfate plus either doxycycline or tetracycline generally preferred. Treatment duration depends on area of acquisition. Quinine sulfate/ clindamycin is recommended during pregnancy. Quinine dosing duration depends on area of acquisition; clindamycin dosing should continue for 7 days regardless of area of acquisition.
	Mefloquine	5 tablets (1,250 mg) as a single dose daily	Associated with severe neuropsychiatric reactions; recommended only when other options cannot be used. If clinical improvement is not seen within 48 to 72 hours, an alternative therapy should be used for retreatment.
P. malariae	Chloroquine	Same as for *P. falciparum*	There is little evidence of chloroquine resistance in *P. malariae*. May be used during pregnancy.
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	

Table 6 continues on the next page.

TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA *(Continued)*			
***Plasmodium* species**	**Drug**	**Dosing**	**Comments**
P. vivax acquired in all areas except Papua New Guinea or Indonesia	Chloroquine	Same as for *P. falciparum*	If patient is nonresponsive, change treatment to one of the three options listed for treatment of *P. vivax* malaria acquired in Papua New Guinea and notify state health department and CDC.
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	
P. vivax acquired in Papua New Guinea or Indonesia	Quinine sulfate plus doxycycline or tetracycline	648 mg every eight hours for three to seven days	High possibility of chloroquine-resistant strains. Options are equally recommended. During pregnancy, treat with quinine for seven days, regardless of area of acquisition. Risk/benefit of adding doxycycline or tetracycline (pregnancy category D) to quinine should be carefully evaluated. Risk/benefit of using atovaquone-proguanil or mefloquine (both pregnancy category C) should be carefully evaluated.
	Atovaquone/ proguanil	1 g/400 mg as a single dose, once daily for three consecutive days	
	Mefloquine	5 tablets (1,250 mg) as a single dose daily	
P. ovale	Chloroquine	Same as for *P. falciparum*	May be used during pregnancy
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	
P. knowlesi	Atovaquone/ proguanil	250 mg/100 mg, four times per day for three days	There is little evidence comparing various medications for the treatment of this relatively new strain.
Source: [46; 189; 190]			*Table 6*

the main test if microscopic analysis is not available, particularly because early treatment is so vital for positive clinical outcomes. The limitations of the rapid tests have shifted attention to PCR-based molecular diagnosis. Although the PCR tests available for malaria are more accurate than either the microscopy or antigen detection systems, the prohibitive costs and need for specialized equipment have made this option less useful [113; 187]. IFA and ELISA tests are available to test for past exposure to the disease [113].

Treatment and Prevention

Treatment for uncomplicated malaria varies based on the region in which the disease was acquired and the infective species (***Table 6*** and ***Table 7***). Some areas have been particularly identified as sensitive to chloroquine, the traditional drug of choice for malaria. Because resistance to chloroquine has increased significantly, it is now generally used only for malaria known to originate from Central America (west of the Panama Canal), Haiti, the Dominican Republic, and most of the Middle East [188]. In all other areas, the organisms are considered to be resistant to the drug, and other agents are used. It is also recommended that, when possible, in vivo assessment of therapeutic efficacy, in vitro studies of parasite susceptibility to drugs in culture, or molecular genotyping be used to establish sensitivity of the parasite to the drug regimen [185].

CDC clinicians are on call at the Malaria Hotline 24 hours per day, seven days per week, to provide advice to healthcare providers on the diagnosis and treatment of malaria. They may reached during business hours 9 a.m. to 5 p.m. Monday through Friday) at (770) 488-7788 or (885) 856-4713. During off hours, weekends, and federal holidays, call (770) 488-7100 and ask to have the malaria clinician on call paged.

Individuals that are known to be traveling to malaria-endemic areas, and areas of resistance in particular, should be counseled regarding antimosquito measures and malarial symptoms prior to departure [191]. Chemoprophylaxis with the most appropriate antimalarial agents should be provided.

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TREATMENT RECOMMENDATIONS FOR SEVERE MALARIA[a]		
Drug	**Dosing**	**Comments**
Quinidine gluconate	IV loading dose: 6.25 mg base/kg (10 mg salt/kg) over one to two hours. Follow with continuous IV infusion 0.0125 mg base/kg/min (0.02 mg salt/kg/min). Alternative regimen: IV loading dose: 15 mg base/kg (24 mg salt/kg) over four hours. Eight hours after loading dose, follow with 7.5 mg base/kg (12 mg/kg salt) over four hours, every eight hours.	At least 24 hours of infusion are recommended. When parasite density is <1% and patient is able to take oral medication, complete treatment course with oral quinine per recommendations for uncomplicated malaria. Reduce maintenance dose by one-third to one-half on the third treatment day in patients with no clinical improvement or in patients with renal failure that persists.
Doxycycline	IV: 100 mg every 12 hours Oral: 100 mg every 12 hours for seven days	
Tetracycline	Oral: 250 mg every six hours for seven days	
Clindamycin	IV: 5 mg base/kg IV every eight hours Oral: 20 mg base/kg/day divided three times/day for seven days	
[a] The regimen for the treatment of severe malaria in the United States consists of quinidine plus either doxycycline, tetracycline, or clindamycin.		
Source: [189]		*Table 7*

BACTERIAL ZOONOTIC DISEASES

Animal products often contain several types of bacteria. The bacteria may be the animal's own flora that contaminates the meat in the process of being slaughtered and prepared for market. Bacterial contamination can also occur from an environmental source during poor handling, either before or after purchase for consumption. Only if the bacterial pathogen originated from the animal is it truly zoonotic. Factory workers who accidentally contaminate a product with a disease they are carrying, as has happened with *E. coli*, can create a public health problem. Because it does not originate from an animal, it is not considered a zoonotic infection in the true sense of the definition. In this section, anthrax, cholera, botulism, the diseases caused by *Salmonella* spp., and brucellosis will be discussed.

ANTHRAX

Anthrax can be transmitted by ingestion of meat from an infected animal, usually a ruminant. The agent of disease is *Bacillus anthracis*. Three forms of anthrax occur in humans, with manifestations depending upon how the organism is contacted; they are cutaneous, gastrointestinal, and inhalation anthrax. The diseases are distinct; however, infection with one form presents a risk for developing the others.

Most cases of anthrax are cutaneous in humans. The pulmonary and gastrointestinal forms are less common. If untreated, the pulmonary (inhalation) form has an 86% to 89% case fatality rate, intestinal 25% to 60%, and the cutaneous form 20% [192].

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2,000 human cases reported annually [193]. The disease typically follows exposure to animals that are infected with anthrax. Cutaneous infections occur when the bacterium or spores enter a cut or abrasion on the skin, such as when handling contaminated wool, hides, or leather.

Gastrointestinal anthrax is not commonly seen; however, outbreaks have occurred in Africa and Asia [193]. GI anthrax follows the ingestion of insufficiently cooked contaminated meat.

Inhalation anthrax is the most lethal form of the disease, but it occurs less frequently as a naturally occurring disease than either the cutaneous or gastrointestinal forms. However, the dissemination of spores could cause widespread disease, and therefore, this is the most likely form of anthrax to be used as a biologic weapon. Prior to the bioterror-related cases in 2001, inhalation anthrax had not been reported in the United States since 1976 [192; 193]. This makes even a single case a cause for alarm today.

The natural incidence of anthrax is rare in the United States, but infection is an occupational hazard among veterinarians, farmers, and individuals who handle animal wool, hair, hides, or bone meal products. It is endemic in Africa and Asia, despite vaccination programs, and is not uncommon in the Middle East, the Indian subcontinent, and Latin America [194]. Most cases are seen after heavy rains, which release the spores and bring them to the surface. Drought also can trigger anthrax spore germination, while flies and vultures spread the spores [194]. The spores produced by the bacteria are extremely resistant in the environment; they have been

documented to survive 22 years in a dry culture [193]. They tolerate freezing and will not be killed by most disinfectants at regular strength concentrations. Methods for sterilizing or inactivating spores on contaminated materials include steam sterilization or ethylene oxide gas sterilization, boiling or using dry heat, or treating with formaldehyde, glutaraldehyde, or hypochlorite for specified periods of time and exposure concentrations; air drying does not destroy the spores [192]. Inhalation of spores is the most common way for the pulmonary form of the disease to be transmitted. When contaminated meat is cut, the spores can be released into the immediate area of the source. This could be in the field or in the kitchen of those who raise their own meat or consume wild ruminant meat, such as deer or elk. Anthrax is a mandatory reportable disease whenever a case is identified in an animal or human.

Clinical Presentation and Diagnosis

Cutaneous anthrax skin infection begins as a raised pruritic lesion or papule that resembles an insect bite. Within one to two days, the lesion develops into a fluid-filled vesicle, which ruptures to form a painless ulcer 1–3 cm in diameter with a necrotic area in the center. Pronounced edema is often associated with the lesions because of the release of an edema-producing toxin by the bacteria. The lymph nodes in the area may become involved and enlarged.

