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Antibiotics Review

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including nurses, nurse practitioners, physicians, physician assistants, and surgical technologists and assistants.

Course Objective
The purpose of this course is to provide a review of the major classes of antibiotics and their characteristics as well as an overview of selected individual agents within each class that are most useful for today's clinical practitioner.

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

1. Describe the general characteristics and mode of action of antibiotics commonly in use.
2. Employ best practice principles for limiting the emergence and transmission of anti-microbial resistant strains within the healthcare environment.
3. Discuss the mechanism of action, pharmacokinetics, and spectrum of activity of natural and extended-spectrum penicillins.
4. Select the most appropriate, cost-effective cephalosporin based on "generational" characteristics and spectrum of activity.
5. Describe the role of carbapenems and monobactams.
6. Discuss the characteristics, expected toxicities, and indications for the use of aminoglycosides, macrolides, and sulfonamides.
7. Outline the mechanism of action, pharmacokinetics, and advantages inherent to quinolones and the tetracyclines.

Faculty
Donna Coffman, MD, attended medical school at the University of Louisville and completed her residency in Family Practice at St. John's Mercy Medical Center in St. Louis, Missouri. She is board-certified in Family Medicine and currently on staff at John Cochran VAMC in St. Louis.

Faculty Disclosure
Contributing faculty, Donna Coffman, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

INTRODUCTION

The number of antibiotic agents available is remarkable, and new agents are added regularly. This course is intended as an overview of the general characteristics of the major antibiotic classes, emphasizing mechanism of action, pharmacokinetics, and potential toxicities, with a brief discussion of the individual member agents and their clinical indications. The purpose of this course is to enlarge clinical perspective and enhance the understanding and confidence required for the selection of appropriate therapy of bacterial infections. The goal is to improve efficacy and safety while limiting the risk for selection and transmission of antimicrobial-resistant pathogens.

Given the large array of available antimicrobial agents, the scope of this course is confined to the eight major classes of antibiotics commonly employed for acute bacterial infection: the penicillins, cephalosporins, carbapenems, aminoglycosides, quinolones, macrolides, sulfonamides, and tetracyclines. A brief discussion of vancomycin and the newer glycopeptide analogues is also included.

For the purposes of the course, it is impractical to list or describe all of the possible adverse effects, recommended uses, and off-label uses of the antibiotics discussed. Before using a specific antimicrobial, it is important to review the manufacturer's package insert and dosing recommendations for the drug.

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GENERAL CHARACTERISTICS OF ANTIBIOTICS

Which classes of antibiotics are associated with a risk for developing *Clostridium difficile*-associated diarrhea?

There are some characteristics that all antibiotics share. All antibiotics can elicit allergic responses, although some are more allergenic than others. Allergic reactions can range from mild, annoying rashes to life-threatening reactions like anaphylaxis and Stevens-Johnson syndrome. In some cases, there is a cross-sensitivity between agents in different classes. In addition, all antibiotics affect normal body flora as well as pathogens, which may result in overgrowth of *Candida* and pathogenic bacteria such as *Clostridium difficile*. Overgrowth of *C. difficile* is a serious complication of antimicrobial therapy that can produce symptoms ranging from mild diarrhea to severe, life-threatening complications, such as pseudomembranous colitis [1]. Most cases resolve with supportive care and discontinuation of the offending antibiotic, but many require treatment. In addition, diarrhea and pseudomembranous colitis can develop weeks after antimicrobial therapy has been discontinued. A high degree of suspicion and judicious use of laboratory testing are the keys to recognizing and managing these complications.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Centers for Disease Control and Prevention, administration of currently available probiotics is not recommended to prevent primary *Clostridium difficile* infection, as there are limited data to support this approach and there is a potential risk of bloodstream infection.

(https://www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSA-SHEA-CDI-guidelines-2010.pdf. Last accessed January 22, 2018.)

Level of Evidence: CIII (Poor evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

ANTIBIOTIC RESISTANCE

What are common ways bacteria gain antibiotic resistance?

Repeated exposure to an antibiotic may lead to the emergence of selective subpopulations of the same or related bacteria now resistant to the therapeutic agent. The Centers for Disease Control and Prevention (CDC) note that approximately 2 million people become infected with bacteria that are resistant to antibiotics, and approximately 23,000 people die annually because of these infections [164]. Mechanisms of microbial resistance include altered cellular permeability (leading to greatly diminished intracellular concentration of the drug), increased efflux of the antibiotic from the cell, and elaboration of deactivating enzymes that alter the antibiotic's interaction at binding sites within the cell wall or cytoplasm [2].

Decreased cell membrane permeability is an important mechanism of bacterial resistance to beta-lactams, quinolones, and vancomycin. Microbial resistance to tetracyclines and quinolones is often mediated by increased efflux of the antibiotic from the cell. Enzymatic deactivation by beta-lactamases is the common mechanism of resistance to penicillins and cephalosporins. Resistance to aminoglycosides may result from altered cytoplasmic membrane transport (influx) or from intracellular enzymes (e.g., phosphotransferases and acetyltransferases) that deactivate the drug.

There are various mechanisms by which the interaction of an antibiotic with its binding site may be altered or bypassed, resulting in loss of antimicrobial activity. One such example, affecting the target site for quinolone activity, is an acquired structural alteration of deoxyribonucleic acid (DNA) gyrase, an enzyme essential for bacterial DNA synthesis. As a result, quinolones are no longer able to bind to the enzyme and the drug loses its antimicrobial effect. Another example is the methylation of ribosomal ribonucleic acid (rRNA) that prevents the binding of macrolides. The effectiveness of trimethoprim/sulfamethoxazole, which acts through disruption of folate synthesis by the cell, may become diminished by the adaptive ability of some bacteria to utilize an alternate metabolic pathway, thereby avoiding the effects of trimethoprim [3].

These resistance mechanisms may be acquired through mutations in the genes that encode for the target or affected transport proteins. As the bacterial cells without the adaptive mutations succumb to the action of the antibiotic, the subpopulation that has the adaptive mutation continues to replicate, replacing the original population with a resistant one.

Bacterial resistance can be transferred from one bacterium to another, or from one bacterial species to related group, by means of plasmids or transposons that gain entry to the cell. These agents 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 [4].

Many strategies have been used in an attempt to circumvent the multiple mechanisms of resistance encountered in bacteria. Among these are the addition of beta-lactamase inhibitors to extended-spectrum penicillins, alteration of

cephalosporin side chains to produce new generations of the drug with broader activity, and pairing two drugs to enhance the antimicrobial effect (e.g. sulfamethoxazole with trimethoprim).

In addition, new categories of antibiotics are being created in an attempt to stay ahead of the rapid evolution of bacterial resistance. Linezolid and tedizolid, the only two FDA-approved drugs in the oxazolidinone category, are examples of this, with linezolid being the first of the two to be developed. Oxazolidinones are a unique category of drugs that prevent formation of the 70S protein synthesis complex in bacteria, and may be useful in the treatment of vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* [149; 171]. Nonetheless, development of resistance in bacteria is relentless.

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 a position paper outlining recommendations for minimizing nosocomial infection and the emergence of resistant organisms [5]. In this paper, the CDC recommended a multistep approach.

The first step recommended by the CDC is to prevent infection. 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 is an effective method to prevent the spread of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

The next step is to tailor medical treatment to fit the infection. Antimicrobial therapy should be based on the likely pathogens or results of culture, so broad-spectrum antibiotics may be avoided when possible. Consideration should be given to pathogens common to the area of infection (e.g., skin, intra-abdominal) and to pathogens common in the environment locally (e.g., hospital environment). Prolonged treatment regimens increase the likelihood of emerging resistance, so the duration of therapy should be carefully monitored and undue prolongation avoided.

The last step is to prevent the transmission of resistant bacteria between patients. A simple, effective method of infection containment is hand washing. As noted in the CDC position paper, participation in hospital infection control programs is also necessary [5]. A coordinated effort to contain pathogens within hospital infection control guidelines makes it easier to prevent the spread of multidrug-resistant bacteria.

EVIDENCE-BASED PRACTICE RECOMMENDATION

A meta-analysis published by the *Cochrane Database of Systematic Reviews* found high-certainty evidence that any professional or structural interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment in the hospital setting.

(http://www.cochrane.org/CD003543/EPOC_improving-how-physicians-working-hospital-settings-prescribe-antibiotics. Last accessed January 22, 2018.)

Level of Evidence: Meta-analysis

Despite the remarkable rate of the development of new antibiotics, the emergence of drug-resistant bacteria continues unabated. Therefore, it is important to use antibiotics wisely to maintain their usefulness for the future.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of the appropriate prescription of antibiotics, particularly in empirical treatment. Furthermore, communication with patients regarding treatment regimens and compliance depends on clear communication between the patient and clinician. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. The interpreter should be considered an active agent in the diagnosis and/or treatment processes, negotiating between two cultures and assisting in promoting culturally competent communication and practice [151].

PENICILLINS

Alexander Fleming discovered penicillin in 1928. After observing that *Penicillium* colonies inhibited the growth of staphylococci on agar plates, Fleming made an extract from the mold and proved that it inhibited bacterial growth. Penicillin became available for general use in the 1940s [150].

MECHANISM OF ACTION

Penicillin is bactericidal, killing susceptible bacteria by interrupting cell wall synthesis. The drug exerts its effect by preventing cross-binding of the peptidoglycan polymers necessary for cell wall formation and by binding with carboxypeptidases, endopeptidases, and transpeptidase ("penicillin-binding proteins" [PBPs]) that participate in cell wall synthesis [6]. Although the exact mechanisms involved are not known, the end result is that the cell wall is structurally weakened and lyses, leading to cell death.

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The basic form of penicillin is structured around the beta-lactam ring (a thiazolidine ring) and can be altered by substituting side chains. By doing so, the antimicrobial spectrum, absorption characteristics, and resistance to beta-lactamase deactivation can be favorably modified.

Bacterial resistance to penicillins may take different forms. The most significant is the bacterial production of beta-lactamases, which can destroy the beta-lactam ring by means of hydrolysis, effectively preventing antimicrobial activity by the agent [7]. In addition, some bacteria are able to prevent binding to the PBPs by various means, including altered binding sites for the penicillins [8].

Various strategies have been employed to circumvent these microbial adaptations. Altering the structure of the penicillin molecule to produce agents that are more resistant to the hydrolysis from the beta-lactamases has resulted in the development of the extended-spectrum penicillins.

Another strategy has been to combine penicillins with other agents that block bacterial beta-lactamases. Examples include amoxicillin plus clavulanic acid, ampicillin plus sulbactam, piperacillin plus tazobactam, and ticarcillin plus clavulanic acid. Clavulanic acid is produced by *Streptomyces clavuligerus*. Sulbactam and tazobactam are derived from the basic penicillin ring. These agents have little intrinsic antimicrobial activity, but they bind irreversibly to many beta-lactamases, preventing hydrolytic activity against the beta-lactam ring.

PHARMACOKINETICS

Penicillins can be separated into groups based on their pharmacokinetics and spectrum of antibacterial activity. These groups are the natural penicillins, the aminopenicillins, the penicillinase-resistant penicillins, and the antipseudomonal penicillins [9].

The Natural Penicillins

The natural penicillins include various penicillin G preparations and penicillin V potassium. Penicillin G is very unstable in stomach acid and must be given parenterally. Penicillin V potassium is more acid-stable and is the appropriate form for oral administration.

The natural penicillins are active against gram-positive organisms such as streptococci, *Enterococcus faecalis*, and *Listeria monocytogenes*. However, most *S. aureus* isolates are now resistant. They are also active against anaerobic species, such as *Bacteroides* species and *Fusobacterium* species. At serum levels achieved by parenteral administration, the natural penicillins are effective against some gram-negative bacteria, such as *Escherichia coli*, *H. influenzae*, *Neisseria gonorrhoeae*, and *Treponema pallidum*. For the treatment of moderate-to-severe infections in which resistant organisms are considered a possibility, reliance upon penicillin alone should be avoided unless the identity and sensitivity of the infecting organism have been confirmed. Labeled uses include treatments for infections of the upper and lower respiratory tract, throat, skin, and genitourinary tract and prophylaxis of recurrent rheumatic fever and pneumococcal infections [149].

The Aminopenicillins

The aminopenicillins have about the same activity as the natural penicillins against susceptible gram-positive organisms, plus improved coverage of selected gram-negative bacilli, including *Enterobacteriaceae*. Amoxicillin/clavulanic acid and ampicillin/sulbactam have better coverage against *H. influenzae* and *Klebsiella* species than the natural penicillins and the aminopenicillins alone.

The aminopenicillins include ampicillin and amoxicillin. Ampicillin can be given parenterally or orally. These agents are useful for the management of sinusitis/bronchitis, endocarditis, meningitis, susceptible urinary tract infection, and salmonellosis [149]. Amoxicillin is the best absorbed of the oral penicillins. It is acid-stable and its absorption, unlike ampicillin, is not much affected by food. Improved absorption is also thought to provide an advantage over ampicillin in reducing the risk of antibiotic-associated diarrhea. Labeled uses include endocarditis prophylaxis and as a component of a multidrug *H. pylori* eradication regimen [149].

The Penicillinase-Resistant Penicillins

The penicillinase-resistant penicillins were developed in response to the emergence of penicillinase-producing *S. aureus*. These penicillins are resistant to hydrolysis by the lactamase produced by the staphylococci, and they include nafcillin and oxacillin, which are parenteral formulations, and dicloxacillin, which is given orally. Methicillin and cloxacillin are no longer available in the United States [149].

While the penicillinase-resistant penicillins are effective against many of the same gram-positive organisms that the natural penicillins are effective against, they lack significant activity against gram-negative or anaerobic organisms. They are, however, notable for their usefulness against penicillin-resistant (methicillin-sensitive) *Staphylococcus* species.

The Antipseudomonal Penicillins

The antipseudomonal penicillins are often also referred to as extended-spectrum penicillins; these include ticarcillin and piperacillin (both of which are parenteral). Mezlocillin, which was also parenteral, and carbenicillin, which was oral, are no longer available in the United States.

These agents retain much of their activity against gram-positive bacteria, but they also have more activity against gram-negative bacteria, including *Pseudomonas aeruginosa*. Additional gram-negative species that are treated by these agents include *H. influenzae*, *Serratia* species, and *Klebsiella* species.

The Addition of Beta-Lactamase Inhibitors

The addition of clavulanic acid, sulbactam, or tazobactam increases the spectrum of activity of the penicillin derivative with which they are combined. They are generally active

THE PENICILLINS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Natural Penicillins					
Penicillin G benzathine	1.2–2.4 MU	50,000 U/kg in one dose Max: 2.4 MU divided between 2 injection sites	IM	Rash, GI upset	Indicated for syphilis and group A strep infections. Note: Do not administer IV (except parenteral/aqueous preparation) or IM near nerve or artery. Cardiopulmonary arrest and death have occurred from accidental IV administration.
Penicillin G benzathine or penicillin G procaine	2.4 MU in one dose	<14 kg: O.6 MU 14 to 27 kg: 1.2 MU in one dose	IM	Rash, GI upset	
Penicillin G (parenteral/ aqueous)	12–24 MU per day	100,000–300,000 U/kg/day in divided doses every 4 to 6 hours Max: 24 MU/day	IM, IV	Rash, GI upset	
Penicillin V potassium	125–500 mg every 6 to 8 hours	Pneumonia (off label): 50–75 mg/kg/day in 3 to 4 divided doses Pharyngitis: 250 mg 2 to 3 times per day	PO	Rash, GI upset	—
Aminopenicillins					
Amoxicillin	250–500 mg every 8 hrs, or 500–875 mg twice daily	Manufacturer recommendation: >3 months and <40 kg: 20–100 mg/kg/day in divided doses every 8 to 12 hrs ≤3 months: 20–30 mg/kg/day divided every 12 hrs AAP recommendation: All infants and children <40 kg: 25–50 mg/kg/day in divided doses every 8 hrs	PO	Rash, diarrhea	Not to be confused with amoxicillin/clavulanate ES formulation. Extended-release tablet 775 mg once daily for adults and children ≥12 years of age
Amoxicillin/ clavulanate	250–500 mg every 8 hrs, or 875 mg every 12 hrs	15–40 mg/kg/day divided every 8 hrs, or 25–45 mg/kg/day divided every 12 hrs Max: 4g/day <3 mos: 30 mg/kg/day every 12 hrs (125 mg/5 mL suspension only)	PO	Rash, diarrhea	Dosing for amoxicillin/ clavulanate is based on the amoxicillin component; the ES formulation of amoxicillin/clavulanate is not interchangeable with the regular suspension and requires product specific dosing.
Ampicillin	250–500 mg every 6 hrs	PO: 50–100 mg/kg/day in 4 divided doses Max: 2–4 g/day IV, IM: 25–200 mg/kg/day every 3 to 4 hrs Max: 12 g/day	PO, IV, IM	Rash, GI symptoms (very common)	The IV form can be given in divided doses or in a continuous infusion.

Table 1 continues on next page.

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THE PENICILLINS *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Ampicillin/ sulbactam	1.5–3 g every 6 hrs IV	≥1 year: IV: 100–400 mg/kg/day every 6 hrs Max: 8 g/day	IV, IM	Rash, diarrhea, local pain at injection or infusion site (very common with IM use)	Dosing for ampicillin/ sulbactam is based on the ampicillin component.
Penicillinase-Resistant Penicillins					
Dicloxacillin	125–500 mg every 6 hrs	<40 kg: 12.5–25 mg/ kg/day in 4 doses divided every 6 hrs >40 kg: 125–250 mg every 6 hrs	PO	Rash, diarrhea	Use with caution in neonates, as elimination of drug is slow.
Nafcillin	IV: 0.5–2 g every 4 to 6 hrs IM: 0.5 g every 4 to 6 hrs	Neonates: 50 mg/kg/ day in 4 divided doses Children: IV: 50–200 mg/kg/day in 4 divided doses IM: 25 mg/kg every 12 hrs	IV, IM	Phlebitis at IV site, neutropenia, rash	Tissue necrosis can occur with IV extravasation.
Oxacillin	0.25–2 g every 4 to 6 hrs	<40 kg: 50–100 mg/ kg/day in divided doses every 6 hrs >40 kg: 250–1,000 mg every 4 to 6 hrs	IV, IM	Phlebitis at IV site, hepatitis, rash	Drug-induced hepatitis is usually reversible if drug is discontinued. Neonatal dosing may require the use of alternate container system/ dosage forms. May contain a significant amount of sodium.
Antipseudomonal Penicillins					
Piperacillin	IV, IM: 3–4 g every 4 to 6 hrs Max: 24 g/day	Neonates: IV, IM: 100 mg/kg every 12 hrs Infants/children: IV, IM: 200–300 mg/kg/day divided every 4 to 6 hrs	IV, IM	Rash, GI upset, phlebitis at infusion site	—
Piperacillin/ tazobactam	IV: 3.375–4.5 every 6 to 8 hrs Max: 18 g/day	Infants 2 to 9 months: 80 mg piperacillin/kg/ dose every 8 hrs Infants and children >9 months: 100 mg piperacillin/kg/dose	IV	Rash, GI upset	Dosing for adults and pediatrics based on traditional infusion method (IV infusion over 30 minutes). Dosage in pediatric patients based on piperacillin component. Pediatric dose is mg/kg/dose, not mg/kg/day.
Ticarcillin or ticarcillin/ clavulanate potassium	<60 kg: 200–300 mg/kg/day divided every 4 to 6 hrs >60 kg: 3.1 g every 4 to 6 hrs Max: 18 g/day	Use adult dosing by weight	IV	Rash, GI upset	Potential warfarin interaction. Ticarcillin/clavulanate doses are based on the ticarcillin component.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
AAP = American Academy of Pediatrics; MU = million units; ES = extra strength.

Source: [148; 149] *Table 1*

against the beta-lactamases produced by *H. influenzae*, *Moraxella catarrhalis*, and *S. aureus*. However, their activity is variable against some of the gram-negative bacteria, such as some species of *Pseudomonas*, *Enterobacter*, *E. coli*, *Klebsiella*, and *Serratia*, due to resistance to these beta-lactamase inhibitors [10].

ABSORPTION/ELIMINATION

While most penicillins can be absorbed via the oral route, the bioavailability varies considerably, and food may interfere with absorption. Penicillin V, amoxicillin, ampicillin, and dicloxacillin can be given orally; the remaining penicillins are either too unstable in the acidic environment of the stomach or must be given intravenously in order to achieve sustained therapeutic levels. Amoxicillin is the best absorbed of the oral penicillins and the least affected by a recent meal.

Once absorbed, these agents are widely distributed throughout the body. Therapeutic concentrations of penicillins are readily achieved in tissues and secretions (e.g., joint fluid, pleural fluid, pericardial fluid, and bile). Low concentrations are found in prostatic secretions, brain tissue, intraocular fluid, and phagocytes. Cerebrospinal fluid (CSF) concentrations vary but are less than 1% of serum concentration when the meninges are normal. When the meninges are inflamed, CSF concentrations may rise to 5% and can be increased by co-administration of probenecid (500 mg 4 times daily) [11; 149]. Concentration in urine is high due to renal clearance mechanisms.

Penicillins are excreted in the kidney by means of glomerular filtration and renal tubular secretion. Probenecid markedly reduces the tubular secretion of the penicillins and decreases the apparent volume of distribution, resulting in higher serum levels. All of the penicillins are excreted to some degree in the bile, but biliary excretion is most important for antipseudomonal penicillins and nafcillin [12].

In patients with mild renal insufficiency, dosage adjustment is not needed, except with the use of ticarcillin [13]. If the creatinine clearance is less than 50 mL/min, then dosage adjustments of parenteral penicillins should be made to avoid excess serum levels. Nafcillin undergoes extensive hepatic metabolism, and the dosage must be adjusted for severe renal and hepatic insufficiency.

SIDE EFFECTS/TOXICITY

What is the only absolute contraindication to administering penicillins?

These drugs are usually well tolerated. However, gastrointestinal (GI) disturbances may occur with all oral penicillins.

Allergy to any of the penicillins is the only absolute contraindication to use of a penicillin agent. However, studies have found that penicillin allergy is less common than previously thought [165; 166; 167; 168]. Traditionally, allergic reactions were believed to occur in up to 10% of patients; however, more recent studies have found the rate to be much lower. While penicillin-induced anaphylaxis death rate estimates are similar to previous statistics (i.e., approximately 0.002% among the general population), the percentage of individuals with a true penicillin allergy as defined by immunoglobulin E (IgE)-mediated reaction is generally less than 10%, with some studies showing a true penicillin allergy rate of only 0.7% [14; 165; 166; 167]. It is also important to note that approximately 90% of patients previously diagnosed with a penicillin allergy will show no reactivity if not exposed to the antibiotic for 10 years or more, due to the absence of a true allergy or loss of allergy over time [165; 167; 168]. Allergy skin testing is the most reliable way to determine true penicillin allergy and may allow for previously avoided antibiotics to be used as indicated.

Reactions commonly misdiagnosed as true allergic responses vary and can include a mild rash (the most common) and urticaria. Rarely, serum sickness, exfoliative dermatitis, and Stevens-Johnson syndrome may develop [12; 149]. These responses were originally thought to develop in response to the beta-lactam ring and its derivatives and, therefore, there is a common misperception that penicillins are cross-reactive with other antibiotics with the same beta-lactam structure (e.g., cephalosporins) [149]. However, the major determinant in the immunologic reaction is now recognized to be the similarity in the side chain of first-generation cephalosporins and penicillins (not the beta-lactam structure), with the reaction nearing 0% in third-generation cephalosporins [165; 166; 167].

Rarely, penicillins may cause hematologic reactions with neutropenia due to reversible bone marrow suppression. Abnormal platelet aggregation may occur, particularly with ticarcillin [15]. Other rare reactions include hepatitis, seizures, interstitial nephritis, and hypokalemia due to local effects in the renal tubules.

DRUG INTERACTIONS

The penicillins should not be given concurrently with tetracycline or other bacteriostatic agents. Penicillin works in cells that are actively synthesizing cell wall components, and if metabolism is prevented, then the actions of penicillin may be impaired. The antipseudomonal penicillins also may affect warfarin metabolism. Therefore, the prothrombin time, using the international normalized ratio (INR), should be monitored [16].

SPECIAL POPULATIONS

The penicillins are pregnancy category B, indicating no adverse events noted in animal studies [17]. These agents are secreted in breast milk, and breastfeeding should be avoided if the infant is allergic to any of the penicillins [18]. Use while breastfeeding may cause modifications of normal intestinal flora and allergic sensitization in the infant [149].

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CEPHALOSPORINS

Giuseppe Brotzu discovered the first cephalosporin in 1948, observing that the fungus *Cephalosporium acremonium* produced a substance that inhibited the growth of *S. aureus* and other bacteria. The initial substance was identified and modified to create the cephalosporins that are now used. The cephamycins were created by adding a methoxy group on the beta-lactam ring of the original compound, based on the structure of cefoxitin, produced by *Streptomyces lactamdurans*. By altering the chemical groups substituted on the basic molecule, greater antimicrobial activity and longer half-lives have been obtained [19].

MECHANISM OF ACTION

Like penicillins, the cephalosporins are beta-lactams in which the beta-lactam ring is joined to a dihydrothiazine ring. Their antimicrobial effect is based on the same mechanism of action as that for the penicillins. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases and other PBPs involved in the synthesis and cross-linking of peptidoglycan [20; 21].

Because each bacterial species has a unique chemical structure in its cell wall, the cephalosporins may have different mechanisms of action by which they inhibit cell wall synthesis.

As with penicillins, resistance to the action of cephalosporins results from mutations in the penicillin-binding proteins (preventing the cephalosporins from binding to them) and from the production of extended-spectrum beta-lactamases that deactivate the drug [22]. An additional source of resistance in gram-negative bacteria is alteration in the cell-membrane porins that normally allow passage of the cephalosporins [23].

Of these mechanisms, the production of beta-lactamase is the most clinically significant. This form of resistance may occur through mutations or may be carried on plasmids [24].

PHARMACOKINETICS

The cephalosporins have been classified in different ways, based on chemical structure and pharmacologic activities. The most commonly used classification system groups the agents into "generations" based on their similarities in antimicrobial coverage.

First-Generation Cephalosporins

The first-generation cephalosporins are most active against aerobic gram-positive cocci. These agents include cefazolin, cephalexin, and cefadroxil, and they are often used for skin infections caused by *S. aureus* and *Streptococcus* and for susceptible urinary tract infections. They have activity against *E. coli* and some activity against *H. influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria.

