Multidrug-Resistant Microbial Infections

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, Florida nurse, or CST/CSFA, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Carol Shenold, RN, ICP, graduated from St. Paul's Nursing School, Dallas, Texas, achieving her diploma in nursing. Over the past thirty years she has worked in hospital nursing in various states in the areas of obstetrics, orthopedics, intensive care, surgery and general medicine.

Mrs. Shenold served as the Continuum of Care Manager for Vencor Oklahoma City, coordinating quality review, utilization review, Case Management, Infection Control, and Quality Management. During that time, the hospital achieved Accreditation with Commendation with the Joint Commission, with a score of 100.

Mrs. Shenold was previously the Infection Control Nurse for Deaconess Hospital, a 300-bed acute care facility in Oklahoma City. She is an active member of the Association for Professionals in Infection Control and Epidemiology (APIC). She worked for the Oklahoma Foundation for Medical Quality for six years.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his postgraduate 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, Carol Shenold, RN, ICP, 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 Planners

John V. Jurica, MD, MPH
Margo A. Halm, RN, PhD, ACNS-BC
Shannon E. Smith, MHSC, CST, CSFA
Randall L. Allen, PharmD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

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

Accreditations & Approvals

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Special Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective

In spite of a growing understanding and application of effective control measures, the problem of multidrug-resistant microbial infection remains a ubiquitous and complex issue for communities and hospitals. Each decade seems to usher in a new generation of common bacterial pathogens that have become resistant to available medications, resulting in ongoing excess morbidity, mortality, and healthcare costs. The purpose of this course is to provide an overview of the basics of antimicrobial resistance mechanisms and to review the classes of multidrug-resistant pathogens currently prevalent in healthcare facilities and the community, including guidelines for prevention and options for therapy.

Learning Objectives

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

1. Describe the effects of antimicrobials and the mechanisms of microbial resistance.
2. Review the etiology of emerging resistant organisms in the healthcare setting.
3. Discuss the impact of and possible control measures for methicillin-resistant *Staphylococcus aureus* (MRSA).
4. List and compare additional resistant organisms that may be encountered in the healthcare setting.
5. Outline ways to control and prevent the development of microbial resistance in healthcare facilities, including patient education and outreach to non-English-proficient patients.

Pharmacy Technician Learning Objectives

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

1. Outline properties of antimicrobials, microbial resistance, and specific resistant organisms.
2. Describe the identification, treatment, and prevention of infection with resistant organisms.

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 course material for better application to your daily practice.

INTRODUCTION

Beginning in the 1940s, the development of antibiotics gave clinicians a weapon against infections that had once been the cause of significant morbidity and mortality. Since that time, new generations of microbes with resistance to available antimicrobials have emerged from time to time, posing serious threats to public health [1; 2]. Organisms that were at one time easily treated, such as staphylococcus and streptococcus, have acquired resistance to many standard antibiotics, making them much harder to treat. *Staphylococcus aureus*, originally susceptible to the semi-synthetic penicillins (methicillin, oxacillin) has evolved resistant strains and is the subject of many investigations to find appropriate therapy. Some strains of *Enterococcus faecium* and *Enterococcus faecalis* have been found to be vancomycin-resistant, prompting the search for other pharmacologic options [1; 3]. Complicating matters is the possibility that vancomycin-resistant enterococci (VRE) may be able to pass along this resistance to other common organisms. In a laboratory setting, VRE has been able to spread its resistance, creating a vancomycin-resistant *S. aureus* (VRSA). The development of resistance is likely exacerbated by the overutilization of antibiotics in the outpatient setting [4; 5; 6; 7; 8; 9].

The risk of contracting infections is much greater in patients with a weakened immune system. This includes the very young, the elderly, patients with acquired immune deficiency syndrome (AIDS), those receiving immunosuppressive therapy, and those being treated with antineoplastic drugs.

The urgency of this situation prompted the Centers for Disease Control and Prevention (CDC) to issue guidelines in 2006 (updated in 2017) that assist in the detection, control, and prevention of infection from resistant organisms [10]. Furthermore, in 2015, the CDC published the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (also referred to as the National Action Plan, the Plan, or CARB), presenting strategic goals aimed at accelerating the U.S. government's response to antimicrobial resistance. The National Action Plan (updated in 2020) aims to identify deficits and collectively combat against antimicrobial resistance in the arenas of health care, public health, veterinary medicine, agriculture, food safety, research, and manufacturing [11; 79]. The CDC addresses its role in the National Action Plan through its Antimicrobial Resistance Solutions Initiative and invests in national infrastructure to detect, respond, contain, and prevent resistant infections across healthcare settings, communities, the food supply, and the environment (water, soil). The Plan has identified five goals for collaborative action, including [11]:

- Slowing the emergence of resistant bacteria and preventing the spread of resistant infections
- Strengthening national surveillance among various healthcare, community, and environmental settings as an effort to combat resistance
- Advancing development and use of rapid and innovative diagnostic testing for identification and characterization of resistant bacteria
- Accelerating basic and applied research and development for new antibiotics, antifungals, other therapeutics, and vaccines

- Improving international collaboration and capacities for antimicrobial-resistance prevention, surveillance, control, and drug research and development

The CDC advises that continued collaboration using these goals as a guideline will continue to reduce the proliferation of multidrug-resistant organisms. Since the inception of the Plan, the CDC has released several encouraging statistics, including [11]:

- From 2011 to 2016, a 5% decrease in outpatient antibiotic prescribing was noted (of that, 16% in children).
- From 2012 to 2017, there was a 27% reduction in the number of antibiotic-resistant infections in hospitals, and a 30% reduction in deaths due to these infections.
- For the first time, swabs are being collected to test for resistant germs, with many initiating a containment response.
- More than 80% of hospitals report having an antibiotic stewardship program meeting the CDC's Core Elements.
- There has been substantial online educational engagement with the Be Antibiotics Aware content (e.g., more than 188 million impressions from public service announcements).

Included in these guidelines is the concept that the proliferation of resistant organisms can be diminished by adherence to good sanitary practices. For example, it has been shown that effective handwashing and proper decontamination techniques are the most critical components of any successful infection control program [1; 11].

EFFECTS OF ANTIMICROBIALS

By its mechanism of action, an antimicrobial can either kill susceptible microbes (i.e., microbicidal) or inhibit their growth (i.e., microbiostatic). Antimicrobial drugs have been developed against the whole range of microbial pathogens, including viruses, bacteria, fungi, and many parasites. With respect to bacterial pathogens, examples of bacteriostatic antibiotics are the tetracyclines, macrolides, sulfonamides, and chloramphenicol. Bactericidal drugs include the beta-lactams, carbapenems, vancomycin, and aminoglycosides [13].

Mechanisms by which antimicrobials act on susceptible organisms include [13]:

- Inhibition of cell wall synthesis (penicillins, cephalosporins, vancomycin)
- Alteration of membrane permeability (polymyxins, amphotericin B, imidazoles)
- Inhibition of protein or nucleic acid synthesis (aminoglycosides, tetracycline, chloramphenicol, erythromycin, rifampin, clindamycin)
- Inhibition of essential folate metabolites (trimethoprim, sulfonamides)

When selecting the appropriate medication to treat an infectious process, there are two concepts to consider: "specific therapy" and "empiric therapy." In specific therapy, the infecting organism has been identified and is known to be sensitive to the antibiotic selected. Empiric therapy refers to initial therapy selected on clinical suspicion, before the results of culture and susceptibility are available, yet the patient is sufficiently ill to warrant treatment. In many cases, the site of the infection or the patient history can provide an indication of the most likely pathogen. An empiric therapy regimen often requires the use of a broad-spectrum antibiotic in the initial treatment stage. Appropriate dosages, routes of administration, and avoidance of drug-drug interactions should be considered in an attempt to eradicate the organism.

SELECTION OF ANTIBIOTICS

When bacterial pathogens are isolated on culture of clinical specimens, the susceptibility to a standard group of candidate antibiotics is determined. The degree of susceptibility is usually reported in one of the following three categories [15]:

- Susceptible: The selected drug is effective at the recommended standard dosage.
- Intermediate: The drug is active, but effectiveness is less predictable; thus, the relationship between the minimum inhibitory concentration (MIC) and the achievable blood and tissue levels should be used to help select the most effective route and dosage of the selected drug.
- Resistant: The selected drug is probably not effective by systemic administration at nontoxic dosages.

When the infecting organism and its susceptibility are known, it is unnecessary to use a broad-spectrum antimicrobial. Broad-spectrum antimicrobials may disrupt the patient's normal flora and cause colonization by resistant strains, super infection, or pseudomembranous colitis. For specific therapy, the safest narrow-spectrum antibiotic should be selected, or, in some situations, a combination of drugs should be used.

MECHANISMS OF BACTERIAL RESISTANCE

There are a variety of ways that bacteria can become resistant to antibiotics. They may develop the ability to decrease the intracellular concentration of the drug, decrease cell membrane permeability, inactivate the drug, change the binding site of the drug, or cause the antibiotic to bypass the targeted binding site [16].

A decrease in the intracellular concentration of the drug may result from a molecular alteration in the cell wall that increases the efflux of the antibiotic from the cell. This is seen in tetracycline and quinolone resistance. Decreased cell membrane permeability can be seen as a bacterial defense in beta-lactam antibiotics and quinolone resistance and in *Pseudomonas aeruginosa* resistance to imipenem. Bacteria can also prevent the influx of the antibiotic by decreasing cytoplasmic membrane transport, as seen with the use of aminoglycosides. Some classes of bacteria have, or acquire, the ability to elaborate enzymes that inactivate the drug, as for example beta-lactamases that deactivate beta-lactams, and the phosphotransferases and acetyltransferases, which deactivate aminoglycosides [17].

There are numerous mechanisms that alter or bypass the binding site of antibiotics. The target of the antibiotic may be altered in the DNA gyrase, preventing the binding of quinolones and the methylation of ribosomal ribonucleic acid (rRNA), and further preventing the binding of macrolides. Bacteria may also bypass a binding site by using an alternative metabolic route, as seen in folate synthesis, thus avoiding the effects of trimethoprim [17; 18].

Bacterial resistance to antibiotics may be acquired through mutations in the genes that are responsible for the target site or the necessary transport proteins. When the bacterial cells without the adaptive mutations are killed by an antibiotic, the cells with the mutation continue to replicate, replacing the original population with a resistant one.

Resistance may also be acquired as a result of the transfer of plasmids or transposons, or through chromosomal and extrachromosomal changes. Plasmids are small segments of DNA that are readily exchanged between bacteria. A plasmid that contains a gene for an adaptive mutation can be shared with a large number of nearby bacteria, which may or may not be the same species. In this manner, resistance can quickly spread from species to species—a process known as lateral or horizontal transfer [17; 19].

Chromosomal and extrachromosomal changes can lead either to drug destruction (e.g., beta-lactamases destroy penicillin and cephalosporin derivatives) or to an alteration of drug-receptor/target sites (e.g., methicillin resistance in *S. aureus*). Although it occurs infrequently, chromosomal resistance results from spontaneous mutation in the gene locus that controls susceptibility to a drug and is usually expressed as a change in the drug-receptor/target site.

Extrachromosomal drug resistance achieved by plasmid exchange is potentially more serious and enables micro-organisms to distribute genetic material more rapidly. Chromosomal change is spread mainly to daughter cells from generation to generation. Extrachromosomal resistance involving plasmids can spread between organisms to different strains and even to different species of bacteria. Chromosomal changes usually mediate resistance to a single antimicrobial, while plasmids usually code for resistance to several antimicrobials [20].

EMERGING RESISTANCE

Shortly after penicillin went into widespread use, the first resistant strain of staphylococcus appeared. As other antibiotics were developed, microbes developed resistance to them as well, via changes in their genetic makeup. Now, the use of any new antibiotic is initiated slowly to delay the development of resistance.

Like many infectious diseases, resistant organisms are more likely to appear first in metropolitan areas due to the close proximity of large numbers of people. However, because travel from state to state and country to country now involves only a matter of days or even hours, drug resistance has become a global issue.

According to 2015–2017 data, 15 pathogen groups accounted for about 86% of reported healthcare-associated infections, the most common being *Escherichia coli* (17.5%), *S. aureus* (11.8%), *Klebsiella* spp. (8.8%), and *Pseudomonas aeruginosa* (8%) [167]. Nearly 20% of cases were associated with drug-resistant phenotypes. This is important to note because, in the last several decades, there has been an increase in the ability of these common bacteria to resist standard antibiotics. Examples of this antibiotic resistance include [13]:

- Ampicillin resistance: *Haemophilus influenzae*, *E. coli*, *Salmonella*
- Penicillin resistance: Pneumococci, meningococci
- Methicillin/oxacillin resistance: *S. aureus*
- Vancomycin resistance: Enterococci
- Imipenem-cephalosporin resistance: *Pseudomonas*
- Carbapenem resistance: *Enterobacteriaceae*

Although some organisms remain sensitive to antibiotics for many years, this is not usually the case. From a historical perspective, the major antibiotic resistance events include [14; 22; 54; 136; 166]:

- Penicillinase-producing *S. aureus*, which first appeared in the late 1950s
- Methicillin-resistant *S. aureus* (MRSA), which appeared in the 1960s
- Aminoglycoside (e.g., gentamicin, tobramycin) resistance among gram-negative bacilli (1970s)
- MRSA resistance to fluoroquinolones (1980s)
- Vancomycin resistance among enterococci (1987–1990s)
- The necessity of combination therapy (usually isoniazid, rifampin, pyrazinamide, and ethambutol) in the treatment of tuberculosis (TB) (1990s)
- Linezolid resistance (first reported in 1999, before the drug had received U.S. Food and Drug Administration [FDA] approval)

- Metallo-beta-lactamase-producing bacteria (1990s)
- Fluoroquinolone-resistant *Clostridium difficile* (2000s)
- Carbapenem-resistant *Enterobacteriaceae* (2000s)
- Multidrug-resistant *Candida auris* (2009)
- Colistin-resistant *E. coli* (2016)

The frightening aspect of these changes is that they have occurred over a relatively short period of time. It is vital to take steps to slow the rate of increased resistance.

The CDC's 2019 report Antibiotic Resistance Threats in the United States provides the most recent estimates of infection and death caused by antimicrobial-resistant pathogens, based on data collected through 2018 [14]. According to this report, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 persons die as a result. A new addition to the CDC 2019 list of pathogens that pose an urgent threat is *Candida auris*, an emerging multidrug-resistant yeast responsible for scattered outbreaks of invasive infection and death in hospitalized patients and nursing home residents.