The incubation period in humans is usually 1 to 10 days but can be prolonged to almost two weeks [193; 195]. To describe the lesion in more detail, picture a painless macular eruption that appears within two to five days, most commonly on an exposed portion of the body. The lesion progresses from a red macule to a pruritic papule, then to a single or ring of vesicles. This is followed by a depressed ulcer and finally a black necrotic eschar that falls off within 7 to 10 days. There is edema associated with the eschar but usually no permanent scarring of the affected area. The symptoms of purely cutaneous anthrax infection can include fever, headache, regional lymph node involvement, and myalgia. The cutaneous form of anthrax may progress to systemic disease, with a fatality rate of up to 20% if untreated [196].

Gastrointestinal anthrax is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea [192; 193].

The first sign of inhalation anthrax is the acute onset of a flu-like illness. If inhalation anthrax progresses to the pneumonic form, the initial symptoms are often followed by a short period of improvement. Next, there is an abrupt development of severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Shock and death usually occur within 24 to 36 hours after the onset of respiratory distress [195]. In the later stages, mortality approaches 100% despite aggressive treatment. Physical findings can be nonspecific. The chest x-ray is usually disease-specific, revealing a widened mediastinum with pleural effusions, but typically without infiltrates [192]. Thoracic trauma can have similar signs, but often with infiltrates. A hemorrhagic mediastinitis often develops.

Laboratory tests of blood products are usually normal if the disease is not disseminated. The *B. anthracis* organism can be obtained for culture or gram stain; however, analysis beyond simple cultures should only be performed in a specialized laboratory environment [196]. On gram stain, the organism can be recognized as a large, rod-shaped, gram-positive, spore-forming bacillus [194]. More positive identification requires lysis by gamma phage and dFA, or most positively by immunohistochemical staining. There is an ELISA test available, but generally only at reference laboratories. A negative culture does not rule out cutaneous anthrax, especially if obtained after antibiotics are started [194].

Treatment and Prevention

Most *B. anthracis* strains are sensitive to a broad range of antibiotics. Either ciprofloxacin or doxycycline is usually recommended for the treatment of anthrax. In the past, penicillin was a first-line treatment, but due to concerns regarding resistance, it is no longer recommended by the CDC or the U.S. military. To be truly effective, antibiotic treatment should be initiated as early as possible. If left untreated, the disease is highly fatal. Immediate prophylaxis with ciprofloxacin 500 mg or doxycycline 100 mg orally twice daily is commonly recommended for cutaneous anthrax [197; 198]. Treatment should continue for 60 days or longer; if the source in known to be from livestock or its products, a 7- to 10-day course is sufficient. If an individual has not been previously vaccinated, a three-dose series of vaccine should also be given subcutaneously at diagnosis and two and four weeks later [192; 198]. For inhalation anthrax treatment in adults, intravenous medications are suggested as the initial treatment and should be combined with one or two other effective agents [196; 198].

In some cases, other antibiotics may be considered, such as the other fluoroquinolones, including levofloxacin, clindamycin, and moxifloxacin; however, use of clindamycin and moxifloxacin are not currently approved for this use by the FDA [197]. Rifampin and linezolid have been suggested as an adjunct treatment, and high-dose penicillins (e.g., amoxicillin, penicillin VK) may be tried if no other antibacterials are available and the strain is susceptible. In general, the cephalosporins are not useful in treating anthrax because the organism produces an enzyme that neutralizes them [197]. Supportive therapy for shock, fluid volume deficit, and adequacy of the airway may be needed.

In 2013, a new antibiotic with significant activity against *B. anthracis*, anthracimycin, was discovered [199]. Although it is not yet FDA-approved, it may have a place in the treatment of anthrax in the future.

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Human-derived anthrax immune globulin (AIG) was used to successfully treat a naturally occurring inhalation anthrax case in Pennsylvania in 2006 [233]. In 2015, the FDA approved AIG for the treatment of inhalation anthrax [234]. Immune globulin administration may be considered in combination with appropriate antibiotics when multiple organ systems are involved or following lack of response to standard therapy.

Vaccination for anthrax can prevent the disease if given prior to contact with the bacillus. However, it can also be used postexposure to help minimize the patient's reaction to the organism. Anthrax Vaccine Adsorbed (AVA) is the only licensed human anthrax vaccine in the United States [192]. The vaccination schedule consists of three injections of 0.5 mL of the vaccine administered subcutaneously in the deltoid region. After the first injection, the follow-up doses are given two and four weeks later. The vaccine is approved only for healthy, nonpregnant adults. There is an adverse reaction incidence of approximately 6% for local inflammation and 2% to 3% for systemic symptoms [46].

There is no data to suggest patient-to-patient transmission of anthrax; therefore, only standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax [198]. There is no need to immunize or provide prophylaxis to patient contacts unless a determination is made that they, like the patient, were exposed to the organism. Standard disinfectants used for hospital infection control are effective in cleaning surfaces contaminated with infected bodily fluids [193].

Proper burial or cremation of humans and animals that have died because of anthrax infection is essential to prevent further transmission of the disease. Serious consideration must be given to cremation. Embalming of bodies could be associated with special risks.

VIBRIO AND CHOLERA

Raw food has a potential for serious zoonotic diseases. Bacteria of the *Vibrio* genus exist in most fish and shellfish habitats. All members of this genus can produce gastrointestinal signs in varying degrees of severity. Raw oysters are one of the more prevalent shellfish to carry *Vibrio* spp. [200]. Ingesting the food items can produce the disease, but handling fish or shellfish contaminated with *Vibrio* can also lead to infection through chapped hands or finger cuts [200].

Cholera, the most well-known of the diseases caused by the *Vibrio* organisms, is caused by *V. cholerae*. Although *Vibrio* infections are much more common in developing countries, outbreaks and individual cases can occur in Europe and North America. Two serogroups of *V. cholerae* cause outbreaks: *V. cholerae* 0139 and *V. cholerae* 01 biotype El Tor. *V. cholerae* 0139 was first identified in Bangladesh in 1992 and is confined to Southeast Asia. *V. cholerae* 01 biotype El Tor has spread rapidly around the world and may be seen in patients returning from foreign countries [201].

Cholera is rarely spread from person to person without the contamination of food or water by animals or people. The organism can live in or on foodstuffs for up to five days at ambient temperatures and for 10 days at 5 to 10 degrees C. Most cases in endemic areas are in young children [201].

Clinical Presentation and Diagnosis

Some cases of cholera are asymptomatic or only produce a mild diarrhea. A major *Vibrio* infection is characterized by a sudden onset of severe enteritis with diarrhea, vomiting, and leg cramps. The usual incubation period is 0.5 to 5 days [201]. Marked dehydration can occur, especially in the instance where reinfection is occurring from a point source. There may be accompanying fever. If the bacteria infect a wound, the site can become necrotic and cellulitis can spread until the infection is no longer localized. Once septicemia occurs, the case fatality rate can be as high as 50%; it may be as high as 25% in wound infection cases [15]. Laboratory diagnosis can be made with gram stain or by culture of the organism.

Treatment and Prevention

The gastroenteritis form of *Vibrio* infection can usually be managed supportively in previously healthy individuals with intravenous followed by oral fluid and electrolyte replacement. It is the very young, the elderly, and patients with chronic disease, who may have a harder time dealing with vibriosis and require antibiotics. Antibiotic use for moderately and severely ill patients has been shown to reduce the volume of stool output, the duration of diarrhea, and the duration of positive stool cultures [202]. Doxycycline is recommended for adults, and azithromycin is recommended as first-line treatment for children and pregnant women.

Care must be taken with cooked shellfish to ensure that handling does not recontaminate the food product just before consumption. As noted, *Vibrio* spp. are relatively tolerant of wide temperature ranges and, consequently, can exist on a food preparation surface for a considerable time.

In 2016, the FDA approved the first cholera vaccine, Vaxchora. This one-dose oral vaccine is approved for adults 18 to 64 years of age traveling to cholera-affected areas [203]. Other preventative measures recommended by the CDC include only drinking safe water, frequently washing hands with soap (or scrubbing hands with ash or sand) and safe water, cooking all foods and eating them hot, and only consuming raw fruits and vegetables that have been peeled recently by oneself.

BOTULISM

Botulinum toxins have gained widespread recognition as a result of the introduction of botulinum type A (Botox) into the field of cosmetology. The toxins have been important medically for many years due to the serious and often fatal consequences of ingesting improperly canned or bottled foods. However, the disease can also be caused by contact with, or ingestion of, contaminated fish and herbivores.

Botulinum toxins are proteins produced by the anaerobic bacterium *Clostridium botulinum* and consist of seven separate but related neurotoxins, denoted A through G. All of the strains produce similar effects when ingested or inhaled. They are among the most toxic compounds known, with an estimated toxic dose of only 0.001 mcg/kg of body weight [204]. These neurotoxins act by binding at the presynaptic nerve terminals and the cholinergic autonomic sites. They also block acetylcholine transmission, causing skeletal muscle weakness and paralysis as well as bulbar palsies [204].