Second-Generation Cephalosporins

The second-generation cephalosporins are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, which are included in this group under this classification system although they are technically cephamycins, also have more coverage against anaerobic bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. influenzae*.

Third-Generation Cephalosporins

The third-generation cephalosporins have enhanced activity and a broader spectrum against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, *Klebsiella*, and other *Enterobacteriaceae*. Of these agents, ceftriaxone has the best activity against gram-positive cocci, specifically *S. pneumoniae* and methicillin-sensitive *S. aureus*. Ceftazidime is active against *P. aeruginosa*. Other cephalosporins in this class include cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory, intraabdominal, and urinary tract infections and for nosocomial infections (because of the high incidence of resistant organisms) [25].

Fourth-Generation Cephalosporins

Cefepime is classed as a fourth-generation cephalosporin because it has good activity against both gram-positive and gram-negative bacteria, including *P. aeruginosa* and many *Enterobacteriaceae*. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections.

Fifth-Generation Cephalosporins

Ceftaroline fosamil is a novel advanced-generation cephalosporin approved by the U.S. Food and Drug Administration (FDA) in 2010, for the treatment of community-acquired bacterial pneumonia and bacterial skin and soft-tissue infections. As with other beta-lactams, ceftaroline exerts its antimicrobial affect by binding to PCP and inhibiting cell wall synthesis. This agent is unique in that it also has a high affinity for PBP2a, which is associated with resistance to methicillin. Consequently, ceftaroline is highly active against methicillin-sensitive and resistant strains of *S. aureus* and against multidrug-resistant *S. pneumoniae* [152]. It is ineffective for *P. aeruginosa*, and its activity against *Enterobacteriaceae* is variable. Beta-lactamase-producing *Enterobacteriaceae* and AmpC mutants are resistant. Prospective clinical trials have shown that the efficacy of ceftaroline is comparable to vancomycin plus aztreonam for the treatment of bacterial skin and soft-tissue infection (including methicillin-resistant *S. aureus* [MRSA]) and to ceftriaxone for the treatment of community-acquired bacterial pneumonia [153]. Among cases of pneumonia caused by *S. pneumoniae*, clinical cure

THE CEPHALOSPORINS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
1st Generation					
Cefadroxil	1–2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	PO	Rash, diarrhea	Can interfere with some urine glucose tests.
Cefazolin	1–2 g every 8 hrs Max: 12 g/day	>1 mo: 25–100 mg/kg/day divided every 6 to 8 hrs Max: 6 g/day	IV, IM	Phlebitis at infusion site, seizure,rash, diarrhea	Can interfere with some urine glucose tests.
Cephalexin	250–1,000 mg every 6 to 12 hrs Max: 4 g/day	>1 yr to <15 yrs: 25–100 mg/kg/day in 3 to 4 divided doses Max: 4 g/day	PO	GI upset, rash	Can interfere with some urine glucose tests.
2nd Generation					
Cefaclor	250–500 mg every 8 hrs	>1 mo: 20–40 mg/kg/day in 2 to 3 divided doses Max: 1 g/day	PO	Rash, GI upset	Can interfere with some urine glucose tests.
Cefotetan	1–2 g every 12 hrs Max: 4–6 g/day	AAP recommendation: 30–50 mg/kg/dose every 12 hrs Max: 4,000 mg/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Disulfiram-like reaction with alcohol. Can interfere with some urine glucose tests. Not recommended for treatment of community-acquired intra-abdominal infections.
Cefoxitin	1–2 g every 6 to 8 hrs Max: 12 g/day	>3 mos: 80–160 mg/kg/day in 4 to 6 divided doses Max: 12 g/day	IV, IM	Phlebitis at infusion site, rash	IM injection is painful. Can interfere with some urine glucose tests. In pediatrics, for group A beta-hemolytic streptococcal infections, antimicrobial therapy should be given for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis.
Cefprozil	250–500 mg every 12 to 24 hrs	>6 mos: 7.5–20 mg/kg every 12 hrs >2 yrs: 7.5–15 mg/kg/day in 2 divided doses, or 20 mg/kg every 24 hrs Max: 1 g/day	PO	Rash, GI upset, elevated liver enzymes	Avoid use in phenylketonuria. Can interfere with some urine glucose tests.
Cefuroxime	PO: 250–500 mg every 12 hrs for 10 days IV, IM: 0.5–1.5 g every 6 to 8 hrs Max: 6 g/day	PO: 20–30 mg/kg/day in 2 divided doses IV, IM: 75–150 mg/kg/day in 3 divided doses Max: 6 g/day	PO, IV, IM	Phlebitis at infusion site, rash, GI upset	Tablets and oral suspension forms require different dose. Oral doses noted here are for tablet formulation. Higher doses can be used for severe infection.
3rd Generation					
Cefdinir	300 mg every 12 hrs, or 600 mg every 24 hrs for 10 days	7 mg/kg/dose twice daily or 14 mg/kg/dose for 10 days Max: 600 mg/day	PO	Rash, diarrhea	Iron and antacids can reduce absorption. Can interfere with some urine glucose tests.
Cefditoren	200–400 mg every 12 hrs for 10 to 14 days	Not studied for patients <12 yrs	PO	GI upset, headache	Interaction with proton-pump inhibitors, H2 blockers, antacids. Contraindicated with milk protein allergy.

Table 2 continues on next page.

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THE CEPHALOSPORINS *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
3rd Generation *(Continued)*					
Cefixime	400 mg/day in 1 or 2 doses	>6 mos and <45 kg: 8–20 mg/kg/day every 12 to 24 hrs Max: 400 mg/day >12 yrs or >50 kg: Use adult dosing	PO	Diarrhea, rash	Can interfere with some urine glucose tests.
Cefotaxime	1–2 g every 4 to 12 hrs	1 mo to 12 yrs and <50 kg: 50–225 mg/kg/day in 3 to 4 divided doses	IV, IM	Phlebitis at infusion site, rash, GI upset	Single dose can be given for GC. Transient arrhythmias have developed after administration of this agent through central venous catheter.
Cefpodoxime	100–400 mg every 12 hrs for 7 to 14 days	10 mg/kg/day in 2 divided doses	PO	Diarrhea, nausea, vomiting	Decreased absorption with antacids and H2 blockers. Can be given as a single dose for GC.
Ceftazidime	500–1,000 mg every 8 hrs	IV: 30–50 mg/kg every 8 hrs Max: 6 g/day AAP recommendation for IV: 90–200 mg/kg/day every 8 hours Max: 6 g/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Can interfere with some urine glucose tests. The L-arginine formulation should not be used in children.
Ceftibuten	400 mg every 24 hrs for 10 days	9 mg/kg/day Max: 400 mg/day for 10 days	PO	Rash, GI upset, headache	Can interfere with some urine glucose tests.
Ceftriaxone	IV, IM: 1–2 g every 12 to 24 hrs	50–100 mg/kg/day in 1 to 2 divided doses Max: 4 g/day	IV, IM	Phlebitis at infusion site, rash	Avoid in neonates with hyperbilirubinemia. Higher doses are used for meningitis. A ceftriaxone-calcium salt can precipitate in the gallbladder, causing sonographically detectable abnormalities.
4th Generation					
Cefepime	IV: 1–2 g every 8 to 12 hrs IM: 0.5–1 g every 12 hrs	IV, IM: 50 mg/kg every 8 to 12 hrs Not to exceed adult dosing	IV, IM	Phlebitis at infusion site, GI upset	Can interfere with some urine glucose tests.
5th Generation					
Ceftaroline fosamil	600 mg every 12 hours for 5 to 14 days	>2 mos to <2 yrs: 8 mg/kg/dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and <33 kg: 12 mg/kg/dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and >33 kg: 400–600 mg every 8 to 12 hrs for 5 to 14 days	IV	Phlebitis at infusion site, GI upset, headache	Slow IV infusion over 60 minutes. Can interfere with some urine glucose tests.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
GC = gonococcal infection.

Source: [148; 149] *Table 2*

rates were higher with ceftaroline (83.3%) than with ceftriaxone (70%) in a phase III clinical trial, and the agent was well tolerated [154].

ABSORPTION/ELIMINATION

What route of elimination is used by most cephalosporins?

The orally administered cephalosporins include cefaclor, cefadroxil, cephalexin, cefprozil, cefuroxime axetil, cefixime, cefpodoxime proxetil, ceftibuten, and cefdinir. In general, the orally administered cephalosporins are absorbed rapidly. Cephalexin, cefadroxil, cefaclor, cefixime, ceftibuten, and cefdinir are nonesterified and are absorbed from the GI tract by active transport in the small intestine. Other agents, such as cefuroxime axetil and cefpodoxime proxetil, are prodrug esters and are passively absorbed. Once absorbed into the cells lining the small intestine, these agents are hydrolyzed and then excreted into the blood stream as active cephalosporins [26].

The presence of food or antacids may increase or decrease the absorption, depending on the drug. Cefuroxime axetil and cefpodoxime proxetil have increased absorption when taken with food. Cefaclor, cefadroxil, and cephalexin have slowed absorption when food is in the stomach. Cefixime, cefprozil, and ceftibuten are not affected by the presence of food. Cefpodoxime is the only cephalosporin whose absorption is decreased by the presence of antacids or H2 antagonists [27].

There is extensive distribution of the cephalosporins into body tissues and fluids. They readily cross the placenta and are also found in synovial fluid. Concentrations in bile and urine are high. Most cephalosporins do not cross into the CSF in sufficient concentration to be recommended for the treatment of meningitis, but there are some exceptions. Cefuroxime, cefotaxime, ceftriaxone, cefepime, and ceftaroline all have good penetration into the CSF [28; 152].

Most cephalosporins are eliminated by the kidney. The exception in the oral cephalosporins is cefixime, half of which is excreted in the urine. The remaining half is partly metabolized to inactive metabolites and partly excreted in the bile. Cefotaxime is deacetylated by the liver to a bioactive metabolite and inactive forms. The deacetylated metabolites are excreted by the kidney. Cefpiramide is excreted predominantly in the bile.

In severe hepatic insufficiency, compensatory changes in renal excretion of the hepatically metabolized drugs may occur [29]. In the presence of severe renal and/or hepatic insufficiency, dosage adjustment of cefotaxime is necessary.

SIDE EFFECTS/TOXICITY

As a group, cephalosporins are relatively well tolerated [30]. The most common complaints are GI upset, resulting in nausea, vomiting, or diarrhea. Thrombophlebitis can occur with intravenous (IV) administration. One to three percent of patients develop an allergic reaction. Rash, fever, eosinophilia, and urticaria can develop. Anaphylaxis is rare. Infrequently, there is some cross-sensitivity with true penicillin allergy (estimated nearly 0%to 10% of cases); this occurs mostly with first-generation cephalosporins [13; 165; 166; 167]. If a patient develops urticaria, anaphylaxis, or angioedema with penicillins or a cephalosporin, avoid using any of the other cephalosporins.

Although uncommon, nephrotoxicity has been reported [31]. Cephalosporins that contain the methylthiotetrazole (MTT) side chain (cefotetan) may induce a disulfiram-like reaction with alcohol ingestion (e.g., flushing, tachycardia, nausea and vomiting, diaphoresis, dyspnea, hypotension, and confusion). This is due to increased circulating acetaldehyde.

Ceftriaxone has been associated with cholelithiasis and cholestatic hepatitis due to precipitation in the bile [32]. Rare reactions include hematologic toxicity with resultant eosinophilia, thrombocytopenia, and leukopenia, all of which resolve after stopping treatment [33]. Rarely, hemolytic anemia develops [34]. Hypoprothrombinemia may occur with cephalosporins with the MTT side chain as a result of interference by the MTT moiety with the synthesis of vitamin-K-dependent clotting factors [35]. For patients at high risk of bleeding, exogenous vitamin K may help alleviate this side effect. False-positive glucosuria testing with a copper reduction test (Clinitest) may occur with many cephalosporins [36].

DRUG INTERACTIONS

The serum levels of all the cephalosporins are increased with co-administration of probenecid. The effects of warfarin may be enhanced by co-administration of cefotetan, cefazolin, cefoxitin, and ceftriaxone.

SPECIAL POPULATIONS

Cephalosporins are generally considered safe to use in pregnancy and are designated as category B. They are excreted in breast milk in low concentrations, and the American Academy of Pediatrics (AAP) considers this compatible with breastfeeding [37; 38].

CARBAPENEMS

Meropenem, imipenem/cilastatin, doripenem, and ertapenem are parenteral synthetic beta-lactams derived from thienamycin, an antibiotic produced by *Streptomyces cattleya* [39]. They have a lactam ring, like the penicillins and cephalosporins, but have a methylene moiety in the ring.

MECHANISM OF ACTION

Like other beta-lactams, the carbapenems inhibit mucopeptide synthesis in the bacterial cell wall by binding to PBPs, leading to lysis and cell death. Bacterial resistance may occur due to a specific beta-lactamase that affects carbapenems. Another significant source of resistance is a mutation that results in the absence of the outer membrane porin, thus

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not allowing transport of the drug into the cell [40]. Cross-resistance may occur between the carbapenems.

PHARMACOKINETICS

Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against anaerobic bacteria, including *Bacteroides* species. They also cover many gram-positive cocci, such as *Enterococcus* and *Streptococcus*, as well as many gram-negative bacteria [41]. Meropenem has somewhat greater activity against gram-negative bacteria, which are not affected by most beta-lactamases. Doripenem has good activity against *Pseudomonas aeruginosa*.

Imipenem and ertapenem are approved by the FDA for use in urinary tract infections, pneumonia, intra-abdominal infections, and skin and soft-tissue infections [149]. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age [149]. Combination meropenem/vaborbactam is approved for the treatment of complicated urinary tract infections caused by susceptible micro-organisms [163].

ABSORPTION/ELIMINATION

Imipenem/cilastatin, meropenem, and ertapenem are given parenterally, as they are unstable in stomach acid. Imipenem is combined with cilastatin, which inhibits dehydropeptidase I in the proximal renal tubular cells. Dehydropeptidase I inactivates imipenem by hydrolysing the beta-lactam ring, so adding the cilastatin allows increased levels of imipenem in the urine and also prevents the production of the nephrotoxic metabolites of imipenem [42]. Meropenem, doripenem, and ertapenem do not require a dehydropeptidase I inhibitor.

Meropenem is well distributed in body tissues and fluids, including the CSF. Imipenem/cilastatin and ertapenem are distributed throughout body tissues, but with only low concentrations in the CSF [43].

Most of the imipenem/cilastatin dose is excreted in the urine. The remaining 20% to 25% of the dose is excreted through an unknown mechanism. Meropenem is excreted unchanged into the urine by means of glomerular filtration and tubular secretion [44]. Ertapenem is metabolized by hydrolysis of the beta-lactam ring, and then both the metabolite and parent drug are excreted in the urine.

The carbapenems require dosage adjustment in patients with renal insufficiency. No changes in dosage are necessary for patients with hepatic insufficiency.

SIDE EFFECTS/TOXICITY

What side effects are associated with the use of imipenem/cilastatin?

The carbapenems are generally well tolerated. Occasional reactions include nausea and vomiting, phlebitis at the infusion site, elevation of liver enzymes, and leukopenia. Seizures may occur. The risk is higher in patients with underlying central nervous system (CNS) disease and in patients with renal disease, which results in high serum levels of the drug [45]. Hypersensitivity reactions may occur, and while there is a degree of cross-sensitivity with penicillins, this risk is lower than previously believed [165; 166; 167]. Carbapenems should be used with caution in patients allergic to the carbapenems or penicillins.

DRUG INTERACTIONS

There are few drug interactions associated with the carbapenems, but probenecid may increase the serum levels of meropenem, ertapenem, and imipenem/cilastatin and should be avoided. Ertapenem cannot be infused with dextrose or other medications. Meropenem may reduce levels of valproic acid [46].

SPECIAL POPULATIONS

Meropenem, doripenem, and ertapenem are pregnancy category B, with animal studies showing no adverse reactions [47]. Imipenem/cilastatin is pregnancy category C, based on studies in monkeys that showed increased embryonic loss and side effects in the mother [48]. No data is available regarding breastfeeding and carbapenem administration.

The safety of doripenem use has not been studied in children. Meropenem has been used in children and is indicated by the FDA for the treatment of pediatric meningitis but has not been studied in infants younger than 3 months of age [49]. Ertapenem can be used in infants older than 3 months of age, and imipenem can be used from birth; these agents are useful for treating complicated infections in pediatric patients (e.g., complicated urinary tract infections).

MONOBACTAMS

Monobactams have a single beta-lactam core, distinguishing them from the other beta-lactam drugs [50]. Aztreonam is the only available example of this class of drugs. Aztreonam was originally extracted from *Chromobacterium violaceum*. It is now manufactured as a synthetic antibiotic.

MECHANISM OF ACTION

As with other beta-lactams, aztreonam inhibits mucopeptide synthesis in the bacterial cell wall by binding to the penicillin-binding proteins of gram-negative bacteria, leading to cell lysis and death. Aztreonam is resistant to most beta-lactamases. Treatment in combination with an aminoglycoside appears to be synergistic against *Pseudomonas*.

PHARMACOKINETICS

Aztreonam does not have significant activity against gram-positive or anaerobic bacteria and is primarily used as an alternative therapy for gram-negative bacterial infections, including *P. aeruginosa* and *Klebsiella*, that are resistant to the first-line beta-lactams or carbapenems. It is indicated for use in pneumonia, soft-tissue infections, urinary tract infections,

THE OTHER BETA-LACTAMS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Carbapenems					
Doripenem	500 mg every 8 hours for 5 to 14 days	Not studied for pediatric use	IV	Headache, rash, nausea, vomiting, diarrhea, phlebitis	Dosage adjustment necessary for renal impairment. Cannot be used in patients with known serious hypersensitivity or history of anaphylaxis to any beta-lactam antibiotic. Seizure risk in patients with CNS disorders.
Ertapenem	1 g/day for 3 to 14 days	15 mg/kg every 12 hrs Max: 1 g/day for 3 to 14 days	IV, IM	Diarrhea, nausea, phlebitis at infusion site	Seizure risk in patients with CNS disorders. IV therapy may be administered for up to 14 days; IM for up to 7 days.
Imipenem/ cilastatin	500–1,000 mg every 6 to 8 hrs Max: 4 g/day	>3 mos: 15–25 mg/kg every 6 hrs Max: 4 g/day	IV	Phlebitis at infusion site, rash	Documentation of cross-allergy with penicillin allergy is limited. Seizure risk in patients with CNS disorders. Adults <70 kg may require decreased dosing.
Meropenem	1.5–6 g/day in 3 divided doses	Infants <3 mos (IV): Gestational age <32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 12 hrs Postnatal age ≥14 days: 20 mg/kg/dose every 8 hrs Gestational age ≥32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 8 hrs Postnatal age ≥14 days: 30 mg/kg/dose every 8 hrs >3 mos and <50 kg: 30–120 mg/kg/day in 3 divided doses Max: 6 g/day >50 kg: Same as adult dosing	IV	Diarrhea, nausea, inflammation at the injection site, headache	Can cause elevated LFTs. Seizure risk in patients with CNS disorders.
Meropenem/ vaborbactam	4 g every 8 hrs for <14 days	Not studied in pediatric patients	IV	Headache, GI symptoms, phlebitis at infusion site	Dosage adjustment necessary for renal impairment.

Table 3 continues on next page.

Source: [148; 149] *Table 3*

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THE OTHER BETA-LACTAMS *(Continued)*					
Monobactams					
Aztreonam	IV: 1–2 g every 8 to 12 hrs Nebulizer: 75 mg 3 times/day at least 4 hours apart for 28 days; do not repeat for 28 days after completion.	>9 mos: 30–50 mg/kg/dose every 6 to 8 hrs Max: 120 mg/kg/day >7 years of age (nebulizer): Same as adult dosing	IV, IM, oral inhalation	Rash, nausea, vomiting, phlebitis at infusion site	Rare cross-sensitivity with allergy to other beta-lactams. For oral inhalation, pretreatment with a bronchodilator is recommended.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. CNS = central nervous system; LFTs = liver function tests (liver enzymes).					
Source: [148; 149]					*Table 3*

and intra-abdominal and pelvic infections that are caused by gram-negative aerobic bacteria.

There is no oral form of aztreonam, and intravenous is the preferred mode of parenteral administration. It is distributed widely in body tissues and fluids, including inflamed meningeal tissue [51]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [52]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [53].

SIDE EFFECTS/TOXICITY

Frequent adverse reactions include elevations of liver enzymes and transient eosinophilia. Less common reactions include phlebitis at the infusion site, rash, diarrhea, and nausea [54].

There have been a few reports of cross-allergy reactions in patients who are allergic to ceftazidime, but patients with penicillin and cephalosporin allergy can usually tolerate aztreonam [55]. Aztreonam is contraindicated in patients with prior allergic reactions to it or to any component of the formulation.

DRUG INTERACTIONS

No drug interactions have been reported with aztreonam [56].

SPECIAL POPULATIONS

Aztreonam is pregnancy category B, based on animal studies that have shown no ill effects of the drug. There is no human data available [57].

Aztreonam is secreted in breast milk in low concentrations; breastfeeding is not recommended because the effects of the drug have not been studied in young infants.

Aztreonam has not been studied for use in children younger than 1 month of age but appears safe in children older than 1 month of age, although it should be noted that manufacturer recommendations are for children older than 9 months of age [149]. It has been shown to be very useful in children with respiratory symptoms of cystic fibrosis [58].

AMINOGLYCOSIDES

The first aminoglycoside, streptomycin, was derived from *Streptomyces griseus* during the 1940s. Actinomycetes were studied for possible antimicrobial byproducts, and it was found that *Micromonospora* and *Streptomyces* produced useful agents. As newer, safer, and more effective aminoglycosides have been developed, the use of streptomycin is now confined primarily to certain management strategies for the treatment of tuberculosis.

MECHANISM OF ACTION

The basic structure of the aminoglycosides is an aminocyclitol ring. Different members of the family have different glycosidic linkages and side groups.

The aminoglycosides have at least two effects on the bacterial cell that ultimately result in cell death. These agents bind negative charges in the outer phospholipid membrane, displacing the cations that link the phospholipids together. This leads to disruption in the wall and leakage of cell contents. In addition, they inhibit protein synthesis by binding to the 30S subunit of the ribosome, causing miscoding and termination [59].

Although resistance to aminoglycosides is less common than with many other antibiotics, it can develop as a result of three known mechanisms. The most common pattern of resistance involves modification of the aminoglycoside molecule itself by enzymes produced by some bacteria. After the aminoglycoside is altered, it cannot bind as well to the ribosomes. The genes that encode for these enzymes are carried on plasmids, allowing rapid transfer of resistance between bacteria. Of

note, amikacin has an S-4 amino 2-hydroxybutyryl (AHB) side chain that protects it against deactivation by many bacterial enzymes and is therefore less susceptible to this bacterial defense mechanism [60].

The binding site for aminoglycosides on the rRNA of the ribosome may also be altered, reducing binding. In addition, mutations that cause reduced uptake of aminoglycosides have been documented [60].

To combat resistances and overcome the relative natural resistance of enterococcus, other agents that target the cell wall are often used in conjunction with the aminoglycosides. Damage to the cell wall from the additional agents may be bactericidal in some cases and also makes the cell wall more permeable to the aminoglycosides [61].

PHARMACOKINETICS

Which aminoglycoside is taken orally as a bowel decontaminant due to its minimal absorption?

The aminoglycosides are effective for the treatment of aerobic gram-negative bacilli, such as *Klebsiella* species, *Enterobacter*, and *P. aeruginosa*. There is very little activity against anaerobes and gram-positive organisms, so combination therapy with a beta-lactam, vancomycin, or other agents active against gram-positive organisms and anaerobes is commonly used. The aminoglycosides are indicated for infections caused by susceptible organisms of the urinary tract, respiratory tract, skin and soft tissues, and sepsis due to gram-negative aerobic bacilli.

The aminoglycosides commonly used at present for treatment of systemic bacterial infection include gentamicin, tobramycin, amikacin, and kanamycin. Aminoglycosides have negligible oral absorption and thus require parenteral administration. They also can be administered directly into body cavities and have a role in the management of pleural and peritoneal infection. Tobramycin is particularly useful for treatment of recurrent *Pseudomonas* infection in patients with cystic fibrosis and can be administered by aerosolized inhalation to facilitate optimal local antimicrobial effect [58]. Neomycin is often used orally as part of a pre-operative bowel decontamination protocol.

The aminoglycosides are widely distributed in extracellular fluid, including pleural fluid, synovial fluid, abscesses, and peritoneal fluid. They are relatively insoluble in lipid, so the volume of distribution is lower in obese patients. They have poor distribution in bile, aqueous humor, bronchial secretions, sputum, and the CSF [9].

Aminoglycosides are excreted unchanged by the kidneys. There is no reduction of dosage necessary in liver failure, as there is no hepatic metabolism of these agents. In renal failure, the dosage must be carefully adjusted based on glomerular filtration rate and measured serum levels. Serum levels should be monitored in all patients with reduced renal function [63].

TOXICITY

The most common adverse effect associated with aminoglycoside usage is renal failure, which is usually reversible when the drug is discontinued. The exact mechanism of renal injury and how that injury results in decreased glomerular filtration is unknown [64]. It appears that, although there is no hepatic metabolism of the aminoglycosides, concomitant liver disease increases the likelihood of the development of nephrotoxicity [65].

Less commonly, vestibular and auditory impairment may develop during treatment with aminoglycosides. These effects are usually reversible, and because there is some data suggesting that there is a genetic predisposition to ototoxicity, this drug class should be avoided in patients who have a family history of ototoxicity with aminoglycosides [66]. When aminoglycoside therapy is expected to exceed five to seven days, baseline testing of auditory function should be performed and monitored weekly for the duration of treatment.

Neuromuscular blockage has also been observed as a side effect. Aminoglycosides may aggravate muscle weakness in patients with neuromuscular disorders, such as myasthenia gravis and Parkinson disease, due to a curare-like effect on neuromuscular function [67].

Hypersensitivity reactions are not common with aminoglycosides, but rash, fever, urticaria, angioneurotic edema, and eosinophilia may occur. Very rare reactions include optic nerve dysfunction, peripheral neuritis, arachnoiditis, encephalopathy, pancytopenia, exfoliative dermatitis, and amblyopia. Bronchospasm and hoarseness have been known to occur with tobramycin inhalation solution [62].