In 2023, the CDC issued a health advisory regarding the emergence of extensively drug-resistant *Shigella* strains [172]. In 2022, about 5% of *Shigella* infections reported to CDC were caused by extensively drug-resistant strains, compared with 0% in 2015. Clinicians treating patients infected with extensively drug-resistant strains have limited antimicrobial treatment options. Currently, there are no data from clinical studies of treatment of extensively drug-resistant *Shigella* to inform recommendations for the optimal antimicrobial treatment of these infections [172].

FACTORS THAT ENCOURAGE THE DEVELOPMENT OF RESISTANCE

As discussed, resistance to antibiotics is an emerging problem in medicine, and its effects are being noted on an ever-increasing scale. Multidrug-resistant organisms are diminishing the ability to control the spread of infectious diseases. The rate at which resistant organisms develop is not solely a function of the use of antimicrobials in humans. It is also influenced by the use of these agents in veterinary medicine, animal husbandry, agriculture, and aquaculture, as has been emphasized in a report on bacterial resistance issued by the U.S. Office of Technology Assessment [24].

IDENTIFIED RISK FACTORS

Patient behaviors are a major contributing factor to antibiotic resistance. Patients frequently stop taking antibiotics when symptoms are alleviated but before an infection is completely eradicated. This suppresses susceptible microbes but may allow partially resistant ones to flourish. Furthermore, many patients with viral infections may demand antibiotics, although the drugs are useless against viral infections, giving hardier bacteria an even greater chance to grow. In some countries, antibiotics are available over the counter, which allows patients to treat themselves, often inappropriately and without the benefit of advice from a physician.

Farmers have learned that by mixing low doses of antibiotics into livestock and poultry feed they can enhance the animals' growth (i.e., the energy the animals would normally use fighting infections may instead be used to promote growth). However, bacteria present in animals may develop resistance to the low levels of antibiotics, which can then be transferred to the bacteria in humans when they consume milk or meat [17; 25]. In instances of food-chain contamination, resistant bacteria can be directly transmitted to humans. Several studies have detected *S. aureus* and MRSA bacteria in samples of meat sold in grocery stores. For example, a study

of 120 retail meat samples from Louisiana grocers found *S. aureus* in 45% of retail pork and 20% of retail beef samples, and MRSA in 5% and 1%, respectively [28].

Parents and guardians of sick children, although well-meaning, also contribute to the kind of misuse of antibiotics that fuels resistant organisms. It is suggested that parents may give their child(ren) previously prescribed or borrowed antibiotics because they wish the child to feel better, to lessen the course of an illness, or the parent is unable to lose essential work time and income to care for their child. This type of antibiotic use is believed to be implicated in the increase of pneumococci resistance to penicillin [12; 26].

The introduction of antimicrobials into the environment (e.g., by aerosolizing fluid from needles or pouring solutions down sinks) can increase antimicrobial resistance in environmental flora. Runoff from farms can have a similar effect. Unfortunately, healthcare professionals are the primary vectors of transmission of micro-organisms from patients and the environment to other patients or to inanimate items or devices.

Research over the last several decades has led to the development of new antibiotics to combat resistant organisms. However, the rate of development has been declining. Possible reasons include slow growth of antimicrobial drug sales and increased regulation by government agencies. In addition, resistance limits the market life of antimicrobial drugs, and there is difficulty converting pharmacologic targets into commercially viable drugs [27]. The net result is a decrease in the availability of new drugs to treat infections caused by resistant organisms.

Healthcare professionals and patients should take responsibility to use antimicrobials wisely and judiciously. Fifty or more years ago, public acceptance was an integral part of establishing quarantines for infectious diseases. The public should again cooperate to help prevent the continuing spread of antibiotic resistance.

The World Health Organization includes the problem of antimicrobial resistance among its list of the 10 most serious threats to public health in 2019 and is working to implement a global action plan designed to address the issue and to encourage prudent use of antimicrobials [139]. To achieve this goal, the global action plan sets out five strategic objectives:

- Improve awareness and understanding of antimicrobial resistance
- Strengthen knowledge through surveillance and research
- Reduce the incidence of infection
- Optimize the use of antimicrobial agents
- Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medications, diagnostic tools, vaccines, and other interventions

NOVEL RISK FACTORS

In addition to the factors that contribute to antibiotic resistance, the COVID-19 pandemic has demonstrated the need for public health preparedness and health system resilience to effectively manage potential novel healthcare crises. In 2022, the CDC released a special report on the impact of the COVID-19 pandemic on antimicrobial resistance in the United States [71]. This report indicated resistant hospital-onset infections and deaths increased at least 15% during the first year of the pandemic due to an increased number of patients, severity of illness, personal protective equipment and lab supply challenges, reduced staff, longer length of stays, and more frequent use of ventilators and catheters [71].

It is difficult to discern the effects that the COVID-19 pandemic had and will continue to have on antibiotic-resistant infections. For example, although ineffective against viruses, it was noted that 80% of patients hospitalized with COVID-19 received an antibiotic, due to the uncertainty of whether the patient was presenting with community-acquired

pneumonia. In contrast to hospital use of antibiotics, between 2019 and 2020, antibiotic use decreased significantly in the outpatient setting due to lower utilization of outpatient health care and less spread of respiratory illnesses as a result of quarantining practices [71].

In addition to an increase in the use of antibiotics during the pandemic, reporting and surveillance also decreased. It was noted that between 2019 and 2020, the CDC's Antibiotic Resistance Lab Network received and tested 23% fewer specimens and isolates [71].

As of 2023, the CDC is estimating that the progress that has been undone will revert to pre-pandemic levels by 2025–2026. In addition, the CDC is exploring investments in infrastructure to better respond to the challenges of antimicrobial resistance and emerging threats simultaneously. Healthcare and community education and preparedness to emerging threats are essential to ensuring the proper use of antibiotics [71].

IMPACT OF RESISTANT PATHOGENS ON HEALTHCARE COSTS

The growth of resistant organisms in healthcare settings has had a significant effect on healthcare costs. Although it is difficult to calculate, researchers estimate that resistant organisms are responsible for up to $20 billion in direct healthcare costs each year, with an additional $35 billion in indirect costs (e.g., lost productivity) [54].

Also added to the equation is the cost of patient treatment involving multidrug therapy or treatment with more expensive single-drug therapies. However, it has been argued that the cost of using more expensive antibiotics, and even using combinations of expensive drugs, is less than the cost of an extended length of stay or a transfer to the intensive care unit (ICU).

The effects of drug resistance can be seen in many aspects of the healthcare delivery system. Nosocomial infections from any organism can increase a patient's length of stay, which may result in a two- to three-fold increase in the cost of the hospital stay. Nosocomial blood stream infection costs more than $40,000 per survivor on average [32]. Add drug resistance to the equation and both the length of stay and the cost of treatment can increase. The prolonged length of stay due to infection may be further extended if the patient must wait for a series of negative cultures in order to be discharged or accepted in transfer to another facility. Compounding this problem is the necessity for hospitals to provide adequate isolation and protective equipment barrier systems when the staff is caring for infected patients. Staff education is time-consuming and costly, as is the barrier equipment that is designed to protect both caregivers and patients. Facilities also are required to invest resources in quality improvement projects in order to monitor the effectiveness of antimicrobial usage and the prevention and control of antimicrobial-resistant organisms [31; 32].

As mentioned, major factors involved in the increased costs due to resistant organisms include increased length of patient stay, staff education, and control measures. Successful attempts to control these factors, and the resultant spread of infections, could result in the savings of billions of dollars every year.

SPECIFIC ORGANISMS AND DISEASES

In addition to the historically important resistant strains, such as penicillinase-producing organisms, several emerging resistant pathogens have gained clinical prominence. These include MRSA, VRE, VRSA, vancomycin-intermediate *S. aureus* (VISA), and Enterobacteriaceae resistant to extended-spectrum cephalosporins and carbapenems. Several diseases, such as TB and pneumonia, also are associated with a list of antibiotics that have become ineffective in their treatment. Cases of multidrug-resistant TB

(MDR-TB) and extensively drug-resistant TB (XDR-TB) are especially difficult to treat [9]. Newer mechanisms of resistance, such as extended-spectrum beta-lactamases and metallo-beta-lactamases, have added to the complexity of the problem of bacterial resistance [22; 33; 34].

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

In the early 1940s, when penicillin first became available, *S. aureus* isolates were highly susceptible. By the early 1950s, 65% to 80% of nosocomial isolates were reported to be resistant to penicillin. Now, more than 90% of community- and hospital-acquired *S. aureus* isolates are penicillin-resistant [13].

The mechanism behind this acquired resistance to penicillin is the production of the enzyme penicillinase. This specific beta-lactamase is able to degrade the drug to an inactive form. The understanding of this mechanism led to the development of several semi-synthetic penicillins (i.e., methicillin, oxacillin, and nafcillin) and the first-generation cephalosporins, which were not susceptible to this particular beta-lactamase [13].

In the early 1960s, methicillin was the first drug to become available to treat infections due to beta-lactamase-producing, penicillin-resistant *S. aureus*. However, strains resistant to methicillin were soon identified in England and shortly after in Continental Europe. In the mid-1970s, MRSA began to be a problem in the United States. Isolates of *S. aureus* resistant to methicillin are also resistant to all other beta-lactam antibiotics, including oxacillin, nafcillin, and cefazolin.

In order to investigate the growing prevalence of MRSA, a large reference laboratory that handles thousands of samples each year investigated the rate of methicillin resistance among isolates of *S. aureus* collected between 1997 and 2004. Researchers found that the highest rate was in isolates from the United States, where 50% of patients with bacteremia had resistant strains. Latin America had a rate of 41%, followed by Asia with 40% and Europe with 26% [35].

The prevalent community-acquired strain in the United States appears to have evolved from the methicillin-susceptible *S. aureus* (MSSA) strain known as ST8. The resistant strains have been designated by the CDC as USA300 and USA400, with USA300 being more common [36; 37]. Both strains are characterized by the Panton-Valentine leukocidin (PVL) gene and the SCCmec IV element, which are responsible for the resistance to beta-lactam antibiotics and rarely identified in healthcare-associated MRSA isolates [38]. The USA400 strains (designated ST1) were first seen in the Midwest in 1966 and appear to have more *S. aureus* toxins than the USA300 strains. The epidemic is predominately caused by the USA300 strain.

Healthy children and adults commonly carry *S. aureus* in the anterior nares. In most individuals, this carriage state is transient, lasting a matter of weeks. At any given time, an estimated 30% of the U.S. population has *S. aureus* nasal carriage [38; 40]. About 2% of the general population carries MRSA in the nose, a rate that increases to 5% among hospitalized patients [39]. As with sensitive strains of *S. aureus*, nasal carriage of MRSA is transient, and carriers are at low risk for developing a serious MRSA infection. Healthcare workers have a 50% to 90% higher *S. aureus* nasal carriage rate than the general population. *S. aureus* can be easily transferred from the anterior nares to the skin and other body areas (e.g., pharynx, axilla, rectum, perineum); consequently, when given a portal of entry, it can cause a significant infection [13; 38]. MRSA infections most commonly present as skin and soft tissue inflammatory lesions (e.g., cellulitis, furuncles) and have been reported as an emerging cause of recurrent skin and soft tissue disease among otherwise healthy persons outside the healthcare setting [38; 41]. In 2005, an estimated 14 million outpatient healthcare visits were related to infections of the skin and soft tissue [42].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Infectious Diseases Society of America recommends an antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.

(https://www.idsociety.org/practice-guideline/skin-and-soft-tissue-infections. Last accessed February 28, 2023.)

Strength of Recommendation/Level of Evidence: Strong recommendation; low-quality evidence

Eradication of nasal *S. aureus* carriage often leads to elimination of the organism from other body sites. However, nasal shedding of organisms does not appear to be important in the direct dispersal of the organism to others. Nosocomial outbreaks have rarely been traced to a "shedder" or to environmental contamination, although the role of the environment remains controversial [43]. Factors more likely involved in the spread of MRSA infections include close skin-to-skin contact between individuals, participation in activities that result in cuts or abrasions, sharing personal items that may be contaminated, poor personal hygiene, and crowded living conditions [38; 43]. *S. aureus* strains causing infection are often of endogenous origin and transmitted from patient to patient via hand carriage by healthcare workers. Invasive infections generally occur as complications resulting from prior skin or soft tissue infections or viral respiratory tract infections, such as influenza [38].

In 2017, an estimated 120,000 people in the United States developed invasive MRSA infection [39; 54]. Of these infections, approximately 75% were healthcare-associated and 25% were community-associated. Some community strains of MRSA appear to be more transmissible, although they are generally not multidrug-resistant, as are some hospital strains [38].

The CDC has noted that epidemiologic and molecular features of MRSA are evolving and, therefore, changing the characteristics that initially made it possible to distinguish community-acquired MRSA from healthcare-acquired MRSA. Reports have described transmission in healthcare settings that are indistinguishable from those associated with community acquisition of infection [44; 45; 46]. These strains could eventually become predominant in both community and healthcare settings [38]. The CDC has stressed, however, that rather than formally categorizing possible MRSA infections as either community- or healthcare-acquired, it is more important to be aware of local resistance patterns for pathogens when diagnosing specific clinical syndromes [38]. A report published by the CDC in 2006 described two outbreaks of MRSA involving otherwise healthy newborns in Chicago and Los Angeles. Although the infections appeared to be superficial, 41% of the cases required hospitalization [47]. In December 2006 and January 2007, 10 cases of severe MRSA community-acquired pneumonia associated with influenza were reported in Louisiana and Georgia, which was a number far higher than expected [48]. Several other community-associated cases of MRSA in otherwise healthy children and adolescents also were reported in 2007, which raised concern regarding the possibility of spreading the organism to additional populations. Surveillance data from 2010 indicated a steady increase in *S. aureus* isolates among community-dwelling adults with pneumonia who are admitted to hospitals in the United States [49]. There have also been reports of community-acquired pneumonia caused by MRSA, including cases of post-influenza pneumonia in young patients. It has therefore been suggested that empiric therapy for pneumonia include coverage for MRSA [41].