Human disease is caused by strains A, B, E, and rarely, F [205]. In the United States, toxin A is found predominantly west of the Mississippi River, while toxin B is found most commonly in the East. Toxin E is found in northern latitudes, such as the Pacific Northwest, the Great Lakes region, and Alaska. The frequency of botulism in native Alaskans is among the highest in the world, as toxin E outbreaks are frequently associated with fish products [204]. The disease can also be caused by wounds infected with *C. botulinum* and is known as "wound botulism." An intestinal form has been reported in infants when the organism is ingested and germinates in the gastrointestinal tract. There is no person-to-person transmission of botulism, and airborne transmission of botulism does not occur naturally [204].

In 2015, potato salad prepared with home-canned potatoes sickened 29 people after it was eaten at a church potluck in Ohio. The coordinated effort by the area hospitals, county and state health departments, and the CDC, which sent 50 doses of botulinum antitoxin from the Strategic National Stockpile, is credited with saving the lives of 28 of the patients and vastly reducing their illness severity and length of hospital stay. The potatoes were bottled using a boiling water canner rather than a pressure canner, which is recommended and able to effectively deactivate spores. This was the largest outbreak of botulism in the United States in nearly 40 years [249].

Clinical Presentation and Diagnosis

Following an incubation period of 2 hours to 8 days, depending on the dose (typically 12 to 72 hours), the early signs and symptoms of diplopia, blurred vision, dry mouth, ptosis, and photophobia appear. This is followed by skeletal muscle weakness and paralysis, which is typified by a descending, symmetrical pattern, ending in respiratory difficulty and eventually respiratory failure. Interestingly, the patient usually remains alert and afebrile, although there may be dysarthria, dysphagia, and dysphonia. The pupils may be dilated and fixed, the gag reflex may be absent, and deep tendon reflexes are diminished or absent. The patient may develop hypotension, cyanosis, and evidence of carbon dioxide retention. In foodborne botulism, all of these findings may be evident in patients within 24 hours of the ingestion of the tainted items [204; 206].

Some cases of botulism may be confused with disorders such as Guillain-Barré syndrome or myasthenia gravis (MG). It has been suggested that the edrophonium (Tensilon) test may be used to differentiate it from MG, but because it may be transiently positive in botulism, its actual usefulness is in doubt [205]. The edrophonium test requires that the patient have a sign, such as ptosis, that can be reversed with an intravenous injection of a cholinesterase agent like edrophonium.

Very limited information can be obtained from laboratory tests. Survivors usually do not develop an antibody response to the toxin because of the subimmunogenic amount of material required to produce major symptoms. In cases of ingested botulinum toxin, culture of the serum or stool may be useful [204]. An ELISA test might possibly detect the toxin on nasal mucous membranes for 24 hours in cases of inhalation.

The recommended test for confirmation of botulism is the mouse neutralization bioassay [204; 206]. This assay can detect as little as 0.03 ng of botulinum toxin within one to four days after exposure.

Treatment and Prevention

There are good antitoxins available; however, they only halt the progression of future symptoms and do not reverse the existing clinical presentation. A licensed heptavalent antitoxin for all known types of botulinum (A, B, C, D, E, F, and G) has been approved by the FDA and is recommended for all cases of botulism in patients other than infants [204; 207]. The antitoxin is of equine origin, which means that skin testing must be performed to help prevent serum sickness or anaphylaxis in susceptible individuals [208]. Intravenous human botulism immune globulin (BIG-IV, BabyBIG) is available for the treatment of patients younger than 1 year of age with infant botulism caused by toxin type A or B. In cases of suspected infant botulism, for consultation, and to obtain BabyBIG, physicians should call (510) 231-7600 [248]. Antibiotics (i.e., penicillin G, chloramphenicol, clindamycin) are useful in wound botulism, but not in foodborne botulism [204].

For patients with symptoms of botulism, the prompt administration of botulinum antitoxin and supportive care can markedly reduce the mortality rate. Supportive care may include ventilatory assistance for several weeks or even months. Treatment is the same for children and adults [204].

Botulism poisoning is not an infection. It is not transmitted from person to person, and only standard precautions are required to control its spread. Because botulism poisoning is not transmittable, patients do not need to be isolated. The CDC recommends that contaminated objects or surfaces be cleaned with 0.1% hypochlorite bleach solution if they cannot be avoided for the hours to days required for natural degradation [209].

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SALMONELLOSIS

The diseases caused by this group of organisms are well known in animals and in humans. Salmonellosis is caused by *Salmonella* spp., of which there are more than 2,500 serotypes. The species is divided into six subgroups or subspecies based on pathogenicity, DNA similarity, common host, and other factors. The classification system is complex, and the diseases that are expressed are quite diverse. Most pathogenic *Salmonella* spp. become localized in the body within the victim's cells [210; 211]. Consequently, after ingestion they are taken up by macrophages, which facilitate their spread through the lymphatic system.

It is from an animal host in the asymptomatic carrier state that many *Salmonella* diseases are transmitted to humans [213]. Domestic and wild animals can be reservoirs for these zoonoses, including domestic and wild reptiles, farm animals, chickens and other poultry (especially ducks), and small mammals. All transmissions to humans are from ingestion [211]. Most transmissions occur from meat, poultry, raw eggs, and milk products, but any food, including vegetables, may become contaminated. It can also be transmitted directly by the fecal-oral route [211]. Infected water sources can also transmit disease, and infected food handlers have been noted to cause sporadic outbreaks. Freezing does not destroy the agent.

Salmonellosis diseases fall into three categories in humans: gastroenteritis, septicemia, and enteric fever. Animal cases are more chronic, and an asymptomatic carrier state is seen in many species after the disease runs its course [213]. The carrier state is also common in humans, with typhoid fever being the most familiar. Inappropriate use of antibiotics can prolong the carrier state. Other examples of diseases seen in humans caused by *Salmonella* include paratyphoid fever and the many forms of gastroenteritis. The case fatality rate is less than 1% and is primarily seen in the young or elderly [211].

Clinical Presentation and Diagnosis

The common presentation of salmonellosis is gastroenteritis with fever, abdominal cramping, vomiting, diarrhea that is often bloody, chills, and weight loss [210; 211]. There is often a history of ingesting a possibly contaminated food product within the past few days, but in many cases a full epidemiologic investigation is necessary to find the source of infection. The symptoms usually appear within 12 to 72 hours after ingestion of the infective organism.

Serum is useful in testing for the enteric fever form *S. typhi* only. Culturing the feces is usually needed to verify the disease [214]. The samples can be serotyped, in most cases, to help identify the exact source of an infection.

Treatment and Prevention

Antimicrobial therapy is not recommended for the usual case of uncomplicated salmonella gastroenteritis, as this tends to be self-limited, lasting about four to seven days; antibiotic treatment does not shorten the duration and may prolong the carrier state, which could have adverse public health consequences if the patient is in close contact with others or is a food handler [211; 214]. Patients with enteric fever presentation or signs of disseminated foci of salmonella infection do require antibiotic treatment. Careful attention to antimicrobial sensitivity testing of the infecting strain is important, as some salmonella strains are multidrug-resistant [212; 214]. Choices for antibiotic therapy for severe infections include fluoroquinolones, third-generation cephalosporins, and ampicillin (for susceptible infections) [214]. Third-generation cephalosporins, which must be given by injection, are widely used in children with serious infections because the quinolones are not generally recommended for this age group. The drugs commonly used in the past, chloramphenicol, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole, are occasionally used as alternatives [211]. For cases in which a carrier state is identified, it is important to treat the individual who is the carrier. It is also especially important to identify sources of drug-resistant strains to avoid outbreaks similar to those in northern California during spring 1997 related to the home production of Mexican-style cheese [215].

In managing clusters of salmonellosis among livestock, fecal samples should be tested and the animal cleared of carrier status only after a series of samples are determined to be free of the bacteria. In the case of infection coming from a food handler, tracking the source will be hastened if the initial case is reported in a timely fashion to allow public health officials to investigate as quickly as possible.

Common sense (e.g., hand washing after handling raw foods or animals/animal feces) prevails in the prevention of these diseases. Avoiding raw eggs, unpasteurized dairy products, and other questionable food products will prevent most cases, as will proper cooking of poultry and meats [210; 213; 214].

According to the World Gastroenterology Organisation, two typhoid vaccines (with limited cost-efficiency) are approved for clinical use to prevent diarrhea associated with *Salmonella typhi* infection.

(https://www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english. Last accessed April 17, 2020.)

Level of Evidence: Expert Opinion/Consensus Statement

BRUCELLOSIS

Brucellosis, also known as undulant fever, is a zoonotic disease caused by infection with a species of *Brucella*. The most common are *B. abortus* (cattle), *B. melitensis* (sheep), and *B. suis* (swine), with rare cases reported due to infection with *B. canis* (canine). *B. melitensis* is thought to be the most virulent, the most prevalent, and the cause of the most severe and acute cases of brucellosis worldwide; it is also the source of most human cases of brucellosis in the United States [216]. According to the USDA, the only known focus of *B. abortus* infection in the United States is among bison and elk in and around Yellowstone National Park [217]. Brucellosis is highly endemic in countries such as Peru, Mexico, Spain, Greece, Iraq, Iran, Jordan, and Kuwait. It is considered a rare disease in the United States, where an average of approximately 100 cases are reported per year, mostly from Florida, California, Virginia, and Texas [218]. Ingesting non-pasteurized milk or cheese is a likely cause for many of these cases [218; 219].