The aminoglycosides are contraindicated in patients with hypersensitivity to the drug. Cross-sensitivity between aminoglycosides does occur. Streptomycin also contains metabisulfite and should be avoided if the patient is allergic to sulfites (more common in asthmatics) [68].

DRUG INTERACTIONS

There are numerous drug interactions that should be taken into consideration when using the aminoglycosides. The risk of nephrotoxicity may be increased with co-administration of other drugs that are nephrotoxic or in patients receiving loop diuretics (e.g., furosemide). Respiratory depression may occur if aminoglycosides are given with nondepolarizing muscle relaxants. Neomycin may affect digoxin levels by altering the bowel flora responsible for the metabolism of digoxin in the GI tract. Gentamicin may also cause increased serum digoxin levels [69].

In vitro deactivation of penicillins due to acylation has been observed, so the drugs should not be mixed in vitro. Tobramycin inhalation solution cannot be mixed in the nebulizer with dornase alfa [70].

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THE AMINOGLYCOSIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Amikacin	5 mg/kg every 8 hrs or 7.5 mg/kg every 12 hrs	15–22.5 mg/kg/day every 8 hrs OR 15–20 mg/kg/dose every 24 hours	IV, IM	Renal failure, vestibular nerve damage, auditory nerve damage	Predisposition to auditory/ vestibular nerve damage may be genetic; check family history. Check serum levels. Doses are based on lean body mass; maintenance dose is based on calculation with creatinine clearance. Additional dose adjustments are needed in renal failure.
Gentamicin	3–5 mg/kg/day in divided doses every 8 to 12 hrs, or 5–7 mg/kg once daily	Infants: 2–2.5 mg/kg/ dose every 6 to 8 hrs	IV, IM, topical		
Kanamycin	5–7.5 mg/kg/day divided every 8 to 12 hrs Max: 1.5 g/day	15 mg/kg/day in 2 to 3 divided doses	IV, IM[a]		
Neomycin	4–12 g/day in 4 to 6 divided doses for 5 to 6 days, or 4 g/ day for an indefinite period	50–100 mg/kg/day in 3 to 4 divided doses	PO, topical	Systemic absorption is possible, resulting in the same side effects as amikacin.	Used as a bowel prep for surgery. Is also formulated in some topical eye, ear, and skin preparations.
Streptomycin	15–30 mg/kg/day or 1–2 g daily	20–40 mg/kg/day every 6 to 12 hrs in divided doses Max: 1 g/dose or 2 g/day	IV, IM	Renal failure, vestibular nerve damage, auditory nerve damage	This is the most ototoxic of aminoglycosides; levels must be monitored closely. Can cause neuromuscular blockade and respiratory paralysis, especially when given soon after muscle relaxants or anesthesia.
Tobramycin	1–2.5 mg/kg every 8 to 12 hrs, or 4–7 mg/kg once daily dose	<5 yrs: 2.5 mg/kg every 8 hrs >5 yrs: 2–2.5 mg/kg every 8 hrs	IV, IM inhalation solution, ophthal-mic oint-ment or solution	Renal failure, vestibular nerve damage, auditory nerve damage	Effects of nondepolarizing muscle relaxants can be increased. Total body weight (as opposed to ideal body weight) should be used for underweight patients.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
[a]IM formulation no longer available in the United States.

Source: [148; 149] *Table 4*

SPECIAL POPULATIONS

Amikacin, streptomycin, tobramycin, and kanamycin are pregnancy category D due to eighth cranial nerve toxicity that has occurred in the fetus with some aminoglycosides. Gentamicin is pregnancy category C due to animal studies that show dose-related nephrotoxicity. Ototoxicity has not been reported with gentamicin, but it may occur. Neomycin is pregnancy category C due to minimal systemic absorption of the oral dose. Despite these categorizations by the manufacturers, some authorities think that these agents may be used if the benefit outweighs the potential risk [71].

Traces of aminoglycosides are excreted in breast milk, but the AAP considers this compatible with breastfeeding because aminoglycosides are very poorly absorbed from the GI tract [38]. However, they may cause alterations in the normal bowel flora of the infant.

Half-life alterations occur in patients at extremes of age. The half-life in neonates and low-birth-weight infants may be considerably prolonged. The elderly may also have a longer aminoglycoside half-life due to an age-related decrease in renal function [62]. Geriatric dosing should be based on ideal body weight estimates [149].

MACROLIDES AND TELITHROMYCIN

The original macrolide, erythromycin, was discovered in 1952 by J.M. McGuire. It is produced by *Saccharopolyspora erythraea* (formerly known as *Streptomyces erythreus*). Semisynthetic derivatives (clarithromycin, azithromycin) have been produced from the original erythromycin, with modifications that improve acid stability, antibacterial spectrum, and tissue penetration.

MECHANISM OF ACTION

The macrolides are bacteriostatic, inhibiting protein synthesis by binding at the 50S ribosomal unit and by blocking transpeptidation and translocation. At high concentrations or with rapid bacterial growth, the effects may be bactericidal [72].

Telithromycin is technically a ketolide, but it is structurally related to the macrolides. It also functions by binding the ribosomal subunit with subsequent inhibition of bacterial protein synthesis. By binding in two places, telithromycin remains active against bacteria that produce methylases, which alter binding at the domain V site on the ribosomal subunit [73].

Many bacteria that are resistant to the penicillins are also resistant to erythromycin. Bacterial resistance may result from decreased permeability of the cell membrane; in addition, an increase in active efflux of the drug may occur by incorporating a transporter protein into the cell wall [74]. The gene for this mechanism is transferred on plasmids between bacteria. Mutations of the 50S ribosomal receptor site may also develop, preventing binding of the erythromycin. Lastly, bacterial enzymes have been described that may deactivate erythromycin [75]. It is likely that this form of resistance is also transferred on plasmids.

Many strains of *H. influenzae* are resistant to erythromycin alone but are susceptible to a combination with a sulfonamide [76]. Erythromycin ethylsuccinate and sulfisoxazole are manufactured as suspensions for use in treating acute otitis media in children older than 2 months of age. They are useful for targeting *H. influenzae*, one of the common pathogens in otitis media in this age group.

PHARMACOKINETICS

Erythromycin has a wide spectrum of activity. Gram-positive bacteria that are usually susceptible to erythromycin include the *Streptococcus* species. Erythromycin is a second-line agent for gram-negative bacteria, such as *H. influenzae* and *M. catarrhalis*. Macrolides are particularly useful for their coverage of atypical bacteria, such as *Mycoplasma* and *Chlamydia*. Some spirochetes and mycobacteria are also susceptible to the macrolides. These drugs are indicated for upper respiratory tract infections, such as sinusitis, otitis media, pharyngitis, and bronchitis. They are also useful in the treatment of pertussis, Legionnaires disease, and diphtheria. Telithromycin, which has a long half-life and can be given once daily, has proved useful for the management of community-acquired pneumonia [149]. However, in 2016, the manufacturer of telithromycin announced the discontinuation of the drug [149].

Erythromycin base is deactivated by gastric acid, so it is formulated in enteric-coated tablets or capsules that protect the drug until it reaches the duodenum, where it is absorbed. Eating increases stomach acid secretion and may slow absorption as a result. The ester forms of the erythromycin base (stearate, estolate, and ethylsuccinate) were all formulated to improve absorption. The estolate is the best absorbed of the three after eating; the ethylsuccinate form is best absorbed in the fasting state [77]. Erythromycin may also be given intravenously.

Clarithromycin and azithromycin have excellent absorption after oral dosing. Clarithromycin and telithromycin may be given with food, but for azithromycin, the presence of food in the stomach causes significant delays in absorption [78].

All the macrolides have extensive tissue distribution, with less than adequate penetration into the brain tissue and the CSF [79]. Erythromycin and azithromycin are primarily excreted unchanged into the bile. Clarithromycin is excreted in the bile and in the urine, both unchanged and as the hydroxy metabolite. Telithromycin undergoes hepatic metabolism and is eliminated mainly in the bile, but also in the urine [80].

It may be necessary to adjust the doses of the macrolides in the presence of severe hepatic insufficiency. Azithromycin and clarithromycin doses may have to be reduced in severe renal failure. Because telithromycin is eliminated by more than one mechanism, hepatic or renal insufficiency is unlikely to affect serum levels unless they are both present [81].

SIDE EFFECTS/TOXICITY

While serious side effects with the macrolides are rare, milder side effects are common. Erythromycin stimulates motility in the GI tract, and this may cause abdominal cramping, diarrhea, nausea, and vomiting. Hepatic dysfunction with or without jaundice has occasionally been reported. There have also been some reports of reversible hearing loss in patients treated with erythromycin in high doses or in the presence of renal insufficiency. With IV erythromycin, prolongation of the QT interval and ventricular tachycardia may occur [82].

Clarithromycin may cause nausea, diarrhea, abnormal taste, dyspepsia, and headache. There have been reports of tooth discoloration that is reversible with professional cleaning. Transient CNS changes with anxiety and behavioral changes, which resolve when the drug is discontinued, have also been reported [83].

Side effects from telithromycin include nausea and diarrhea in up to 10% of treated patients [84]. Occasional side effects include headache, dizziness, vomiting, reversible liver function test (LFT) elevation, and hepatitis. Reversible vision

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THE MACROLIDES AND TELITHROMYCIN					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Macrolides					
Azithromycin	PO: 250–600 mg/day, or 1–2 g/day IV: 250–500 mg/day	PO: 5–12 mg/kg/day Max: 500 mg/day Otitis media: 30 mg/kg as single dose (not to exceed 1,500 mg)	PO, IV, ophthalmic drops	GI upset	One dose of 1 g given PO can be used for non-GC urethritis/cervicitis. Interaction with pimozide/cyclosporine.
Clarithromycin	250–500 mg every 12 hrs, or 1 g/day extended-release formulation for 7 to 14 days	>6 mos of age: 7.5 mg/kg every 12 hrs	PO	GI upset, metallic taste	Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions. Special dosing combined with omeprazole and amoxicillin is one regimen used for *H. pylori* treatment.
Erythromycin	Base: 250–500 mg PO every 6 to 12 hrs Max: 4 g/day Ethylsuccinate: 400–800 mg PO every 6 to 12 hrs Max: 4 g/day Lactobionate: 15–20 mg/kg/day IV in 4 divided doses, or 0.5–1 g IV every 6 hrs, or continuous infusion over 24 hrs (Max: 4 g/day)	Base: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Ethylsuccinate: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 4 g/day Stearate: 30–50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Lactobionate: 15–50 mg/kg/day IV in 4 divided doses Max: 4 g/day	PO, IV, ophthalmic solution, topical ointment, gel, or pad	GI intolerance (common), phlebitis at IV infusion site	Inhibits liver CYP 450 enzymes 3A4 and 1A2, resulting in multiple significant drug interactions.
Fidaxomicin	200 mg twice daily for 10 days	Not studied in pediatric patients	PO	Nausea, abdominal pain	Used for treatment of diarrhea due to *C. difficile*
Ketolides					
Telithromycin[a]	800 mg every 24 hrs for 7 to 10 days	Not studied for children <13 yrs of age >13 yrs: Use adult dosing	PO	Nausea, diarrhea	Occasionally causes visual changes (reversible). Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions. Cases of serious or fatal respiratory failure have occurred in patients with myasthenia gravis.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
Non-GC = nongonococcal infection.
[a]Drug discontinued by manufacturer in 2016.

Source: [148; 149] *Table 5*

blurring and diplopia occurs in 1% of patients [84]. Exacerbations of myasthenia gravis have been reported as well. QT interval elongation may occur, so telithromycin should be avoided in patients at risk for arrhythmias [84].

Allergic reactions to macrolides are rare, but may include rash and eosinophilia. Very rarely, severe reactions such as Stevens-Johnson syndrome have occurred. The drugs are contraindicated in patients with known hypersensitivity to the macrolides.

DRUG INTERACTIONS

Drug interactions are extensive. Erythromycin and clarithromycin are inhibitors and substrate for the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A4). If they are given with a drug that is primarily metabolized by CYP3A, the drug serum levels may be increased and/or prolonged [85]. Erythromycin and clarithromycin are contraindicated with concurrent use of cisapride, pimozide, astemizole, or terfenadine. Serum levels of theophylline, cyclosporine, digoxin, ergotamine, carbamazepine, benzodiazepines, warfarin, amiodarone, and tacrolimus may also be affected by concurrent administration with erythromycin and clarithromycin. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors levels may also be elevated, with increased risk for rhabdomyolysis [86].

Azithromycin is not likely to interact with drugs metabolized by CYP3A4. However, azithromycin interacts with pimozide, potentially resulting in QT interval prolongation and arrhythmia [87]. Co-administration with pimozide is therefore contraindicated. Levels of cyclosporine could potentially be increased and therefore should be monitored closely [88].

Telithromycin is metabolized in the liver, partly by the P450 enzyme system and partly by other mechanisms. It may interact with the following drugs: cisapride, pimozide, quinidine, procainamide, dofetilide, rifampin, ergot alkaloids, itraconazole, ketoconazole, midazolam, digoxin, cyclosporine, carbamazepine, hexobarbital, phenytoin, tacrolimus, sirolimus, metoprolol, theophylline, and statins. Telithromycin is contraindicated in patients allergic to macrolides or telithromycin. It should not be given with cisapride or pimozide [84]. An interaction between warfarin and telithromycin has also been reported [89].

SPECIAL POPULATIONS

Erythromycin is pregnancy category B, with an erythromycin estolate preparation as the preferred form because it is less likely to cause hepatotoxicity. Surveillance studies have not shown any increase in adverse outcomes. The CDC recommends the use of erythromycin for the treatment of *Chlamydia* during pregnancy [90]. Azithromycin is also category B, based on animal studies. It has been used safely to treat *Chlamydia* in pregnant women [91]

Clarithromycin is pregnancy category C, based on the finding that it causes growth retardation in monkeys and adverse effects on other mammals. A postmarketing surveillance study did not find any evidence of teratogenicity, but another study found a higher rate of spontaneous abortion in those treated with clarithromycin [92; 93].

Erythromycin is excreted in breast milk, but the AAP considers it usually compatible with breastfeeding [38]. Clarithromycin is excreted in breast milk in lactating animals, but the effects have not been studied in humans. There have been some reports of infantile hypertrophic pyloric stenosis following treatment of newborns with erythromycin [94].

QUINOLONES

The first quinolone, nalidixic acid, was introduced in 1962. It was developed as a result of chloroquine synthesis. Later, derivatives with broader spectrum antimicrobial coverage were produced, leading to the current class of quinolone drugs. As with other classes of synthetic and semisynthetic antimicrobials, alterations of side chains affect antimicrobial activity and pharmacokinetics [95].

MECHANISM OF ACTION

Quinolones cause bacterial cell death by inhibiting DNA synthesis. They inhibit DNA gyrase and DNA topoisomerase, enzymes that mediate DNA supercoiling, transcription, and repair [96]. The exact mechanism by which this leads to cell death has not yet been determined.

Bacterial resistance develops as a result of spontaneous mutations that change the binding sites for quinolones on the DNA gyrase and the DNA topoisomerase [97]. Mutations that decrease the ability of quinolones to cross the cell membrane also occur. Some of these resistances may be transferred from other bacteria by means of plasmids [98].

PHARMACOKINETICS

The quinolones are active against many gram-positive cocci, gram-negative bacilli, and atypical bacteria (e.g., *Legionella*, *Mycoplasma*). Quinolone activity against streptococci and anaerobes, at achievable serum levels, is relatively poor, although newer agents, such as moxifloxacin, have better coverage for anaerobes [99]. Gram-negative coverage includes *Campylobacter*, *Enterobacter*, *E. coli*, *H. influenzae*, *Klebsiella*, *Salmonella typhi*, *Shigella*, and *Vibrio cholerae*. Indications for the use of quinolones include urinary tract infections, non-gonococcal infections of the urethra and cervix, pneumonia, sinusitis, soft-tissue infections, and prostatitis. Ciprofloxacin is indicated for post-exposure prophylaxis for anthrax, and levofloxacin has an indication for the treatment of inhalation anthrax infection. The quinolones are absorbed well after oral administration, and peak serum levels in the elderly and those with reduced renal function approximate those achieved with intravenous usage. Food may delay the time to reach peak serum concentration but does not decrease

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total absorption. The drugs are distributed well throughout all tissues, including the prostate, although the levels in the CSF and prostatic fluid are lower than serum levels [100].

Clearance mechanisms vary between the quinolones. Levofloxacin and ofloxacin are mainly cleared by renal excretion and have minimal hepatic clearance [101]. Moxifloxacin is mainly excreted nonrenally. Moxifloxacin is metabolized, via glucuronide and sulfate conjugation in the liver, to an inactive metabolite [102].

Norfloxacin, ciprofloxacin, and gemifloxacin have mixed routes of elimination. Norfloxacin has some hepatic metabolism to active metabolites; the metabolites and parent drug are excreted by the kidney. About 30% of the dose of norfloxacin is excreted in the stool, in the bile, and as unabsorbed drug. As much as 50% of the ciprofloxacin dose is excreted renally, and 40% is excreted in the bile after hepatic metabolism. Approximately 60% of gemifloxacin is excreted in the feces, and the remainder is excreted in the urine.

In renal insufficiency, the quinolones that are primarily excreted renally and those with mixed routes of elimination require dosage adjustments [103]. Moxifloxacin doses do not have to be adjusted for mild hepatic insufficiency, although this has not been studied in severe hepatic insufficiency [102].

SIDE EFFECTS/TOXICITY

The most common side effect with the use of quinolones is GI upset. Less common side effects include headache, insomnia, dizziness, peripheral neuropathy, tendon rupture, elevated liver enzymes, and interstitial nephritis [104; 105]. Rarely, hematologic toxicities have occurred, resulting in hemolytic anemia (more likely to occur in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency), aplastic anemia, and agranulocytosis [106]. Very rarely, hepatic necrosis and hepatic failure have been reported [107].

Although allergic reactions are not common, they may occur and range from a rash to severe reactions, such as Stevens-Johnson syndrome. Very rare cases of severe fatal hypoglycemia have been reported with concurrent treatment with glyburide and ciprofloxacin [108]. Use quinolones with caution in patients with medical problems that predispose the patient to seizures.

There is also a risk of disabling peripheral neuropathy associated with the use of oral or injectable fluoroquinolones [155]. The onset can be rapid, and patients should be advised to contact their healthcare provider if any signs or symptoms develop. In these cases, the fluoroquinolone should be stopped and an alternative non-fluoroquinolone drug used, unless the benefit of continued treatment outweighs the risk [155].

In 2018, the FDA strengthened the warnings about the risks of mental health side effects (e.g., disorientation, agitation, delirium) and serious blood sugar disturbances (including hypoglycemic coma) associated with fluoroquinolones [176].

DRUG INTERACTIONS

Drug interactions are common and vary among the quinolones. Antacids may decrease the absorption of these agents. Iron supplements and other supplements with divalent and trivalent cations cause quinolone-cation complexes and impair absorption [109]. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) appears to increase the risk of seizures [110].

Theophylline, phenytoin, warfarin, and mexiletine levels may be elevated in patients concurrently treated with ciprofloxacin. Serum levels or prothrombin time should be monitored, and the doses of these drugs should be altered as appropriate. Dosage adjustments are not typically needed with other quinolones [111].

SPECIAL POPULATIONS

Quinolones are not recommended during pregnancy. Animal studies have demonstrated arthropathy in immature animals [112]. It is presumed that quinolones are excreted in breast milk, and due to the risk for arthropathy, breastfeeding while taking a quinolone should be avoided.

It is unclear if these effects cause clinically significant changes in humans, so there is debate over whether it is safe to use the drugs in children [113]. Quinolones have been used in pediatric patients with cystic fibrosis, but they should only be used in patients younger than 18 years of age if the benefits outweigh the risks [114].

SULFONAMIDES

Sulfonamides, the first true antibiotics, are derived from azo dyes. The first agent was sulfachrysoidine, used in 1935, which released sulfanilamide in vivo [115]. Modifications were made to the sulfanilamide to reduce side effects, resulting in the development of the modern sulfonamides. Many of the sulfonamides are no longer used as parenteral agents, but they continue to be used as topical agents or for treatment in specific conditions (e.g., prophylaxis for drug-resistant malaria). Some of these agents are no longer available in the United States but are still commonly used in other countries.

MECHANISM OF ACTION

The sulfonamides are bacteriostatic, exerting their effect as competitive antagonists of para-aminobenzoic acid (PABA). They inhibit dihydropteroate synthase from using PABA to synthesize dihydropteroic acid, a precursor of folic acid. The lack of folic acid intermediates ultimately results in impaired synthesis of nucleotides. Bacteria that use pre-formed folate are not susceptible to the bacteriostatic action. Silver sulfadiazine is one exception, as it exerts its effects on the cell membrane and cell wall and is bactericidal.

Unfortunately, bacterial resistance to sulfonamides is common, with cross-resistance between agents frequently occurring. Mutations that result in additional production of PABA

THE QUINOLONES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Besifloxacin	1 drop 3 times daily (4 to 12 hrs apart) for 7 days	Same as adult dosing	Ophthalmic drops	Headache	Contact lenses should not be worn during treatment
Ciprofloxacin	PO: 250–750 mg every 12 hrs IV: 200–400 mg every 12 hrs	PO: 20–30 mg/kg/day in 2 divided doses Max: 1.5 g/day IV: 20–30 mg/kg/day in 2 divided doses Max: 800 mg/day	PO, IV, topical, otic, ophthalmic solution or ointment	GI upset, headache	Photosensitivity can occur. Antacids decrease absorption. Can prolong QT interval. Quinolones may cause tendon inflammation and rupture and may exacerbate myasthenia gravis associated muscle weakness.
Delafloxacin	PO: 45 mg every 12 hrs for 5 to 14 days IV: 300 mg every 12 hrs for 5 to 14 days	Not studied in pediatric patients	PO, IV		
Gatifloxacin	Day 1: 1 drop every 2 hrs while awake Max: 8/day Days 2–7: 1 drop 2 to 4 times/day	>1 yr: same as adult dosing	Ophthalmic drops	Headache, GI upset, conjunctival irritation, keratitis	
Gemifloxacin[a]	320 mg once daily for 5 to 7 days	N/A	PO	GI upset, headache, rash	
Levofloxacin	250–750 mg/day for 5 to 14 days	N/A	PO, IV, ophthmalmic drops, inhalation	GI upset, headache, phototoxicity	
Moxifloxacin	400 mg/day for 5 to 14 days	N/A	PO, IV, ophthalmic drops	GI upset, headache	
Norfloxacin[a]	400 mg every 12 hrs, or 800 mg as a single dose for GC	N/A	PO	GI upset, headache	Antacids decrease absorption.
Ofloxacin	200–400 mg every 12 hrs	N/A	PO, otic, ophthalmic drops		
Ozenoxacin	Apply thin layer to affected area (up to 100 cm^2) twice/day for 5 days	Infants >2 mos to 12 yrs: Same as adult dosing, except treated area may only be up to 2% of total body surface area (Max: 100 cm^2) >12 yrs: same as adult dosing	Topical	<1% experience rosacea-like face eruption, seborrheic dermatitis	Novel drug for treatment of impetigo caused by *Staphylococcus aureus* or *Streptococcus pyogenes*

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
[a]No longer available in the United States.

Source: [148; 149] *Table 6*

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or changes in the enzyme binding sites for sulfonamides are responsible for the resistance [116]. Genes for these resistant mutations may be carried on plasmids, allowing rapid transfer to other similar bacteria and resulting in more rapid development of resistance patterns than through random mutation alone [117].

One method for improving bacterial activity against potentially resistant strains is the addition of trimethoprim [118]. Trimethoprim is a competitive inhibitor of dihydrofolate reductase, another enzyme active in the synthesis of folate. Trimethoprim resistance is also common [119].

PHARMACOKINETICS

The sulfonamides can be divided into four groups based on absorption and excretion characteristics. They are classified as short-to medium-acting agents, long-acting agents, agents limited to activity in the GI tract, and topical agents.

The Short- to Medium-Acting Sulfonamides

The first group, the short- to medium-acting agents, includes sulfisoxazole, sulfamethoxazole, and sulfadiazine. Sulfisoxazole is partly metabolized to *N*-acetyl sulfisoxazole; both the drug and the metabolite are excreted in the urine [120]. Because of a limited spectrum of action, sulfisoxazole is indicated primarily for uncomplicated urinary tract infection and chloroquine-resistant malaria. Sulfamethoxazole is combined with trimethoprim and is indicated for *Pneumocystis jiroveci* prophylaxis and treatment, upper respiratory tract infections, and urinary tract infections. The only FDA indication for sulfadiazine is toxoplasmosis [149].

The Long-Acting Sulfonamides

The long-acting agents have been associated with severe allergic reactions and for the most part been replaced in use by the less-toxic sulfonamides. The last long-acting agent available in the United States was sulfadoxine, which is given as a combination with pyrimethamine; however, as of 2018, this agent is no longer available. This drug was reserved for the treatment of drug-resistant malaria and certain cases of *Toxoplasma gondii* infestation. Pyrimethamine inhibits dihydrofolate reductase in *Plasmodium* species during the erythrocytic stage [149].

Sulfadoxine/pyrimethamine is absorbed quickly from the small intestine and, like the shorter acting agents, is widely distributed in tissue and body fluids [149].

Sulfonamides Limited to Gastrointestinal Tract Activity

The agents limited to the GI tract are very poorly absorbed and have been used for reducing bacterial flora in the bowel before surgery. The only available agent in this class is sulfasalazine, which is used in the treatment of ulcerative colitis. Although absorption of sulfasalazine from the intact intestine is very low, inflammation in the bowel may result in significant absorption of the metabolite sulfapyridine.

Topical Sulfonamides

The topical sulfonamides include mafenide acetate and silver sulfadiazine, which are used in the treatment of burns. Mafenide is used less often because it may cause a metabolic acidosis as a result of carbonic anhydrase inhibition. An additional topical agent is sulfacetamide, which is used in ophthalmic and lotion formulations. Topical sulfonamides may be absorbed systemically, and if large burn areas are treated, absorption may be significant [149].

ABSORPTION/ELIMINATION

The sulfonamides are quickly absorbed after administration unless they have been altered to stay in the lumen of the intestine (e.g., sulfasalazine). After absorption, they are acetylated in the liver into a toxic but inactive form. The acetylated form is mostly excreted in the urine, with a small amount excreted in bile. These drugs are widely distributed throughout body tissue and fluids, including the CSF and peritoneal fluid [121].