In 1970, 62 selected hospitals in 31 states in the United States began routinely reporting their nosocomial infection surveillance data for aggregation into a national database, which became the National Nosocomial Infections Surveillance (NNIS) System. The number of participating hospitals grew to approximately 300 hospitals in 37 states by 2004, when data reporting was concluded. The hospitals reported data about infections in ICUs, high-risk nurseries, and surgical units [50; 51]. In 2005, the NNIS system was replaced by the National Healthcare Safety Network (NHSN). In 2006, the NHSN began reporting data from former NNIS

participants. Participation increased sharply in 2007 due to mandated reporting laws enacted in several states [51].

As far back as the early 1990s, NNIS data indicated that *S. aureus* was a leading cause of nosocomial infection, accounting for 12% of cases. It was the most common isolate for cases of nosocomial pneumonia at 20%, for skin and soft tissue infections at 19%, and the second most common organism causing primary bacteremia at 16%. In 1993, the total number of hospital stays associated with MRSA was estimated to be less than 2,000 [52]. In 2005, approximately 368,600 hospital stays in the United States were attributable to infection with MRSA. This represented a 30% increase between 2004 and 2005 [52]. Other sources have cited an increase from 20% in 1999 to approximately 60% in 2003 [10].

The CDC, however, reported a decrease in these numbers from 2005 to 2011 [39; 54]. Among patients with severe healthcare-associated MRSA infections diagnosed after hospital discharge, the rate of infection decreased 27%, and among patients with severe hospital-onset disease, the rate decreased 54% [39; 54]. These data (extracted from the Active Bacterial Core Surveillance Program) were based on input from nine diverse metropolitan areas, which represented the largest population (approximately 15 million) yet evaluated for changes in the incidence of MRSA infections.

Risk Factors and Transmission of MRSA

While MRSA has been found in hospitals of all sizes, the highest rates have been found in larger hospitals and in federally supported institutions. Although first seen primarily in large, metropolitan teaching hospitals, MRSA has been documented in increasing numbers in long-term care facilities. A 2012 study showed that large hospitals in urban centers act as proliferation and transmission hubs, where patients acquire disease and carry resistant novel strains into the community and especially to regional clinics through referrals [169]. It is theorized that willingness to travel long distances for medical treatment and centralized specialist treatment centers have contributed to the widespread distribution of MRSA.

MRSA frequently colonizes in older, debilitated patients and presents the great risk of being transferred between long-term care and acute-care facilities [170]. Antibiotic use may encourage colonization, and once colonized or infected, a patient may harbor MRSA for months. Then, because of close living conditions, the spread can be rapid. When these patients are then transferred to an acute-care setting, they bring the resistant organisms with them [13; 170].

As noted, MRSA is thought to be transmitted within institutions from patient to patient primarily via hand carriage of healthcare workers who have been contaminated by contact with colonized or infected patients or with devices, items, or environmental surfaces that have been contaminated with body fluids containing MRSA. Colonized or infected healthcare workers may also be reservoirs [43]. The role of the environment seems to be less important, except in burn units, ICUs, and other special facilities where prevention and control measures should be tailored to the area's unique needs and population [11]. Other risk factors for acquiring MRSA during hospitalization vary and depend on the population studied and specific circumstances. Important risk factors include prolonged hospitalization, the length of the period preceding antimicrobial therapy, stay in an ICU or burn unit, or exposure to a colonized or infected patient [13; 43].

One study conducted in Australia identified risk factors for the development of MRSA, including being male, admission due to trauma, immunosuppression, presence of a central line or indwelling urinary catheter, and a past history of MRSA infection. The study also found that MRSA bacteria are more likely to be associated with adverse outcomes and death [55]. Subsequent studies have confirmed the association [56; 57].

In regards to community-acquired MRSA, the CDC has investigated clusters among athletes, military recruits, children, Pacific Islanders, Alaska Natives, Native Americans, men who have sex with men, and prisoners [58; 59; 60; 61; 62; 63; 64; 65]. Factors that increase the risk of spreading MRSA skin infections include close skin-to-skin contact, openings in the

skin such as cuts or abrasions, contaminated items and surfaces, crowded living conditions, and poor hygiene [38]. Recent studies have also documented the emergence of community-acquired MRSA strains in healthcare settings [66; 67].

Preventing and Controlling MRSA

Prevention of MRSA infection has been listed among the safe healthcare practices established by the Agency for Healthcare Research and Quality (AHRQ) and the National Quality Forum. In 2004, the Institute for Healthcare Improvement (IHI) established the *100,000 Lives Campaign* as a challenge to save 100,000 patient lives through healthcare interventions, such as infection prevention. Building on the success of that campaign, the IHI established the *5 Million Lives Campaign* in December 2006 and added reducing MRSA infection to its list of interventions [68]. The U.S. Department of Health and Human Services called for a 25% reduction of MRSA bacteremia in hospitals and a 50% reduction of MRSA invasive infections in the general population by 2013 [69]. By 2014, MRSA bacteremia in hospitals had reduced 13% and MRSA invasive infections in the general population dropped 36% [69]. In the 2019 report, MRSA had reduced an additional 21% compared with 2015 data [14; 69].

According to the 2019 national data analysis, the rate of MRSA bloodstream infections has decreased substantially in the past decade. From 2005 to 2016, the incidence of hospital-onset and community-onset MRSA bloodstream infection declined 74% and 40%, respectively [140]. For the most part, the decline in hospital-onset MRSA infection occurred in the early period (2005–2012); since 2013, the annual rate of hospital-onset MRSA bloodstream infection has not changed significantly. Adjusted community-onset MRSA bloodstream infection rates have continued to decline by 6.9% per year. This decrease in the incidence of severe MRSA infection is likely attributable to the surge in efforts to reduce the number of MRSA infections in the hospital and other healthcare settings, thereby reducing also the numbers of hospital-associated MRSA infections occurring in the community.

Although much progress has been made in reducing the incidence of serious MRSA infection in healthcare settings, *S. aureus* infection remains a significant cause of morbidity and mortality in the United States. A 2019 trend analysis estimates that nearly 120,000 *S. aureus* bloodstream infections and 20,000 associated deaths occurred in the United States in 2017 [140]. This estimate includes healthcare- and community-onset infections caused by methicillin-sensitive and -resistant strains. Suggested strategies for further prevention of *S. aureus* infections include better adherence to CDC recommendations for preventing device- and procedure-associated infections and for interrupting transmission, combined with tailored interventions such as patient decolonization.

Evidence-based guidelines are at the heart of strategies to prevent and control drug-resistant infections. These guidelines have been developed primarily by the CDC and the World Health Organization, infection-related organizations, and other professional societies. The strongest recommendations for preventing and controlling MRSA outbreaks in the hospital or long-term care setting include the use of Contact Precautions (e.g., cohorting patients with MRSA, limiting patient transport) and Standard Precautions (e.g., strict hand washing, gloving, gowning) by all healthcare workers [43]. Outbreaks of MRSA infection have occurred commonly among surgical patients in burn units and in ICUs, and many outbreaks have been traced directly to carriage on the hands of healthcare workers [72]. Patient-to-patient transmission in healthcare settings, usually via the hands of healthcare workers, is a major factor in the incidence of MRSA in acute-care facilities. Hand hygiene is the most basic and single most important preventive measure, yet compliance rates among healthcare workers have averaged only 30% to 50% [70; 73; 78]. One large-scale study found that hand hygiene compliance is further diminished when gloves are worn [162].

SUMMARY OF STRATEGIES FOR PREVENTION OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND OTHER DRUG-RESISTANT MICRO-ORGANISMS
System to identify patients with antibiotic-resistant colonization or infection
Feedback of information to clinicians
Education
Hand hygiene
Environmental decontamination
Dedicated equipment
Masks
Cohorting
Antimicrobial stewardship
Active surveillance testing
Decolonization therapy
Compliance with hand hygiene
Compliance with cleaning protocols
Compliance with Contact Precautions
Source: [11; 80; 163; 164] *Table 1*

Guidelines for the management of MRSA and other drug-resistant micro-organisms published by the CDC and the Society for Healthcare Epidemiology of America (SHEA) focus on the prevention of drug-resistant infections and the judicious use of antibiotics (i.e., antimicrobial stewardship) (***Table 1***) [11; 80; 163; 164]. As noted, the CDC's National Action Plan for Combating Antimicrobial Resistance, which is based on the CDC's National Action Pan, summarized recommendations according to five overall strategies [11]:

- Surveillance
- Strengthen national surveillance efforts
- Development and use of rapid and innovative diagnostic tests
- Accelerate basic and applied research
- Improve international collaboration for prevention, surveillance, control, and drug research and development

Universal surveillance of MRSA at hospital admission has been suggested as a measure to help prevent the transmission of this infection in the healthcare setting; however, the CDC guideline states that the evidence on universal surveillance is limited and recommends surveillance only in specific subpopulations, defined in the context of the infection characteristics of the facility [80]. Since the publication of the guideline, conflicting data have been reported.

In 2008, the FDA approved the first rapid blood test for the detection of MRSA, which allows clinicians to more effectively identify and treat patients with the organism [81]. The BD GeneOhm StaphSR Assay is able to distinguish between MRSA and methicillin-susceptible strains of *S. aureus* and provides results within two hours. The FDA recommends that the test be used in conjunction with other diagnostic techniques and only in patients suspected of having an infection with *S. aureus*; it should not be used to either monitor treatment or rule out complications [81]. Since 2008, several rapid tests have been FDA approved, including the KeyPath MRSA/MSSA Blood Culture Test, the BD MAX MRSA Assay, Xpert MRSA/SA BC Assay [130].

Treatment of MRSA

Vancomycin has been the preferred treatment for both community-acquired and healthcare-associated MRSA. However, concerns have been raised about its efficacy, particularly over its slow bactericidal activity, emergence of resistant strains, and possible "MIC creep" among susceptible strains [82].

Strains of MRSA with reduced susceptibility to vancomycin were first discovered in Japan in 1996. Resistant strains are called VISA and VRSA. Several documented cases of VRSA infection have occurred worldwide, with most occurring in the United States, but as of 2014, these instances are exceedingly rare and are able to be treated with other FDA-approved antimicrobials [83; 124]. In January 2011, the American Society of Health-System Pharmacists, the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists published consensus-based recommendations for vancomycin dosing and monitoring [82].

Other oral agents that are usually active against MRSA include clindamycin, fluoroquinolones, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX). Although not specifically FDA-approved for the treatment of MRSA infection, clindamycin is approved for the treatment of serious infections due to *S. aureus*. Fluoroquinolones are not routinely recommended because resistance can emerge with monotherapy [82]. Among the tetracyclines, minocycline is the most active, followed by doxycycline and tetracycline [82]. As a group, they are about 90% effective. TMP-SMX is not FDA-approved for the treatment of any staphylococcal infection; however, it has become an important option for outpatient treatment of community-acquired MRSA [82].

Several parenteral medications are also useful for both community-acquired and healthcare-associated MRSA infections. These include daptomycin, linezolid, and tigecycline. Daptomycin is a cyclic lipopeptide with bactericidal activity against susceptible gram-positive bacteria, including most isolates of MRSA. At present, daptomycin is usually the preferred alternative therapeutic agent for invasive MRSA infections for which sensitivity to vancomycin is marginal and/or the clinical response is unsatisfactory. Linezolid is FDA-approved for the treatment of skin and soft-tissue infections and nosocomial pneumonia due to MRSA. Although resistance to linezolid has been a rare occurrence, a clinical outbreak of linezolid-resistant *S. aureus* was reported in 2010 [82; 84]. Tigecycline is a derivative of the tetracyclines. Caution should be used when treating patients with bacteremia with tigecycline due to its demonstrated bacteriostatic activity against MRSA. An increase in all-cause mortality noted in phase III and IV clinical trials prompted the FDA to issue a warning regarding the use of tigecycline in patients with serious infections [82]. Daptomycin is FDA-approved for adults with *S. aureus* bacteremia. A possible cross-resistance between daptomycin and vancomycin has been reported [82].

The combination drug quinupristin/dalfopristin has also been advocated for severe infections; however, it has side effects that have led to a significant number of patients requiring discontinuation of therapy [82].

MRSA is far from being the only difficult resistant organism in healthcare, but it was one of the first to draw major attention to the growing problem of resistant organisms. MRSA has the potential to affect almost all hospital populations; however, if proper hand washing procedures are followed and antibiotic prescription patterns are monitored and controlled, it may be possible to reduce the number of infections. Research is ongoing for a vaccine against MRSA.

VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE)

Enterococci are catalase-negative, gram-positive, facultative anaerobic cocci that have classically belonged to the Lancefield group D streptococci. In the mid-1980s, they were officially classified into their own genus. Of the many species of enterococci, the clinically important types are *E. faecalis*, accounting for 80% to 90% of clinical isolates of enterococci, and *E. faecium*, the second most commonly isolated species, making up 5% to 16% of clinical isolates [13]. *E. faecium* is the most difficult to treat of all the enterococcal species because it is often resistant to both vancomycin and ampicillin [85].

Enterococci are normally found in the intestinal tract and the female genital tract, as well as in the environment. When they cause a pathologic process, the usual result is a urinary tract infection (UTI), bacteremia, wound infection, or endocarditis [9].

Enterococci are often antibiotic-resistant, opportunistic pathogens recovered from patients who have received multiple courses of antibiotics over prolonged periods. These organisms were established as a cause of endocarditis and UTIs in the early 1900s. By the 1980s, subtypes of the species were known to be a common cause of nosocomial infections. The emergence of enterococci with vancomycin resistance has been followed by an increase in the frequency of infection with this species.

Vancomycin is a tricyclic glycopeptide antibiotic with many useful properties, including the ability to be administered either orally or parenterally. Vancomycin was historically effective against the organism until VRE were reported in Europe in 1988. VRE were subsequently reported in the United States in 1989 and have become a worldwide problem since that time. A study on burn patients showed a greater than 20-fold increase in the frequency of VRE by 1993. By 2006, the organism was found in over 10% of "high-risk" patients, defined as patients who had a hospital admission or antibiotic therapy within the past year [86; 87]. Vancomycin resistance has been associated with increased mortality, length of hospital stay, admission to ICU, surgical procedures, and costs. A patient's risk of acquiring VRE has been shown to increase significantly when more than 50% of the ICU population consists of patients colonized with VRE. The risk also increases when the number of days of exposure to a VRE patient exceeds 15 days [10].

As noted, VRE poses treatment difficulties because the resistance has often appeared in the more ampicillin-resistant strains of *E. faecium*. These strains also are typically resistant to multiple other antimicrobial drugs, including erythromycin, tetracycline, fluoroquinolones, rifampin, and the aminoglycosides [85]. Because most enterococci are inherently resistant to many antibiotics, it is believed that the genes for intrinsic resistance reside in the chromosomes.