Clinical Presentation and Diagnosis

The brucellae are a group of gram-negative cocci bacillary organisms. The most common way to become infected is by drinking or eating unpasteurized milk or cheese products derived from sheep, goats, or cows. Meat packing and laboratory worker infections suggest that *Brucella* is highly infectious via direct contact with carcasses or by inhalation aerosol route [219]. It is estimated that inhalation of only 10–100 bacteria is sufficient to cause disease in humans. The incubation period is 5 to 60 days, and many infections are asymptomatic under natural conditions. Large aerosol doses may shorten the incubation period and increase the clinical attack rate. Brucellosis infection has a low mortality rate (2% to 5% of untreated cases), with most deaths caused by endocarditis or meningitis. It is an incapacitating disease in its natural form [198; 219].

Acute brucellosis presents as a flu-like illness, with fever, headache, joint pain, sweats, chills, and general weakness as common complaints. Cough and pleuritic chest pain may be present, but may not correlate with radiographic results. Chest x-rays may show lung abscesses, single or miliary nodules, and pleural effusions. Gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, and constipation, colitis, or an infiltrative hepatitis occur in up to 70% of adult cases and less frequently in children. Hepatomegaly and splenomegaly can occur in as many as 45% to 63% of cases. Peripheral joint involvement may vary from pain on range of motion to joint immobility and effusion, usually involving the hips and sacroiliac joints [219]. Meningitis occurs in less than 5% of brucellosis cases and may be an acute presenting illness of a chronic syndrome, occurring late in the course of a persistent infection [219]. Behavioral disturbances in children and psychoses may occur in the meningoencephalitic form of the disease.

Laboratory studies for *Brucella* spp. are most productive if accomplished early in the course of the disease. The organism is slow-growing and should be incubated for about three weeks before a negative result can be reported. Cultures can be obtained from blood, urine, CSF, or even bone marrow. Serologic testing is the most common diagnostic procedure, with rising titers or an agglutination titer of more than 1:100 being a good indication that brucellosis is the diagnosis [218].

Many other procedures have been utilized, including IFA, ELISA, and counter immunoelectrophoresis. The microagglutination test is still considered to be the gold standard test. This test allows for the differentiation of an acute (predominately IgM) infection versus a relapse (predominately IgG). Identification is made by culturing *Brucella* spp. from blood or bone marrow [198; 218].

Treatment and Prevention

Brucellosis is treatable with antibiotics, but due to the intracellular nature of the infectious process, treatment usually requires combination therapy over a long duration. Optimal antibiotic therapy for brucellosis has been studied; however, recommendations differ [218]. Doxycycline (200 mg daily) plus rifampin (600–1,200 mg daily) for six weeks may be appropriate for uncomplicated disease in adults [12; 218]. Fluoroquinolones (e.g., ciprofloxacin) have been used as monotherapy but carry a high relapse rate; adding these agents to doxycycline offers no specific advantages over other combination regimens but may be preferred in areas where resistance to rifampin is high [218]. The WHO guidelines for treatment of acute brucellosis recommend [218]:

- Doxycycline (100 mg) twice daily plus rifampin (600–900 mg/day) given orally for six weeks. This regimen is more convenient but may increase the risk of relapse.
- Doxycycline (100 mg) orally twice daily for six weeks and streptomycin (1 g/day IM) for two to three weeks. This regimen is believed to be more effective, mainly in preventing relapse. Gentamicin can be used as a substitute for streptomycin and has shown equal efficacy.
- Ciprofloxacin-based regimens have shown efficacy equal to that of doxycycline-based regimens.

A 2012 Cochrane review found that a regimen consisting of doxycycline for six weeks plus streptomycin for two to three weeks was more effective than one consisting of doxycycline plus rifampicin for six weeks [220]. The investigators also found that a regimen consisting of a fluoroquinolone plus rifampicin for six weeks was as effective overall as doxycycline plus rifampin (based on low-quality evidence) and was slightly better tolerated.

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Limited data are available regarding the treatment of brucellosis in pregnant women. TMP-SMZ has been effective, either as monotherapy or in combination with rifampin or gentamicin [218].

For children younger than 8 years of age, a regimen of rifampin and TMP-SMZ for six weeks is the therapy of choice. Relapses occur in about 5% of patients and are due to sequestered rather than resistant organisms [221; 222]. Arthritis may occur in recurrent cases. For complications, such as endocarditis or meningoencephalitis, triple therapy including rifampin, a tetracycline, and an aminoglycoside has been recommended [12; 218].

Prevention is largely limited to those occupations for which brucellosis is a risk, as naturally occurring forms of the disease have been drastically limited in the United States through the use of animal vaccines. However, food and animal products imported from other countries can pose a risk. Avoidance of high-risk food products, particularly unpasteurized dairy products, is an important step in avoiding the disease [219]. For those in direct contact with *Brucella* spp. cultures, prophylaxis may be considered [223].

PARASITIC ZOONOTIC DISEASES

Parasitic zoonoses may be the most widespread in the world [224]. Although they generally produce a much greater morbidity than mortality, these diseases have an enormous impact on economic and social well-being in many countries. Fortunately, most of the diseases are endemic in areas outside North America and only involve travelers or immigrants in the United States and Canada.

There are multitudes of parasitic organisms that affect animals, many of which can then be transmitted to humans. Trichinosis, tapeworm infestation, and anisakiasis will be discussed as examples due to their similar morphology.

TRICHINOSIS

Trichinosis, also known as trichinellosis, is caused by the nematode *Trichinella spiralis*. It is common in Europe and the United States and is a reportable disease [225]. Several other *Trichinella* spp. are found around the world in carnivorous mammals and birds. The typical hosts of the worm in North America are pigs, rats, and bears. Less commonly, humans, dogs, cats, wolves, and horses can also be hosts. In the host, the adult organism typically lives in the intestine. There, it produces larvae, which penetrate the intestinal wall and migrate into skeletal muscle, where they encyst.

Infection occurs when infected meat of a host is consumed. The common source in this country is undercooked pork, especially from small farm operations that feed uncooked meat scraps to the animals or from pig cannibalism [225]. People have been infected from consumption of horse and bear meat as well.

Clinical Presentation and Diagnosis

The symptoms of infection are initially diarrhea, vomiting, fever, and abdominal distress. This is followed by flu-like symptoms from the muscle infection. In this stage, patients may have headaches, chills, cough, arthralgia, and myalgia. In severe infections, there can be myocarditis, paresis, central nervous system involvement, and respiratory distress. There have been fatalities from the disease [225].

The initial symptoms usually appear one to two days after ingesting the contaminated food product, with the later signs and symptoms showing up after about two to eight weeks. A detailed patient history is very helpful in identifying this zoonosis, and cases frequently present in an isolated small group or family.

Some of the *Trichinella* larvae may be passed in the feces, which can assist in diagnosis. Laboratory analysis includes antibody detection, muscle biopsy, and microscopy. The patient may have a pronounced eosinophilia [225].

Treatment and Prevention

Treatment should begin as soon as possible once the diagnosis is suggested. The CDC suggests the anthelmintics mebendazole and albendazole as possible therapeutic medications, although they are not FDA approved for this purpose. Steroids may be required for severe symptoms [46; 225; 226].

Adequate cooking of meat products will kill the organisms. This usually means obtaining an internal temperature of 170 degrees F. Pork can also be frozen for 20 days at 5 degrees F (if less than 6 inches thick) to assure safety. Thorough cooking of wild game meats will provide protection, but the freezing regimen is not always effective. In addition, curing by salting, smoking, or drying does not always kill the nematodes or cysts. Interestingly, microwaving does not consistently inactivate the organism, but ionizing irradiation has been used successfully to provide protection [225].

TAPEWORMS

The cestodes that produce the common human tapeworm infestation belong to the *Taeniidae* family. The most frequently seen in the United States are *Taenia saginata*, or beef tapeworm, and *Taenia solium*, the pork tapeworm. *Taenia asiatica* is limited to Asia and seen mostly in the Republic of Korea, China, Taiwan, Indonesia, and Thailand. *T. solium* can also cause cysticercosis [14]. *Dipylidium caninum* is found in dogs and cats and produces the disease dipylidiasis, most frequently seen in children younger than 8 years of age [227]. Humans are the only definitive hosts for *T. saginata* and *T. solium*, with pigs and cattle being common sources of the infestation.

All tapeworm organisms cause the disease process after being ingested by the victim in food or by direct contact, in the case of dipylidiasis. In addition, *D. caninum* can also be transmitted by ingesting infected fleas [227].