The sulfonamides undergo acetylation and glucuronidation in the liver. Both the unchanged and metabolized forms are excreted in the urine through glomerular filtration and renal tubular secretion.

Mafenide may be used in renal failure, but monitoring of acid-base balance is recommended. Dosage and frequency of administration of other sulfonamides must be adjusted in renal failure based on serum levels. No data is available on dosing in hepatic insufficiency.

SIDE EFFECTS/TOXICITY

Allergic reactions with rash and itching are relatively common. Nausea, vomiting, diarrhea, headache, and photosensitivity may occur. Rare but severe hypersensitivity reactions, including vasculitis, anaphylaxis, serum sickness, and Stevens-Johnson syndrome, may occur [122]. Sulfacetamide lotion also contains metabisulfite, which may cause an allergic reaction in patients allergic to sulfites.

Sulfonamide ophthalmic preparations may cause local irritation. The topical mafenide may cause pain or burning locally. Systemic reactions may develop during treatment with ophthalmic and topical preparations of sulfonamides due to systemic absorption.

Less common reactions include metabolic acidosis that may occur with absorption of mafenide due to a byproduct, (rho) carboxybenzenesulfonamide, that inhibits carbonic anhydrase. Very rare reactions with sulfonamides include blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia, hemolytic anemia), hepatitis and hepatocellular necrosis, and toxic nephrosis due to crystalluria [123]. Hemolysis is more likely to develop in patients with G6PD deficiency [124].

Sulfonamides are contraindicated in patients who are known to be allergic to sulfa drugs and in cases where there have been previous adverse effects to sulfonamides.

THE SULFONAMIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Short- to Medium-Acting					
Sulfadiazine	2–4 g/day in 3 to 6 divided doses	>2 mos (initial): 75–150 mg/kg/day in 4 to 6 divided doses >2 mos (maintenance): 150 mg/kg/day in 4 to 6 divided doses Max: 6 g/day	PO	Rash, pruritus	Multiple drug interactions. Contraindicated in infants <2 mos of age.
Sulfamethoxazole/ trimethoprim	PO: 1–2 DS tablets every 12 to 24 hrs IV: 8–20 mg TMP/ kg/day in 2 to 4 divided doses	>2 mos PO: 6–20 mg TMP/kg/day in 2 divided doses IV: 6–20 mg TMP/ kg/day every 12 to 24 hours Max single dose: 160 mg TMP/dose	PO, IV	Rash, pruritus	Multiple drug interactions. Weight-based dosing recommendations based on trimethoprim content.
Long-Acting					
Sulfadoxine/ pyrimethamine[a]	Single dose of 3 tablets (total: sulfadoxine 1,500 mg and pyrimethamine 75 mg)	Weight-based dosing: Sulfadoxine 25–70 mg/kg and pyrimethamine 1.25–3.5 mg/kg as a single dose	PO	Folic acid deficiency, blood dyscrasias, GI upset	For malaria prophylaxis: A single dose should be carried for self-treatment in the event of febrile illness when medical attention is not immediately available. Note: Discontinue at first sign of rash, myelosuppression, or active bacterial/fungal infection.
Limited to GI Tract					
Sulfasalazine	RA: Initial: 0.5–1 g every 6 to 8 hrs Maintenance: 2 g/ day in divided doses UC: Initial: 3–4 g in evenly divided doses every 8 hours Titrate to 4–6 g in 4 divided doses	>2 yrs: 40–60 mg/kg/ day in 3 to 6 divided doses	PO	Anorexia, headache, GI upset	Contraindicated with hypersensitivity to salicylates, sulfasalazine, sulfonamides, or mesalamine.
Topical					
Mafenide	Cream: Apply 1.6 mm thick layer to burn area every 12 or 24 hrs Solution: Wet dressing gauze every 4 hrs or as needed	Use adult dosing	Cream, powder for solution	Burning at application site, rash, allergic reaction	Used for treatment of second- and third-degree burns to prevent infection. Burn area should be covered with cream/wet at all times. Apply with sterile gloved hand.
Silver sulfadiazine	Apply 1.6-mm layer to burn area once or twice daily	Use adult dosing	Cream	Rash, allergic reaction	

Table 7 continues on next page.

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THE SULFONAMIDES *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Sulfacetamide	Dosage varies with the preparation.	Use adult dosing	Prepared in complex with other topical medications as a solution or ointment	Rash, local irritation	Combinations with fluorometholone, prednisolone, and phenylephrine are available, each with differing dosing, indications, and contraindications. Common for ophthalmic and topical use.

Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.
DS = double strength; RA = rheumatoid arthritis; TMP = trimethoprim; UC = ulcerative colitis.
[a]Not currently available in the United States.

Source: [148; 149] *Table 7*

DRUG INTERACTIONS

Warfarin, phenytoin, and sulfonylureas may all be potentiated due to displacement of the drugs from serum albumin by the sulfonamides [125]. Cyclosporine levels may be decreased, and levels should be monitored [126]. Administration of PABA may antagonize the effects of sulfa drugs.

SPECIAL POPULATIONS

Sulfa drugs should be avoided in pregnancy near term due to the increased potential for kernicterus in the newborn [127]. Animal studies with sulfamethoxazole show bone abnormalities and a higher incidence of cleft palate.

Mafenide, sulfacetamide ophthalmic drops, and sulfadiazine are pregnancy category C. Sulfacetamide lotion has not been studied in pregnancy. Silver sulfadiazine is pregnancy category B, based on animal studies that showed no ill effects [128].

Sulfonamides are excreted in breast milk. Sulfamethoxazole and sulfisoxazole are considered compatible with breastfeeding by the AAP, although they should be avoided if hyperbilirubinemia or G6PD deficiency is present [38]. Sulfacetamide lotion and silver sulfadiazine have not been studied in breastfeeding but would presumably also be excreted in breast milk; use with caution in breastfeeding women [149].

Because of the risk of neonatal kernicterus, use of sulfonamides should be avoided in the newborn. Sulfacetamide eye drops have not been studied in children younger than 2 months of age [149].

TETRACYCLINES

Chlortetracycline, the first tetracycline, was developed in 1948 as a product of *Streptomyces aureofaciens*. Chlortetracycline was altered to produce tetracycline. Doxycycline and minocycline are semisynthetic derivatives.

Tetracyclines bind to the 30S ribosomal subunit, blocking the binding of aminoacyl transfer-RNA [129]. This results in inhibition of protein synthesis, with bacteriostatic effects.

Bacterial resistance is typically the result of mutations that either prevent entrance of tetracyclines into the cell or increase the export of tetracycline out of the cell [130]. The resistance may be transmitted by plasmids [131].

MECHANISMS OF ACTION AND PHARMACOKINETICS

The tetracyclines have a broad spectrum of activity that includes aerobic gram-positive and gram-negative bacilli, atypical bacteria (such as *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Mycoplasma pneumoniae*), and spirochetes (such as *Borrelia burgdorferi*). Tetracycline is also a second-line agent for *T. pallidum*. It is approved by the FDA for treatment of rickettsial infections, typhus, Rocky Mountain spotted fever, trachoma, nongonococcal urethritis, and lymphogranuloma venereum [149].

As a result of decades of clinical and agricultural use, the prevalence of resistance to tetracyclines is now high among common gram-positive and gram-negative pathogens. For this reason, and because they are bacteriostatic, the role of tetracyclines is limited for treatment of most pyogenic infections. Primary indications for this class are atypical

infections (e.g. mycoplasma and chlamydia) and zoonoses (e.g. tularemia and brucellosis).

The tetracyclines may be divided into three groups based on their pharmacokinetic traits. These groups are the short-acting group, intermediate-acting group, and long-acting group. The varying half-lives are the result of different rates of renal excretion [149].

Short-Acting Tetracyclines

The short-acting tetracyclines include oxytetracycline and tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. Oxytetracycline is no longer available in the United States [149]. Tetracycline is inexpensive but requires dosing every six hours for most indications. A less frequent dosage protocol is commonly used for the treatment and prevention of acne [149].

Intermediate-Acting Tetracyclines

The only intermediate-acting agent available in the United States is demeclocycline. Demeclocycline is no longer used as an antibiotic but rather has been used as an off-label drug to treat the syndrome of inappropriate antidiuretic hormone (SIADH) [132]. However, studies have suggested that there is limited high-quality evidence to suggest that demeclocycline is effective in managing this condition, and European clinical practice guidelines recommend against the use of demeclocycline for the management of hyponatremia in patients with SIADH [149; 169].

Long-Acting Tetracyclines

The long-acting tetracycline agents, doxycycline and minocycline, are the more recently developed drugs. The main difference between these and the short-acting agents is that these may be dosed less frequently (once or twice daily), which is an advantage in ensuring compliance. The spectrum of bacterial coverage is essentially the same and the indications are the same, with the additional indication for the treatment of inhalation anthrax as part of a multidrug regimen.

ABSORPTION/ELIMINATION

Of the tetracyclines, which drug is mainly excreted in the urine?

Tetracycline is well absorbed after an oral dose taken in the fasting state. Doxycycline and minocycline are well absorbed after an oral dose and may be given with or without food.

The tetracyclines are well distributed throughout body tissues and fluids; distribution in the CSF is adequate for the treatment of some infections [133; 134]. The excellent tissue penetration results in the ability of the drug to cross into the dentin, where the tetracycline permanently chelates with the calcium [135].

Most of the tetracycline dose is excreted unchanged into the urine by glomerular filtration, although there is some biliary excretion as well. Nonrenal, possibly hepatic, mechanisms account in large part for excretion of doxycycline and minocycline. Only 20% to 26% of doxycycline and 4% to 19% of minocycline is excreted in the urine [136].

Tetracycline should be avoided in the presence of renal insufficiency, because it accumulates rapidly in the serum in the presence of decreased renal function. Doxycycline may be used in renal failure, as it will be excreted into the bile [137]. Because tetracyclines have been known to cause hepatic toxicity, they should not be used in patients with hepatic insufficiency [138].

SIDE EFFECTS/TOXICITY

Tetracyclines commonly cause GI upset, including nausea, vomiting, and diarrhea. They also cause staining and deformity of the teeth in children younger than 8 years of age. Photosensitivity, idiopathic intracranial hypertension, esophageal ulceration, and hepatotoxicity occur rarely [149].

Minocycline is often associated with vertigo, nausea, and vomiting, and it may increase azotemia in renal failure. In addition, prolonged use of minocycline may cause reversible discoloration of the fingernails, the sclera, and the skin [139]. Minocycline has been associated with a lupus-like reaction [140].

Allergic reactions to tetracyclines are not common but may range from mild rashes to anaphylaxis. Tetracyclines are contraindicated in patients who have shown hypersensitivity to any tetracyclines.

DRUG INTERACTIONS

Several types of drug interactions result in alterations in serum levels of tetracyclines. Agents that alkalinize the urine will increase excretion of the tetracyclines. Polyvalent metal cations (calcium, aluminum, zinc, magnesium, and iron) and bismuth decrease absorption [141]. Drugs that induce hepatic enzymes may decrease the half-life of doxycycline.

Interactions that affect the efficacy of other drugs also occur. The bactericidal effect of penicillins may be decreased by co-administration with tetracyclines. Concurrent use of oral contraceptives may make the contraceptive less effective [142; 143]. The effects of warfarin are increased, probably because tetracyclines depress plasma prothrombin activity, resulting in a synergistic effect [144]. Digoxin effects may be increased because of changes in the bowel flora that are responsible for digoxin metabolism [145].

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THE TETRACYCLINES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range[a]**	**Route**	**Common Side Effects**	**Comments**
Short-Acting					
Tetracycline	250–500 mg every 6 to 12 hrs	25–50 mg/kg/day in 4 divided doses	PO	Photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption.
Intermediate-Acting					
Demeclocycline	150 mg every 6 hrs or 300 mg every 12 hrs	≥8 years: 8–12 mg/kg/day in 2 to 4 divided doses	PO	GI upset, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Long-Acting					
Doxycycline	PO: 100–200 mg/day in 1 to 2 divided doses IV: 100 mg every 12 hrs	<45 kg: 2–5 mg/kg/day in 1 to 2 divided doses Max: 200 mg/day >45 mg: Same as adult dosing	PO, IV	Phlebitis at IV site, photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Minocycline	Initial: (IV, PO): 200 mg Maintenance: (IV): 100 mg every 12 hrs Max: 400 mg/day Maintenance (PO): 100 mg every 12 hrs, OR 100–200 mg initially, followed by 50 mg 4 times daily	Initial: (IV, PO): 4 mg/kg/dose Maintenance: 2 mg/kg/dose every 12 hrs Max: 400 mg/day	PO, IV	GI upset, tooth enamel deformities in children <8 yrs of age	
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. SIADH: syndrome of inappropriate antidiuretic hormone hypersecretion. [a]All pediatric doses are for children older than 8 years of age.					
Source: [148; 149]					*Table 8*

SPECIAL POPULATIONS

Tetracycline and doxycycline are pregnancy category D because of impaired bone development in the fetus. Hypoplasia of the enamel and discoloration of fetal teeth may occur, and maternal hepatic toxicity has been reported as well [146; 147].

Tetracyclines are excreted into the breast milk in small amounts. Most exposed infants have very low blood levels of the drug and probably are not at risk [38]. Tetracyclines should not be used in children younger than 8 years of age because of the risk for tooth deformity.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Optometric Association asserts that tetracycline and its derivatives should not be given to children younger than 8 years of age or pregnant or nursing women.

(https://www.aoa.org/documents/optometrists/CPG-10.pdf. Last accessed January 22, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

VANCOMYCIN

Vancomycin is the oldest member of the glycopeptide antibiotics class, a group of large molecules that inhibit bacterial cell wall synthesis. Glycopeptides have a high binding affinity for peptides found only in bacterial cell walls. This interaction disrupts peptidoglycan polymerization, the late-stage reaction that imparts rigidity to the cell wall [156]. Gram-positive organisms, both cocci and bacilli, are highly susceptible to glycopeptides.

Vancomycin was developed more than 50 years ago as an alternative intravenous therapy for serious staphylococcal and streptococcal infections in patients allergic to beta-lactams. In this early period, vancomycin usage was associated with a high incidence of vestibular and renal toxicity. The cause was attributed in large part to impurities in the formulation, a problem solved in subsequent years. At present, the major role for vancomycin is in the treatment of serious infections caused by MRSA, methicillin-resistant *S. epidermidis* (MRSE), and ampicillin-resistant enterococci. An oral formulation is available for the treatment of *C. difficile*-associated diarrhea/colitis.

MECHANISMS OF ACTION AND PHARMACOKINETICS

Vancomycin is not absorbed by the intestinal tract and must be administered by intravenous infusion, with the exception of the formulation for the treatment of *C. difficile*-associated diarrhea/colitis [149]. The determination of a safe, effective dosage regimen, and decisions regarding monitoring of therapy, are complex matters that require consideration of multiple factors, including the site and severity of infection, the patient's weight and renal function, the susceptibility of the infecting organism, and the anticipated duration of therapy [157]. The usual adult dose is 15–20 mg/kg/dose every 12 hours. The rate of infusion should be no more than 500 mg/hour, as rapid infusion causes an uncomfortable generalized erythroderma ("red man" syndrome). The red man syndrome is a histamine-mediated flushing that occurs during or immediately following infusion and does not mandate discontinuation unless slowing the infusion rate fails to mitigate the reaction.

ABSORPTION/ELIMINATION

Vancomycin is cleared almost entirely by the kidneys. Prolonged usage at excessively high therapeutic serum levels has been associated with nephrotoxicity and ototoxicity. In treating patients with invasive staphylococcal infection and MRSA, it is considered important to use the maximum dosage (target trough serum vancomycin level of 15–20 mcg/mL) in order to assure optimal therapeutic effect [157]. The serum creatinine and trough vancomycin level (target <20 mcg/mL) should be monitored once or twice weekly in such cases, as well as in all patients who are elderly or have impaired renal function.

SIDE EFFECTS/TOXICITY

Apart from the (avoidable) red man syndrome, vancomycin administration is well tolerated and side effects are uncommon. As with beta-lactams and sulfonamides, vancomycin is a good sensitizing agent; allergic manifestations such as fixed drug eruptions and drug fever are relatively common. Vancomycin nephrotoxicity does occur. The incidence is low, the exact mechanism is poorly understood, and the impact is usually reversible upon discontinuation of the drug. Risk factors for nephrotoxicity include total daily dose in excess of 3–4 grams, trough serum vancomycin levels >20 mcg/mL, pre-existing renal disease, concomitant use of other nephrotoxic drugs (e.g. aminoglycosides), and duration of therapy longer than one week [158].

In 2017, the FDA published a safety review that indicated that use of intraocular vancomycin prophylactically during cataract surgery, alone or in a compound formula, should be avoided because of the risk of hemorrhagic occlusive retinal vasculitis [149; 170].

Reversible neutropenia, presumably from bone marrow toxicity, is sometimes seen in patients receiving prolonged vancomycin therapy (e.g., for endocarditis and osteomyelitis). Oral vancomycin is not absorbed and thus imposes no risk of nephrotoxicity or ototoxicity.

LIPOGLYCOPEPTIDES

In response to the increasing prevalence of multidrug resistance among clinical isolates of staphylococci and streptococci, glycopeptide analogues (lipoglycopeptides) with enhanced activity and favorable pharmacokinetics have been developed. In comparison to vancomycin, the lipoglycopeptides have greater potency against gram-positive bacteria, are active against vancomycin-resistant strains, and appear to be less likely to lead to emergence of resistant organisms [159; 160]. As with vancomycin, lipoglycopeptides must be administered intravenously. The lipophilic side chain prolongs plasma half-life and helps anchor these agents to the outer structure of the bacterial cell. In animal studies, lipoglycopeptides have proven effective in treating a variety of serious gram-positive infections, including bacteremia, pneumonia, and endocarditis [159; 160]. Clinical studies of efficacy in humans have been limited to date.

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At present, three lipoglycopeptides, telavancin, dalbavancin, and oritavancin, have been approved by the FDA for the treatment of acute bacterial skin and soft-tissue infection. Clinical trials have shown equivalent or superior efficacy against MRSA skin infection compared with vancomycin [160; 161; 171]. The side effect profile is mild and comparable to other effective regimens. Reported adverse effects include headache, nausea, pruritus, pain at injection site, and fever.

Of note, a risk/benefit analysis should be conducted when using telavancin in patients with pre-existing moderate-to-severe renal impairment treated for hospital-acquired or ventilator-associated bacterial pneumonia, as mortality is increased compared with administration of vancomycin [149].

Dalbavancin has the advantage of a prolonged plasma half-life (6 to 10 days), allowing for weekly administration and perhaps obviating the need for an indwelling central line. In adults and children 12 to 17 years of age, the best-studied treatment protocol is 1 g IV, followed by 500 mg weekly [161; 162]. In a randomized trial comparing dalbavancin (1 g IV on days 1 and 8) with vancomycin (IV for 3 days followed by the option of oral linezolid to complete 10 to 14 days) for treatment of skin infection, the clinical response outcomes were similar in both treatment arms. For patients with *S. aureus* infection, including MRSA, clinical success was observed in 90.6% of patients treated with dalbavancin and 93.8% of those who received vancomycin-linezolid [161].

INVESTIGATIONAL ANTIOBIOTICS FOR DRUG-RESISTANT MICRO-ORGANISMS

Researchers continue to seek new methods and drugs to aid in the prevention of antibiotic resistance. Progress has been made in recent years, with two new antibiotics void of cross-resistance to existing antibiotics being discovered through soil sample screening: teixobactin and pseudouridimycin.

Teixobactin, a cyclic depsipeptide antibiotic, works by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid), inhibiting bacterial cell wall biosynthesis [172; 173]. Teixobactin has been shown effective at treating an array of gram-positive pathogens, including MRSA, vancomycin-resistant *Enterococcus*, and *Mycobacterium tuberculosis*, with no known cross-resistance to other antibiotics [172; 173]. With reports in 2016 of efficient syntheses of two teixobactin analogues, this class of drugs may be part of the solution to bacteria resistant to currently available antibiotics [172; 173].

Pseudouridimycin, a nucleoside-analog inhibitor, acts by inhibiting bacterial RNA polymerase, an enzyme responsible for bacterial RNA synthesis, through a binding site. The structure is similar to rifampin, an antitubercular agent that inhibits the enzyme; however, the mechanism of action does differ so as not to cause a cross-reaction with rifampin [174; 175]. Pseudouridimycin has been shown effective for a broad spectrum of drug-sensitive and drug-resistant bacteria.

Researchers are currently attempting to conduct synthesis of these two new classes of drugs with varying, but promising, success. Although it may take several years for these or other new antibiotics with no cross-resistance to be developed, promising progress is continuing, and researchers estimate that, once approved, resistance to these novel drugs could take decades, rather than years, to develop [172; 173; 174; 175].

CONCLUSION

Antibiotics are commonly used drugs that have diverse actions, side effects, and toxicities. The large number of antibiotics available makes it challenging to understand the characteristics of each antimicrobial class, including important information such as indications, action, dosage, and toxicities. Knowing the general characteristics by antibiotic class and having experience with one or two key agents within each class improves recall and facilitates the selection of the most appropriate antibiotic for a given bacterial infection.

An understanding of the mode of action, spectrum of activity, and potential toxicity enables the practitioner to tailor a therapeutic regimen that is specific and of appropriate duration. This in turn lessens the likelihood developing microbial resistances and reduces risk of adverse effects.

It is important to remember that the indications given by the FDA are guidelines. Many antibiotics are used for off-label purposes, and occasionally in doses that differ from those recommended for the usual indications. This may be necessary when faced with managing severe and life-threatening infections or for special populations, such as premature infants, neonates, and the elderly. Before using a specific agent, one should always consider carefully reviewing the detailed information (package insert) provided by the manufacturer.

Customer Information/Evaluation insert located between pages 64–65.

Gastroesophageal Reflux Disease in Adults

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, and members of the interprofessional healthcare team involved in the diagnosis, treatment, and care of patients with gastroesophageal reflux disease (GERD).

Course Objective
The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately diagnose, treat, and care for patients with GERD.

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

1. Outline the incidence and prevalence of gastroesophageal reflux disease (GERD).
2. Describe the patient, social, and economic impact of GERD.
3. Identify risk factors for GERD.
4. Review the natural history and pathophysiology of GERD.
5. Appropriately categorize GERD according to underlying pathology.
6. Identify signs and symptoms of GERD.
7. Select appropriate diagnostic tests for patients with suspected GERD.
8. Analyze the pharmacologic treatment of GERD.
9. Outline the treatment options for refractory GERD.
10. Describe surgical options for GERD treatment.

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

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

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

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is recognized as a complex clinical entity, primarily a motility disorder with impaired lower esophageal sphincter (LES) structure and function playing a central role. However, GERD is widely seen as a simple disorder of acid over-secretion resolved by proton pump inhibitor (PPI) medication. While PPIs are the backbone of clinical management for patients with suspected GERD, many patients remain symptomatic even after initiating treatment. The diverse underlying pathology of GERD symptom presentation requires proper diagnosis to effectively target with therapy. There is also evidence associating long-term PPI therapy with concerning adverse effects. This course will disentangle the conflicting and sometimes confusing clinical guidance and evidence that characterizes the large volume of publications on GERD, empowering primary care clinicians with the clarity and direction to improve the clinical care of these patients.

DEFINITIONS AND DESCRIPTIONS

Non-erosive reflux disease (NERD) accounts for what proportion of the overall GERD population?

Acid reflux: Esophageal reflux with pH <4 [1].

Dyspepsia: A condition with epigastric pain that may include epigastric fullness, nausea, vomiting, or heartburn [2].

Eosinophilic esophagitis: An immune-mediated inflammatory disease of the esophageal mucosal layer, mainly caused by GERD [3].

Erosive esophagitis (also referred to as reflux esophagitis or erosive GERD): GERD symptoms with visible esophageal mucosal injury during endoscopy [4].

Esophagitis: Inflammation of the esophageal mucosa, usually associated with symptoms of heartburn, chest pain, or dysphagia (difficulty swallowing) [3].

Functional gastrointestinal disorders (FGIDs): Disorders of gut-brain interaction, with gastrointestinal (GI) symptoms related to any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut micro-biota, and altered central nervous system (CNS) processing [5]. Rome IV, the 2016 guideline for the diagnosis and management of GERD, eliminated the vague, potentially stigmatizing term "functional" and replaced FGIDs with disorders of gut-brain interaction, but recognized functional is an embedded terminology that will take time to replace [10]. With this terminology introduced in 2016, this course uses functional for consistency with the published literature.

Functional esophageal disorders (FEDs): FGIDs with esophageal symptoms (i.e., chest pain, heartburn, dysphagia) not adequately explained by structural, inflammatory, or motor abnormalities. Also includes reflux hypersensitivity. Treatment markedly differs from GERD [6].

Gastroesophageal reflux disease (GERD): A condition defined by troublesome symptoms, impaired quality of life, and/or mucosal damage or complications resulting from reflux of gastric fluid into the esophagus, oropharynx, and/or respiratory tract [7].

GERD symptoms: Term used to describe heartburn and/or regurgitation symptoms, independent of actual GERD diagnosis.

Heartburn: A rising, burning sensation in the chest or throat.

Non-erosive reflux disease (NERD): GERD symptoms in the absence of visible esophageal mucosal injury during endoscopy; accounts for 70% of the GERD population [4; 7; 8].

Reflux (also referred to as gastroesophageal reflux or GER): An event in which stomach contents leak upward, or reflux, into the esophagus [9].

Regurgitation: Refluxed gastric content reaches the throat or mouth.

Visceral (esophageal) hypersensitivity: Lowered pain threshold and heightened sensitivity to noxious GI stimuli, such as acid reflux [6].

EPIDEMIOLOGY OF GERD

Symptoms suggestive of GERD affect an estimated 30% of Western populations, and the prevalence continues to increase [11]. A comparison of GERD prevalence in different continents showed the highest rates in North America [11]. As noted, the prevalence of NERD in the GERD population is roughly 70% [12].

Among adult residents of Olmsted County, Minnesota (home of the Mayo Clinic), 18.1% had GERD (defined by at least weekly heartburn and/or regurgitation) [13]. Combining these data with results from three other U.S. studies with similar GERD definitions found a prevalence of 18.1% to 27.8% and a sample size-weighted average prevalence of 19.8% [11].