Risk Factors for VRE

Several risk factors have been identified for VRE, including age older than 60 years, prior hospitalization, placement in the ICU, major underlying disease, surgery, immunosuppression, exposure to invasive devices, and long-term antibiotic therapy [125]. The reservoirs most often identified in outbreaks of VRE include infected or colonized patients, healthcare workers' hands, and contaminated inanimate objects. Risk of transmission is greatly increased in patients receiving care at multiple facilities and in patients who are transported between acute care, ambulatory and/or chronic care, and long-term care environments [9; 11; 72].

Treatment of VRE

During the 1990s virtually no antimicrobial agents were available to treat VRE infections. Although this has changed, resistance to each new agent has emerged in clinical isolates [11]. The antibiotics with known effectiveness in vitro against VRE include linezolid, daptomycin, and tigecycline. Most experience has been with linezolid; unfortunately, a linezolid-resistant strain has been found in 10% to 20% of the isolates in some institutions. Tigecycline may be considered a drug of choice because it has good activity against gram-negative bacilli and anaerobes. Most VRE infections arise from an intra-abdominal source and may be present with other organisms, making tigecycline an effective choice [88].

Quinupristin/dalfopristin has emerged as an approved option for treatment of VRE. It is a streptogramin with bacteriostatic activity against vancomycin-resistant *E. faecium* but not against *E. faecalis* [89; 90]. Myalgia/arthralgia is the most frequently reported treatment-limiting adverse effect. In vitro studies of quinupristin/dalfopristin combined with ampicillin or doxycycline have shown enhanced activity against VRE; however, the clinical use of combined therapy has not been established [89]. Studies comparing the efficacy and safety of quinupristin/dalfopristin to linezolid found that the two drugs had comparable clinical responses [91].

ERYTHROMYCIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

There has been a considerable amount of interest in and discussion about MRSA. However, other forms of resistant *S. aureus* also exist, such as erythromycin-resistant *S. aureus* (ERSA). Fortunately, the choice of antibiotics is not as severely limited in the case of ERSA as with MRSA. Therefore, ERSA has not received the same amount of attention, but it and other resistant organism outbreaks have encouraged researchers to develop a molecular analysis of bacterial isolates that may allow the identification of endemic strains of bacteria during an outbreak. This would facilitate a greater probability of identifying the source of the outbreak and help with the choice of a proper antibiotic [92]. Pulsed-field gel electrophoresis (PFGE) remains the gold standard for ERSA typing due to its high discriminatory power [93; 94]. Penicillin (and alternately, amoxicillin) is the treatment of choice [54]. In patients who cannot tolerate penicillin, clindamycin is a good choice as a substitute for erythromycin, but reports have shown that some strains have developed resistance to both antibiotics [54; 95; 96; 97; 98].

PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

Streptococcus pneumoniae infections are a leading cause of morbidity and mortality in the United States, resulting in an estimated 150,000 hospitalizations due to pneumonia (5% to 7% mortality rate), 2,000 cases of meningitis (8% mortality rate in children and 22% among adults), and more than 4,00 cases of bacteremia (20% overall mortality rate and up to 60% mortality rate in older adults) [99]. Additionally, *S. pneumoniae* causes up to 20% of all acute otitis media infections [99]. It is also a major cause of sinus infections. Despite the availability of rapid tests (e.g., Binax NOW), the diagnosis of *S. pneumoniae* infection is usually presumptive and the therapy usually empiric. The full impact of the problem is difficult to assess because infection with a drug-resistant strain only became a reportable condition as of 2010 in the CDC's National Notifiable Diseases Surveillance System [102; 103].

In the 1940s, all *S. pneumoniae* were exquisitely susceptible to penicillin. Minute concentrations of penicillin not only inhibited the growth of these organisms, but also killed them by rapid lysis. It was not until the 1960s that reports of strains of pneumococci with intermediate levels of penicillin resistance began to appear. In 2019, there were approximately 30,300 cases of invasive pneumococcal disease in the United States; up to 30% of those cases are resistant to one or more antibiotics [105]. Compounding the problem is the fact that patients with pneumococcal pneumonia also show resistance to many other antibiotics, including some macrolides, tetracycline, and TMP-SMX [102; 106].

The mechanism of pneumococcal resistance to penicillin involves alterations in one or more of the penicillin-binding proteins that are important in the synthesis of the bacterial cell wall. Many strains of *S. pneumoniae* are penicillin resistant due to this mechanism, including some that also are resistant to cephalosporins, macrolides, tetracyclines, and clindamycin. All of the multidrug-resistant strains in the United States remain sensitive to vancomycin and linezolid; most remain sensitive to broad-spectrum quinolones [107].

Penicillin resistance occurs in a number of different pneumococcal serotypes, but it appears to be much more prevalent among those types that most frequently cause disease in children. This is consistent with the hypothesis that many of these organisms originate in children and spread to adults. This concept is supported by the occurrence of outbreaks of resistant pneumococci in childcare facilities.

One of the concerns regarding this organism is the frequency of its identification among the very young and the very old, in which infections act more quickly and can be more difficult to treat. Pneumococcus is the most commonly identified cause of bacterial pneumonia and bacterial meningitis. Children younger than 2 years of age and adults 65 years of age and older account for more nearly 40% of all cases [100]. Another concern is the propensity of penicillin-resistant pneumococci toward resistance

to multiple antibiotics. In areas where multiple resistant strains are common, the therapeutic choices for the treatment of life-threatening infections may be limited to drugs that are either toxic for the patient or in limited use [109].

Risk Factors for Penicillin-Resistant *S. Pneumoniae*

Crowded conditions, such as those found in day care centers, and prior beta-lactam antibiotic therapy are the principal predisposing factors to colonization and disease. Populations at greatest risk include the elderly, children younger than 2 years of age, African Americans, American Indians, Alaska Natives, and persons with underlying medical conditions, including human immunodeficiency virus (HIV) infection and sickle-cell disease [99]. Acute otitis media and meningitis are the two conditions caused by resistant pneumococci that are the most difficult to treat [102]. Treating meningitis is especially challenging when caused by a strain of *S. pneumoniae* that is highly resistant to penicillin and third-generation cephalosporins [101]. The concentration of beta-lactams in cerebrospinal fluid and middle ear fluid are frequently inadequate to allow prompt elimination of some intermediate and highly resistant pneumococcal strains.

Pneumococci are easily spread from person to person by respiratory droplets or through direct inoculation of secretions [99]. The organism may spread from patients to hospital staff; the carrier rates among nurses caring for patients with pneumococcal pneumonia can be high. This increases the probability of nosocomial dissemination of resistant pneumococci, especially if the infection is not detected when the patient is admitted. Penicillin resistance has its most dramatic effects in patients with pneumococcal meningitis.

Treatment of Penicillin-Resistant *S. Pneumoniae*

For community-acquired pneumonia, the consensus opinion is to use azithromycin in otherwise healthy patients who can be treated as outpatients. Older patients or those with comorbidities usually respond well to a beta-lactam agent, such as ceftriaxone or high-dose amoxicillin/clavulanate plus a macrolide [110]. The organism is uniformly susceptible to vancomycin and imipenem [106]. As penicillin-resistant *S. pneumoniae* continues to increase in the United States, there are signs of emerging fluoroquinolones-resistant strains as well.

Some experts believe that the use of therapeutic agents, such as ceftriaxone or clindamycin for acute otitis media and vancomycin or rifampin for meningitis, may be necessary. Although drugs with high levels of activity against penicillin-resistant pneumococci may solve this problem, antimicrobial drugs alone probably will not provide the final answer.

Immunization Against Penicillin-Resistant *S. Pneumoniae*

Pneumococcal vaccines have been improved over time by broadening the coverage of serotypes in the vaccine to include those that are causing the most common invasive infections. In the past, a single agent, the 23-valent polysaccharide vaccine (PPSV23) (Pneumovax), had been recommended for use in selected adults with conditions of impaired immunity, and for all adults older than 65 years of age [74]. This vaccine provided some protection against 85% to 90% of the pneumococcal serotypes that cause invasive disease in these populations [77]. In 2021, PCV15 (replacing PCV13) and PCV20 were introduced for adults [111].

The use of pneumococcal conjugate vaccines in the pediatric age group has been followed by a reduction in the incidence of pneumococcal disease among children, and, indirectly, among adults as well. By 2013, the incidence of invasive pneumococcal disease caused by serotypes represented in the PCV13 vaccine had declined in the adult population older than 65 years of age by approximately 50% compared with 2010 [171]. In 2012, upon approval by the FDA, the ACIP recommended the use of PCV13 for adults with immune deficits and other conditions that impose a heightened risk for invasive pneumococcal infection. After reviewing additional data in 2014, the ACIP extended its recommendation for PCV13 use to all adults older than 65 years age [171].

In 2021, the ACIP again amended its recommendation for PCV use in older adults, based on sharp declines in pneumococcal disease among adults since the advent of PCV13 use in children [171]. The ACIP now recommends a routine single dose of PCV20 for adults older than 65 years of age. Alternatively, one dose of PCV15 may be administered followed by PPSV23 given at least one year after the PCV15 dose. A minimum interval of eight weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid (CSF) leak to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups [74; 171]. Current information, schedules, and guidance for adult immunizations is maintained at the CDC/ACIP website at https://www.cdc.gov/vaccines/schedules.

CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

Enterobacteriaceae are gram-negative bacilli that form part of the human intestinal flora and are spread easily among humans by way of hand carriage and contaminated food and water. These bacteria are among the most common pathogens causing cystitis, pyelonephritis, peritonitis, pneumonia, and catheter-associated infections. *Enterobacteriaceae* are also able to share newly acquired genetic material through horizontal gene transfer, mediated principally by plasmids and transposons. High-level antimicrobial resistance caused by cabapenemases acquired and shared in this manner has increasingly been reported in *Enterobacteriaceae* over the past 15 years, in the United States and worldwide [135].

Infection with carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenemase-producing *Enterobacteriaceae* is an emerging and important challenge in healthcare settings because CRE are resistant to nearly all antibiotics [30; 54]. Healthy persons in the community setting usually do not become infected with highly resistant *Enterobacteriaceae*. CRE infection most often occurs in hospitals, nursing homes, and other healthcare settings where broad-spectrum antibiotic usage and risk factors for infection (e.g., indwelling catheters, medical devices, surgical wounds) are prevalent. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and carbapenem-resistant *E. coli* are the species of CRE most commonly encountered in the United States, with an estimated 13,100 healthcare-associated infections each year resulting in approximately 1,100 deaths [14]. Half of patients who acquire a CRE bloodstream infection will die from the infection, but fortunately, this invasive form of CRE infection is relatively uncommon. If CRE becomes a problem in one facility in a community, then typically there is propagation to other facilities in the region as well. To help protect patients and prevent transmission, the CDC has provided CRE-specific guidance for clinicians and hospital staff in the form of a CRE toolkit, updated in 2013 and 2015 [30].

Klebsiella accounts for most healthcare-associated infections such as urinary tract infections and pneumonia. The bacterial enzyme, carbapenemase, was first identified in *K. pneumoniae* isolates, but can also be produced by other organisms, such as *E. coli*. *K. pneumoniae* carbapenemase (KPC)-producing bacteria have rapidly emerged as a cause of multidrug-resistant infections worldwide [33].

The isolates that harbor KPCs are able to hydrolyze a broad spectrum of beta-lactams, including the penicillins, cephalosporins, and carbapenems. This is worrisome as the carbapenems are often the agents of last resort for resistant gram-negative infections [9; 14; 137; 138].

Risk Factors

Limited functional status and complete dependence upon healthcare personnel for activities of daily living have been identified as independent risk factors for infection and colonization with CRKP [80]. Infections have been associated with high rates of morbidity and mortality among persons with prolonged hospital stays, the critically ill, and those exposed to invasive devices, such as ventilators or central venous catheters [30].

Diagnosis

KPC-producing bacteria often are misidentified by routine susceptibility testing and incorrectly reported as sensitive to all carbapenems. Resistance to ertapenem is common and may be a better indicator of the presence of KPCs. Proficiency testing studies have shown both false resistance and false susceptibility with imipenem and meropenem [141; 142; 143; 144]. Guidelines published in 2009 by the Clinical and Laboratory Standards Institute (CLSI) recommend that CRE with elevated MICs be tested for the presence of carbapenemases using the modified Hodge test (MHT). The MHT has demonstrated sensitivity and specificity exceeding 90% [30].

Infection control measures do not always detect all resistance problems, but they may help to limit the spread of KPCs. Surveillance, cohorting patients colonized and infected with KPC bacteria, and intensifying hygiene and cleaning practices are effective strategies to control the spread of KPCs [30; 141; 142; 143; 144]. The CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) have developed guidelines for CRE infection prevention and control [30].

Treatment

The optimal treatment of infections caused by KPC-producing bacteria has not been well established; however, most KPC-producing organisms are susceptible to tigecycline. Polymyxins used as monotherapy have demonstrated low success rates; their use in combination therapy has demonstrated higher success rates [138; 143]. Polymyxins may be less nephrotoxic than previously believed, but caution with their use has been recommended. Furthermore, polymyxin resistance in KPC-producing organisms increasingly has been reported [143].

MULTIDRUG-RESISTANT *ACINETOBACTER BAUMANNII*

Acinetobacter is a group of bacteria commonly found in soil and water. Of the more than 30 differentiated species, *Acinetobacter baumannii* is the most clinically relevant. Prior to the 1970s, most *A. baumannii* were fully susceptible to antibiotics. In the last few decades, multidrug-resistant *A. baumannii* has emerged as a major cause of healthcare-associated infections, including bacteremia, pneumonia, meningitis, and urinary tract and wound infections, accounting for an estimated 80% of reported infections [145; 146; 147]. There have also been reports of pan-resistant *A. baumannii*. The increased use of broad-spectrum antibiotics and the technologic improvements in invasive medical procedures have contributed to the ability of this pathogen to develop multiple resistance mechanisms [147].