The lifecycle begins with egg packets within proglottids being released into the environment by a carrier. The eggs can survive for months on the ground or on most surfaces [14]. Once ingested, the organisms invade the intestinal wall of the victim and migrate to striated muscle, where they become cysticerci. The cysticerci can persist for years in an animal and cause significant morbidity. In humans, an adult tapeworm develops over a period of about two months. It attaches to the small intestine, where it can reside and excrete multitudes of proglottids for many years.

Clinical Presentation and Diagnosis

The symptoms of infestation with *T. saginata* are minimal, with mild abdominal pain being the most common finding. The clinical presentation of *T. solium* is even more minimal. It is usually the discovery of proglottids in the stool that signals the presence of the infestation [14]. Infrequently, the pork tapeworm progresses to cysticercosis, which can cause central nervous system symptoms if it invades the brain.

Dipylidiasis is typically asymptomatic; however, a severe worm burden can cause local pruritus, abdominal pain, allergic manifestations, and intestinal obstruction. The disease is often identified by the parent noting "rice stools" in a child's diaper [14; 228].

Microscopic identification of the eggs and proglottids in the feces is diagnostic. This may not be possible until three months after infection because the adult tapeworm must first be present. Repeated examinations may be necessary to find the organisms, especially in light infestations. Antibody detection methods can be useful in the early stages of the disease, before the presence of proglottids in the stool. The differentiation of the species of *Taenia* requires more detailed analysis, with examination of the gravid proglottids or the scolex of the organism [14; 228].

Treatment and Prevention

Treatment with antiparasitic medication is usually very effective. The CDC recommends praziquantel, although it is not yet approved for this use by the FDA [14; 46]. The usual anthelmintics (i.e., albendazole or praziquantel) have been used for the treatment of neurocysticercosis [229]. Treatment of dipylidiasis in adults and children can be with praziquantel or albendazole (off-label use) [46].

Prevention of dipylidiasis in pets and humans is aided by the control of fleas with pet medications or flea collars. Good hygiene and refraining from sleeping with or kissing the animal will also help prevent the infestation. Good sanitary practices are also the best way to prevent taeniasis [227].

ANISAKIASIS

There are many fish-borne zoonotic diseases, including ciguatera poisoning, tetrodotoxin poisoning from pufferfish, and infestations of *Diphyllobothrium* tapeworms. Because of the increasing consumption of uncooked fish in North America, there has been an increased awareness of anisakiasis. *Anisakis simplex* is a nematode (roundworm) found in several types of ocean fish and marine animals. It has been known in Japan for centuries, but it was first described in detail in the Netherlands in 1960 [230].

The adult nematodes reside in the intestines of marine mammals such as dolphins and sea lions. These mammals excrete the eggs, which are ingested by crustaceans. Fish then eat the crustaceans and become intermediate hosts, as the larvae imbed themselves in their flesh. Commonly affected fish include mackerel, salmon, squid, rockfish, anchovies, sardines, hake, and herring [230; 231]. After ingestion by humans, the larvae attach themselves to the gastric mucosa or penetrate the stomach or intestinal wall. This can lead to abscess formation or eosinophilic granulomatosis. A severe allergic reaction often occurs, which causes more morbidity than the local effects of the adult nematodes [231].

Clinical Presentation and Diagnosis

Patients may suffer a marked allergic response, including urticaria, angioedema, bronchospasm, and anaphylaxis, within 24 hours of eating raw or undercooked fish [232]. The latency of the reaction ranges from 15 minutes to 26 hours, with 5 hours after consumption being the mean [231]. Gastrointestinal symptoms of abdominal pain, diarrhea, fullness, nausea, and vomiting are often mild, although the vomiting may be violent enough to expel some of the larvae [232]. If the organisms lodge in the bowel, they can produce a granulomatous response, mimicking Crohn disease, after about one to two weeks [231]. They can also be found in organs or areas outside the gastrointestinal tract, such as the peritoneum and liver [230].

Diagnosis can be made by endoscopy, during which the 2-cm larvae can be seen and removed. The organisms can also be seen on biopsy specimens obtained during the endoscopic procedure or surgery [232].

Treatment and Prevention

The treatment of choice is removal of the organisms during fiberoptic endoscopy or surgery [231; 232]. Successful treatment of anisakiasis with albendazole 400 mg orally twice daily for 6 to 21 days has been reported in cases with a strong presumptive diagnosis based on history and/or serology [232]. Prevention is almost absolute if raw or uncooked fish is avoided. However, this is not practical in many parts of the world, including the United States. Fortunately, most chefs trained in handling and preparing raw fish can spot tainted fish. Freezing at negative 4 degrees F for at least seven days

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will kill the larvae, as will "blast-freezing" at negative 31 degrees F for 15 hours [232]. Irradiation of fish can also kill the organisms as will the cooking of thawed or fresh fish. Salting, in high concentration, and smoking may provide some prevention but not enough to assure a safe product [250]. When smoking, the flesh must reach 65 degrees C to kill the parasites.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of diagnosing many zoonotic diseases, particularly those that are rare or that display similar signs and symptoms to other conditions. Furthermore, communication with patients regarding diagnostic procedures, treatment regimens, and prevention of zoonotic diseases depends on clear communication between the patient and clinician. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. The interpreter should be considered an active agent in the diagnosis and/or treatment processes, negotiating between two cultures and assisting in promoting culturally competent communication and practice [50]. This is particularly an issue for zoonotic diseases that commonly originate in countries outside the United States, for which English will be a second language for some or many of the patients.

In the increasingly multicultural landscape of the United States, interpreters are a valuable resource to help bridge the communication and cultural gap between patients or caregivers and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When interacting with patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve understanding and outcomes.

CONCLUSION

The zoonotic diseases, in their many forms, have produced widespread morbidity and mortality. From the very old zoonoses, such as plague and rabies, to the relatively new diseases, like avian influenza and West Nile encephalitis, these diseases can be expected to cause disease in humans well into the future.

This course presented a spectrum of the more common zoonoses and briefly reviewed the background, clinical presentation, diagnostic procedures, treatment, and preventive measures associated with the individual diseases. It is vital for medical professionals to have a working knowledge of the zoonoses that they may encounter. Particularly considering the globalization of commerce and travel, early diagnosis and effective treatment can protect against potential outbreaks and pandemics.

Customer Information/Answer Sheet/Evaluation insert located between pages 104–105.

COURSE TEST - #94923 ANIMAL-RELATED HEALTH RISKS

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 15 credit activity must be completed by April 30, 2023.

1. Which of the following diseases was known to be transmitted from animals to humans in the 1300s?
A) *Rabies*
B) *Tularemia*
C) *Tinea cruris*
D) *Liver flukes*

2. In what decade did the electron microscope allow us to first see viruses?
A) *The 1920s*
B) *The 1930s*
C) *The 1940s*
D) *The 1950s*

3. An animal that can support an infective agent of a zoonotic disease is called a
A) *host.*
B) *zooan.*
C) *vector.*
D) *carrier.*

4. In a dead-end or aberrant host, the organism cannot
A) *reproduce.*
B) *transmit disease.*
C) *survive even briefly.*
D) *Both A and B*

5. A more serious zoonotic disease transmitted by an arthropod vector is
A) *malaria.*
B) *Lyme disease.*
C) *Rocky Mountain spotted fever (RMSF).*
D) *All of the above*

6. The two types of transmission from animals to humans are
A) *direct and indirect.*
B) *direct and reservoir.*
C) *indirect and complete.*
D) *incomplete and complete.*

7. Plague would be reported in which zoonotic disease class?
A) *1*
B) *2*
C) *3*
D) *4*

8. Nematode infection can cause
A) *giardiasis.*
B) *listeriosis.*
C) *trichinosis.*
D) *Lyme disease.*

9. Which of the following is NOT a bacterial zoonotic agent?
A) *Taenia solium*
B) *Bacillus anthracis*
C) *Rickettsia rickettsii*
D) *Bartonella henselae*

10. Stage 1 of Lyme disease may present with a characteristic skin lesion in 70% to 80% of cases. It is usually described as a(n)
A) *lesion looking like impetigo.*
B) *linear, raised rash of an erythema.*
C) *macular, papular, flesh-colored rash.*
D) *expanding bull's-eye lesion of erythema migrans.*

11. The International Lyme and Associated Diseases Society suggests that acute Lyme disease in adults should be treated with
A) *a carbapenem.*
B) *watchful waiting.*
C) *gentamicin and ciprofloxacin.*
D) *either doxycycline, amoxicillin, or cefuroxime.*

12. Which type of tularemia is mainly due to inhalation or ingestion of infected spores?
A) *Bovar*
B) *Typhoidal*
C) *Oculoglandular*
D) *Ulceroglandular*

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13. The symptoms of RMSF usually appear how long after a tick bite?
A) *1 to 2 days*
B) *2 to 14 days*
C) *2 to 3 weeks*
D) *60 days*

14. Most West Nile virus infections are subclinical and unapparent. Approximately what percentage of those who contract the virus will develop West Nile fever?
A) *Less than 1%*
B) *5%*
C) *20%*
D) *50%*