American studies conducted after 1995 show a significantly higher prevalence of GERD than studies conducted before 1995. Among various ethnicities, the incidence of GERD is higher in white individuals, likely related to lifestyle rather than genetic factors [7]. GERD incidence increases with age, especially after 40 years [4].

GERD and functional GI disorders (defined by Rome criteria) frequently co-occur and overlap. In a large study, 83% of patients with irritable bowel syndrome with constipation (IBS-C) had comorbid GERD and/or functional dyspepsia [14].

EXTRAESOPHAGEAL MANIFESTATIONS OF GERD

Extraesophageal manifestations of GERD are typically pulmonary or ear/nose/throat (ENT) and may represent associated symptoms or complications. GERD can be considered a co-factor in the development of asthma, chronic cough, or laryngitis, and GERD-related esophageal disease is associated with chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, and pneumonia [15; 16]. In a study of 6,000 patients with erosive esophagitis or NERD, 30% had extraesophageal manifestations of GERD, including chronic cough (13.3%), laryngeal disorders (10.6%), and asthma (4.5%) [17]. Microaspiration (or "silent" aspiration) of gastric contents is thought to underlie the high prevalence of respiratory disorders in GERD. With multiple irritant and corrosive elements in gastric contents, this effect may be independent of aspirate acidity [18].

Hoarseness and Laryngitis

Hoarseness occurs more frequently in patients with weekly GERD symptoms. Patients with chronic laryngitis often lack typical GERD symptoms of heartburn and regurgitation, but esophageal inflammation is present in 19% to 40%. Abnormal esophageal presence of acidic reflux was found in 55% to 79% of patients with chronic hoarseness and 18% to 70% of those with posterior laryngitis [16; 19; 20; 21].

Chronic Cough

GERD is the third most common cause of chronic cough in adults, after postnasal drip and asthma. The frequency of chronic cough in patients with no, infrequent, or frequent GERD symptoms is 11%, 15%, and 22%, respectively. GERD may be the primary cause in 10% of patients with chronic cough [16; 17; 22].

Non-Cardiac Chest Pain

Non-cardiac chest pain is recurrent chest pain that can be difficult to distinguish from ischemic heart pain, diagnosed after a cardiac cause is excluded. GERD is the most important esophageal cause of non-cardiac chest pain [16]. In a community study, 53% of patients with non-cardiac chest pain experienced heartburn and 58% experienced acid regurgitation. Non-cardiac chest pain was reported by 37% of patients with at least weekly heartburn symptoms, 30.7% with infrequent heartburn (less than weekly), and 7.9% of those without GERD symptoms. Around 50% of patients with non-cardiac chest pain show abnormal esophageal acid exposure [23].

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Asthma

GERD is present in 50% to 80% of adults with asthma, and 65% to 77% of adults with asthma report GERD-related symptoms [24]. Roughly 35% of patients with asthma show abnormal esophageal pH [25]. In 341 patients with severe or difficult-to-treat asthma despite standard treatment, 46.3% were diagnosed with GERD at 12- to 15-year follow-up [26]. The prevalence of asthma in patients with GERD increased over five years, from 4.5% to 7.8% [27].

FUNCTIONAL ESOPHAGEAL DISORDERS

Functional Chest Pain

The prevalence of functional chest pain is unknown and is largely inferred from studies of non-cardiac chest pain. Population surveys estimate the lifetime prevalence of functional chest pain at 19% to 33%, but this includes chest pain from GERD, eosinophilic esophagitis, and esophageal motor disorders [23; 28].

Within non-cardiac chest pain cohorts, 50% to 60% have GERD, 15% to 18% have esophageal dysmotility, and 32% to 35% have functional chest pain. The prevalence appears gender-equal but is higher in patients younger than 55 years of age [29].

Functional Heartburn

The prevalence of heartburn is difficult to estimate because its diagnosis is linked to ambulatory reflux testing and PPI response, both of which have limited ability to differentiate from GERD. Up to 70% of patients with heartburn have normal endoscopy findings and are categorized by the presence or absence of abnormal acid exposure, symptom-reflux association, and PPI response [30]. Functional heartburn is found in roughly 50% of PPI nonresponders and 25% of PPI responders [6; 31].

Reflux Hypersensitivity

The epidemiology of reflux hypersensitivity is unknown but can be inferred from the NERD population. An estimated 37% to 60% of patients with NERD have normal esophageal presence of acidic reflux (measured by ambulatory pH testing) off their PPIs. Less than 10% show acid sensitivity [6; 32; 33].

Functional Dysphagia

Functional dysphagia is considered the least prevalent functional esophageal disorder, but the true prevalence is unknown. A population survey of functional disorders estimated that 7% to 8% of dysphagia was unaccounted for by exclusionary criteria, and another study found 0.6% of patients with functional GI disorder complained of frequent dysphagia [6; 34; 35].

GENDER DIFFERENCES IN THE GERD SPECTRUM

Gender differences are found across the GERD spectrum. Differences in GERD symptom expression have been suggested, with women more likely to have heartburn, regurgitation, belching, and extraesophageal symptoms than men [36]. Testing of subjects without reflux symptoms or GERD using ambulatory 24-hour esophageal pH monitoring, which evaluates esophageal acid presence, suggests women experience fewer reflux events, lower total reflux time, and fewer periods with pH <4 [37; 38]. This suggests differences in upper GI response to reflux exposure, with greater sensitivity and symptoms in women despite less noxious acid exposure. However, men are more likely to develop pathologic changes of the esophagus [38]. Women are more likely to have partial response to PPIs, persistent GERD symptoms despite PPI treatment, and a need for PPI dose escalation [14; 39; 40].

PATIENT, SOCIETAL, AND ECONOMIC IMPACT

Which GERD symptoms have the greatest negative impact on patient quality of life?

The frequency and severity of reflux-related symptoms falls on a continuum. Some individuals have occasional, mild heartburn that is not troublesome. Such persons do not meet diagnostic criteria for GERD, and symptoms should be managed with low-intensity, as-needed treatments and lifestyle adjustments [7].

In patients who meet the criteria for GERD, symptoms can impose a serious negative burden on quality of life. Disruptive GERD (more than once weekly symptoms) increases patient time off from work and decreases work productivity. These patients often have sleep impairment and decreases in physical functioning compared with patients with infrequent symptoms. Nocturnal GERD has a greater negative impact on quality of life compared with daytime symptoms. Nocturnal symptoms and sleep disturbances are critical to assess when evaluating the patient with GERD [15]. One nationwide survey of 1,000 adults with heartburn at least once a week found that 79% reported nocturnal heartburn. Of these respondents, 75% reported sleep disruption and 40% reported impaired functioning the next day. In addition, 71% were taking over-the-counter medications, but only 29% rated this approach as effective [16; 41].

Considering the potentially severely deleterious effects on productivity, sleep, and quality of life, GERD criteria were loosened in recognition that once-weekly reflux events can be disruptive in some patients. Even mild symptom severity, when experienced two or more times per week, can be impairing on quality of life [7]. Reflux symptoms in NERD can be as severe as those experienced by patients with esophageal erosion and mucosal damage [42].

Regulatory and treatment guidelines focus on individual upper GI disorders, but clinicians often see patients with overlapping conditions. These patients experience more frequent and more bothersome symptoms, a greater negative impact on work and school activities, and are more likely to seek physician care [14].

GERD accounts for 8.9 million outpatient visits each year, with an estimated annual cost of $24 billion. The annual cost of upper GI endoscopy is estimated at $12.3 billion [43]. PPI therapy is the first-line treatment for GERD and represents a substantial proportion of associated costs [1]. In 2009, more than 119 million prescriptions for PPIs were filled, making this class of medications the third-highest in sales in the United States ($13.6 billion) [44]. This figure does not include the cost burden to patients from over-the-counter purchase of PPIs.

ESOPHAGEAL COMPLICATIONS

GERD results from stomach and bile acid reflux through the LES into the distal esophagus. The stomach is lined by a mucinous columnar epithelium to withstand the acidic environment required for digestion. However, the esophagus is lined by squamous epithelium, which can become inflamed with exposure to the acidic contents of reflux [45].

Left untreated, continued esophageal acid exposure can lead to persistent inflammation (esophagitis), erosive esophagitis, and scarring, fibrosis, or strictures. Barrett esophagus can occur with refractory GERD due to histopathologic changes in the lower esophageal epithelium. Barrett esophagus may develop into a malignant dysplasia and is a risk factor for esophageal adenocarcinoma [46].

ESOPHAGITIS AND EOSINOPHILIC ESOPHAGITIS

Esophagitis is an inflammatory condition of the esophageal mucosa, usually associated with symptoms of heartburn, chest pain, and dysphagia. As noted, the esophageal wall has limited defense against injury from gastric acid, which can induce erosive or nonerosive esophagitis [3; 47].

Erosive esophagitis is esophagitis with more extensive reflux-induced injury, such as inflammation or ulceration [48]. Eosinophilic esophagitis is an immune-mediated inflammatory disease, characterized by eosinophilic infiltration of the esophageal mucosal layer [49]. Eosinophilic esophagitis was first described in the 1970s and became a distinct clinical entity in the early 1990s. GERD is the main cause of eosinophilic esophagitis [3].

Stricture formation is a consequence of untreated erosive esophagitis or eosinophilic esophagitis that develops over time into a diffusely narrow-caliber esophagus. Dominant strictures can potentially cause persistent dysphagia [50]. Length of delay in diagnosis correlates with the presence of fibrostenotic features [51].

BARRETT ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

Barrett esophagus is a pre-malignant condition whereby the normal esophageal squamous epithelium becomes replaced by metaplastic columnar epithelium. Most cases result from chronic GERD. Barrett esophagus is found in 1.3% to 1.6% of the general population and in 5% to 15% of patients with symptomatic GERD during endoscopy [45].

The main concern with Barrett esophagus is the increased risk for esophageal adenocarcinoma, an outcome with a poor prognosis and high mortality rate [7; 45]. Patients with Barrett esophagus have at least a 20-fold increased risk of developing esophageal adenocarcinoma, but fewer than 4% of patients with Barrett esophagus develop the malignancy [52]. Why Barrett esophagus develops in some patients with GERD and not in others is unclear, but risk factors include male gender, white race, and increased age. Obesity, especially abdominal adiposity, is a strong risk factor for GERD, erosive esophagitis, and Barrett esophagus [45].

Men are more likely to develop pathologic changes of the esophagus, and women have a higher average age (often post-menopause) of esophageal adenocarcinoma onset than men. Beneficial effects of estrogen, including possible anti-inflammatory action and promotion of esophageal epithelial resistance against refluxate, may account for the lower rates and delayed onset in women [38].

STRICTURE

Strictures are advanced forms of esophagitis. Chronic, deep esophageal injury from acid reflux leads to circumferential fibrosis, typically in the mid-to-distal esophagus and visible by endoscopy. Strictures can result in dysphagia to solid meals and vomiting of nondigested foods. As a rule, the presence of esophageal stricture indicates that surgical consultation is needed for the patient [53].

PREDISPOSING AND RISK FACTORS FOR GERD

Which GERD risk factors are associated with compromised function of the lower esophageal sphincter (LES)?

Predisposing factors for GERD include conditions that weaken the LES (e.g., hiatal hernia, pregnancy), increase pressure on the stomach (e.g., obesity, pregnancy, asthma), or affect transit of food from the stomach to the small intestine (e.g., diabetes, peptic ulcer disease, connective tissue disorders) [45].

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OBESITY

Overweight (body mass index [BMI] 25–29.9) and obesity (BMI ≥30) are risk factors for GERD. GERD occurs in up to 70% of obese patients, and symptoms increase with weight gain [16]. Higher BMI and larger waist circumference are associated with the development of GERD complications, including Barrett esophagus [7].

With higher BMI, gastric compression from visceral adiposity increases the separation between the crural diaphragm and the LES, compromising the functional integrity of this antireflux barrier. Obese patients are also likely to have hiatal hernias, which contribute to reflux risk [54].

HIATAL HERNIA

Hiatal hernias are frequently seen in patients with reflux disease. Many patients with hiatal hernias do not have symptomatic reflux, and large hernias (>3 cm) have substantially greater association with GERD than smaller hernias [53; 55].

Large hiatal hernias in patients with GERD are associated with higher amounts of acid reflux and delayed esophageal acid clearance. Large hernias can separate the LES from the crural diaphragm and decrease LES tone, which weakens the gastroesophageal barrier and leads to its functional incompetence. Hiatal hernias are found in 25% of patients with non-erosive GERD, 75% of those with erosive GERD, and more than 90% of patients with Barrett esophagus [4; 56]. Laparoscopic hernia repair should be performed when a large hiatal hernia is present in patients with GERD who remain symptomatic despite twice-daily PPIs [55].

PREGNANCY

GERD symptoms, particularly heartburn, are common during pregnancy. Symptoms can begin in any trimester, with severity increasing throughout the pregnancy. Predictors of heartburn are advanced gestational age, heartburn before pregnancy, and parity, while maternal age is inversely related to heartburn. Race, pre-pregnancy BMI, and weight gain are unrelated to symptom severity. Despite its frequent occurrence in pregnancy, heartburn usually resolves after delivery. The amount of weight gain during pregnancy predicts persistent GERD symptoms one year post-delivery [15].

GERD diagnosis and treatment during pregnancy are based on symptoms; diagnostic testing and ambulatory pH monitoring are generally not required for most patients. In pregnant patients who require testing, upper endoscopy is the test of choice, but it should be reserved for patients whose symptoms are refractory to medical therapy or with suspected complications of GERD. If possible, endoscopy should be delayed until after the first trimester [15].

DIETARY FACTORS

High dietary fat intake is linked to a greater risk of GERD and erosive esophagitis. Carbonated drinks are also a risk factor for heartburn during sleep in patients with GERD. The role of coffee and alcohol as risk factors is unclear; they may increase heartburn in some patients, but the mechanism is unknown. Specific dietary factors will trigger reflux symptoms in some patients, and despite lack of confirmation in randomized controlled trials, these patients should identify and avoid trigger foods or beverages [7]. Excessive, long-term alcohol use has been associated with progression to esophageal malignancy, but this may be independent of an effect of alcohol on GERD. Smoking, like alcohol, is associated with an increased risk of malignancy.

MEDICATIONS

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for anti-inflammatory, analgesic, and antipyretic effects. NSAIDs act by inhibiting cyclo-oxygenase-1 and -2 (COX-1 and COX-2). COX is an enzyme that converts arachidonic acid to inflammatory mediators (e.g., prostaglandins, thromboxanes). By blocking this conversion, NSAIDs reduce pain and inflammation [57]. However, prostaglandins are important for GI protection and other normal physiologic processes. NSAIDs are associated with adverse GI effects ranging from dyspepsia, heartburn, and abdominal discomfort, to peptic ulcer with life-threatening or fatal complications from upper GI bleeding and perforation. Symptoms are unreliable indicators of upper GI mucosal damage, and risks are similar for short-course and long-term NSAID therapy. NSAIDs are also associated with cardiovascular, hepatic, and renal adverse effects [58].

Combining NSAIDs and selective serotonin reuptake inhibitors (SSRIs) increases the risk of upper GI bleeding greater than either drug alone. NSAIDs with SSRIs can markedly decrease serotonin platelet content, which impairs platelet aggregation in response to injury. This can prolong bleeding time, increase gastric acid secretion, and potentially promote ulcers and perforation. Combining SSRIs and NSAIDs should be avoided, if possible [59; 60; 61; 62].

The recommended approach to mitigate upper GI risk is switching to or initiating the COX-2 inhibitor-dominant NSAID celecoxib and starting a PPI [63]. PPIs can reduce or resolve GERD-like symptoms of heartburn and dyspepsia and are more effective than histamine-2 receptor antagonists (H2RAs). Treatment adherence should be assessed, especially in the elderly [58].

NSAID-induced GI toxicity can also involve non-gastric intestinal ulceration and bleeding. PPIs do not prevent, and may aggravate, intestinal damage by inducing gut dysbiosis. Celecoxib has better intestinal tolerability than other NSAIDs, but this advantage is partially lost by adding a PPI [64; 65; 66]. Given the GI and cardiovascular risk profiles of NSAIDs, the appropriateness of NSAID prescriptions should be assessed. These agents are indicated to control inflammation and pain, rather than pain alone [58].

Other Medications

Increased GERD symptoms are also associated with beta-adrenergic agonists, anticholinergics, nitrates, phosphodiesterase type 5 (PDE5) inhibitors, theophylline, calcium channel blockers, and benzodiazepines [57].

Medication-Induced Esophagitis

Esophageal mucosa damage can be induced by commonly prescribed drugs, but this is under-appreciated due in part to sparse attention in the published research. Drug-induced esophagitis is characterized by dysphagia, chest pain, and/or odynophagia. Endoscopic findings of ulcers or erosions are usually confined to the middle third of the esophagus [67]. Antibiotics (e.g., doxycycline, amoxicillin, ciprofloxacin, metronidazole, rifaximin) are the primary cause of drug-induced esophagitis and are potentially more damaging than NSAIDs [3].

COMORBID CONDITIONS

Diabetes, metabolic syndrome, cardiovascular disease, and sleep apnea are seen frequently in patients with GERD. This may be due in part to overweight and obesity, common risk factors for GERD and its comorbidities. GERD is frequently comorbid with functional GI syndromes, such as IBS [7]. The lifetime prevalence of IBS in patients with GERD is 71% [68].

Patients with diabetes are more prone to developing GERD and may present with atypical manifestations. Although there are several proposed mechanisms for the higher prevalence of GERD in patients with diabetes, this complex interrelationship requires further research [69]. Studies involving treatment options for comorbid disease suggest conflicting drug-drug interactions.

NATURAL HISTORY OF GERD

GERD is a chronic disease. Approximately 70% of patients with GERD experience chronic or relapsing symptoms and require long-term intermittent, on-demand, or continuous acid suppressant therapy, mostly with PPIs, while others may require antireflux surgery [55]. A large longitudinal population study found that among those with GERD at study initiation, GERD persisted for 10 years in 33% [70]. Patients with GERD followed clinically may have more severe and chronic illness than persons with GERD followed in the community. However, in a community study, the rate of chronic, unabated GERD was high and showed a substantial and persistent symptom burden.

Around 10% of patients with NERD may progress to erosive esophagitis and manifest more severe reflux disease. Erosive esophagitis is a major risk factor for Barrett esophagus, and the presence of erosive esophagitis at baseline was associated with a fivefold increased risk of Barrett esophagus at five-year follow-up [71].

The long-term natural history of functional heartburn is incompletely known. Up to 67% of patients with functional heartburn remain symptomatic two years after diagnosis, while symptom intensity and frequency decrease in 20%. This suggests functional heartburn is durable in most patients [6].

PATHOGENESIS AND PATHOPHYSIOLOGY

What is the core pathology of GERD?

GERD is widely assumed to arise from acid over-secretion. However, GERD symptoms can result from non-acidic reflux, and the core pathology in GERD involves impaired structure and function of the lower esophagus.

NORMAL STRUCTURE AND FUNCTION

Upper GI

Infrequent or occasional gastroesophageal reflux is normal, particularly after a large meal. The reflux is diluted with saliva, and the esophagus clears the diluted refluxed acid with peristaltic action (a part of esophageal motility). A fully functioning LES, with normal pressure and a normal frequency of transient relaxation episodes, is a crucial physiologic defense against damage from reflux. The LES performs this function with assistance from the diaphragmatic crura, which relies on gastroesophageal junction positioning in the abdomen. This abdominal positioning enables the crura to essentially function as an external sphincter [46].

The crura and LES normally relax during swallowing. Relaxations not initiated by swallowing are termed transient LES relaxations. Transient LES relaxations are also part of normal LES function unrelated to swallowing or peristaltic action, but allow gas to be vented from the stomach (belching) as a normal function. Gastric distention can trigger reflux during transient relaxation and may underlie postprandial reflux [4; 56].

Normal LES function is illustrated by air swallowing when drinking carbonated beverages in the upright position. The ingested air accumulates in the proximal stomach to cause distention. This elicits transient relaxations of the LES, allowing the ingested gas (air) to be vented as a belch. Air swallowing during eating and drinking is normal [72].

To function properly, the LES sustains a higher than normal tone from increased calcium, mediated by excitatory cholinergic neurons. The resting LES has higher intracellular levels of calcium than adjacent esophageal muscle, and decreased LES calcium levels are found in GERD [46].

Persons without GERD have a balance between the aggressive forces associated with injury and irritation of the esophagus and the defensive forces that impede reflux and help clear the refluxate. The primary aggressive forces are reflux causticity and volume burden, and defensive forces

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are related to the antireflux barrier, clearance mechanisms, and tissue resistance at the cellular level [73].

Gastric Acid Release

In parietal cells that line the stomach wall, proton pumps produce stomach acid by moving hydrogen ions from the parietal cell into the stomach lumen against a concentration gradient. Proton pump release of acid is prompted by signaling from acetylcholine, released by vagal nerve endings; gastrin, a local hormone produced by G cells in the antrum; and histamine, produced by enterochromaffin-like cells in the stomach wall [74]. Gastric acid kills micro-organisms, assists digestion, and facilitates absorption of iron, calcium, and vitamin B12 [75]. It also plays a crucial role in filtering out bacteria and in preventing development of enteric infections [76].

As discussed, PPIs are the foundation of GERD management. They directly inhibit hydrogen ion exchange and acid release prompted by all three stimulatory signaling agents, thus blocking the proton pump. H2RAs only block H2 receptors on the parietal cells, leaving gastrin and acetylcholine as potential signaling stimuli. PPIs are more potent inhibitors of gastric acid secretion than H2RAs [74].

PATHOPHYSIOLOGY

Anti-Reflux Barriers

Reflux occurs when the normal function of antireflux barriers between the stomach and esophagus become impaired. GERD develops when reflux of gastric contents is large or aggressive enough to cause troublesome symptoms and/or complications and adversely affect health-related quality of life [58]. The primary factor in GERD pathogenesis is defective function of the LES and the diaphragmatic crura antireflux barrier [48].

LES incompetence results in frequent transient LES relaxations, defined as LES relaxation occurring in absence of swallowing, lasting longer than 10 seconds, and associated with crural diaphragm inhibition [77]. Frequent or longer-lasting transient LES relaxations result in reflux of gastric fluid through the gastroesophageal junction. Most reflux events (about 90%) occur during transient LES relaxations rather than low resting LES pressure [48; 77]. Mechanisms more likely with hiatal hernia include low gastroesophageal junction pressure, strain, or air swallow-associated reflux [77].

Symptoms develop when offensive factors in reflux make repeated contact with esophageal mucosa [58]. Potential esophageal injury from reflux increases as more elements of esophageal defense break down [78]. With LES compromise, increasing contact with caustic, corrosive reflux elements can induce esophageal mucosal injury and degrade esophageal mucosal defense by impairing mucosal resistance and esophageal clearance of acid and reflux [48]. Other pathogenic factors can include delayed gastric emptying and hiatal hernia [58]. As discussed, pathophysiologic mechanisms of GERD are exaggerated in obese patients [79].

In patients with GERD, reflux markedly increases after meals due to increased transient LES relaxations to accommodate food-induced gastric expansion. Despite the buffering effect of food, the pH of reflux into the distal esophagus is acidic due to a "pocket" of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as a reservoir for acid reflux [58; 80].

Esophageal Injury

As discussed, GERD causes reflux esophagitis, reflux esophagitis causes Barrett esophagus, and the metaplasia of Barrett esophagus predisposes to esophageal adenocarcinoma. Until recently, the presumed cause of reflux esophagitis was caustic, chemical injury induced by acid and pepsin in reflux. Repeated exposure made the esophageal squamous epithelium permeable to acid, causing epithelial cell death that triggers a proliferative response to repair epithelial injury [81].

Reflux esophagitis is now shown to develop as a cytokine-mediated inflammatory injury. Instead of direct destruction of epithelial cells, acid and bile salts in reflux induce these cells to release pro-inflammatory cytokines. The cytokines initially attract T lymphocytes that trigger the basal cell proliferation characteristic of GERD-induced injury. The inflammatory cells recruit neutrophils to the site of injury, ultimately mediating the epithelial damage [81].

Barrett esophagus develops through metaplasia, a process whereby one type of tissue replaces another type of tissue. Acid and bile reflux damages the squamous mucosa of the distal esophagus. This mucosal damage can heal through regeneration of more squamous epithelium, or through columnar metaplasia, whereby columnar cells replace the damaged squamous cells [81; 82].

Non-acidic elements of reflux (e.g., pepsin, trypsin) also induce esophageal mucosal injury, esophagitis, and GERD. Most patients with NERD show non-acid-reflux-induced alteration in esophageal epithelium. Dilation of spaces between adjacent esophageal epithelial cells is the hallmark feature of microscopic esophagitis and increases penetration of hydrogen ions, pepsin, and bile into esophageal submucosa. Non-acid reflux is mostly alkaline from the presence of duodeno-gastric biliary reflux. Acid and duodeno-gastric biliary reflux act synergistically to induce lesions and increase the risks of Barrett esophagus and esophageal adenocarcinoma [83]. PPIs are very effective at healing inflammation caused by acid reflux but do not suppress duodeno-gastric biliary reflux [81; 82].

GERD Symptom Pain and Discomfort

Most reflux events do not produce GERD symptoms, but symptom-producing events tend to involve lower pH, longer acid clearance time, and higher total acid exposure. In some cases, weekly acidic or non-acidic reflux can also produce symptoms [56; 84].

HYPERSENSITIVITY, ABNORMAL ACID EXPOSURE, AND REFLUX-RELATED DISORDERS				
Symptom Contributor	**Erosive Esophagitis**	**Non-Erosive Reflux Disease**	**Reflux Hypersensitivity**	**Functional Heartburn**
Acid exposure	++++	+++	++	+
Esophageal hypersensitivity	+	++	+++	++++
Key: ++++, strongly influenced; +, weakly influenced.				
Source: [6]				*Table 1*

The relationship between symptom severity and endoscopic findings is non-linear. Severe GERD symptoms can occur with negative endoscopic findings, while endoscopic findings of erosive esophagitis, Barrett esophagus, hemorrhagic esophageal stricture, or esophageal adenocarcinoma can be asymptomatic [56; 85].

In patients with chronic pain or upper GI disorders without obvious pathology on imaging, the symptoms are termed "functional," a reference to the apparent lack of structural pathology (and explanation). Functional pain symptoms are now known to reflect durable abnormalities in peripheral and CNS pain signaling and processing. This also explains functional esophageal symptoms.