Risk Factors

The main characteristics of *A. baumannii* are its tolerance to desiccation and ability to survive for prolonged periods in the environment. Isolates have been detected on hospital bed rails as many as nine days following discharge of an infected patient. Digestive tract colonization is common in hospitalized patients. Patients in ICUs and those with prolonged hospital stays may be particularly vulnerable to infection with *A. baumannii*. Clinical outcomes are worse and mortality rates as high as 54% have been reported in ICUs. *A. baumannii* wound infections associated with a healthcare setting have also been reported in military personnel in Iraq and Afghanistan [145; 150; 151]. Most of the reported outbreaks have been attributed to multidrug-resistant isolates, with limited available treatment options [152; 153; 154; 155]. Use of Contact Precautions, hand hygiene, thorough environmental cleaning, and cohorting patients has been emphasized to control the spread of infection [145; 147].

Diagnosis

The pathologic changes associated with *A. baumannii* infection are not normally distinguishable from those caused by other aerobic gram-negative bacilli, such as *Enterobacter* species or *P. aeruginosa*, making diagnosis difficult. The primary task is to differentiate colonization from infection [156].

Treatment

A. baumannii has become resistant to almost all available antimicrobials. Carbapenems remain the treatment of choice, even though increasing carbapenem-resistant *Acinetobacter* isolates have been reported worldwide. Most isolates remain sensitive to colistimethate, which is clinically effective. Other treatment options include high-dose ampicillin/sulbactam and tigecycline. It remains unclear whether combination therapy is more effective than monotherapy [145].

MULTIDRUG-RESISTANT *PSEUDOMONAS AERUGINOSA*

The gram-negative bacteria *P. aeruginosa* are a leading cause of healthcare-associated infections (32,600 in 2017), which often can be life-threatening (resulting in 2,700 deaths in 2017) and challenging to treat [168]. *P. aeruginosa* is commonly found in soil and water and occurs regularly on the surfaces of plants and occasionally on the surfaces of animals. As an opportunistic pathogen, *P. aeruginosa* exploits a break in host defenses in order to initiate infection [157]. The increasing frequency of multidrug-resistant strains of *P. aeruginosa* is worrisome due to the limited availability of other effective agents.

P. aeruginosa is naturally resistant to many antimicrobials, and an estimated 13% of isolates are multidrug-resistant [54; 168]. Multidrug-resistant *P. aeruginosa* is resistant to all or nearly all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems. Rates of resistance have been reported to be increasing both worldwide and within specific institutions, such as ICUs. The emergence of multidrug resistance during treatment of *P. aeruginosa* has been associated with increased mortality, hospital stay, and hospital cost when compared with patients with susceptible infections or baseline resistance [158].

Risk Factors

The populations reported to be at greatest risk of infection from *P. aeruginosa* include patients who are immunocompromised, those with prolonged hospital stays and prolonged use of antimicrobials, and those being mechanically ventilated. In patients hospitalized with cancer, cystic fibrosis, and burns, the case fatality rate from *P. aeruginosa* infection is nearly 50%. According to CDC estimates, the number of hospital-associated MDR *P. aeruginosa* infections has declined in recent years, from 46,000 cases in 2012 to 32,600 cases in 2017. This trend is attributed to ongoing infection control measures and appropriate antibiotic use [168]. Small retrospective case-control studies have identified advanced age, intravenous drug abuse, and the use of specific antimicrobials as potential risk factors for infection with multidrug-resistant *P. aeruginosa*; however, larger studies are needed to confirm these findings [158].

Diagnosis

Diagnosis of *P. aeruginosa* infection depends upon isolation and laboratory identification of the bacterium. A culture should be obtained from the site of infection (i.e., blood, skin lesions, drainage fluid, urine, cerebrospinal fluid, or eye). *P. aeruginosa* can be identified based upon its gram morphology, inability to ferment lactose, a positive oxidase reaction, and its ability to grow at 42°C. Localized infection may produce a fruity smell, and pus may be greenish. Fluorescence under ultraviolet light may help with the early identification of *P. aeruginosa* colonies. Fluorescence is also used to suggest the presence of *P. aeruginosa* in wounds [33; 157].

Treatment

Patients with severe multidrug-resistant *P. aeruginosa* infections should be treated with combination therapy that consists of an antipseudomonal beta-lactam and an aminoglycoside or fluoroquinolone (rather than aminoglycoside and fluoroquinolone combinations), to provide adequate therapy and improve patient outcomes. Colistin with adjunctive therapy, such as a beta-lactam or rifampin, may be a useful agent when antimicrobial options are limited; however, patients should be monitored closely for toxicities associated with this agent [158; 168].

CEPHALOSPORIN-RESISTANT *NEISSERIA GONORRHOEAE*

Neisseria gonorrhoeae is the bacterium responsible for gonorrhea, the second most commonly reported sexually transmitted infection (STI) in the United States. Gonorrhea can affect the reproductive tract in women, and the urethra, mouth, throat, eyes, and rectum of both women and men. Gonorrhea plays an additional, major role in facilitating the acquisition and transmission of HIV. In 2018, a total of 1.6 million new cases of gonorrhea were reported in the United States; however, many cases are asymptomatic and therefore not reported, making the true incidence likely higher [127].

Due to its efficient DNA uptake mechanism, *N. gonorrhoeae* has developed resistance to most antimicrobials, such as sulfonamides, penicillin, tetracyclines, fluoroquinolones, and quinolones, which resulted in treatment recommendations that rely primarily on oral cephalosporins. Surveillance of the emergence and spread of cephalosporin-resistant *N. gonorrhoeae* prompted the CDC to recommend against cephalosporin monotherapy (particularly oral administration) for the treatment of gonorrhea [29; 131; 132; 133].

Risk Factors

Factors that may increase the risk of gonorrhea infection include younger age, new or multiple sex partners, and previous diagnosis of gonorrhea. Women and men younger than 25 years of age, including sexually active adolescents, are at highest risk, accounting for 50% of all reported infections. Other risk factors include inconsistent condom use, sex work, and drug use. The risk factors for pregnant women are the same as for nonpregnant women [127; 134].

Diagnosis

Specific diagnosis of *N. gonorrhoeae* infection may be performed by testing endocervical, vaginal, urethral (men only), pharyngeal, rectal (persons who have receptive anal intercourse), or urine specimens, using culture or nucleic acid testing [128]. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected treatment failure following the updated treatment regimen should culture relevant clinical specimens and perform antimicrobial susceptibility testing of *N. gonorrhoeae* isolates (i.e., disk diffusion, Etest, or agar dilution) [29]. Clinicians may also consult a specialist for guidance in clinical management and report the case to the CDC through state and local public health authorities. All persons diagnosed with gonorrhea also should be tested for other STIs, including chlamydia and syphilis. As gonococcal infection can facilitate HIV transmission, HIV testing is strongly encouraged [29; 128].

Treatment

On the basis of experience with other bacteria that have developed antimicrobial resistance rapidly, the CDC previously favored combination therapy using two antimicrobials with different mechanisms of action (e.g., a cephalosporin plus azithromycin) to improve treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins. In 2020, the CDC updated its guidelines with consideration to antimicrobial stewardship and now recommend a single dose of ceftriaxone 500 mg IM for treatment of uncomplicated urogenital, anorectal, and pharyngeal *N. gonorrhoeae* infection [29]. Use of azithromycin is no longer recommended, and doxycycline is only recommended for coadministration when the patient is coinfected with *Chlamydia trachomatis* (100 mg twice daily for seven days) [29; 75].

MULTIDRUG-RESISTANT *CANDIDA AURIS*

Candida auris is an emerging multidrug-resistant yeast that has caused isolated cases of invasive infection and outbreaks of candidiasis in healthcare settings worldwide [149; 159]. It is difficult to identify by standard laboratory methods and may be misidentified or result in inappropriate management and further spread of infection unless specific methodology is applied. The annual number of reported cases of *C. auris* infection in the United States has increased from fewer than 5 in 2015 to 323 in 2019 [14]. Most *C. auris* cases in the United States have been identified in the New York City, New Jersey, and Chicago areas, followed by outbreaks in California and Florida.

Risk Factors

C. auris, like other *Candida* species, readily colonizes the skin and mucous membranes of patients confined to hospital and other facilities where antibiotic usage is common. Under conditions of poor host defense, such colonization can lead to serious illness, including bloodstream infection and death. Risk factors include prolonged confinement in a healthcare facility, indwelling central venous or urinary catheters, and previous antibiotic or antifungal medications. Prolonged patient colonization and persistence of viable yeasts on environmental surfaces facilitate spread of *C. auris* between patients in healthcare facilities.

C. auris should be suspected whenever a clinical isolate is identified as an unusual *Candida* species or the yeast isolate cannot be identified to species level. *C. auris* infection is a nationally notifiable condition. Healthcare facilities and laboratories that suspect they have a patient with *C. auris* infection are urged to contact state or local public health authorities and the CDC immediately for guidance [161].

Treatment

The response to antifungal therapy is variable and unpredictable; mortality rates of 30% to 60% have been reported in association with outbreaks in some parts of the world [149]. Options for the treatment of *C. auris* infection are limited because of resistance to one or more of the available classes of antifungal drugs. In a study of isolates from 54 cases in five countries outside the United States, 93% of isolates were resistant to fluconazole, 35% were resistant to amphotericin-B, and 7% were resistant to echinocandins; 41% were resistant to two antifungal classes and 4% were resistant to all three classes [53].

For simple colonization (including asymptomatic, catheter-associated candiduria), management should center on infection control measures to include hand hygiene, Contact Precautions, environmental disinfection, and in the setting of urinary colonization, removal of any indwelling catheter. The recommended initial choice of therapy for patients with clinical signs of infection is an echinocandin (e.g., caspofungin, micofungin) at standard dosing [161; 149].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Infectious Diseases Society of America, lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable treatment alternative for infection with *Candida* spp. resistant to other antifungal agents.

(https://www.idsociety.org/practice-guideline/candidiasis. Last accessed February 28, 2023.)

Strength of Recommendation/Level of Evidence: Strong recommendation; high-quality evidence

Prevention and Control of Spread

The CDC provides specific guidance for infection prevention and control of *C. auris* transmission. The primary control measures for prevention of transmission in healthcare settings include adherence to hand hygiene, Standard and Contact Precautions, cleaning and disinfecting the patient care environment and reusable equipment, screening contacts of newly identified cases and carriers, and laboratory surveillance of clinical specimens any new transmission events [161].

MYCOBACTERIUM TUBERCULOSIS

It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*; although the majority represent latent (asymptomatic) infection, about 10 million persons develop clinically active TB each year [104]. During the period 1985–1992, there was a resurgence of TB in the United States, accompanied by a rise in the isolates resistant to first-line drugs. In 1989, the Advisory Council for the Elimination of Tuberculosis (ACET) published a plan for eliminating TB in the United States by 2010. This has turned out to be an unrealistic goal [112]. In 2000, according to a report published by the Institute of Medicine (IOM), the annual rate of decline in new cases of TB was 7.5%. Assuming an increase to a 10% rate of decline from 2000–2010, along with the development of new tools that would double the rate to 20% thereafter, the IOM has indicated that it would take until 2035 to achieve TB elimination [112]. Unfortunately, the 2010 rate was 36-fold higher than the elimination goal, making the 2035 goal unfeasible [76]. Stop TB

USA projected TB elimination by 2052 among non-Hispanic white residents born in the United States, with persistence for additional decades for U.S.-born minorities and foreign-born residents [76].

Based on results from the National Tuberculosis Surveillance System, the CDC has reported that there were 7,882 new cases of TB reported in the United States in 2021, a rate of 2.4 cases per 100,000 persons, down from the rate of 4.2 per 100,000 reported in 2011, though relatively stable since 2013. In should be noted that the 2021 incidence statistics are 12% lower than those of collected in 2019, but it is unclear if this decline is COVID-19 pandemic-related, when underdiagnosis and public healthcare restraints were at their peak [104]. The rate was higher among foreign-born persons residing in the United States than among native-born individuals. Although the number of cases in the United States has been declining since 1992, the CDC has indicated that the decline may in part be due to better defined clinical and laboratory criteria for the diagnosis [113].

M. tuberculosis is the etiologic agent for the common disease in humans and differs from the mycobacterium organisms that cause disease in cattle and birds. It has different properties than *Mycobacterium leprae*, the causative agent of leprosy. *M. tuberculosis* is neither gram-positive nor gram-negative; as such, it does not have the characteristics of either. Rather, the bacteria are described as "acid fast," denoting their inability to absorb certain dyes and stains.

Infection with *M. tuberculosis* begins with inhalation of infected droplet nuclei into the lower recesses of the respiratory tract, followed by a brief bacillemia. In most healthy persons with intact immunity, a macrophage-mediated cellular immune response terminates progression and renders the infection inactive. This is referred to as latent or dormant (i.e., asymptomatic) infection. Up to 13 million persons in the United States are infected with the latent or asymptomatic form of TB [114]. In these persons, the tuberculin skin test will be positive, although there is no active disease and the individual is not infectious. If the disease becomes active, it should be treated [115; 116]. Reactivation of latent TB occurs most commonly in persons with weakened immune systems, especially in those with HIV infection [117]. Some authorities have suggested that individuals with latent TB also should be treated in an effort to control the spread of the disease [110]. Approximately 5% to 10% of persons who do not receive treatment for latent infection will develop active TB. The risk is highest during the first several years after infection [118].

In the 1950s, streptomycin was found to effectively treat TB; however, resistance soon developed, not only to streptomycin but also to several other antibiotics, including rifampin, isoniazid, pyrazinamide, and ethambutol, all of which had previously shown reasonable effectiveness against TB. MDR-TB was subsequently defined by the CDC as *M. tuberculosis* bacilli that are resistant to at least the two most effective antituberculosis drugs, isoniazid and rifampicin. The emergence of MDR-TB has become a serious threat to elimination of the disease [114]. XDR-TB has been defined as *M. tuberculosis* bacilli that are resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) [119; 120]. Because of its resistance to both first- and second-line drugs, treatment of patients with XDR-TB often is ineffective. XDR-TB is of particular concern in patients with HIV or other immunodeficiency [119].

Risk Factors for *M. Tuberculosis*

As noted, the spread of TB in the United States has often correlated with immigration into the country by individuals from areas where the disease is endemic. Mexico, Laos, Vietnam, Africa, Eastern Europe, Russia, and South Korea are common countries of origin of MDR-TB cases introduced into the United States [118]. The incidence of TB among foreign-born individuals is 15.8 times higher than in U.S.-born individuals [104]. The incidence of MDR-TB cases among foreign-born individuals is 17.5 times higher than in U.S.-born individuals [121]. The increase in these cases has primarily been seen in urban areas, where close contact with large numbers of people compounds the risk [115].