15. Some imaging studies may be helpful after the development of West Nile meningoencephalitis. The test that has proved to be of most help is a(n)
A) *MRI.*
B) *CT scan.*
C) *skull x-ray.*
D) *nuclear medicine brain scan.*

16. A diagnosis of rabies must be made before symptoms appear. All of the following tests are used, EXCEPT:
A) *Antibody analysis of serum*
B) *Immediate neuroimaging procedures*
C) *Skin biopsy to examine nerves at the base of hair follicles*
D) *Samples of brain tissue of animals to look for Negri bodies*

17. In humans, lymphocytic choriomeningitis (LCM) is characterized by
A) *insidious onset.*
B) *a flu-like illness lasting only a few days.*
C) *rapid onset and very often fatal prognosis.*
D) *severe and incapacitating fever and diarrhea.*

18. A firm diagnosis of variant Creutzfeldt-Jakob disease (vCJD) can only be made by
A) *prion culture.*
B) *brain biopsy or autopsy.*
C) *a rise in specific antibody titers.*
D) *extensive physical examination.*

19. The diagnosis of toxoplasmosis is usually made by
A) *cell culture.*
B) *physical examination.*
C) *brain biopsy of the patient.*
D) *indirect immunofluorescent antibody tests of IgG and IgM.*

20. Treatment of toxoplasmosis in people with normal immune systems
A) *is rarely necessary.*
B) *is limited to supportive measures.*
C) *should begin as soon as possible after diagnosis.*
D) *None of the above*

21. Of the three types of anthrax, which has the highest fatality rate if untreated?
A) *Glandular*
B) *Inhalation*
C) *Cutaneous*
D) *Gastrointestinal*

22. Cholera is rarely spread from person to person without
A) *an insect vector.*
B) *germinating in an unexposed area.*
C) *heat and ultraviolet light to stimulate the organism.*
D) *the contamination of food or water by animals or people.*

23. There are good antitoxins available for botulism. These antitoxins
A) *prevent future cosmetic applications.*
B) *reverse the existing clinical presentation.*
C) *are only available for military personnel.*
D) *only halt the progression of future symptoms.*

24. The symptoms of salmonellosis usually appear
A) *within 6 hours after ingestion of the infective organism.*
B) *within 12 to 72 hours after ingestion of the infective organism.*
C) *one week from the time of the ingestion of the infective organism.*
D) *several weeks from the time of the ingestion of the infective organism.*

25. Salting, in high concentration, and smoking appear to provide what prevention against anisakiasis (fish tapeworm infestation)?
A) *No protection at all*
B) *More protection than "blast freezing."*
C) *Complete eradication of the organism*
D) *Some prevention, but not enough to assure a completely safe product*

Be sure to transfer your answers to the Answer Sheet insert located between pages 104–105.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

NetCE Continuing Education

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RISK MANAGEMENT

#41472 • 5 Credits

Book By Mail – $28 • **ONLINE – $20**

Mandate: CT, MA, PA, RI, TX

Purpose: With patient safety as the priority, risk management should focus on the avoidance of medical errors, as they are, along with inadequate informed consent, the most common assertions in malpractice claims in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to engage in risk management practices, including a variety of proven strategies to avoid malpractice.

Audience: This course is designed for physicians, physician assistants, and nurse practitioners seeking to enhance their knowledge of risk management strategies, especially in the outpatient setting.

Additional Approvals: ABIM, ABA, ABP, ABPath, ABO

Special Approvals: This course meets the Texas requirement for 2 hours of ethics/professional responsibility education and meets 5 hours of risk management education for Connecticut, Massachusetts, Pennsylvania, and Rhode Island physicians.

MEDICAL ETHICS FOR PHYSICIANS

#47173 • 5 Credits

By Mail – $28 • **ONLINE – $20**

Mandate: CT, MA, MI, NV, PA, RI, TX

Purpose: The purpose of this course is to briefly review the history, theory, and practical application of ethical principles to issues that arise in clinical practice.

Audience: This course is designed for physicians and interested healthcare professionals.

Additional Approvals: ABIM, ABA, ABP, ABPath, ABO

Special Approvals: This course meets the Michigan, Nevada, and Texas requirements for ethics/professional responsibility education and meets the Connecticut, Massachusetts, Pennsylvania, and Rhode Island requirements for risk management education.

SAFE CLINICAL USE OF FLUOROSCOPY

#90470 • 10 Credits

By Mail – $48 • **ONLINE – $40**

Mandate: CA, MA (PAs)

Purpose: The purpose of this course is to provide healthcare providers with an understanding of the challenges encountered when using fluoroscopy in clinical practice and the tenets of safe fluoroscopy use in clinical practice.

Audience: This course is designed for physicians, nurses, radiology technicians, surgical technicians, and all healthcare staff involved in ensuring safe clinical use of fluoroscopy.

Additional Approvals: ABIM, ABA, ABP, ABO

Special Approvals: This course meets the California requirement for 4 hours of education in radiation safety for the clinical uses of fluoroscopy and 10 hours of education on the application of x-ray to the human body. This course meets the Massachusetts physician assistant requirement for 4 hours of fluoroscopic imaging education.

MEDICAL ERROR PREVENTION AND ROOT CAUSE ANALYSIS

#91333 • 2 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: FL

Purpose: The purpose of this course is to satisfy the requirement of the Florida law and provide all licensed healthcare professionals with information regarding the root cause process, error reduction and prevention, and patient safety.

Audience: This course is designed for all licensed healthcare professionals.

Additional Approvals: ABIM, ABP, ABPath, ABO

Special Approvals: This course fulfills the Florida requirement for 2 hours of education on the Prevention of Medical Errors.

PROMOTING THE HEALTH OF GENDER AND SEXUAL MINORITIES

#91792 • 5 Credits

By Mail – $28 • **ONLINE – $20**

Mandate: CT, DC, NJ

Purpose: The purpose of this course is to provide healthcare professionals with strategies that promote cultural competency when treating and caring for these patients, supporting the concept of patient-centered care.

Audience: This course is designed for all members of the interdisciplinary team, including physicians and nurses, working in all practice settings.

Additional Approvals: ABIM, ABP, ABO

Special Approvals: This course meets the Connecticut, District of Columbia, and New Jersey requirements for cultural competency and LGBTQ education.

TYPE 2 DIABETES: TREATMENT STRATEGIES FOR OPTIMAL CARE

#94522 • 5 Credits

Book By Mail – $28 • **ONLINE – $20**

Purpose: The purpose of this course is to provide healthcare providers with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support.

Audience: This course is designed for all physicians, physician assistants, pharmacists, and pharmacy technicians involved in the care of patients with type 2 diabetes.

Additional Approvals: ABIM, ABP, ABO

Selected Course Availability List *(Cont'd)*

HIV/AIDS: EPIDEMIC UPDATE FOR WASHINGTON

#94733 • 7 Credits

By Mail – $36 • **ONLINE – $28**

Mandate: WA

Purpose: The purpose of this course is to address those problems in the discussion of epidemiology, organism characteristics, pathophysiology, transmission, clinical manifestations, complications, treatment advancements, prevention, ethical and legal aspects of care, and workplace concerns.

Audience: This course is designed for all physicians and allied healthcare professionals in Washington involved in the care of patients with HIV/AIDS.

Additional Approvals: ABIM, ABP, ABPath, ABO

Special Approvals: This course is designed to fulfill the Washington requirement for HIV/AIDS education. Participants will receive 7 hours of continuing education for completing this course.

PRESCRIPTION OPIOIDS AND PAIN MANAGEMENT: THE TENNESSEE GUIDELINES

#95130 • 2 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: TN

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with clinical guidance for management of chronic pain and opioid prescription drug use that conforms with Tennessee Department of Health guidelines and with clinical tools designed to assess the risk of drug-seeking and diverting behaviors. The goal is to promote best practice patient care and prevent the growing public health problem of drug misuse, diversion, and overdose.

Audience: This course is designed for all clinicians who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approvals: ABIM, ABA, ABP, ABO

Special Approvals: This course is designed to meet the Tennessee requirement for 2 hours of education on the prescribing of controlled substances, including instruction in the Tennessee Chronic Pain Guidelines.

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

#95150 • 3 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: AR, CA, CO, CT, KY, MA, MI, NE, NV, NJ, NM, NY, OR, VT, WA, WI

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Audience: This course is designed for all physicians, osteopaths, physician assistants, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approvals: ABIM, ABA, ABP, ABO

Special Approvals: This course meets 3 hours of opioid prescribing education for Arkansas, Nebraska, New Jersey, Vermont, Washington, and Wisconsin physicians and physician Assistants. This course meets 3 hours of pain management education for California, Massachusetts, Michigan, New Mexico, and Oregon physicians and physician assistants. This course meets the Colorado requirement for 2 hours of substance abuse and opioid education. This course meets the Connecticut requirement for 1 hour of risk management education. This course meets 3 hours of pain management and addiction education for Kentucky physicians and physician assistants. This course meets the Nevada requirement for 2 hours of ethics education, as it relates to addiction. This course is designed to meet the New York requirement for 3 hours of education in pain management, palliative care, and addiction every 3 years for those who are authorized to prescribe controlled substances.