Reflux events become bothersome and distressing through complex mechanisms. Proteinase-activated receptor 2 (PAR2) and transient receptor potential vanilloid-1 (TRPV1) are thought to play key roles. Esophageal expression of PAR2 is activated by acid or weakly acidic reflux exposure. PAR2 releases interleukins (IL-8, IL-1b) and other inflammatory cytokines, promoting inflammatory injury in the esophageal mucosa [86; 87]. The sensation of heartburn is generated by visceral sensory neurons within the deep layers of esophageal mucosa [81]. When activated by PAR2, acid, and other inflammatory mediators, visceral sensory neurons upregulate the expression of chemosensitive receptors TRPV1 and acid-sensing ion channel 3 (ASIC3), which release pain mediators that generate heartburn symptoms [88; 89]. Repeated activation can induce inflammatory and neuroinflammatory effects and promote visceral hypersensitivity [90]. Elevated levels of IL-8 are found in biopsy specimens from patients with GERD and NERD, and high levels of IL-8 in biopsies of patients with NERD predict symptomatic recurrence [91; 92; 93].

Psychologic stress can increase the perception of heartburn and aggravate GERD symptoms [38]. Acute stress can enhance sensitivity to intraesophageal acid perception in patients with reflux esophagitis or NERD, and greater emotional response to stress correlates with increased perceptual response to acid [94; 95]. Previous reports have revealed that low quality of life was severe in patients with extraesophageal symptoms. The quality of life of patients with GERD is also associated with psychologic factors [38; 96; 97].

Functional Esophageal Disorders

Esophageal hypersensitivity contributes most strongly to which reflux-related disorder?

Reflux-related esophageal disorders fall on a spectrum, based on interaction between esophageal hypersensitivity and acid exposure and its contribution to reflux symptoms. On one end, symptom contribution from abnormal acid exposure dominates erosive esophagitis; on the other end, contribution from hypersensitivity dominates functional heartburn. Acid exposure and hypersensitivity both contribute to symptoms in reflux hypersensitivity and NERD (***Table 1***) [6].

Patients with functional esophageal disorders present with reflux-related esophageal symptoms (e.g., heartburn, chest pain) not adequately explained by structural, inflammatory, or major motor abnormalities. In these patients, clinical findings typically include [6; 10]:

- Normal endoscopy
- Absence of mechanical obstruction or biopsy-confirmed eosinophilic esophagitis
- Absence of esophageal motor disorder (e.g., achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm)
- Esophageal acid exposure absent or borderline (i.e., pH 4–7)

Structural, motor, or inflammatory abnormality can be present, but a pathologic finding is not sufficient or necessary for diagnosis.

In the context of normal or borderline functional testing, symptom perception is driven by mechanisms that include hypersensitivity from peripheral and/or central sensitization, altered central processing of visceral stimuli, and altered autonomic activity. Altered pain perception with heightened visceral sensitivity and symptom perception and lowered symptom thresholds to chemical, mechanical, or emotional stimuli are consistently shown [1; 98].

Esophageal tissue injury, inflammation, and repetitive mechanical stimuli can all sensitize peripheral afferent nerves. Esophageal hypersensitivity can remain long after resolution of the original insult [6; 99].

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Psychologic features are an important aspect of functional esophageal disorders. With recurrent or long-standing states of psychologic stress, centrally mediated processes can alter autonomic nervous system activity and modulate spinal transmission of nociceptive signals. Peripherally, gut mucosa permeability can be altered by mast cell degranulation [100]. These mechanisms contribute to exaggerated perception of physiologic stimuli [6].

SYMPTOMS ASSOCIATED WITH GERD

What are possible extraesophageal manifestations of GERD?

As noted, the typical symptoms of GERD are heartburn and regurgitation [46; 101]. Heartburn is defined as a burning, retrosternal, rising sensation associated with meals. Clinicians should be aware this definition is often misunderstood by the general population and clarify the nature of symptoms discussed when the term is used. Regurgitation is the effortless appearance of gastric contents in the throat or mouth without associated nausea or retching.

Although heartburn and regurgitation are cardinal features of GERD, they lack sensitivity and specificity in diagnosis. GERD is found in 54% of patients with heartburn-dominant symptoms and 29% with regurgitation-dominant symptoms. This is because heartburn and regurgitation can also be presenting symptoms of a variety of other disorders [1; 58].

In addition to these cardinal symptoms, patients may display atypical symptoms and/or extraesophageal manifestations of GERD, including [7; 46; 73]:

- Gastric
  - Nausea
  - Belching
  - Slow digestion
  - Early satiety
  - Epigastric pain
  - Bloating
- Respiratory
  - Non-cardiac chest pain
  - Chronic cough
  - Asthma
- ENT
  - Laryngopharyngeal reflux
  - Hoarseness
  - Sore throat
  - Otitis media
  - Pharyngeal pain
  - Globus
  - Chronic rhinosinusitis
  - Repetitive throat clearing
- Dental
  - Enamel erosion
  - Other dental manifestations

ALARM FEATURES

Alarm features are associated with, but are not specific to, GERD and are symptoms and signs associated with gastric cancer, complicated ulcer disease, or other serious conditions requiring urgent evaluation. They include [7; 46; 101]:

- Recurrent nausea and vomiting
- Dysphagia or odynophagia (painful swallowing)
- Unintentional weight loss
- GI tract bleeding
- Persistent pain
- Evidence of iron deficiency or anemia
- Duration of symptoms longer than five years or less than six months
- Epigastric mass or other abnormalities on physical examination
- Family history of esophageal or gastric adenocarcinoma

EVIDENCE-BASED PRACTICE RECOMMENDATION

The University of Michigan recommends that patients with warning or alarm signs and symptoms suggesting complications from GERD should be referred to a specialist.

(https://www.med.umich.edu/1info/FHP/practiceguides/gerd/gerd.12.pdf. Last accessed September 7, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

DIAGNOSIS OF GERD

GERD is diagnosed based on frequent reflux events (one or more events per week) with troublesome symptoms, impaired patient quality of life, and/or mucosal damage or complications from reflux of gastric contents into the esophagus, oropharynx, and/or respiratory tract [7]. Although heartburn and regurgitation are the classic presentation of GERD, other presentations considered markers include dyspepsia and a general gastric discomfort that includes nausea, abdominal pain, and bloating, and non-cardiac chest pain, which can be the presenting symptom after diagnostic workup excludes cardiac causes [15; 46].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the University of Michigan, if classic symptoms of heartburn and acid regurgitation dominate a patient's history, then they can help establish the diagnosis of GERD with sufficiently high specificity, although sensitivity remains low compared with 24-hour pH monitoring.

(https://www.med.umich.edu/1info/FHP/practiceguides/gerd/gerd.12.pdf. Last accessed September 7, 2018.)

Level of Evidence: B (Controlled trials, no randomization)

Publications on the GERD diagnostic process increasingly point to the need for a more tailored approach, but the initial empiric PPI trial remains the standard of care.

EMPIRIC PPI TRIAL

Patients presenting with typical symptoms of GERD and no alarm features typically receive a presumptive diagnosis of GERD, confirmed by positive response to an empiric trial of PPI therapy. With a PPI trial, patients are prescribed once-daily PPIs for four to eight weeks. Nonresponders receive dose escalation to twice-daily PPIs for eight weeks. All PPI responders continue PPI therapy. The emphasis on the empiric PPI trial as a diagnostic and therapeutic tool is based on the premise that GERD symptoms and severity are proportional to exposure of esophageal tissue to acidic reflux. By targeting this core pathophysiology, response to PPI acid suppression therapy reliably confirms the diagnosis of GERD [1; 73; 101].

The empiric PPI trial has advantages of being simple, cost-effective, and informative of whether further investigation is required [46; 101]. The clinical approach that emphasizes the empiric PPI trial as a diagnostic and therapeutic tool has been endorsed by professional organizations including the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), the American College of Physicians (ACP), the American Society of Gastrointestinal Endoscopy (ASGE), and the World Gastroenterology Organization [7; 15; 102; 103; 104; 105].

Although empiric PPI trials have clear utility in ease and practicality, over-reliance has come under increasing criticism. This dissent centers on the diverse symptom profile and pathogenesis of reflux presentations that require management guided by symptom presentation and focused diagnostic testing instead of the uniform PPI trial approach [73]. A substantial placebo response is shown during empiric PPI trials, and PPI response widely varies by presenting symptom and underlying mechanism. This model has led to 30% to 60% of patients unsatisfied with their treatment, high levels of inappropriate PPI use, and failure to address visceral hypersensitivity, which amplifies symptom perception and complicates patient coping [73; 106; 107].

To better align initial management with disease complexity, updated practice recommendations for GERD were published by the Italian Society of Pharmacology and Italian Association of Hospital Gastroenterologists in 2016 and the AGA in 2017 [58; 73]. In addition, guidelines for dyspepsia by the ACG and the Canadian Association of Gastroenterology (CAG) were updated in 2017, and recommendations for functional esophageal disorders by the Rome Foundation were revised in 2016 [2; 6]. With growing evidence of adverse effects with long-term PPIs, safe PPI prescribing recommendations by the AGA and PPI deprescribing guidelines by the University of Ottawa in Ontario, Canada, were both published in 2017 [63; 108].

As of 2018, clinical guidance for GERD management is conflicting and appears to be in a transition phase. In aggregate, the most useful approach retains the PPI trial while incorporating diagnostic advances that identify underlying causes of GERD symptoms to better inform treatment selection.

DIAGNOSTIC WORKUP

As mentioned, patients presenting with heartburn and acid regurgitation (sometimes with non-cardiac chest pain or dysphagia) are considered to have suspected GERD, confirmed by response to an empiric PPI trial. PPI nonresponse does not rule out GERD, but prompts diagnostic testing [1]. Typical GERD symptoms can reflect non-GERD conditions with or without abnormal (pathologic) esophageal acid exposure, and GERD can be erosive or non-erosive [48; 109]. With extraesophageal symptoms associated with GERD, reflux is more often a co-factor than an etiology, and these patients should receive proper evaluation for non-GERD causes such as allergic, pulmonary, or ENT disorders [110].

Phenotypic characterization, a key diagnostic concept, means that different underlying pathologies can look similar in symptom expression. The underlying pathologies in GERD-related disorders differ in treatment response, and effective therapeutic targeting hinges on diagnostic findings [55]. Dual phenotypic characterization is recommended. With this approach, esophageal structure and function are both assessed and diagnosed if abnormal. Endoscopy and biopsy assessment of structure and pH-impedance monitoring plus manometry assessment of function establish the proper diagnosis in most cases [55].

Structural and Histologic Assessment

Upper GI Endoscopy

GERD can be diagnosed by what endoscopy findings?

Endoscopy identifies and documents reflux-related esophageal mucosal damage; the presence and severity of reflux disease complications, such as erosive esophagitis, Barrett esophagus, or peptic ulcers; and anatomic abnormalities, such as hiatal hernia, masses, and strictures [110]. Upper GI endoscopy is the most common initial test in patients with GERD symptoms and PPI nonresponse and is performed

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urgently in patients with alarm features [1; 111]. This procedure consists of an endoscope being fed down the esophagus into the stomach and duodenum, where a small camera sends video images to a monitor screen for close inspection of the esophageal lining [112].

Endoscopic findings of esophagitis, esophageal erosion, eosinophilic esophagitis, or Barrett esophagus are highly suggestive of chronic esophageal epithelial exposure to reflux [48]. Erosive esophagitis is visually graded during endoscopy using Los Angeles (LA) classification [30].

GERD is diagnosed when endoscopy shows erosive esophagitis, and further testing is usually not needed. However, esophagitis is present in only 33% of patients with GERD symptoms and the absence of esophagitis does not rule out GERD. Patients with negative endoscopy should receive functional assessment [73].

Esophageal Biopsy

Esophageal biopsy specimens allow histologic assessment of esophageal mucosal injury. Biopsies are obtained during endoscopy to confirm or rule out suspicions of eosinophilic esophagitis (suggested by esophageal symptoms) or Barrett esophagus (suggested during endoscopy) [73]. Biopsies can also identify dilated distal intercellular spaces, a possible mechanism of GERD symptoms. Esophageal biopsy is not recommended in suspected GERD with normal endoscopy [73].

Functional Assessment

pH Monitoring

pH monitoring in the distal esophagus measures the extent of acid exposure using either a trans-nasal catheter (24 hours) or wireless, capsule-based pH testing (48 hours) [1; 110]. The capsule-based approach is preferred because it increases detection. Extension of pH monitoring to 96 hours is an option. This increases pathologic findings and diagnostic yield over 24- and 48-hour pH monitoring in more complex patients [113].

Wireless pH monitoring uses a small capsule, endoscopically attached to the esophageal wall, to record and transmit pH data to a receiver worn on the belt. Patients push a button when experiencing symptoms. The capsule detaches and is excreted 7 to 10 days later [112].

pH monitoring measures:

- Acid exposure time (i.e., the percentage of time esophageal pH is <4)
- Number of acid reflux episodes
- Number of episodes lasting longer than five minutes
- Longest reflux episode

Esophageal acid exposure time is the most useful indicator of pathologic acid reflux. Off-PPI testing assesses symptom provocation by acid reflux events; on-PPI testing measures persistent esophageal acid exposure despite PPI acid suppression [48].

In patients with GERD symptoms, NERD is diagnosed with negative endoscopy and pathologic acid reflux. Further testing is performed when endoscopy and pH monitoring are negative.

Esophageal Impedance Monitoring

Non-acid reflux is undetectable by standard pH monitoring but can induce symptoms in patients with GERD or functional esophageal disorders and is common in patients maintained on PPIs [48]. Impedance monitoring is a valuable test in patients with suspected GERD but negative pH testing, atypical or extraesophageal symptoms, or refractory GERD [4].

Esophageal impedance monitoring detects changes in the resistance of electrical current on a catheter placed into the esophagus. Impedance monitoring is usually combined with pH monitoring to record antegrade or retrograde movement of liquid and gas into the esophagus and to identify reflux as acidic, weakly acidic, or weakly alkaline [4]. Acid reflux is defined as a pH <4 in the esophagus; non-acid reflux is pH >4. The latter includes weakly acidic (4 <pH<7) and weakly alkaline (pH ≥7) reflux [1].

High-Resolution Esophageal Manometry

Functional assessment of the LES and the esophageal body is performed by esophageal manometry. High-resolution manometry (HRM) is often used with esophageal impedance; some devices combine both. HRM uses a catheter, inserted transnasally, with closely spaced sensors that measure the intraluminal pressure of the entire esophagus during swallowing [77]. In patients with GERD symptoms or NERD with poor PPI response, HRM identifies altered esophageal motility, impaired LES function, and/or transient LES relaxations to explain symptom persistence [55; 114]. HRM is also valuable in excluding possible underlying esophageal motility disorders [115]. HRM is combined with 48-hour pH testing to assess patients with [1; 73]:

- Persistent esophageal symptoms during PPI therapy to exclude non-GERD causes
- Recurrent symptoms after PPI discontinuation
- Atypical symptoms (e.g., chest pain, asthma) in patients without esophagitis

It should also be conducted before antireflux surgery for diagnostic confirmation.

Gastric Scintigraphy

Gastroparesis (delayed gastric emptying) is an important contributor to GERD symptoms in many patients. These patients generally have negative endoscopy findings and greater odds of PPI nonresponse. With suspicion of gastroparesis, a four-hour gastric emptying scintigraphy is used [110; 116].

Barium Swallow

Achalasia is an esophageal motility disorder with incomplete LES relaxation, increased LES pressure, and esophageal body aperistalsis, leading to poor clearance and esophageal dilation. Aside from dysphagia to solids and liquids, patients with achalasia may experience heartburn and regurgitation. Barium swallow with HRM can differentiate achalasia and other esophageal motility disorders from GERD [48].

The University of Michigan asserts that barium radiography has limited usefulness in the diagnosis of GERD and is not recommended.

(https://www.med.umich.edu/1info/FHP/practiceguides/gerd/gerd.12.pdf. Last accessed September 7, 2018.)

Strength of Recommendation/Level of Evidence: IIIB (Generally should not be performed based on controlled trials with no randomization)

AMERICAN GASTROENTEROLOGICAL ASSOCIATION RECOMMENDATIONS

The diagnostic process is relatively straightforward until patients with GERD symptoms show negative endoscopic, pH, and impedance findings. At this point, the diagnostic pathway becomes vague, but it is clarified by practice recommendations from the AGA and the Rome Foundation.

The AGA has stated that treatment guidelines emphasizing empiric PPI trials should be rewritten to stress the importance of clinical management guided by symptom presentation, anatomy, and focused diagnostic testing [73]. To this end, the AGA published a novel approach to GERD management in 2017, guided by the four GERD symptom domains identified by the National Institutes of Health and based on patient-reported outcomes [117]:

- Liquid and food sensations
  (e.g., reflux sensations, regurgitation)
- Painful sensations
  (e.g., heartburn, chest pain)
- Belching and hiccups
  (supragastric and gastric belching)
- Head and neck sensations
  (e.g., ENT and respiratory symptoms)

While GERD diagnosis lacks a criterion standard, the AGA states that focused diagnostic testing based on clinical history and GERD symptom domains can identify the diverse GERD-related phenotypes. This, in turn, best informs the optimal management approach [73].

The AGA stresses the importance of considering visceral hypersensitivity and psychosocial distress when patients fail PPIs and diagnostic testing is negative. In any GERD symptom domain, these factors can exacerbate the primary symptoms and adversely impact patients' ability to cope with symptoms [73].

Patients with Food and Liquid Sensation

Primary regurgitation and reflux symptoms (e.g., reflux into throat and mouth, wet burps, choking on liquid or food reflux) may reflect esophageal dysmotility or rumination syndrome. The step-wise diagnostic process outlined by the AGA starts with endoscopy to detect mechanical obstruction, eosinophilic esophagitis, or hiatal hernia [73]. With negative endoscopy, esophageal HRM is used. With meal-related regurgitation or suspected rumination syndrome, postprandial HRM is indicated.

In these patients, PPI response is less than 50%, because symptoms often result from reflux burden/volume instead of reflux acidity [118]. Reflux volume can reflect esophagogastric junction distensibility [48]. With hypotensive gastroesophageal junction or impaired esophageal motility on HRM, the next step is to assess with pH-impedance testing.

With abnormal reflux on PPI, dose-escalation benefit is unlikely and treatment addresses other pathophysiology [73]. With incompetent gastroesophageal junction and/or hiatal hernia, antireflux surgery is indicated to restore antireflux barrier function. Without hiatal hernia or hypotensive gastroesophageal junction, patients may still benefit from antireflux surgery. Transient LES relaxations may drive reflux with normal gastroesophageal junction pressure and anatomy; in these patients, use baclofen for reflux inhibition.

Patients with Painful Sensations

Pain (e.g., chest pain, heartburn, throatburn) is a primary symptom of GERD, and PPI response is often sufficient to guide management [73]. In cases of PPI nonresponse, endoscopy is used to explore alternative diagnoses. With negative endoscopy, pH-impedance testing off-PPI should be done to assess esophageal acid exposure, type of reflux event, and reflux/symptom correlation.

With normal impedence testing findings, functional heartburn or chest pain is the likely diagnosis, so HRM should be done to rule out esophageal motility disorders. Patients with positive HRM may have reflux hypersensitivity or refractory GERD (abnormal acid exposure with or without reflux symptom correlation) [6]. With confirmed pathologic acid exposure, pH-impedance testing on-PPI is used to assess PPI-refractory reflux mechanism (e.g., impaired gastric acid suppression, continued reflux, functional overlap) [73; 119]. For patients with functional heartburn/chest pain or reflux hypersensitivity, pain modulators and behavioral therapies are indicated to target visceral hypersensitivity. Patients with reflux hypersensitivity may also require PPIs and baclofen for reflux inhibition.

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Patients with Belching Syndromes

Aerophagia is a functional GI disorder of repetitive troublesome belching and abdominal discomfort from excessive air swallowing, also associated with visceral hypersensitivity [72; 110]. Other belching syndromes include [72; 110]:

- Gastric belching (the venting of gas from the stomach)
- Supragastric belching (esophageal air ingestion followed by immediate expulsion before reaching the stomach)
- Rumination syndrome (a behavioral condition with symptoms of postprandial belching and regurgitation often mistaken for GERD)

It is important to distinguish supragastric from gastric belching, because supragastric belches do not originate from the stomach, making transient LES relaxation therapy ineffective.

The first step in assessing these patients is the use of HRM/impedance testing to differentiate belching type, rumination syndrome, or GERD [73; 110; 120; 121]. PPIs may reduce heartburn or chest pain with a transient LES relaxation-mediated belching syndrome. If only belching is present (not other reflux symptoms), PPIs should be discontinued. Patients with supragastric belching or rumination syndrome should be referred to behavioral therapy or a speech pathologist.

If postprandial HRM/impedance is negative for gastric belching, pH-impedance testing is indicated to assess belching pattern and reflux burden [73]. With normal reflux burden and gastric belching, patients may benefit from reflux inhibition with baclofen. Patients with gastric belching and abnormal reflux burden may benefit from the addition of PPIs. Antireflux surgery should be used cautiously in belching syndromes, as the risks of gas bloat and worsening supragastric belching can be substantial.

Patients with Head and Neck Sensations

In the context of presumed GERD, prominent ENT and/or respiratory symptoms are challenging; non-reflux cause is likely. PPI response is comparable to placebo in randomized trials [19]. The extent of symptom association with GERD guides initial management [15; 73]. Without close symptom association, clinicians should focus on non-reflux causes. With closer symptom association, pH-impedance testing off-PPI should be used to guide management decisions. Patients with normal results are unlikely to benefit from PPI dose escalation, but patients with abnormal esophageal acidity may benefit from antireflux procedures, with the caveat that symptoms are more refractory.

FUNCTIONAL ESOPHAGEAL DISORDERS: ROME IV CRITERIA

Functional esophageal disorders are diagnosed and classified using Rome Foundation criteria, which has changed over time to incorporate new scientific evidence. Functional esophageal disorders are highly prevalent in patients with suspected GERD, but their consideration in the GERD diagnostic process is often neglected. It is essential to include these disorders, because treatment is distinct from other GERD-related disorders [5].

Functional esophageal disorders do not progress along a tangible organic natural history, with chronicity reflecting greater pathophysiology and disease burden [6]. All functional esophageal disorders require the following for diagnosis [6]:

- Diagnostic criteria present in the past three months
- Symptom onset at least six months before diagnosis
- Symptom frequency two or more days per week (or one or more days per week for functional chest pain and functional dysphagia)
- Absence of major esophageal motor disorders (e.g., achalasia/gastroesophageal junction outflow obstruction, diffuse esophageal spasm, aperistalsis, hypercontractile peristalsis)

Functional Chest Pain

Functional chest pain is a subtype of non-cardiac chest pain. Initial cardiac evaluation is required in both, because history and physical examination do not reliably differentiate esophageal from cardiac chest pain. Functional chest pain is defined as recurring, unexplained, retrosternal chest pain of presumed esophageal origin, not explained by reflux disease or other mucosal or motor processes and with pain differing from heartburn [6].

Clinical Evaluation and Diagnosis

After exclusion of a cardiac cause, further workup is necessary and is guided by common underlying causes of non-cardiac chest pain and clinical evaluation findings [6; 122]. With high prevalence in GERD, a high-dose PPI trial is used to assess for a possible GERD trigger of chest pain. With PPI nonresponse, pH-impedance testing off-PPI is recommended if suspicion of GERD remains. Endoscopy with biopsy is recommended to rule out eosinophilic esophagitis and Barrett esophagus. HRM may be considered when GERD is ruled out, because major motor disorders are exclusion criteria.

In order to diagnose functional chest pain, all of the following criteria must be present [6]:

- Retrosternal chest pain or discomfort, after cardiac causes are ruled out
- No associated esophageal symptoms, such as heartburn and dysphagia

- No evidence that acid reflux or eosinophilic esophagitis is the cause of symptoms

Functional Heartburn

The definition of functional heartburn has evolved from a NERD-spectrum disorder in Rome III to a stand-alone functional esophageal diagnosis in Rome IV [123]. The current diagnosis emphasizes a lack of conclusive evidence for GERD; the absence of symptom-reflux correlation and PPI nonresponse alert to a possible functional disorder [6].

Clinical Evaluation and Diagnosis

Functional heartburn is diagnosed after careful history identifies heartburn as the dominant symptom and stepwise evaluation is negative for GERD, eosinophilic esophagitis, and esophageal motor disorders. Most patients are identified by PPI nonresponse, a core diagnostic criteria [6; 124]. After nonresponse to PPI trial, endoscopy and esophageal biopsies are used, regardless of esophageal mucosa appearance, to assess for reflux esophagitis, Barrett esophagus, eosinophilic esophagitis, or a nonpeptic inflammatory process. pH-impedance testing is used to identify acidic reflux and symptom/reflux correlation.

Diagnosis of NERD is made when there is evidence of abnormal esophageal acid exposure. When symptoms correlate with weakly acidic/non-acidic reflux events, the diagnosis is reflux hypersensitivity. Functional heartburn is diagnosed with normal esophageal acid and no symptom/reflux correlation. Diagnostic criteria are [6]:

- Burning retrosternal discomfort or pain
- No symptom relief despite optimal PPI therapy
- No evidence that reflux (abnormal acid exposure or symptom/reflux correlation) or eosinophilic esophagitis is the cause of symptoms

GERD (proven by endoscopy and pH testing) and PPI nonresponse may reflect [6]:

- True refractory reflux (abnormal acidity during pH-impedance testing on-PPI)
- Overlapping functional heartburn and GERD (normal acid exposure, no symptom/reflux correlation during pH-impedance testing on-PPI)
- Overlapping reflux hypersensitivity and GERD (normal acid exposure, symptom/ reflux association during pH-impedance testing on-PPI)

Reflux Hypersensitivity

Reflux hypersensitivity describes heartburn or chest pain symptoms, endoscopy negative for reflux injury, and pH-impedance testing negative for abnormal acid burden but positive for symptom triggering by non-acidic reflux [6].

Clinical Evaluation and Diagnosis

As with functional chest pain and functional heartburn, an empiric PPI trial begins the diagnostic process for reflux hypersensitivity. Partial or poor PPI response points to functional heartburn or reflux hypersensitivity. Endoscopy should be used to rule out esophagitis, Barrett esophagus, and eosinophilic esophagitis [124].