ANTITUBERCULOSIS DRUGS CURRENTLY IN USE IN THE UNITED STATES	
First-Line Drugs	**Second-Line Drugs**
Isoniazid (INH) Rifampin (RIF) Ethambutol (EMB) Pyrazinamide (PZA) Rifabutin[a,b] Rifapentine[b]	Capreomycin Cycloserine Ethionamide p-Aminosalicylic acid Amikacin/kanamycin[a] Levofloxacin[a] Gatifloxacin[a] Moxifloxacin[a] Streptomycin (SM)[b] Bedaquiline
[a]Not approved by the FDA for use in the treatment of tuberculosis (TB). [b]Of the approved drugs INH, RIF, EMB, and PZA are considered first-line agents and form the core of initial treatment regimens. Rifabutin and rifapentine may also be considered first-line agents under specific situations. SM was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations, such as drug intolerance or resistance.	
Although not approved by the FDA for TB, the fluoroquinolones are used relatively often to treat TB caused by drug-resistant organisms or for patients who are intolerant of some of the first-line drugs. Rifabutin is not approved to treat TB but is approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection. It is useful for treating TB in patients concurrently taking drugs that have unacceptable interactions with other rifamycins.	
Source: [23; 126]	*Table 2*

Other factors that increase the risk of *M. tuberculosis* infection include poor nutrition, intravenous drug use, close contact with large groups of people (e.g., in schools, nursing homes, dormitories, long-term care facilities, homeless shelters, prisons), and HIV or other immunologic deficiencies. Close contact with an individual who has active TB is a major risk factor, especially if there is contact with aerosols or sputum. The organism is contained in droplet nuclei, which can be inhaled and deposited into the alveoli when someone is exposed to a cough or sneeze [117; 118; 122; 123].

Treatment of *M. Tuberculosis*

Intensive educational efforts at a level appropriate for the culture, language, age, and reading level of the patient, should be initiated as soon as TB is suspected. These efforts should include information about the disease, treatment regimen and expected outcomes, and potential drug side effects, and should also include a thorough discussion of infection control measures. A list of drugs used for the treatment of TB in the United States is included in ***Table 2*** [23; 126].

The CDC, the American Thoracic Society, and the IDSA provide updated guidance for the treatment of TB, most recently in 2016 [23]. Additionally, the National Institutes of Health (NIH) has joined in developing guidelines for those with special needs, such as patients who have HIV. These guidelines also discuss the appropriate treatment of pregnant women and children [23; 129]. The CDC and the NIH additionally advise that practitioners consult an expert before attempting to treat a patient diagnosed with TB. Advice is usually available from local public health authorities.

Therapy should be initiated on the basis of strong clinical (or laboratory) suspicion, without waiting for culture confirmation of the diagnosis or sensitivity testing results. The recommended strategy is to use a multi-drug regimen administered in a two-step process: an initial four-drug intensive phase protocol for eight weeks, followed by a maintenance phase regimen to complete a total six- to nine-month course of therapy [21; 23; 126]. The recommended intensive phase regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol. This approach covers the possibility that infection is caused by a resistant strain and provides a quick "knockdown effect" designed to maximize the rate of clinical improvement, eliminate the risk of transmission, and prevent the emergence of resistant strains. After eight weeks, when culture and sensitivity results are known, pyrazinamide and ethambutol are discontinued in cases of presumed drug-sensitive infection, and isoniazid and rifampin are continued for an additional 18 to 24 weeks [23].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For the treatment of multidrug-resistant TB, the American Thoracic Society, the Centers for Disease Control and Prevention, the European Respiratory Society, and the Infectious Diseases Society of America suggest using at least five drugs in the intensive phase of treatment and four drugs in the continuation phase of treatment.

(https://www.atsjournals.org/doi/10.1164/rccm.201909-1874ST. Last accessed February 28, 2023.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, very low certainty in the evidence

For patients with known isoniazid- and rifampin-susceptible *M. tuberculosis*, ethambutol may be omitted from the initial phase regimen; moreover, directly observed therapy (DOT) administered five days of each week is an acceptable alternative to daily treatment [23]. The continuation phase of this regimen, isoniazid and rifampin for 18 weeks, is then continued either by daily dosage or DOT five days per week. There are somewhat similar regimens have the same initial phase, with the continuation phase utilizing twice weekly doses of isoniazid and rifampin or once weekly doses of isoniazid with the addition of pyrazinamide or ethambutol. In each case, the choice is influenced by severity of disease, clinical response, ease of follow-up, and issues of compliance [21; 23].

Clinical practice guidelines for the treatment of drug-resistant tuberculosis were published in 2019, prepared jointly by the CDC, the American Thoracic Society, the IDSA, and the European Respiratory Society [117]. These guidelines suggest using at least five drugs in the intensive phase of treatment and four drugs in the continuation phase, and expanding the duration of intensive-phase treatment to about 7 months and the total duration of antituberculous therapy to between 15 and 21 months. The specific regimen will vary in relation to the known or suspected susceptibility pattern of a given case. In order of strength of recommendation, selection of an oral drug(s) to add to the standard regimen includes the following choices: a fluoroquinolone (levofloxacin or moxifloxacin), bedaquiline, linezolid, clofazimine, and cycloserine [117]. Because patients with AIDS are usually taking antiretroviral and other medications, it is necessary to be especially diligent in recognizing possible drug interactions when these patients are also being treated for TB [23].

Assuring patient adherence to the treatment regimen is a critical goal of the overall management plan, not only for speedy control of infection and resolution of illness, but also to prevent emergence of resistance and limit transmission to others. It is strongly recommended that all patients be observed while taking their medication to be certain that they are conforming to the regimen. This is referred to as DOT and has been shown to markedly improve therapeutic results and enable early identification of nonadherence, adverse drug reactions, and clinical worsening of TB [23]. In most communities, a patient is assigned a public health case manager who assesses needs and barriers that may interfere with treatment adherence. With active input from the patient, family, and healthcare providers, the case manager, together with the patient, develops an individualized "case management plan" designed to address identified needs and barriers.

ENTEROBACTERALES

Enterobacterales are a large order of bacteria, including *E. coli* and *K. pneumoniae*. These bacteria are increasingly producing extended-spectrum beta-lactamase (ESBL), enzymes that inactivate most penicillins, cephalosporins, and aztreonam [165]. In 2017, there were an estimated 197,400 cases of ESBL-producing Enterobacterales among hospitalized patients and 9,100 deaths in the United States [148]. This represented a 53% increase compared to the 2012 rate [165]. These pathogens generally remain susceptible to carbapenems, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, and other non-β-lactam agents [165].

Risk Factors

ESBL-producing Enterobacterales are most commonly encountered in healthcare settings, including hospitals and nursing homes [148]. As with many other resistant organisms, previous antibiotic use, previous hospitalization, catheterization (for urinary tract infections), and immunosuppression are potential risk factors.

Diagnosis

Routine EBSL testing is typically available [165]. As such, diagnosis of ESBL-producing Enterobacterales is made in patients with Enterobacterales infection that does not respond to ceftriaxone.

Treatment

For cystitis caused by ESBL-producing Enterobacterales, the recommended first-line agents are nitrofurantoin or trimethoprim-sulfamethoxazole; alternative options include amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin (for *E. coli* only), ciprofloxacin, levofloxacin, ertapenem, meropenem, or imipenem-cilastatin. The preferred options for pyelonephritis or complicated urinary tract infections are ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole. Available options for infections outside the urinary tract include meropenem, imipenem-cilastatin, and ertapenem [165].

METHODS OF PREVENTING RESISTANCE

Many strategies have been used in an attempt to circumvent the multiple mechanisms of resistance that have developed in bacteria in the community and in healthcare settings. Examples of these strategies include adding beta-lactamase inhibitors to penicillin drugs; combining sulfa drugs with pyrimethamine, trimethoprim, and erythromycin; and chemically altering cephalosporins to create additional generations of the antibiotic. In addition, entirely new categories of antibiotics are being created in an attempt to stay ahead of the rapid evolution of bacterial resistance. Linezolid, the first oxazolidinone, is an example of this. It is a unique drug, approved in 2002 for use in the United States, that prevents formation of the 70S protein synthesis complex in bacteria and may be useful in the treatment of VRE and MRSA. Several other oxazolidinone drugs are being developed or are in clinical trials.

In light of the efficient means by which bacteria develop resistance, it is important to avoid practices that contribute to the process. The CDC has issued several position papers and action plans outlining recommendations for minimizing nosocomial infections and the emergence of resistant organisms [10; 11; 39]. Three general strategies based upon a multi-step approach are needed to combat microbial resistance: infection prevention, individualized treatment, and transmission prevention.

INFECTION PREVENTION

Many infections in hospitalized or institutionalized patients are the direct result of indwelling urinary catheters, central venous catheters, and intubation. These invasive medical devices should be avoided unless they are clearly indicated. In addition, proper vaccination of medical staff and patients to prevent infection is an effective method to prevent the spread of *S. pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* [10; 11].

Part of preventing infection is accomplished through effective patient education strategies. Including patients in the process allows the steps taken in the hospital or office setting to continue into the community. It is important for healthcare professionals to emphasize to patients the need for good hygiene, including proper cough cover, hand washing technique, and avoidance of public places when ill.

Because the prevalence of some resistant organisms is higher among immigrant and/or refugee groups, language and understanding may become an issue. When possible, patient education materials should be provided in the patient's native language. 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. Interpreters are more than passive agents who translate and transmit information back and forth 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. Use of a translator to ensure patient understanding of and compliance with infection control measures is recommended when indicated.

INDIVIDUALIZED TREATMENT

The next step involves tailoring medical treatment to fit the infection. Antimicrobial therapy should be based on the likely pathogens or culture results; broad-spectrum antibiotics should be avoided whenever possible. Consideration should be given to pathogens common to the area of infection (e.g., skin, intra-abdominal), pathogens common in the local environment (e.g., hospital environment), and pathogens common to the geographical region (e.g., the southwestern United States). Prolonged treatment regimens can allow more time for the development of resistance, so the duration of therapy should be considered as well [10]. It is important to use new antibiotic agents wisely to maintain their usefulness for the future.

PREVENTION OF TRANSMISSION

Another step is to prevent transmission of resistant bacteria between patients. A simple, effective method of infection containment is hand washing [11]. Participation in hospital infection control programs also is necessary [20]. A coordinated effort to contain pathogens according to hospital infection control guidelines makes it easier to prevent the spread of multidrug-resistant bacteria.

Education in basic infection control practices, such as Contact Precautions, should not be confined only to direct clinical caregivers. Any person entering a patient's room, from physicians to maintenance personnel, increases the possibility of the organism progressing from that room to another patient's room or other hospital areas. All persons in contact with a patient infected with a resistant organism should be diligent about necessary precautions.

Cohorting patients who have resistant organisms is an accepted practice to control transmission and involves placing patients with similar infections together in rooms. This is effective unless an immunocompromised patient who has been treated successfully is placed in the same room with a patient who is still infectious. In these cases, transmission is possible. Cross-contamination also is a constant danger in the hospital setting. Resistant infections can be particularly dangerous in acute-care facilities that involve treatment of immunocompromised patients, such as oncology wards. All long-term care facilities, including acute or subacute facilities or skilled nursing facilities, face the same length of stay, cohorting, and discharge difficulties, as do short-term acute-care facilities.

In 2016, Congress appropriated $160 million for the CDC to utilize in the effort to combat the problem of antimicrobial resistance, and again appropriated more than $182 million in 2022 to support this effort. The CDC has implemented the Antibiotic Resistance Solution Initiative, improving national infrastructure to detect, respond, and contain resistant infections across healthcare settings and communities. The largest portion of this funding is being used to support the 50 state health departments, the six largest local health departments, and Puerto Rico [108].

CONCLUSION

Resistance to antimicrobials is a problem that has existed since the medications were first utilized. Although there is an increased level of awareness about the problem, the lack of universal conformity to good preventive practice has allowed the continuing spread of resistant organisms. The presented timeline of the development of some of the more prominent resistant organisms gives a good indication of the present state of the problem.

The bacteriostatic and bactericidal effects of the antimicrobials and some of the mechanisms of bacterial resistance have been described in this course. A considerable amount of research continues on the subject. Specific examples of microbial resistance were examined in detail, including MRSA, VRE, and penicillin-resistant *S. pneumoniae*. The effects of resistance on the treatment of TB and *S. pneumoniae* have been significant, as described.