MEDICAL MARIJUANA AND OTHER CANNABINOIDS

#95172 • 5 Credits

Book By Mail – $28 • **ONLINE – $20**

Mandate: OR

Purpose: The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.

Audience: This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana and other cannabinoids.

Additional Approvals: ABIM, ABP, ABO

Special Approvals: This course meets the Oregon requirement for 3 hours of medical marijuana education.

ALZHEIMER DISEASE

#96153 • 15 Credits

Book By Mail – $68 • **ONLINE – $60**

Mandate: CA, MA, NV, OR, RI

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

Additional Approvals: ABIM, ABPath, ABO

Special Approvals: This course meets the Massachusetts, Nevada, Oregon, and Rhode Island requirements for Alzheimer disease and dementia education. This course meets the California requirement for geriatric medicine education.

ANXIETY DISORDERS

#96181 • 15 Credits

Book By Mail – $68 • **ONLINE – $60**

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Additional Approvals: ABIM, ABP

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Selected Course Availability List *(Cont'd)*

HUMAN TRAFFICKING AND EXPLOITATION
#96312 • 5 Credits
By Mail – $28 • **ONLINE – $20**
Mandate: MI
Purpose: The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health professionals can identify and intervene in cases of exploitation.
Audience: This course is designed for physicians and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approvals: ABIM, ABP, ABO
Special Approvals: This course meets the Michigan requirement for training in identifying victims of human trafficking.

SUICIDE ASSESSMENT AND PREVENTION
#96441 • 6 Credits
By Mail – $32 • **ONLINE – $24**
Mandate: CT, NV, TX, WA
Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.
Audience: This course is designed for physicians and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.
Additional Approvals: ABIM, ABP, ABO
Special Approvals: This course meets the Connecticut requirement for Behavioral Health education. This course is approved by the Nevada State Board of Medical Examiners to fulfill 2 hours of Suicide Prevention and Awareness education. This course meets the Texas requirement for medical ethics/professional responsibility education. This course is approved by the State of Washington Department of Health to fulfill the requirement for Suicide Prevention training for healthcare professionals. Approval number TRNG.TG.60715375-SUIC.

SEXUAL ASSAULT
#97022 • 3 Credits
By Mail – $23 • **ONLINE – $15**
Mandate: CT, SC, TX
Purpose: The purpose of this course is to address knowledge gaps, enhance clinical examination and management skills, and improve treatment outcomes for victims of sexual assault.
Audience: This course is intended for physicians and other healthcare professionals who may be called upon to provide care to victims of sexual assault.
Additional Approvals: ABIM, ABP, ABPath, ABO
Special Approvals: This course meets the Connecticut requirement for sexual assault education, the South Carolina requirement for encouraged education in domestic violence, and the Texas requirement for forensic evidence education for those who perform examinations on sexual assault survivors.

SEXUAL HARASSMENT PREVENTION: THE ILLINOIS REQUIREMENT
#97080 • 1 Credit
By Mail – $23 • **ONLINE – $15**
Mandate: IL
Purpose: The purpose of this course is to provide health and mental health professionals with clear knowledge of the consequences of sexual harassment and the skills to help combat harassment in the workplace.
Audience: This course is designed for physicians, physician assistants and all members of the interprofessional healthcare team who may act to prevent sexual harassment.
Additional Approvals: ABIM, ABA, ABP, ABO
Special Approvals: This course is designed to fulfill the Illinois requirement for sexual harassment education.

RECOGNIZING AND REPORTING HUMAN TRAFFICKING IN FLORIDA
#97110 • 2 Credits
By Mail – $23 • **ONLINE – $15**
Mandate: FL
Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals an in-depth, practical review of human trafficking, including the definition and scope of the problem, the means of identification and assessment of individuals who may be victims, guidance on reporting of cases, and interventions and resources available to victims.
Audience: This course is designed for all health and mental health professionals in Florida who may identify and intervene in cases of human trafficking and exploitation.
Additional Approvals: ABIM, ABP, ABO
Special Approvals: This course meets the Florida requirement for Human Trafficking education.

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE
#97382 • 15 Credits
Book By Mail – $68 • **ONLINE – $60**
Mandate: CA, IA, MA, NJ, OR, RI, VT
Purpose: The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the benefits and barriers to optimum palliative care at the end of life.
Audience: This course is designed for all members of the interdisciplinary team, including physicians, physician assistants, nurse practitioners, nurses, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.
Additional Approvals: ABIM, ABA
Special Approvals: This course fulfills 11 hours of education on the appropriate care of the terminally ill for California-licensed physicians who must complete 12 hours of pain management and the appropriate care of the terminally ill. This course meets the Iowa, Massachusetts, New Jersey, Oregon, Rhode Island, and Vermont requirements for end-of-life education.

Selected Course Availability List *(Cont'd)*

HUMAN TRAFFICKING AND EXPLOITATION: THE TEXAS REQUIREMENT

#97470 • 5 Credits

By Mail – $28 • **ONLINE – $20**

Mandate: TX

Purpose: The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.

Audience: This course is designed for Texas physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

Additional Approvals: ABIM, ABA, ABP, ABO

Special Approvals: This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT

#97533 • 2 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: NY

Purpose: The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of New York for child abuse victims.

Audience: This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

Additional Approvals: ABIM, ABP, ABPath, ABO

Special Approvals: This course is approved by the New York State Education Department to fulfill the requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW

#98393 • 10 Credits

Book By Mail – $48 • **ONLINE – $40**

Purpose: Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Audience: This course is primarily designed for physicians, pharmacists, and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

Additional Approvals: ABIM, ABP, ABO

INFECTION CONTROL: THE NEW YORK REQUIREMENT

#98642 • 5 Credits

By Mail – $28 • **ONLINE – $20**

Mandate: NY

Purpose: The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

Additional Approvals: ABIM, ABA, ABP, ABPath, ABO

Special Approvals: This course is approved by the New York State Department of Health to fulfill the requirement for 4 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #TP02078.

ABIM CME MOC ACCREDITED

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of a course constitutes permission to share the completion data with ACCME.

PART 2 MOC

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

MOCA

Designated activities contribute to the patient safety CME requirement for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements.

Participants will earn CC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pathology area of Lifelong Learning (Part II).

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA
COLLÈGE ROYAL DES MÉDECINS ET CHIRURGIENS DU CANADA

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What You Should Know About…

Tickborne Diseases

Patient Education Handout
A service for patients

This page is perforated for easy removal.

UNDERSTAND the problem

Some of the most common tickborne diseases in the United States include Lyme disease, Rocky Mountain spotted fever, tularemia, and babesiosis. In 2018, state and local health departments reported 47,743 cases of tickborne disease to the CDC. The most common reported disease is Lyme disease (70.5%), followed by anaplasmosis/ehrlichiosis (12.8%), spotted fever rickettsiosis (11.6%), and babesiosis (4.5%). These diseases have the potential to cause significant illness and even death if unidentified and/or untreated.

Ticks transmit pathogens that cause disease through the process of feeding. Depending on the tick species and its stage of life, preparing to feed can take from 10 minutes to 2 hours. When the tick finds a feeding spot, it grasps the skin and cuts into the surface to drink the host's blood. Ticks also can secrete small amounts of saliva with anesthetic properties so that the animal or person can't feel that the tick has attached itself. If the tick contains a pathogen, the organism may be transmitted to the host animal from this saliva.

WHO is at risk

Anyone, including infants and children, is at risk for tickborne disease after an exposure. Of the many different tick species found throughout the world, only a select few bite and transmit disease to people. Of the ticks that bite people, different species of ticks transmit different diseases. The characteristics of a few of the most common species in the United States are outlined below.

American Dog Tick (*Dermacentor variabilis*)

Where Found: Widely distributed east of the Rocky Mountains. Also occurs in limited areas on the Pacific Coast

Transmits: Tularemia and Rocky Mountain spotted fever

The highest risk of being bitten occurs during spring and summer. Dog ticks are sometimes called wood ticks. Adult females are most likely to bite humans.

Blacklegged or Deer Tick (*Ixodes scapularis*)

Where Found: Widely distributed across the eastern United States

Transmits: Lyme disease, *anaplasmosis*, *B. miyamotoi* disease (a form of relapsing fever), ehrlichiosis, babesiosis, and Powassan virus disease

The greatest risk of being bitten exists in the spring, summer, and fall. However, adults may be out searching for a host any time winter temperatures are above freezing. Stages most likely to bite humans are nymphs and adult females.

Brown Dog Tick (*Rhipicephalus sanguineus*)

Where Found: Worldwide

Transmits: Rocky Mountain spotted fever (in the southwestern United States and along the U.S.-Mexico border)

Dogs are the primary host for the brown dog tick in each of its life stages, but the tick may also bite humans or other mammals.