A reflux hypersensitivity diagnosis hinges on sensitivity to reflux events. Acid parameters should be in the normal range on- and off-PPI [125]. Reflux hypersensitivity differs from functional heartburn by significant symptom/non-acidic reflux correlation [6; 33]. The diagnostic criteria are [6]:

- Retrosternal symptoms, including heartburn and chest pain
- Normal endoscopy and no evidence that eosinophilic esophagitis is the cause for symptoms
- Symptoms triggered by reflux events, despite normal acid exposure on pH or pH-impedance testing

A PPI response does not exclude this diagnosis.

Functional Dysphagia

Functional dysphagia is a sensation of abnormal bolus transit through the esophageal body in the absence of structural, mucosal, or motor abnormalities to explain the symptom. Diagnosis requires exclusion of oropharyngeal mechanisms of dysphagia, structural lesions in the tubular esophagus, GERD, eosinophilic esophagitis, and major motor disorders [6].

Clinical Evaluation and Diagnosis

Careful history should be obtained for patients with suspected functional dysphagia to exclude oropharyngeal dysphagia and to detect conditions that mimic or contribute to dysphagia (e.g., globus, xerostomia, odynophagia) [6; 126; 127; 128]. PPI trial and upper endoscopy with biopsy can exclude GERD and eosinophilic esophagitis. Barium contrast using solid boluses is indicated to detect subtle strictures often overlooked on endoscopy and other obstructive processes, such axial hiatal hernias.

In the absence of structural lesions, HRM should be used to exclude major motor disorders. During HRM, multiple rapid swallows, water drinking, or food ingestion can improve detection of obstructive motor mechanisms that explain dysphagia. Borderline or minor motor disorders are compatible with functional dysphagia.

The diagnostic criteria for functional dysphagia are [6]:

- Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus
- No evidence that esophageal mucosal or structural abnormality is the cause of symptoms
- No evidence that reflux or eosinophilic esophagitis is the cause of symptoms

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ESOPHAGEAL DISORDERS

Erosive Esophagitis

Esophageal erosions are observable during endoscopy and visually graded using the LA classification, which provides endoscopic stratification of esophagitis severity [30]:

- Grade A: One or more mucosal breaks ≤5 mm, does not extend between the tops of two mucosal folds
- Grade B: One or more mucosal breaks >5 mm, does not extend between the tops of two mucosal folds
- Grade C: One or more mucosal breaks that are continuous between the tops of two or more mucosal folds but involve less than 75% of the circumference
- Grade D: One or more mucosal breaks that involve ≥75% of the esophageal circumference

Mucosal breaks are areas of slough or erythema with discrete demarcation from adjacent, more normal-looking mucosa. In a validation study, severity of esophageal acid exposure was significantly related to the severity grade of esophagitis. Pre-treatment esophagitis grades A through C were significantly related to heartburn severity, PPI treatment outcomes, and risk for symptom relapse off of PPIs [30].

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic disorder characterized by an aberrant inflammatory response involving local production of eotaxin-3, a chemokine that attracts eosinophils to the esophageal mucosa. Eosinophils cause local tissue damage and recruit and/or activate other effector cells, such as mast cells, which facilitate esophageal fibrous remodeling [129]. Progressive loss of tissue elasticity from inflammatory cell infiltration can elicit motor abnormalities [3; 130].

Patients with eosinophilic esophagitis that does not respond to PPIs are diagnosed with "true eosinophilic esophagitis;" good PPI response or abnormal acid reflux on pH testing results in a diagnosis of GERD. The term "PPI-responsive eosinophilic esophagitis" was coined for the latter group, despite nearly identical clinical, endoscopic, and histologic features in both groups [129]. GERD is associated with eosinophilic esophagitis and should be ruled out by pH testing [48].

Therapy in patients with PPI-responsive eosinophilic esophagitis can reverse the inflammatory signature, but PPI response as diagnostic exclusion for eosinophilic esophagitis has been controversial [129]. In 2017, the first practice guidelines that eliminated the eosinophilic esophagitis vs. PPI-responsive eosinophilic esophagitis dichotomy were published [131]. In this guideline, diagnostic criteria for eosinophilic esophagitis are organized into three categories [131]:

- Clinical features
  - Symptoms of esophageal dysfunction with dysphagia
  - Food impaction
  - Abdominal pain
  - Nausea
  - Reflux-like symptoms
- Histologic features
  - Esophageal eosinophil-predominant inflammation limited to the esophagus
  - Detection of 15 eosinophils in at least one high-power field
- Other causes ruled out
  - Eosinophilic gastroenteritis
  - Crohn disease
  - Hypereosinophilic syndrome
  - Parasites
  - Drug hypersensitivity
  - Achalasia
  - Vasculitis
  - Connective tissue disorders

Barrett Esophagus

As noted, reflux injury to the esophageal squamous epithelium can lead to Barrett esophagus, a metaplastic process whereby the squamous cells are replaced by columnar epithelium-containing goblet cells [48]. Patients with Barrett esophagus may experience heartburn, regurgitation, or less commonly, dysphagia or a globus sensation, but others remain asymptomatic [45].

The ACG states that Barrett esophagus diagnosis requires endoscopic detection of columnar metaplasia plus biopsy confirmation of metaplasia with goblet cells [132]. In contrast, the British Society of Gastroenterology and the GERD Society Study Committee in Japan state that the presence of goblet cells is not required to diagnose Barrett esophagus, with diagnosis based solely on endoscopic detection of columnar metaplasia [45; 133; 134].

DYSPEPSIA

Dyspepsia is a common GI condition of epigastric pain, and dyspeptic symptoms are common in patients with GERD, especially with frequent reflux-related symptoms [58]. Rome IV minimized the diagnosis of GERD in those with dyspepsia by excluding patients with heartburn and acid regurgitation [135].

This definition is best suited for clinical research, but it is less relevant in clinical practice, because many patients have overlapping GERD and dyspepsia symptoms [2; 136]. To improve relevance in the real-world clinical setting, dyspepsia criteria were jointly updated in 2017 by the ACG/CAG [2]. They are:

- Predominant epigastric pain lasting at least one month

- Associated with any other upper GI symptom (e.g., epigastric fullness, nausea, vomiting, heartburn), but epigastric pain is the primary feature

Functional dyspepsia is dyspepsia in which endoscopy (and other tests, when relevant) has ruled out apparent pathology that explain symptoms.

Based on their definition of dyspepsia and functional dyspepsia, recommendations for clinical management were published by ACG/CAG, presented sequentially for patients who fail initial or subsequent therapies [2]. The ACG/CAG states this guideline does not apply to patients with alarm features in the absence of epigastric pain; to patients with epigastric pain that suggests a pancreatic or biliary source; or to patients with other alarm features that require non-endoscopic testing [2].

Patients with dyspepsia should undergo noninvasive testing for *Helicobacter pylori*. If testing is positive, treatment should focus on this infection. When patients are *H. pylori*-negative or remain symptomatic after *H. pylori* eradication, PPIs should be prescribed. With nonresponse to PPIs or *H. pylori* eradication therapy, prokinetic therapy and a tricyclic antidepressant should be offered [2]. With nonresponse to medications, psychologic therapy should be explored.

Endoscopy is not suggested for patients younger than 60 years of age to investigate alarm features or exclude upper GI neoplasia. However, endoscopy is indicated to exclude upper GI neoplasia in patients 60 years of age and older. Motility studies are suggested in selected patients when gastroparesis is strongly suspected.

INITIAL MANAGEMENT OF GERD

The objective of GERD treatment is to control symptoms, heal the esophagus, and prevent recurrent esophagitis or other complications by reducing gastric acidity and decreasing esophageal reflux [46; 53; 137]. The diverse clinical presentation and underlying pathology of GERD has imposed significant challenges in long-term symptomatic management. A patient-centered, individualized approach can optimize patient outcomes across the GERD spectrum, and the following elements are important for clinicians to consider in all patients: a secure and clear diagnosis, early patient engagement, adherence to therapy, and a targeted approach [55].

A secure and differentiated diagnosis is vital, especially in PPI-refractory GERD. Extraesophageal symptoms and their relationship to pathologic acid exposure should be evaluated, because abnormal perception frequently contributes to symptom expression and therapy response.

Early patient engagement is important to help patients' understanding of their GERD symptoms, long-term implications on quality of life, and possible complications of strictures, extraesophageal symptoms, Barrett esophagus, and cancer. This information-sharing empowers patients to take ownership and control of their chronic disease management and minimizes undue fear and anxiety [55; 138].

Clinicians should emphasize the importance of lifelong adherence to dietary and lifestyle measures to prevent relapse or exacerbations, even during long-term PPI or postsurgical remission. Unless such measures are understood and practiced by patients, therapy is likely to fail. Medically or surgically refractory GERD often originates from poor dietary habits and weight gain [55; 139].

Most patients respond well to PPIs, but many can require changes in dose timing, dose doubling, switching to alternative or adjunctive agents, or endoscopic antireflux therapy or antireflux surgery [55]. A tailored, treat-to-target approach that considers long-term safety, tolerability, and patient preference is highly preferable to therapy based on empiricism or cost savings.

LIFESTYLE INTERVENTIONS

Which lifestyle modifications have the strongest evidence support in reducing GERD symptoms?

Before making pharmacologic recommendations to patients, consider lifestyle modifications that can considerably improve symptoms alone or combined with other strategies. During history-taking and physical examination, note the presence of risk factors for GERD, including agents or physical states that decrease pressure in the LES and increase transient LES relaxations. When these factors are present and modifiable by patient behavior change, they are targets for lifestyle interventions [46].

Most commonly, patients are recommended to avoid foods that decrease LES pressure and to minimize behaviors that predispose to increased esophageal acid exposure [46]. In contrast to the extensive data on acid inhibiting medication in GERD, relatively few studies are published on lifestyle intervention [140]. Lifestyle modifications with the strongest evidence support are weight loss and head-of-bed elevation [46].

Weight Loss

Weight gain and weight loss are associated with an increase and decrease in reflux symptoms, respectively, in both normal and overweight individuals [54]. Weight loss in overweight or obese patients with GERD symptoms is one of the most strongly supported lifestyle modification interventions. Several randomized controlled trials and well-designed observational studies have shown reduced reflux symptoms and esophageal acid exposure with weight loss, with a dose-dependent decreased presence of reflux symptoms following weight reduction [140].

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The AACE/ACE recommends all overweight or obese patients with GERD should undergo weight loss, with the goal loss of 10% of body weight or greater. PPI therapy should be administered during dietary and weight-loss interventions [141]. Bariatric and other surgical options for obese patients may be considered.

Head-of-Bed Elevation

The recumbent position is associated with worsening of esophageal pH values and GERD symptoms. Several randomized controlled trials have demonstrated improvement in GERD symptoms and esophageal pH values with head-of-bed elevation. Wood or cement blocks may be placed under the feet of the bed to raise the head end 6 to 10 inches. Wedges can also be inserted between the mattress and box-spring to elevate the body from the waist up and are available at drugstores and medical supply stores. Stacking pillows is ineffective [15; 140]. Some patients may invest in adjustable beds that allow for easy personalization of this elevation. Patients with nocturnal GERD symptoms may find substantial relief from head-of-bed elevation and avoiding meals three hours before bedtime, especially foods with high fat content [46].

Smoking Cessation

Tobacco smoking reduces LES pressure and salivary bicarbonate secretion, which facilitates reflux and decreases acid buffering [140]. However, smoking cessation has shown inconsistent benefits in GERD [15]. A large prospective study of 29,610 participants found smoking cessation was associated with decreased severe reflux symptoms in normal-weight individuals on PPI treatment (versus those who continued daily smoking), but no effect was found in overweight or obese individuals. This was thought to reflect the minimal added contribution from smoking compared with obesity in GERD pathophysiology, with smoking a more important factor in non-obese individuals [142].

Foods and Beverages

Consumption of chocolate and carbonated beverages has been found to decrease LES pressure, but cessation of these agents does not necessarily raise LES pressure, decrease transient relaxations, or improve GERD symptoms [46]. Clinicians routinely recommend patients with GERD avoid coffee and caffeinated beverages, but whether coffee or caffeine itself is a factor in the pathophysiology of GERD is unclear; studies show conflicting results [54].

Protein and dietary fat have shown opposite effects on the LES; protein ingestion increases LES pressure, and fat ingestion decreases LES pressure. Ingestion of total fat, saturated fat, and cholesterol were higher in patients with GERD symptoms than those without symptoms in one study, but this effect only held in patients with BMI >25 [54; 143; 144].

A study examined dietary guideline adherence in 317 patients with GERD and whether adherence was related to reflux symptom severity and frequency. Compared with GERD-free controls, patients with GERD, even with moderate-severe or frequent symptoms, were as likely to consume tomato products and large-portion meals and were significantly more likely to consume soft drinks and tea and eat fried and high-fat foods. The results held when PPI users were excluded. If dietary modification is effective in reducing GERD, the results suggest substantial potential for nondrug interventions for many patients with GERD [145]. BMI was not analyzed separately.

Clinical trials have failed to consistently capture the aggravating effect of the consumption of chocolate, carbonated beverages, alcohol, coffee/caffeine, spicy foods, tomatoes or tomato sauce, citrus, or fatty foods on GERD symptoms. The equivocal findings are partly due to methodology problems [146]. More recent evidence supports the role of certain trigger foods, while population studies endorse decreased reflux symptoms with specific diets [139]. Specific foods or beverages are clearly GERD symptom triggers for some patients. When triggers are identified, their avoidance can bring considerable symptom relief [15].

Interestingly, a comparison of patients with GERD who performed Ramadan fasting and those who did not found significant reductions in GERD symptoms and severity in the fasting group before the end of the month compared with the non-fasting group [147].

Medications

Common medications that facilitate decrease in LES pressure and increase in transient relaxations include beta-adrenergic agonists, anticholinergics, nitrates, PDE-5 inhibitors (e.g., sildenafil, tadalafil), theophylline, calcium channel blockers, and benzodiazepines [46]. As discussed, regular use of NSAIDs is linked to a range of adverse GI effects; concurrent use of NSAIDs and SSRIs further elevates risks of upper GI ulceration and bleeding [108]. In patients prescribed these medications, possible contribution to GERD symptoms should be discussed. It is also worth revisiting if a patient has poor response to acid suppressant medications to determine if therapeutic alternatives are feasible.

NSAIDs should be discontinued whenever possible. If this is not feasible, PPI therapy should be initiated and NSAID dose reduction considered. PPIs are more effective than H2RAs in reducing NSAID-induced upper GI injury [148].

Misoprostol is a prostaglandin analogue also used for gastroprotection during NSAID use and is approved by the U.S. Food and Drug Administration (FDA) for prevention of NSAID-induced ulcer disease. Misoprostol is more effective than H2RAs in preventing NSAID-induced mucosal injury and equally effective as PPI in ulcer prevention with NSAID use. However, GI side effects, especially diarrhea, can limit patient tolerability [148].

ANTACIDS AND HISTAMINE-2 RECEPTOR ANTAGONISTS

GERD is a chronic disease, and proper treatment should be preventive in nature instead of reactive. PPIs are the standard of care, but less potent interventions may be suitable for some patients [46].

Antacids

Antacids are popular for treating occasional mild episodes of reflux and use different combinations of three basic salts—magnesium, calcium, and aluminum—with hydroxide or bicarbonate ions to neutralize gastric acid [9]. Antacids only provide quick, short-acting relief for 30 to 60 minutes, do not promote healing of erosive esophagitis, and only neutralize acid already secreted [78]. The role of antacids in the treatment of GERD is limited to patients with known triggers or breakthrough symptoms not effectively controlled by other medications. If used, antacids should be taken after each meal and at bedtime. Patients should receive education on the differences between occasional indigestion and GERD so they do not try to self-treat and subsequently fail to achieve relief [46].

Histamine-2 Receptor Antagonists

Cimetidine, ranitidine, famotidine, and nizatidine are currently the FDA-approved H2RA agents for the treatment of GERD and are available over the counter. H2RAs decrease gastric acid secretion in a reversible fashion by blocking the action of histamine on H2 receptors of gastric parietal cells. The inhibition of acid secretion results in an increase in gastric pH and a decrease in pepsin activity. Over-the-counter formulations are available at a dose that is typically half the lowest standard prescription dosage [46].

This class of drugs is uniformly safe and well tolerated. The risk of adverse effects is slightly increased with cimetidine because it interacts with cytochrome P-450, potentially leading to drug-drug interactions [78].

Taken in standard divided doses, H2RAs can achieve symptom relief in some patients with milder or intermittent GERD. However, H2RAs have a dose ceiling; dose escalation above the recommended range does not further improve response. Over-the-counter H2RAs are particularly useful when taken before reflux. The peak potency of antacids and H2RAs is similar, but H2RAs have a much longer duration of action—up to 10 hours [78].

The ACG practice guidelines recommend H2RA use as a maintenance option in patients without erosive disease if patients experience heartburn relief [15]. A main limitation of H2RAs is tachyphylaxis (development of tolerance), often within two weeks of daily use. This pharmacologic phenomenon results in declining acid suppression and limits the regular use of H2RAs in clinical practice [149].

PPI THERAPY

Evidence from a systematic review of publications and practice guidelines addressing safe and appropriate PPI use were synthesized into an expert consensus statement on appropriate indications and treatment durations for PPI therapy (***Table 2***) [150; 151]. The consensus statement reflects current knowledge based on published evidence and real-world clinical use that may not have been available to the FDA when PPI indications were approved.

The initial PPI approved for use in the United States was omeprazole, followed by lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole. Most are now available in generic forms [152]. Their introduction and widespread use revolutionized the management of acid-related diseases and minimized the role of surgery [153]. By 2015, PPIs ranked in the top 10 national health-related drug expenditures in the United States [151].

PPIs are substituted benzimidazoles and are the most potent inhibitors of gastric acid secretion available. They block the final common pathway of acid secretion in gastric parietal cells by irreversibly binding to and inactivating the proton pump [148]. For gastric secretory activity to be restored, new enzymes need to be resynthesized, a process that normally takes two to five days [78].

As discussed, in patients without alarm features, management of GERD usually begins with an empiric PPI trial [154]. An initial trial of once-daily PPIs for at least eight weeks is recommended by the ASGE and the ACG, with four to eight weeks recommended by the ACP [15; 103; 111]. With nonresponse to once-daily PPIs, twice-daily PPI is initiated. Patient response and adherence is assessed after eight weeks before PPI failure/nonresponsiveness is concluded [63; 154]. Some argue that incomplete response to once-daily PPI is sufficient to define PPI failure, but twice-daily dosing achieves adequate symptom control and eliminates residual acid reflux in 20% to 30% of patients with once-daily PPI nonresponse [16; 155; 156].

The American Society for Gastrointestinal Endoscopy suggests that repeat esophagogastroduodenoscopy be performed in patients with severe erosive esophagitis after at least an eight-week course of PPI therapy to exclude underlying Barrett esophagus or dysplasia.

(https://www.asge.org/docs/default-source/education/practice_guidelines/doc-endoscopy_in_the_managment_of_gerd.pdf. Last accessed September 7, 2018.)

Level of Evidence: Low quality

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INDICATIONS FOR APPROPRIATE PPI THERAPY
FDA-Approved Indications for PPI Therapy
Treatment of GERD Healing of erosive esophagitis Maintenance of healed erosive esophagitis Risk reduction for gastric ulcer associated with NSAIDs *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence in combination with antibiotics Zollinger-Ellison syndrome and other hypersecretory conditions Short-term and maintenance treatment of duodenal ulcer
Long-Term PPI Therapy Appropriate
Barrett esophagus, asymptomatic patients with Barrett esophagus[a] Healing/maintenance of healed Los Angeles grade C or D erosive esophagitis PPI-responsive esophageal eosinophilia Idiopathic (*H. pylori*- and NSAID/aspirin-negative) peptic ulcer disease Zollinger-Ellison syndrome[b] PPI-responsive GERD/NERD[c, d] Patients at risk for ulcer-related bleeding from NSAIDs, for the duration of regular NSAID use[a] Anti-platelet therapy in patients at high-risk for upper GI complications (i.e., age older than 65 years; concomitant use of corticosteroids or anticoagulants; or a history of peptic ulcer disease) Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
Short-Term PPI Therapy Appropriate (4 to 12 Weeks)
Healing of Los Angeles grade A or B erosive esophagitis Eosinophilic esophagitis *H. pylori* eradication (combined with antibiotics)[e] Stress ulcer prophylaxis in high-risk patients (e.g., critically ill patients) Functional dyspepsia Treatment and maintenance of peptic ulcer disease Prior to endoscopy for acute upper GI bleeding Following endoscopic treatment of a high-risk ulcer GI bleed
PPI Use Not Appropriate
Corticosteroid users without concomitant NSAID therapy To prevent bleeding from hypertensive gastropathy in patients with cirrhosis Acute pancreatitis Stress ulcer prophylaxis in non-critically ill hospitalized patients not at high-risk for ulcer formation and GI bleeding
PPI Use of Uncertain Benefit
PPI-nonresponsive GERD Extradigestive GERD (e.g., asthma, pseudoangina, dysphoria)
GERD = gastroesophageal reflux disease, GI = gastrointestinal, NERD = non-erosive reflux disease, NSAID = nonsteroidal anti-inflammatory drug. [a]AGA recommendation [b]Requires three to four times the usual dose [c]PPI taper should be attempted to lowest effective dose, on-demand dosing, or intermittent dosing. [d]AGA recommends the dose of long-term PPIs should be periodically re-evaluated so the lowest effective PPI dose can be prescribed to manage the condition. [e]One- to two-week PPI course appropriate
Source: [63; 150; 151] *Table 2*

PPI Efficacy

GERD and NERD

Numerous clinical trials have shown PPIs to be superior to H2RAs, antacids, and sucralfate in alleviating GERD symptoms. PPIs result in a significantly faster healing rate of peptic ulcers (12% per week) and heartburn (11.5% per week) compared with H2RAs (6% and 6.4% per week, respectively) [148]. Long-term PPI maintenance is also more effective in preventing recurrence of reflux esophagitis (80% PPIs vs. 49% H2RAs) and esophageal strictures (46% PPIs vs. 30% H2RAs) [63].

A meta-analysis of 98 randomized controlled trials evaluated PPI and H2RA effectiveness after four to eight weeks in adults with GERD. Effectiveness (defined as esophageal healing and GERD symptom relief) and tolerability (defined as discontinuation from ineffectiveness, adverse effects, or nonadherence) was calculated for low- and high-dose daily use; high doses were uniformly more effective [157]. The agent with top-ranked effectiveness was esomeprazole (40 mg/day), followed by rabeprazole (40–50 mg/day) and pantoprazole (80 mg/day). Best tolerability was noted with omeprazole (40 mg/day), then pantoprazole (40 mg/day), lansoprazole (60 mg/day), and the H2RA ranitidine (1,200 mg/day). However, sponsorship bias was detected. Higher PPI outcomes in studies with pharmaceutical company funding may have led to overestimated esophageal healing efficacy [157].

Once-daily PPIs for eight weeks heals reflux esophagitis in more than 80% of patients, and this is further improved by twice-daily dose escalation. Esomeprazole achieves higher short-term healing rates of reflux esophagitis than omeprazole, lansoprazole, and pantoprazole, but this advantage is negligible in less severe esophagitis. PPIs are effective for symptom relief in erosive and non-erosive disease, but efficacy in reducing regurgitation is considerably lower than with heartburn [158; 159].

The belief that PPIs have lower efficacy in NERD was dispelled by a meta-analysis showing that PPI efficacy for NERD was comparable to erosive disease when functional testing using pH-HRM or pH-impedance testing was added to confirm NERD after negative endoscopy findings [58; 160].

GERD practice guidelines and review papers often state that PPIs lack meaningful differences in potency. However, a comparative study of PPI efficacy in intragastric pH control, measured by percentage of time at pH >4 over 24 hours, found relative potencies, compared with omeprazole (1.00; reference), of 0.23 for pantoprazole, 0.90 for lansoprazole, 1.60 for esomeprazole, and 1.82 for rabeprazole [161]. This pharmacodynamic non-equivalence should be considered when prescribing or switching PPIs [58].

Short-term PPIs are generally well-tolerated, with infrequent adverse reactions including flatulence, headache, diarrhea, abdominal pain, and nausea. These reactions are often self-limiting or can be addressed by switching to a different agent [151].

Extraesophageal Manifestations

In contrast to typical symptoms, PPI efficacy in extraesophageal manifestations of GERD is less clear-cut. PPIs are usually given twice-daily for extended periods, but evidence is not strong enough to allow clear recommendations to be made for patients with only extraesophageal symptoms. Nonetheless, an empiric PPI trial can be the initial approach to diagnose and treat the potential underlying cause of extraesophageal disease [58].

As noted, GERD is the most common and best-studied cause of non-cardiac chest pain, and PPIs are the initial pharmacologic approach in these patients. Patients with non-cardiac chest pain and endoscopic or pH-monitoring evidence of GERD tend to improve, but not resolve, with PPI therapy. In contrast, GERD-negative patients show little or no PPI response. The therapeutic benefit of PPIs in patients with chronic cough is demonstrated, but efficacy in reflux laryngitis is much weaker. Asthma and GERD often coexist, and while asthma medications can trigger GERD, PPIs may improve asthma control [58].

Dyspepsia

Dyspeptic symptoms are common in patients with GERD, especially with frequent reflux-related symptoms. In these patients, PPI therapy improves epigastric pain, belching, bloating, and early satiety, but lacks benefit with nausea and vomiting [162]. PPI efficacy in functional dyspepsia occurs at standard doses, but long-term PPI therapy for functional dyspepsia is not indicated [58].

Dyspeptic symptoms may worsen with PPI therapy or new symptoms (especially postprandial fullness) may emerge from PPI-induced inhibition of gastric motility and delayed gastric emptying. In these cases, patients should be switched to the H2RA ranitidine or nizatidine. In addition to antisecretory activity, these agents display cholinergic-like activity and accelerated gastric emptying [58; 163].

Optimal Use and Duration

Optimizing PPI Use

To achieve maximum response, it is important that patients receive correct instructions on how to use PPIs. The timing of PPI administration is essential. Patients are usually initiated on once-daily dosing, which must be taken 30 to 60 minutes before the first meal of the day, as the agents are most effective after a prolonged fast (i.e., overnight). Proton pumps are highly active during the postprandial period, and with a plasma half-life of one to two hours, PPIs reach peak concentration at the time of a meal [101; 148]. If increased acid suppression is required, a second dose taken 30 to 60 minutes before the evening meal is more effective than doubling the morning dose [101].