Although new antimicrobials continue to be produced, the IDSA has reported that the pipeline of new drugs is drying up. Pharmaceutical companies are increasingly losing interest in performing the expensive, risky, and time-consuming research and development needed to identify and clinically test new antimicrobials, which are generally less profitable than drugs used to treat chronic health conditions or lifestyle issues. Furthermore, none of the drugs in development are capable of treating microbes that are resistant to all currently available drugs [160]. This makes it critical that healthcare providers be the first defense against the continuing spread of resistant organisms. Therefore, this course has presented methods for preventing resistance, including the proper choice of narrow-spectrum antimicrobials, adequate hand washing, cohorting patients, and other methods of eliminating the transfer of organisms.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Centers for Disease Control and Prevention. Preventing emerging infectious diseases: a strategy for the 21st century: overview of the updated CDC plan. *MMWR*. 1998;47(RR15):1-14.
2. Giblin TB, Sinkowitz-Cochran RL, Harris PL, et al. Clinicians' perceptions of the problem of antimicrobial resistance in health care facilities. *Arch Intern Med*. 2004;164(15):1662-1668.
3. Rice LB. Emergence of vancomycin-resistant enterococci. *Emerg Infect Dis*. 2001;7(2):183-187.
4. Chouake J, Krausz A, Adler BL, Cohen HW, Nosanchuk JD, Friedman A. Management of cutaneous abscesses by dermatologists. *J Drugs Dermatol*. 2014;13(2):611-616.
5. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. *Br J Gen Pract*. 2003;53(496):871-877.
6. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev*. 2005;19(4):CD003539.
7. Lin MY, Hayden MK. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus: recognition and prevention in intensive care units. *Crit Care Med*. 2010;38(8 suppl):S335-S344.
8. Kerwat K, Kerwat M, Graf J, Wulf H. Resistance to antibiotics and multiresistant pathogens. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 2010;45(4):242-243.
9. Centers for Disease Control and Prevention. Diseases and Organisms in Healthcare Settings. Available at https://www.cdc.gov/HAI/organisms/organisms.html. Last accessed February 1, 2023.
10. Siegel JD, Rhinehart E, Jackson M, Chiarello L, the Healthcare Infection Control Practices Advisory Committee. Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006. Available at https://www.cdc.gov/infectioncontrol/pdf/guidelines/mdro-guidelines.pdf. Last accessed February 1, 2023.
11. Centers for Disease Control and Prevention. U.S. Action and Events to Combat Antimicrobial Resistance. Available at https://www.cdc.gov/drugresistance/us-activities.html. Last accessed February 1, 2023.
12. Miao R, Wan C, Wang Z, et al. Inappropriate antibiotic prescriptions among pediatric inpatients in different type hospitals. *Medicine (Baltimore)*. 2020;99(2):e18714.
13. Murray PR, Rosenthal KS, Pfaller MA (eds). *Medical Microbiology*. 9th edition. Philadelphia, PA: Elsevier; 2020.
14. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019. Available at https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Last accessed February 1, 2023.
15. Turnidge J, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. *Clin Microbiol Rev*. 2007;20(3):391-408.
16. Kaye KS, Fraimow HS, Abrutyn E. Pathogens resistant to antimicrobial agents: epidemiology, molecular mechanisms, and clinical management. *Infect Dis Clin North Am*. 2000;14(2):293-319.
17. Stokowski LA. Antimicrobial Resistance: A Primer. Available at https://www.medscape.com/viewarticle/729196. Last accessed February 1, 2023.
18. Neu HC. Overview of mechanisms of bacterial resistance. *Diagn Microbiol Infect Dis*. 1989;12(4 suppl 1):S109-S116.
19. Normark BH, Normark S. Evolution and spread of antibiotic resistance. *J Intern Med*. 2002;252(2):91-106.
20. Shlaes DM, Gerding DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance. Guidelines for the prevention of antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol*. 1997;18(4):275-291.
21. Neff M. Practice guidelines: ATS, CDC, and IDSA update recommendations on the treatment of tuberculosis. *Am Fam Physician*. 2003;68(9):1854, 1857-1858, 1861-1862.
22. Goossens H. Antibiotic Resistance: Highlights of the 16th European Congress on Clinical Microbiology and Infectious Diseases. Available at https://www.medscape.org/viewarticle/530824. Last accessed February 1, 2023.
23. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147-e195.
24. Tenover FC, Hughes JM. The challenges of emerging infectious diseases: development and spread of multiply-resistant bacterial pathogens. *JAMA*. 1996;275(4):300-304.
25. Centers for Disease Control and Prevention. Antibiotic Resistance and NARMS Surveillance. Available at https://www.cdc.gov/narms/faq.html. Last accessed February 1, 2023.
26. Evans G. The day-care connection to drug resistance: parental pressure leads to antibiotic pressure. *Healthcare Infect Prev*. 2000:1-2.
27. Metlay JP, Powers JH, Dudley MN, Christiansen K, Finch RG. Antimicrobial drug resistance, regulation, and research. *Emerg Infect Dis*. 2006;12(2):183-190.
28. Pu S, Han F, Ge B. Isolation and characterization of methicillin-resistant Staphylococcus aureus strains from Louisiana retail meats. *Appl Environ Microbiol*. 2009;75(1):265-267.

29. Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines: Gonococcal Infections. Available at https://www.cdc.gov/std/tg2015/gonorrhea.htm. Last accessed February 1, 2023.
30. Centers for Disease Control and Prevention. Facility Guidance for Control of Carbapenem-Resistant *Enterobacteriaceae* (CRE): November 2015 Update CRE Toolkit. Available at https://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf. Last accessed February 1, 2023.
31. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. *JAMA*. 1996;275(3):234-240.
32. Chen YY, Wang FD, Liu CY, Chou P. Incidence rate and variable cost of nosocomial infections in different types of intensive care units. *Infect Control Hosp Epidemiol*. 2009;30(1):39-46.
33. Mulvey MR, Grant JM, Plewes K, Roscoe D, Boyd DA. New Delhi metallo-ß-lactamase in *Klebsiella pneumoniae* and *Escherichia coli*, Canada. *Emerg Infect Dis*. 2011;17(1).
34. Rawat D, Nair D. Extended-spectrum ß-lactamases in gram negative bacteria. *J Glob Infect Dis*. 2010;2(3):263-274.
35. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY antimicrobial surveillance program, 1997–1999. *Clin Infect Dis*. 2001;32(suppl 2):S114-S132.
36. Montgomery CP, Boyle-Vavra S, Adem PV, et al. Comparison of virulence in community-associated methicillin-resistant *Staphylococcus aureus* pulsotypes USA300 and USA400 in a rat model of pneumonia. *J Infect Dis*. 2008;198(4):561-570.
37. McCaskill ML, Mason EO Jr, Kaplan SL, Hammerman W, Lamberth LB, Hulten KG. Increase of the USA300 clone among community-acquired methicillin-susceptible *Staphylococcus aureus* causing invasive infections. *Pediatr Infect Dis J*. 2007;26(12):1122-1127.
38. Gorwitz RJ, Jernigan DB, Powers JH, Jernigan JA, and participants in the Centers for Disease Control and Prevention-Convened Experts' Meeting on Management of MRSA in the Community. *Strategies for Clinical Management of MRSA in the Community: Summary of an Experts' Meeting Convened by the Centers for Disease Control and Prevention*. Atlanta, GA: Centers for Disease Control and Prevention; 2006.
39. Centers for Disease Control and Prevention. What CDC is Doing to Combat MRSA. Available at https://www.cdc.gov/mrsa/tracking. Last accessed February 1, 2023.
40. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001–2004. *J Infect Dis*. 2008;197(9):1226-1234.
41. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003–2004 influenza season. *Emerg Infect Dis*. 2006;12:894-899.
42. McCaig LF, McDonald LC, Mandal S. Jernigan DB. *Staphylococcus aureus*-associated skin and soft tissue infections in ambulatory care. *Emerg Infect Dis*. 2006;12(11).
43. Centers for Disease Control and Prevention. MRSA: Healthcare Settings. Available at https://www.cdc.gov/mrsa/healthcare/index.html. Last accessed February 1, 2023.
44. Bratu S, Eramo A, Kopec R, et al. Community-associated methicillin-resistant *Staphylococcus aureus* in hospital nursery and maternity units. *Emerg Infect Dis*. 2005;11(6):808-813.
45. Healy CM, Hulten KG, Palazzi DL, Campbell JR, Baker CJ. Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Clin Infect Dis*. 2004;39(10):1460-1466.
46. Saiman L, O'Keefe M, Graham PL 3rd, et al. Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. *Clin Infect Dis*. 2003;37(10):1313-1319.
47. Centers for Disease Control and Prevention. Community-associated methicillin-resistant *Staphylococcus aureus* infection among healthy newborns—Chicago and Los Angeles County, 2004. *MMWR*. 2006;55(12):329-332.
48. Centers for Disease Control and Prevention. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza: Louisiana and Georgia, December 2006–January 2007. *MMWR*. 2007;56(14):325-329.
49. Dean N. Methicillin-resistant *Staphylococcus aureus* in community-acquired and health care-associated pneumonia: incidence, diagnosis, and treatment options. *Hosp Pract (Minneap)*. 2010;38(1):7-15.
50. National Center for Infectious Diseases. National Nosocomial Infections Surveillance (NNIS) System Report, Data Summary from January 1992 through June 2004, Issued October 2004. Available at https://www.cdc.gov/nhsn/PDFs/dataStat/NNIS_2004.pdf. Last accessed February 1, 2023.
51. Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in U.S. intensive care units, 1997–2007. *JAMA*. 2009;301(7):727-736.
52. Elixhauser A, Steiner C. Infections with Methicillin-Resistant *Staphylococcus aureus* (MRSA) in U.S. Hospitals, 1993–2005. Available at https://www.hcup-us.ahrq.gov/reports/statbriefs/sb35.pdf. Last accessed February 1, 2023.
53. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. *Clin Infect Dis*. 2017;64:134-140.

54. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. Available at https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Last accessed February 1, 2023.
55. Selvey LA, Whitby M, Johnson B. Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia: is it any worse than nosocomial methicillin-sensitive *Staphylococcus aureus* bacteremia? *Infect Control Hosp Epidemiol*. 2000;21(10):645-648.
56. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. *Infect Control Hosp Epidemiol*. 2007;28(3):273-279.
57. Wang FD, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial *Staphylococcus aureus* bacteremia. *Am J Infect Control*. 2008;36(2):118-122.
58. Centers for Disease Control and Prevention. Community-associated methicillin-resistant *Staphylococcus aureus* infections in Pacific Islanders—Hawaii, 2001–2003. *MMWR*. 2004;53(33):767-770.
59. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities—Georgia, California, and Texas, 2001–2003. *MMWR*. 2003;52(41):992-996.
60. Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. *MMWR*. 2003;52(33):793-795.
61. Zinderman CE, Conner B, Malakooti MA, LaMar JE, Armstrong A, Bohnker BK. Community-acquired methicillin-resistant *Staphylococcus aureus* among military recruits. *Emerg Infect Dis*. 2004;10(5):941-944.
62. Adcock PM, Pastor P, Medley F, Patterson JE, Murphy TV. Methicillin-resistant *Staphylococcus aureus* in two child care centers. *J Infect Dis*. 1998;178(2):577-580.
63. Lee NE, Taylor MM, Bancroft E, et al. Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men. *Clin Infect Dis*. 2005;40(10):1529-1534.
64. Groom AV, Wolsey DH, Naimi TS, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. *JAMA*. 2001;286(10):1201-1205.
65. Baggett HC, Hennessy TW, Rudolph K, et al. Community-onset methicillin-resistant *Staphylococcus aureus* associated with antibiotic use and the cytotoxin Panton-Valentine leukocidin during a furunculosis outbreak in rural Alaska. *J Infect Dis*. 2004;189(9):1565-1573.
66. D'Agata EM, Webb GF, Pressley J. Rapid emergency of co-colonization with community-acquired and hospital-acquired methicillin-resistant *Staphylococcus aureus* strains in the hospital setting. *Math Model Nat Phenom*. 2010;5(3):76-73.
67. Popovich KJ, Weinstein RA, Hota B. Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains? *Clin Infect Dis*. 2008;46(6):787-794.
68. McCannon CJ, Hackbarth AD, Griffin FA. Miles to go: an introduction to the 5 Million Lives campaign. *Jt Comm J Qual Patient Safe*. 2007;33(8):477-484.
69. U.S. Department of Health and Human Services. HAI National Action Plan. Available at https://www.hhs.gov/oidp/topics/health-care-associated-infections/hai-action-plan/index.html. Last accessed February 1, 2023.
70. Makhni S, Umscheid CA, Soo J, et al. Hand hygiene compliance rate during the COVID-19 pandemic. *JAMA Intern Med*. 2021;181(7):1006-1008.
71. Centers for Disease Control and Prevention. 2022 Special Report: COVID-19 U.S. Impact on Antimircrobial Resistance. Available at https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf. Last accessed February 1, 2023.
72. Khan TM, Kok YL, Bukhsh A, et al. Incidence of methicillin resistant *Staphylococcus aureus* (MRSA) in burn intensive care unit: a systematic review. *Germs*. 2018;8(3):113-125.
73. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. Available at https://www.ncbi.nlm.nih.gov/books/NBK144035. Last accessed February 1, 2023.
74. Murthy N, Wodi AP, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2023. *MMWR*. 2023;72(6):141-144.
75. Centers for Disease Control and Prevention. Update to CDC's Treatment Guidelines for Goncoccoal Infection, 2020. Available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm. Last accessed February 1, 2023.
76. Reves RR, Nolan CM. Tuberculosis elimination in the United States: an achievable goal or an illusion? *Am J Respir Crit Care Med*. 2012;186(3):i-iii.
77. Immunization Action Coalition. Pneumococcal: PCV. Available at https://www.immunize.org/resources/pneumococcal-pcv.asp. Last accessed February 25, 2023.
78. Larson EL, Quiros D, Lin SX. Dissemination of the CDC's hand hygiene guideline and impact on infection rates. *Am J Infect Control*. 2007;35(10):666-675.
79. Centers for Disease Control and Prevention. A Public Health Action Plan to Combat Antimicrobial Resistance. Available at https://www.cdc.gov/drugresistance/pdf/action-plan-2012.pdf. Last accessed February 1, 2023.
80. Siegel JD, Rhinehart E, Jackson M, Chiarello L, the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Available at https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines-H.pdf. Last accessed February 1, 2023.