Gulf Coast Tick (*Amblyomma maculatum*)

Where Found: Coastal areas along the Atlantic coast and the Gulf of Mexico

Transmits: *Rickettsia parkeri* rickettsiosis, a form of spotted fever

Larvae and nymphs feed on birds and small rodents, while adult ticks feed on deer and other wildlife. Adult ticks have been associated with transmission of *R. parkeri* to humans.

Lone Star Tick (*Amblyomma americanum*)

Where Found: Widely distributed in the southeastern and eastern United States

Transmits: *Ehrlichia chaffeensis* and *E. ewingii* (which cause human ehrlichiosis), Heartland virus, tularemia, and southern tick-associated rash illness (STARI)

A very aggressive tick that bites humans. The adult female is distinguished by a white dot or "lone star" on her back. Lone star tick saliva can be irritating; redness and discomfort at a bite site does not necessarily indicate an infection. The nymph and adult females most frequently bite humans and transmit disease.

Rocky Mountain Wood Tick (*Dermacentor andersoni*)

Where Found: Rocky Mountain states and southwestern Canada from elevations of 4,000 to 10,500 feet

Transmits: Rocky Mountain spotted fever, Colorado tick fever, and tularemia

Adult ticks feed primarily on large mammals. Larvae and nymphs feed on small rodents. Adult ticks are primarily associated with pathogen transmission to humans.

Western Blacklegged Tick (*Ixodes pacificus*)

Where Found: Along the Pacific coast, particularly northern California

Transmits: Anaplasmosis and Lyme disease

Nymphs often feed on lizards, as well as other small animals. As a result, rates of infection are usually low (~1%) in adults. Stages most likely to bite humans are nymphs and adult females.

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WHAT are the signs and symptoms

Many tickborne diseases can have similar signs and symptoms. The most common symptoms of tick-related illnesses are fever/chills, aches and pains, and rash.

With all tickborne diseases, patients can experience fever at varying degrees and time of onset. Tickborne disease symptoms also include headache, fatigue, and muscle aches. With Lyme disease you may also experience joint pain. The severity and time of onset of these symptoms can depend on the disease and the patient's personal tolerance level.

Lyme disease, STARI, Rocky Mountain spotted fever, ehrlichiosis, and tularemia can result in distinctive rashes. In Lyme disease, the rash is usually a circular rash called erythema migrans. The rash of STARI is nearly identical to that of Lyme disease, with a red, expanding "bull's eye" lesion that develops around the site of a lone star tick bite. The rash seen with Rocky Mountain spotted fever varies greatly from person to person in appearance, location, and time of onset. In the most common form of tularemia, a skin ulcer appears at the site where the organism entered the body. The appearance of the rash of ehrlichiosis ranges from macular to maculopapular to petechial.

HOW are tickborne diseases treated and prevented

If you have been bitten by a tick and develop the symptoms described within a few weeks, a healthcare provider should evaluate the following before deciding on a course of treatment:

- Your symptoms
- The geographic region in which you were bitten
- Diagnostic tests, if indicated by the symptoms and the region where you were bitten

Tickborne diseases can result in mild symptoms treatable at home to severe infections requiring hospitalization. Although easily treated with antibiotics, these diseases can be difficult for physicians to diagnose. However, early recognition and treatment of the infection decreases the risk of serious complications. So, see your doctor immediately if you have been bitten by a tick and experience any of the symptoms described here.

Prevention of tick bites is the best approach. Especially during warmer months, all people should take steps when they go outdoors and return from time outdoors.

Before You Go Outdoors

- Know where to expect ticks. Ticks live in grassy, brushy, or wooded areas, or even on animals. Many people get ticks in their own yard or neighborhood.
- Treat clothing and gear with products containing 0.5% permethrin.
- Use EPA-registered insect repellents containing DEET, picaridin, IR3535, Oil of Lemon Eucalyptus (OLE), para-menthane-diol (PMD), or 2-undecanone.

While Outdoors

- Avoid wooded and brushy areas with high grass and leaf litter.
- Walk in the center of trails.

After You Come Indoors

- Check your clothing for ticks.
- Examine gear and pets.
- Shower soon after being outdoors.
- Check your body for ticks after being outdoors.

This information is reprinted from materials provided by the Centers for Disease Control and Prevention.

This handout is provided to you by NetCE and your healthcare provider. For more information, please consult your physician.

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✓	Course #	Course Title / Credits	Price
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	94300	Fibromyalgia / 3 Credits	$15
	91783	Smoking and Secondhand Smoke / 10 Credits	$40
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Please print name (as shown on credit card)

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/
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Special Offer (before June 30, 2021) $99

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I would like my certificates mailed for an additional $6 _____

Additional Courses _____

Subtotal _____

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Do not include Sales Tax $ 0
(Applicable sales tax is included for sales made to California addressees.)

Grand Total _____

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(Refer to pages 114–118)

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State License # Exp.

State License # Exp.

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License Type: (circle one) MD / PA / DO / OPA / Other:

Address

City State Zip

Phone ( )

Fax Number ( )

Email

(Incomplete information may delay processing.)

Please transfer your selected courses from pages 114–118 to this form.

Payment must accompany this form. To order by phone, please have your credit card ready.

Course #	Credits	Price	Course #	Credits	Price	Course #	Credits	Price
Sub Total $			Sub Total $			Sub Total $		
						Total Price	$	

To read and complete online with no extra shipping charges, please go to www.NetCE.com.

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Please print name (as shown on credit card)

Credit card #

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Expiration date

Security code

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Signature

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Additional Courses

Subtotal

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Answer Sheet

(Completion of this form is mandatory)

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Please note the following:

- In accordance with changes to the *AMA PRA Category 1 Credit™* system, physicians must complete and pass a post-test to receive credit.
- A passing grade of at least 70% must be achieved on each course test in order to receive credit.
- Darken only one circle per question.
- Use pen or pencil; please refrain from using markers.
- **Information on the Customer Information form must be completed.**
- **Include the completed and signed mandatory Evaluation.** Your postmark or fascimile date will be used as your completion date.

#97280 PAIN MANAGEMENT PEARLS: OPIOIDS AND CULTURE—2 CREDITS Please refer to pages 10–11.

Expiration Date: 07/31/23 *May be taken individually for $15*

	A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍

#94300 FIBROMYALGIA—3 CREDITS Please refer to pages 27–28.

Expiration Date: 07/31/23 *May be taken individually for $15*

	A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍

#91783 SMOKING AND SECONDHAND SMOKE—10 CREDITS Please refer to pages 62–63.

Expiration Date: 05/31/22 *May be taken individually for $40*

	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍	11.	❍	❍	❍	❍	16.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍	12.	❍	❍	❍	❍	17.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍	13.	❍	❍	❍	❍	18.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍	14.	❍	❍	❍	❍	19.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍	15.	❍	❍	❍	❍	20.	❍	❍	❍	❍

#94923 ANIMAL-RELATED HEALTH RISKS—15 CREDITS Please refer to pages 112–113.

Expiration Date: 04/30/23 *May be taken individually for $60*

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	11.	❍	❍	❍	❍	21.	❍	❍	❍	❍
2.	❍	❍	❍	❍	12.	❍	❍	❍	❍	22.	❍	❍	❍	❍
3.	❍	❍	❍	❍	13.	❍	❍	❍	❍	23.	❍	❍	❍	❍
4.	❍	❍	❍	❍	14.	❍	❍	❍	❍	24.	❍	❍	❍	❍
5.	❍	❍	❍	❍	15.	❍	❍	❍	❍	25.	❍	❍	❍	❍
6.	❍	❍	❍	❍	16.	❍	❍	❍	❍					
7.	❍	❍	❍	❍	17.	❍	❍	❍	❍					
8.	❍	❍	❍	❍	18.	❍	❍	❍	❍					
9.	❍	❍	❍	❍	19.	❍	❍	❍	❍					
10.	❍	❍	❍	❍	20.	❍	❍	❍	❍					

Evaluation

(Completion of this form is mandatory)

MD21

Last Name _____ First Name _____ MI _____

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To receive continuing education credit, completion of this Evaluation is mandatory.

Please read the following questions and choose the most appropriate answer for each course completed.

1. Was the course content new or review?
2. How much time did you spend on this activity, including the questions?
   (Physicians should only claim credit commensurate with the extent of their participation in the activity.)
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing this course, did you identify the necessity for education on the topic to improve your professional practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
11. Are you more confident in your ability to provide patient care after completing this course?
12. Do you plan to make changes in your practice as a result of this course content?
13. May we contact you later regarding planned changes in your practice and changes in treatment or health status of your patients as a result of this activity?

#97280 2 Credits	**#94300** 3 Credits	**#91783** 10 Credits	**#94923** 15 Credits
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#97280 Pain Management Pearls: Opioids and Culture — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#94300 Fibromyalgia — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#91783 Smoking and Secondhand Smoke — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#94923 Animal-Related Health Risks — If you answered YES to question #12, what change(s) do you plan to make in your practice? _____

_____

_____

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