81. U.S. Food and Drug Administration. FDA Clears First Quick Test for Drug-Resistant Staph Infections. Available at https://wayback.archive-it.org/7993/20170114031912/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm161552.htm. Last accessed February 1, 2023.
82. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(1):1-38.
83. Saravolatz LD1, Pawlak J, Johnson LB. In vitro susceptibilities and molecular analysis of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* isolates. *Clin Infect Dis*. 2012;55(4):582-586.
84. Morales G, Picazo JJ, Baos E, et al. Resistance to linezolid is mediated by the *cfr* gene in the first report of an outbreak of linezolid-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2010;50(6):821-825.
85. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med*. 2000;342:710-721.
86. McManus AT, Goodwin CW, Pruitt BA Jr. Observations on the risk of resistance with the extended use of vancomycin. *Arch Surg*. 1998;133(11):1207-1211.
87. Furuno JP, McGregor JC, Harris AD, et al. Identifying groups at high risk for carriage of antibiotic-resistant bacteria. *Arch Intern Med*. 2006;166(5):580-585.
88. Squires RA, Postier RG. Tigecycline for the treatment of infections due to resistant gram-positive organisms. *Expert Opin Investig Drugs*. 2006;15(2):155-162.
89. Linden PK. Treatment options for vancomycin-resistant enterococcal infections. *Drugs*. 2002;62(3):425-441.
90. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis*. 2003;36(4):473-481.
91. Raad I, Hachem R, Hanna H, et al. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* infections. *J Antimicrob Chemother*. 2004;53(4):646-649.
92. Fang FC, McClelland M, Guiney DG, et al. Value of molecular epidemiologic analysis in a nosocomial methicillin-resistant *Staphylococcus aureus* outbreak. *JAMA*. 1993;270(11):1323-1328.
93. Trindade PA, McCulloch JA, Oliveira GA, Mamizuka EM. Molecular techniques for MRSA typing: current issues and perspectives. *Braz J Infect Dis*. 2003;7(1):32-43.
94. Ross TL, Merz WG, Farkosh M, Carroll KC. Comparison of an automated repetitive sequence-based PCR microbial typing system to pulsed-field gel electrophoresis for analysis of outbreaks of methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2005;43(11):5642-5647.
95. Levin TP, Byungse S, Axelrod P, Truant AL, Fekete T. Potential clindamycin resistance in clindamycin-susceptible, erythromycin-resistant *Staphylococcus aureus*: report of a clinical failure. *Antimicrob Agents Chemother*. 2005;49(3):1222.
96. Kader AA, Kumar A, Krishna A. Induction of clindamycin resistance in erythromycin-resistant, clindamycin susceptible and methicillin-resistant clinical staphylococcal isolates. *Saudi Med J*. 2005;26(12):1914-1917.
97. Gherardi G, De Florio L, Lorino G, Fico L, Dicuonzo G. Macrolide resistance genotypes and phenotypes among erythromycin-resistant clinical isolates of *Staphylococcus aureus* and coagulase-negative staphylocci, Italy. *FEMS Immunol Med Microbiol*. 2009;55(1):62-67.
98. Schmitz FJ, Sadurski R, Kray A, et al. Prevalence of macrolide-resistance genes in *Staphylococcus aureus* and *Enterococcus faecium* isolates from 24 European university hospitals. *J Antimicrob Chemother*. 2000;45(6):891-894.
99. Centers for Disease Control and Prevention. Pneumococcal Disease: Clinical Features. Available at https://www.cdc.gov/pneumococcal/clinicians/clinical-features.html. Last accessed February 1, 2023.
100. Centers for Disease Control and Prevention. ABCs Report: *Streptococcus pneumoniae*, 2020. Available at https://www.cdc.gov/abcs/downloads/SPN_Surveillance_Report_2020.pdf. Last accessed February 1, 2020.
101. Kietzman C, Tuomanen E. Acute bacterial meningitis: challenges to better antibiotic therapy. *ACS Infect Dis*. 2019;5(12):1987-1995.
102. Centers for Disease Control and Prevention. Manual for the Surveillance of Vaccine-Preventable Diseases: Pneumococcal Disease. Available at https://www.cdc.gov/vaccines/pubs/surv-manual/chpt11-pneumo.html. Last accessed February 1, 2023.
103. Centers for Disease Control and Prevention. 2020 National Notifiable Diseases Surveillance System Event Code List. Available at https://ndc.services.cdc.gov/event-codes-other-surveillance-resources. Last accessed February 1, 2023.
104. Centers for Disease Control and Prevention. Tuberculosis (TB): Data and Statistics. Available at https://www.cdc.gov/tb/statistics/default.htm. Last accessed February 1, 2023.
105. Centers for Disease Control and Prevention. Pneumococcal Disease: Drug Resistance. Available at https://www.cdc.gov/pneumococcal/clinicians/drug-resistance.html. Last accessed February 24, 2023.
106. McCracken GH Jr. Emergence of resistant *Streptococcus pneumoniae*: a problem in pediatrics. *Pediatr Infect Dis J*. 1995;14(5):424-428.
107. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.
108. Centers for Disease Control and Prevention. What CDC is Doing: Investments and Action. Available at https://www.cdc.gov/drugresistance/solutions-initiative. Last accessed February 1, 2023.
109. Gold HS. Antimicrobial-drug resistance. *N Engl J Med*. 1996;335:1445-1453.

110. Institute for Clinical Systems Improvement. *Community-Acquired Pneumonia in Adults*. Bloomington, MN: Institute for Clinical Systems Improvement; 2006.
111. Centers for Disease Control and Prevention. Pneumococcal Vaccine Recommendations. Available at https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html. Last accessed February 25, 2023.
112. Geiter L (ed). *Ending Neglect: The Elimination of Tuberculosis in the United States*. Washington, DC: National Academy Press; 2000.
113. Centers for Disease Control and Prevention. Decrease in reported tuberculosis cases—United States, 2009. *MMWR*. 2010;59(10):289-294.
114. Centers for Disease Control and Prevention. Latent TB Infection in the United States, Published Estimates. Available at https://www.cdc.gov/tb/statistics/ltbi.htm. Last accessed February 1, 2023.
115. Blumberg HM, Leonard MK Jr, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. *JAMA*. 2005;293(22):2776-2784.
116. Epstein L. Tuberculosis among health care workers. *Am J Nurs*. 2007;107:21.
117. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200:e93-e142.
118. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR*. 2005;54(RR17):1-147.
119. Centers for Disease Control and Prevention. Multidrug-Resistant Tuberculosis (MDR-TB) Fact Sheet. Available at https://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm. Last accessed February 1, 2023.
120. Centers for Disease Control and Prevention. Revised definition of extensively drug-resistant tuberculosis. *MMWR*. 2006;55(43):1176.
121. Granich RM, Oh P, Lewis B, Porco TC, Flood J. Multidrug resistance among persons with tuberculosis in California, 1994–2003. *JAMA*. 2005;293(22):2732-2739.
122. Telenti A, Iseman M. Drug-resistant tuberculosis: what do we do now? *Drugs*. 2000;59(2):171-179.
123. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. *MMWR*. 1994;43(RR13):1-132.
124. Centers for Disease Control and Prevention. VISA/VRSA in Healthcare Settings. Available at https://www.cdc.gov/HAI/organisms/visa_vrsa/visa_vrsa.html. Last accessed February 1, 2023.
125. Centers for Disease Control and Prevention. VRE in Healthcare Settings. Available at https://www.cdc.gov/HAI/organisms/vre/vre.html. Last accessed February 1, 2023.
126. Centers for Disease Control and Prevention. Tuberculosis: Treatment for Latent TB Infection and TB Disease. Available at https://www.cdc.gov/tb/topic/treatment/default.htm. Last accessed February 1, 2023.
127. Centers for Disease Control and Prevention. Gonorrhea: CDC Detailed Fact Sheet. Available at https://www.cdc.gov/std/gonorrhea/stdfact-gonorrhea-detailed.htm. Last accessed February 1, 2023.
128. Workowski KA, Berman S, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR*. 2010;59(RR12):1-110.
129. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV, National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. 2023 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-andadolescent-opportunistic-infection. Last accessed February 1, 2023.
130. U.S. Food and Drug Administration. FDA Clears First Test to Quickly Diagnose and Distinguish MRSA and MSSA. Available at https://wayback.archive-it.org/7993/20170114063448/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm254512.htm. Last accessed February 1, 2023.
131. Bala M, Sood S. Cephalosporin resistance in *Neisseria gonorrhoeae*. *J Glob Infect Dis*. 2010;2(3):284-290.
132. National Institute of Allergy and Infectious Diseases. Antimicrobial Resistance Threats. Available at https://www.niaid.nih.gov/research/antimicrobial-resistance-threats. Last accessed February 1, 2023.
133. Deguchi T, Nakane K, Yasuda M, Maeda S. Emergence and spread of drug resistant *Neisseria gonorrhoeae*. *J Urol*. 2010;184(3):851-858.
134. U.S. Preventive Services Task Force. Chlamydia and Gonorrhea: Screening. Available at https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/chlamydia-and-gonorrhea-screening. Last accessed February 1, 2023.
135. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011;17(10):1791-1798.
136. Centers for Disease Control and Prevention. Discovery of First *mcr-1* Gene in *E. coli* Bacteria Found in a Human in United States. Available at https://www.cdc.gov/media/releases/2016/s0531-mcr-1.html. Last accessed February 1, 2023.
137. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis*. 2009;9(4):228-236.
138. Hirsch EB, Tam VH. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug resistant infection. *J Antimicrob Chemother*. 2010;65(6):1119-1125.

139. World Health Organization. Global Action Plan on Antimicrobial Resistance. Available at https://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html. Last accessed February 1, 2023.

140. Kourtis AP, Hatfield K, Baggs J, et al. Vital Signs: epidemiology and recent trends in methicillin-resistant and in methicillin-susceptible *Staphylococcus aureus* bloodstream infections—United States. *MMWR*. 2019;68:214-210.

141. Cuzon G, Naas T, Nordmann P. KPC carbapenemases: what is at stake in clinical microbiology? *Pathol Biol (Paris)*. 2010;58(1):39-45.

142. Tenover FC, Kalsi RK, Williams PP, et al. Carbapenem resistance in *Klebsiella pneumoniae* not detected by automated susceptibility testing. *Emerg Infect Dis*. 2006;12(8):1209-1213.

143. Chen LF. *Klebsiella pneumoniae* Carbapenemase: Extended-Spectrum Beta-Lactamase Continues to Go Global. Available at https://www.medscape.com/viewarticle/587949. Last accessed February 13, 2020.

144. Arnold RS, Thom KA, Sharma S, Phillips M, Kristie Johnson J, Morgan DJ. Emergence of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *South Med J*. 2011;104(1):40-45.

145. Bassetti M, Righi E, Esposito S, Petrosillo N, Nicolini L. Drug treatment for multidrug-resistant *Acinetobacter baumanni* infections. *Future Microbiol*. 2008;3(6):649-660.

146. Garnacho-Montero J, Amaya-Villar R. Multiresistant *Acinetobacter baumannii* infections: epidemiology and management. *Curr Opin Infect Dis*. 2010;23(4):332-339.

147. Gootz TD, Mara A. *Acinetobacter baumannii*: an emerging multidrug-resistant threat. *Expert Rev Anti Infect Ther*. 2008;6(3):309-325.

148. Centers for Disease Control and Prevention. ESBL-Producing Enterobacterales in Healthcare Settings. Available at https://www.cdc.gov/hai/organisms/ESBL.html. Last February 1, 2023.

149. Tsay S, Kallen A, Jackson BR, et al. Approach to the investigation and management of patients with *Candida auris*, an emerging multidrug-resistant yeast. *Clin Infect Dis*. 2018;66:306-311.

150. Baran G, Erbay A, Bodur H, et al. Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. *Int J Infect Dis*. 2008;12(1):16-21.

151. Abbo A, Carmeli Y, Navon-Venezia S, Siegman-Igra Y, Schwaber MJ. Impact of multidrug-resistant *Acinetobacter baumannii* on clinical outcomes. *Eur J Clin Microbiol Infect Dis*. 2007;26:793-800.

152. Jeong SH, Bae IK, Park KO, et al. Outbreaks of imipenem-resistant *Acinetobacter baumannii* producing carbapenemases in Korea. *J Microbiol*. 2006;44(4):423-431.

153. Nemec A, Krízová L, Maixnerová M, et al. Emergence of carbapenem resistance in *Acinetobacter baumannii* in the Czech Republic is associated with the spread of multidrug-resistant isolates of European clone II. *J Antimicrob Chemother*. 2008;62(3):484-489.

154. Chim H, Tan BH, Song C. Five-year review of infections in a burn intensive care unit: high incidence of *Acinetobacter baumannii* in a tropical climate. *Burns*. 2007;33(8):1008-1014.

155. Wang H, Guo P, Sun H, et al. Molecular epidemiology of clinical isolates of carbapenem-resistant *Acinetobacter* spp. from Chinese hospitals. *Antimicrob Agents Chemother*. 2007;51(11):4022-4028.

156. Mazumder SA. Acinetobacter. Available at https://emedicine.medscape.com/article/236891-overview. Last accessed February 13, 2020.

157. Todar K. *Todar's Online Textbook of Bacteriology*. Available at http://textbookofbacteriology.net/index.html. Last accessed February 1, 2023.

158. Obritsch MD, Fish DN, MacLaren R, Jung R. Nosocomial infections due to multidrug-resistant *Pseudomonas aeruginosa*: epidemiology and treatment options. *Pharmacotherapy*. 2005;25(10):1353-1364.

159. Centers for Disease Control and Prevention. *Candida auris*. Available at https://www.cdc.gov/fungal/candida-auris/index.html. Last accessed February 1, 2023.

160. Infectious Diseases Society of America. *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates...A Public Health Crisis Brews*. Alexandria, VA: Infectious Diseases Society of America; 2004.

161. Centers for Disease Control and Prevention, Candida auris: Information for Laboratorians and Health Professionals. Available at https://www.cdc.gov/fungal/candida-auris/health-professionals.html. Last accessed February 1, 2023.

162. Fuller C, Savage J, Besser S, et al. "The dirty hand in the latex glove:" a study of hand hygiene compliance when gloves are worn. *Infect Control Hosp Epidemiol*. 2011;32(12):1194-1199.

163. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Cont Hosp Epidemiol*. 2003;24(5):362-386.

164. Calfee DP, Salgado CD, Classen D, et al. Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals. *Infect Cont Hosp Epidemiol*. 2008;29(suppl 1):S62-S80.

165. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). *Clin Infect Dis*. 2021;72(7):1109-1116.

166. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 2001;45(4):1151-1161.

167. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2015–2017. *Infect Control Hosp Epidemiol.* 2020;41(1):1-18.

168. Centers for Disease Control and Prevention. Multidrug-Resistant *Pseudomonas aeruginosa* in Healthcare Settings. Available at https://www.cdc.gov/hai/organisms/pseudomonas.html. Last accessed February 1, 2023.

169. McAdam PR, Templeton KE, Edwards GF, et al. Molecular tracing of the emergence, adaptation, and transmission of hospital-associated methicillin-resistant *Staphylococcus aureus*. *Proc Natl Acad Sci U S A.* 2012;109(23):9107-9112.

170. Barnes SL, Harris AD, Golden BL, Wasil EA, Furuno JP. Contribution of interfacility patient movement to overall methicillin-resistant *Staphylococcus aureus* prevalence levels. *Infect Control Hosp Epidemiol.* 2011;32(11):1073-1078.

171. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/= 65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR.* 2019;68:1069-1075.

172. Centers for Disease Control and Prevention. CDC Health Advisory: Increase in Extensively Drug-Resistant Shigellosis in the United States. Available at https://emergency.cdc.gov/han/2023/pdf/CDC_HAN_486.pdf. Last accessed February 25, 2023.

Evidence-Based Practice Recommendations Citations

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10-e52. Available at https://www.idsociety.org/practice-guideline/skin-and-soft-tissue-infections. Last accessed February 28, 2023.

Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1-e50. Available at https://www.idsociety.org/practice-guideline/candidiasis. Last accessed February 28, 2023.

Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med.* 2019;200(10):e93-e142. Available at https://www.atsjournals.org/doi/10.1164/rccm.201909-1874ST. Last accessed February 28, 2023.