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With initial therapy, patients must adhere to daily use. The antisecretory action of PPIs increases with consecutive daily dosing, and full steady-state acid inhibition is achieved after four to five days. Steady-state acid inhibition is lost with non-adherence to daily use [148].

Treatment Duration and Discontinuation

With evidence that links long-term PPI use to potential risks, GERD practice guidelines recommend PPI dose reduction or discontinuation in some patients. In 2017, the AGA recommended that after a three- to six-month treatment course with good PPI response, patients with uncomplicated GERD should attempt to stop or reduce PPIs because patients who cannot reduce PPIs face the likelihood of lifelong PPI use [63]. In these patients, esophageal pH-impedance monitoring distinguishes acid-related disorders from a functional syndrome. The best candidates for this strategy may be patients with primarily atypical symptoms and those who lack obvious predisposition to GERD from central obesity or large (>3 cm) hiatal hernia.

PPIs can be very difficult to quit, and 75% to 90% of patients with GERD relapse in the initial six months after PPI discontinuation. This is attributed to the chronicity of GERD and NERD and contribution from PPIs, as abrupt cessation may be followed by rebound acid hypersecretion and symptom exacerbation [58; 101; 164].

Before continuing a likely long-term PPI treatment, or for patients already on long-term PPIs, an attempt to stop PPI therapy should be considered. Tapering is more effective as a discontinuation strategy than abrupt withdrawal, patient education, or lifestyle modifications [165]. Weight loss can also be an effective strategy in obese/overweight patients. One study found 54% of patients remaining adherent to a hypocaloric diet were able to stop PPIs, and 32% reduced their PPI dose by 50% [166].

PPIs can induce parietal cell proliferation to promote a hyperacidity state after discontinuation. This rebound hyperacidic can create a dependence on continued PPI use [167]. In a study of 120 healthy volunteers, rebound acid hypersecretion occurred after 8 weeks of PPI treatment, and 44% experienced acid-related symptoms 9 to 12 weeks after discontinuation. The authors concluded patients should taper off PPIs more gradually than is commonly suggested [168]. These results have been replicated in other studies as well [56; 169; 170].

Because relapse frequency and severity are highly variable among patients, long-term PPI maintenance should be individualized based on clinical characteristics of the patient. Strategies include continuous/daily use, intermittent cycles of daily use, and on-demand/symptom-driven therapy. Infrequent reflux symptoms are less likely to be chronic and may respond to a different approach [58].

An alternative approach is a PPI step-down, in which the dose is reduced to determine the minimum needed. This involves a gradual reduction in dose or frequency and may include a goal of switching to "as-needed" therapy. The step-down approach allows patients to implement lifestyle modifications and find the lowest dose they need for adequate symptom control [101]. While full-dose PPIs are superior to half-dose in maintaining remission, step-down dosing with esomeprazole 20 mg maintained a significantly higher proportion of patients with GERD in symptomatic remission than lansoprazole 15 mg or pantoprazole 20 mg [158]. Because PPIs do not correct the underlying esophageal motor abnormalities of GERD, patients may require continuous acid suppression treatment to maintain remission [58].

The AGA guideline for long-term use of PPIs concludes the best current approaches to mitigate potential risks of long-term PPIs are to avoid prescribing when PPIs are not indicated and to reduce their use to the minimum dose when PPIs are indicated [63]. The AGA states most patients with uncomplicated GERD can reduce from twice-daily to once-daily PPI dosing, 33% can successfully transition from PPIs to H2RAs, and 16% are able to transition off all acid suppression. Patients with non-erosive disease who cannot transition off PPIs are usually satisfied with on-demand PPI therapy. Because PPI reduction is often successful in uncomplicated GERD, it is recommended that clinicians periodically re-evaluate patients to ensure they are taking the lowest dose sufficient to manage their condition [63].

Patients with complicated GERD (e.g., erosive disease) are usually unable to successfully reduce PPIs. Patients with good symptom control from daily PPIs who cannot reduce face lifelong PPI therapy. Assessment for an acid-related disorder with esophageal pH-impedance monitoring is recommended. This testing shows a subset of patients with poor correlation between symptoms and acidic reflux events, and strenuous efforts should be made to discontinue or reduce PPIs in these patients [63].

A Canadian guideline was published in 2017 to help clinicians identify when to taper or stop PPI therapy. In adults with upper GI symptoms who have completed a minimum four-week course of PPI treatment with resolution of upper GI symptoms, the following is recommended [108]:

- Decrease the daily dose or stop and change to on-demand (as-needed) use.
- Consider an H2RA as an alternative to PPIs.
- Patients with erosive disease, or who require daily NSAIDs, should continue their regular-dose PPI.

Criteria have also been proposed that may predict greater success halting PPIs in elderly patients living in care facilities. PPI discontinuation outcomes were evaluated in 27 elderly residents (mean age: 80 years) taking a PPI for more than six months who met all of the following criteria: 1) no indica-

tion for long-term PPIs; 2) not currently experiencing GI symptoms; 3) no previous PPI discontinuation without success; and 4) no anxiety when medications are discontinued. PPIs were stopped without taper with participants receiving medical monitoring and support. After eight weeks, 70% remained asymptomatic and did not need PPIs to manage GI symptoms [171].

PPI Chemoprevention in Barrett Esophagus

With Barrett esophagus of any mucosal length, long-term PPI use for potential chemopreventive effects against neoplastic transformation is advocated by the ACG and the AGA, but is not recommended by the British Society of Gastroenterology [63; 132; 172]. The evidence supporting this practice is inconsistent. A meta-analysis of observational studies found PPI use associated with a 71% reduction in risk of esophageal adenocarcinoma and/or high-grade dysplasia in Barrett esophagus, but another study concluded standard PPI therapy was unable to normalize esophageal exposure to acid in most patients with Barrett esophagus [173; 174]. Individually tailored maximal acid suppression is needed to control GERD and to achieve any chemopreventive effect in Barrett esophagus [58].

PPI SAFETY CONCERNS

PPI Overuse

Following their introduction and uptake into clinical practice, PPIs became highly successful in managing patients with GERD. However, once PPIs are taken regularly, many patients remain on long-term PPIs often indefinitely, especially the elderly [58]. PPIs are available over the counter and are used indiscriminately for treating conditions without appropriate indication [74]. PPI prescriptions doubled from 1999 to 2012, and an estimated 53% to 69% of PPI prescriptions are written for inappropriate indications—cases in which the benefits of PPI use may not justify the risks [175; 176]. PPIs are often overprescribed, rarely deprescribed, and frequently started inappropriately during a hospital stay, with their use extended to long-term without appropriate medical indication [177].

Use of PPIs appears disproportionate to prescribing guidelines and to the prevalence of acid-related diseases of GERD and NSAID-related gastropathy. Contributing to the continuous increase in PPI use over the last decade is inappropriate prescribing for inappropriate purposes, including prevention of gastroduodenal ulcers in low-risk patients; stress-ulcer prophylaxis in patients receiving corticosteroid therapy or anticoagulant treatment without risk factors for gastroduodenal injury; functional dyspepsia; and mistaken diagnosis of acid-related disorder [153]. The widespread overuse and inappropriate use of PPIs is especially concerning in the elderly, who have greater risk of long-term PPI-related adverse outcomes and drug-drug interactions [58].

Other Safety Concerns

Awareness that PPI use may be associated with adverse effects has increased since they were first approved for marketing. The FDA issued safety warnings for potential increased risk of osteoporosis-related fractures and *Clostridium difficile* infection associated with PPI therapy in 2010 and 2012, respectively [178]. In 2015, the American Geriatrics Society recommended avoiding PPI use longer than eight weeks in older adults, due to potential risk of *C. difficile* infection, bone loss, and fractures [179]. Reports also associate PPIs with increased risk of community-acquired pneumonia, vitamin B12 deficiency, dementia, and kidney disease [178].

The association between PPI exposure and increased risk of acute interstitial nephritis, chronic kidney disease, kidney disease progression, end-stage renal disease, and rare but potentially fatal hypomagnesemia is strong [177]. The data linking PPI use with increased risk of *C. difficile* infection are convincing, but the magnitude of risk is very low [148]. The relationship between PPI use and risk of community-acquired pneumonia or cardiovascular events is inconsistent and weak [177]. The duration of PPI therapy that may elevate the risks of some adverse effects is not known [178].

Of note, PPI use and mortality risk were examined in a study of Veterans Affairs healthcare system patients. Among patients newly prescribed PPIs or H2RAs and followed a median 5.71 years, PPI use was associated with a 25% greater risk of death compared with H2RAs [177]. Among new users of PPI therapy, risk of death was associated with greater PPI exposure. Compared with PPI use ≤30 days, the risk of death increased by 31% with 181 to 360 days of exposure and 51% with 361 to 720 days of PPI exposure [177]. Cause of death was not reported in this study, but the authors state the heightened risk of death was likely mediated by adverse events associated with PPI use, including kidney disease, dementia, hypomagnesemia, *C. difficile* infection, and/or osteoporotic fracture [177].

PPIs may also adversely impact microbial biodiversity of the GI tract. The gut microbiome is important in maintaining overall health, and alterations in its biodiversity can promote pathologic conditions. *Streptococcus* spp. are over-represented in biopsies of patients with gastritis and may contribute to the development of peptic ulcer disease. PPI use favors relative streptococcal abundance independent of *H. pylori* status and may explain the persistence of dyspeptic symptoms in patients on PPI therapy. Patients on long-term PPIs also have increased risk of enteric infections. PPI overuse may significantly shift the GI microbiome toward a less healthy state, with significant changes in the microbial composition of gastric and intestinal microbiota [76].

Considering the high prevalence of PPI use, the adverse events associated with PPI use may have public health implications. Given the potential for these risks, limiting the duration and use of PPIs to medically indicated conditions seems warranted [148; 177; 178].

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Safety of Over-the-Counter PPIs

PPI safety concerns mostly originate from studies evaluating their prescription use, but over-the-counter use differs in several relevant ways. Patients prescribed PPIs generally take higher doses over longer treatment durations for more severe underlying conditions than over-the-counter users. In contrast, over-the-counter PPIs are generally used for shorter durations at lower dose ranges. A concern with over-the-counter PPI use is that direct consumer access without physician direction may promote inappropriate use. Real-world-use data suggest the opposite; persons using over-the-counter PPIs tend to self-select appropriately based on symptoms and are more likely to take the appropriate or fewer number of doses [180]. When over-the-counter PPI use is consistent with label instructions, a consensus panel of experts concluded that available evidence does not suggest an association with substantial health risks [180].

MANAGEMENT OF GERD IN PATIENTS NONRESPONSIVE TO PPIs

MEDICATION OPTIONS IN PPI-REFRACTORY GERD

If switching to rabeprazole or esomeprazole is ineffective, it is essential to assess for other disorders that may be the cause of persistent symptoms in PPI nonresponders. pH testing and HRM assess bolus clearance, reflux episodes, transient LES relaxations, and the integrity of the antireflux barrier, providing important information for treatment targeting. Excluding functional disorders is critical, as these patients are managed differently from those with pathologic reflux [149].

Pharmacologic options are available to target various mechanisms of PPI-refractory GERD, including transient LES relaxations with reflux, incomplete acid suppression, impaired esophageal clearance, and delayed gastric emptying. Targeting these mechanisms may improve symptoms and eliminate the need for antireflux surgeries [149].

An important criticism of the body of published evidence on non-PPI medications is the pervasive neglect of phenotyping to determine the underlying mechanism of symptom persistence. Without phenotyping, many patients with functional symptoms have been included in these studies, making assessment of efficacy in target populations difficult [73; 149]. The medications discussed in the following sections should be added to PPIs (rather than used alone), because their efficacy alone is less-evaluated and may be poor [1; 181].

H2RAs

H2RAs may improve PPI gastric acid suppression, particularly nocturnal acid breakthrough that occurs in up to 75% of patients on PPIs [149].

Adding ranitidine 300 mg or famotidine 40 mg before bed improved overall symptoms (72%) and night-time symptoms (74%) in patients taking PPIs [182]. Compared with PPI alone, adding a night-time H2RA for PPI nonresponse significantly reduced nocturnal acid breakthrough (17% vs. 64%) and percent intragastric time pH <4 (18% vs. 31.5%). Esophageal acid exposure (1.9% vs. 3.3%) and positive acid reflux/symptom correlation (0% vs. 10%) were lower but not significantly different [149; 183]. Night-time H2RAs may help suppress nocturnal acid breakthrough, but tachyphylaxis limits their long-term use [149].

Promotility/Prokinetic Agents

Agents with prokinetic properties are proposed as adjunctive medications for PPI nonresponse when delayed gastric emptying is a suspected symptom contributor. Metoclopramide and domperidone are selective dopamine receptor antagonists that may improve esophageal peristalsis, accelerate esophageal acid clearance, increase LES basal pressure, and improve gastric emptying. Other possible agents include revexepride, prucalopride, and mosapride [149].

A select group of PPI nonresponders may benefit from adjunctive promotility agents. However, mosapride, the most-studied agent, is not approved in the United States. Domperidone reduced symptom scores better than PPI alone, but is also not approved and carries significant arrythmogenic risks [149]. Metoclopramide is associated with several adverse effects and use in GERD has been limited by safety concerns [184; 185]. In patients with persistent GERD symptoms despite PPI treatment, two randomized controlled trials found revexepride no more effective than placebo in controlling regurgitation and reflux [186; 187]. A small randomized controlled trial of prucalopride in patients with GERD and ineffective esophageal motility suggested this drug may be useful in augmenting peristalsis in these patients [188].

Transient LES Relaxation Inhibitors

Which medication can decrease transient LES relaxation-related acidic and nonacidic reflux episodes?

Baclofen acts as an agonist of gamma-aminobutyric acid (GABA) type B receptors and is prescribed to decrease transient LES relaxation-related acidic and non-acidic reflux episodes [149]. Baclofen physiologically inhibits transient LES relaxations, and studies measuring baclofen effects with pH-impedance monitoring show significant reductions in postprandial acid- and non-acid-related symptoms in patients with heartburn by reducing transient LES relaxations, increasing LES tone, and decreasing reflux episodes. Studies have also demonstrated that baclofen reduces the number of postprandial and non-acid reflux events, nocturnal reflux activity, and belching episodes [46; 48]. In patients with symptomatic GERD treated with daily omeprazole plus baclofen 10 mg or placebo, baclofen significantly reduced the rates of heartburn (46% vs. 4%) and regurgitation (54% vs. 4%) [189]. Baclofen may be particularly beneficial for

patients with abnormally high non- or weakly-acidic reflux events [149]. However, baclofen requires adherence to twice or three times daily dosing, and common side effects include drowsiness, fatigue, and confusion [101].

Mucosal Protective Agents

Especially in patients with NERD, PPI response is often partial or limited and symptom relief requires additional medications. Esophageal mucosal protection from acidic and non-acidic contents is another approach to PPI nonresponse. Some of these agents target the gastric acid pocket in the proximal stomach, a contributor to the pathogenesis of postprandial reflux [190].

Alginates

Alginate is a polysaccharide derived from seaweed that binds water in the acid pocket to form a viscous gel, displacing the acid pocket distally below the diaphragm. Sodium bicarbonate, often added to alginate, is converted to carbon dioxide and forms bubbles trapped within the gel. This changes the gel to a lighter substance that rises to the surface of gastric contents and floats, hence the term "raft-forming agent." Alginates offer a supplemental mechanism of acid suppression [191; 192].

Gaviscon is a common raft-forming alginate formulation. In a randomized controlled trial of 136 patients with persistent reflux symptoms taking once-daily PPIs, adding alginate (10 mL four times/day) for seven days led to significantly greater reductions in reflux score and number of nights with symptoms than placebo [193].

A review of 14 studies in patients with NERD or atypical GERD symptoms found alginate-based therapies more effective in resolving reflux symptoms than placebo or antacids, and somewhat less effective than PPIs or H2RAs [192]. This review evaluated alginate monotherapy, but in practice, alginates are typically added to PPIs. Alginate-antacid formulations show efficacy comparable to single-dose omeprazole in patients with NERD [190].

Mirgeal is an alginate formulation that combines glycyrrhetinic acid and anthocyanosides, both of which have mucosal protective properties. Use in combination with PPIs showed greater reflux symptom control in patients with NERD and poor PPI response compared with alginic acid plus PPI [149].

Sucralfate

Sucralfate is a salt of sucrose sulfate and aluminum hydroxide that creates a physical barrier to block esophageal mucosa exposure to, and diffusion of, hydrochloric acid, pepsin, and bile salts. As an add-on to PPIs, sucralfate can further reduce GERD symptoms and may help induce mucosal healing and reduce recurrent esophagitis during maintenance therapy [190; 194].

Hyaluronic Acid and Chondroitin Sulfate

Hyaluronic acid is involved in several key processes, including cell signaling and wound repair and regeneration. Chondroitin sulfate has possible benefits in inflammatory diseases. Formulations that combine hyaluronic acid and chondroitin sulfate have been introduced and evaluated as treatment of reflux disease [195].

In adults with NERD and poor PPI response, hyaluronic acid/chondroitin sulfate (four times per day) for 14 days led to significantly greater reductions in heartburn and regurgitation symptom intensity than placebo. Onset of effect within 30 minutes was more frequent with hyaluronic acid/chondroitin sulfate than placebo (60% vs. 30%). Complete remission was attained by 50% with hyaluronic acid/chondroitin sulfate and 10% with placebo [195].

A larger randomized controlled trial evaluated improved symptom relief with hyaluronic acid/chondroitin sulfate plus PPI compared with PPI alone in 154 patients with NERD. After two weeks of hyaluronic acid/chondroitin sulfate or placebo, significant reduction in total symptom score (on measures of heartburn, acid regurgitation, retrosternal pain, and acid taste in mouth) was reached by 52.6% with hyaluronic acid/chondroitin sulfate and 32.1% with placebo. The synergistic effect of hyaluronic acid/chondroitin sulfate and PPI treatment suggests mucosal protection added to acid suppression could improve symptom control in patients with NERD [153].

Based on current knowledge, mucosal protective compounds cannot replace PPIs, but show promise in PPI-refractory GERD or NERD in combination with PPIs [149; 190]. The ACG states there is no role for sucralfate or other membrane-protectors, but these agents may represent the only effective medication protection against biliary reflux injury of the esophageal mucosa [15; 83].

Pain Modulators

Compared with healthy subjects, patients with non-cardiac chest pain demonstrate higher pain sensation with esophageal exposure to balloon distension, acid infusion, and electrical and thermal stimulation [196]. In these patients, esophageal hypersensitivity results from sensitization of both peripheral afferent nerves (peripheral sensitization) and spinal dorsal horn neurons (central sensitization). Esophageal hypersensitivity and objective pathology can occur together; around 30% of patients with non-cardiac chest pain have abnormal esophageal findings on HRM [198].

Most PPI-refractory patients have NERD or functional symptoms, making treatment with pain modulators a reasonable option. Antidepressants are the most-studied medications for this indication and include tricyclic antidepressants (e.g., imipramine, nortriptyline), SSRIs (e.g., sertraline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), and trazodone. Doses used are lower than in depression, and randomized controlled trials have found them effective

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in reducing esophageal pain, especially in patients with esophageal hypersensitivity [197; 199]. Antidepressants act by modulating the esophagus-brain axis. Patients with NERD and painful heartburn received functional magnetic resonance imaging (off-PPI) after 21 days of nortriptyline or placebo. Acid-induced activation in prefrontal cortex, caudate, insula, cingulate, and hippocampus brain areas were significantly reduced with nortriptyline compared with placebo [200].

A systematic review of 15 randomized controlled trials found that, compared to baseline, antidepressants increased esophageal pain thresholds 7% to 37%, reduced functional chest pain 18% to 67%, and reduced heartburn in patients with GERD 23% to 61%. Antidepressants modulate esophageal sensation, reduce functional chest pain, and may benefit a subgroup with GERD [201]. In these patients, PPI therapy can (and should) be discontinued when ineffective. The clinical relevance of distinguishing functional heartburn from esophageal hypersensitivity is unclear [202].

In patients with non-cardiac chest pain, chest pain was reduced by 50% to 63% with venlafaxine, sertraline, or imipramine, compared with 1% to 15% in those randomized to placebo. This improvement was independent of effects on depression. Side effects are the main drawback with antidepressant therapy for esophageal hypersensitivity and can adversely impact their tolerability and lead to discontinuation. Antidepressant study drop-out rates as high as 53% have been reported in this population, highlighting the need for safer, more tolerable drugs [1; 203].

Novel Agents

Vonoprazan

A novel potassium-competitive acid blocker, vonoprazan, has demonstrated more potent and sustained acid suppressive effects than the PPIs lansoprazole, esomeprazole, and rabeprazole [149]. The metabolism of vonoprazan is not impacted by genetic polymorphisms of CYP2C19, which impair the efficacy of some PPIs. Vonoprazan was comparable to lansoprazole for the treatment of erosive esophagitis and overall shows more favorable pharmacodynamic and pharmacogenetic properties compared to PPIs. As of 2018, vonoprazan is not approved in the United States, but this may change in the future [149].

Melatonin

Melatonin is an important signaling molecule in gut motility and gut-liver communication, and the esophageal mucosa possesses large numbers of melatonin-binding sites [56]. Exogenous melatonin is thought to control GERD symptoms by stimulating production of nitric oxide and prostaglandin E2, inhibiting gastric acid secretion, reducing inflammatory cytokines, and preventing acid/pepsin-induced esophagitis. Melatonin is not conventional therapy but may represent an alternative for patients lacking benefit from PPIs [46].

Clinical trials in GERD are limited, but published results suggest improvements in heartburn, epigastric pain, and LES function [46]. Ramelteon is a melatonin (MT) receptor agonist with high affinity for MT1 and MT2 receptors, essentially a pharmaceutical version of melatonin that is FDA-approved for insomnia. Ramelteon is considerably more expensive than melatonin but is produced under quality control not found with melatonin supplements, because the quality and purity of supplements are unregulated in the United States. In one study, patients with frequent heartburn and/or regurgitation and chronic insomnia received ramelteon 8 mg or placebo before bed for four weeks. Ramelteon led to significant decreases in symptom scores (vs. placebo) for daytime heartburn, night-time heartburn, 24-hour heartburn, and 24-hour acid regurgitation. Insomnia severity scores were significantly reduced with ramelteon compared with placebo. Ramelteon also led to improvements in sleep efficiency and sleep latency. No significant adverse events were observed [204].

OPTIMIZING PPI ADHERENCE

Up to 40% of patients report persistent GERD symptoms despite PPI therapy [149]. An important cause of PPI failure is treatment non-adherence, with inadequate dosing or poor timing [48].

Treatment adherence should be assessed to determine true PPI nonresponse, because PPIs are often taken inappropriately; 27% of patients with GERD dose their PPI correctly and only 12% dose optimally [205]. There is poor understanding of PPI pharmacokinetics, with nearly 70% of primary care physicians and 20% of gastroenterologists incorrectly instructing patients about when to take doses [206].

PPI failure can result from taking PPIs incorrectly. As noted, gastric acid production is stimulated by food, and PPIs inactivate proton pumps only during acid production. Thus, PPI effectiveness is lost by failure to dose 30 to 60 minutes before a meal. Patients may take PPIs at bedtime for nighttime symptoms, which is far less effective than before meals. Taking PPIs infrequently or as-needed, before stable efficacy is achieved, significantly reduces their benefit [1].

SWITCHING TO ANOTHER PPI

Another reason for PPI failure is variation in PPI metabolism. PPIs are primarily metabolized by the hepatic cytochrome (CY) P450 enzymatic system. CYP2C19 and CYP3A4 are the most important isoenzymes in metabolic degradation of PPIs. CYP2C19 polymorphisms (genetic variations) are common and influence the rate of serum clearance and elimination of metabolized drugs. Patient genotypes include extensive metabolizers (normal) and rapid/ultra-rapid metabolizers [48].

Omeprazole is extensively metabolized by CYP2C19. Rapid/ultra-rapid metabolizers show lower serum levels of omeprazole, reduced efficacy from rapid drug clearance, and lower rates of endoscopic healing, remission, and GERD symptom response with CYP2C19-dependent PPIs [1]. Measuring a patient's PPI metabolizer genotype is expensive, but

switching to a CYP2C19-independent PPI (rabeprazole or esomeprazole) is a simple, conservative measure that may be useful in patients with incomplete acid suppression from other PPIs [149].

REFRACTORY HEARTBURN AND NOCTURNAL HEARTBURN

PPIs tend to be more effective in postprandial reflux control during the daytime than in night-time heartburn [207]. PPI-refractory heartburn is more common in NERD than erosive disease. Once-daily PPIs may control symptoms, but nocturnal intragastric acidity often remains elevated enough to produce nocturnal acid breakthrough in these patients [208]. In patients with persistent nocturnal acid breakthrough despite twice-daily PPIs, adding an H2RA at bedtime may control nocturnal acid breakthrough and associated esophageal acidification, but development of tolerance to the H2RA is likely [58].

PPI PARTIAL RESPONDERS

PPI partial responders are patients with some improvement in GERD symptoms but a significant remaining symptom burden despite optimized PPIs. Assessment of this patient population suggests functional GI disorders are common [73].

ANTIREFLUX SURGERY

Antireflux surgery was introduced when acid reflux was the presumed cause of GERD. Refinements in antireflux surgery and the introduction of minimally invasive options may eliminate or markedly reduce GERD symptoms by structurally restoring anatomic failure of the LES antireflux barrier—the primary underlying pathology [83].

Outcomes after any surgical management of refractory GERD are highly dependent on adherence to strict surgical indications and appropriate patient and procedure selection [209]. Guidelines for patient-procedure matching have been established (***Table 3***).

LAPAROSCOPIC FUNDOPLICATION

Fundoplication was introduced in 1955 and subsequently modified to laparoscopic fundoplication in 1991 by Dr. Rudolph Nissen, hence the term Nissen fundoplication surgery (NFS) [156]. NFS is also referred to as laparoscopic antireflux surgery or laparoscopic Nissen fundoplication. It is considered the criterion-standard antireflux surgery approach [15; 55; 210].

With NFS, the gastric fundus is used as a wrap to tightly augment the LES in order to reduce reflux episodes [101]. While effective at preventing reflux, this technique also prevents the normal venting of swallowed air (belching) and reduces normal reflux episodes, which can result in side effects of gas bloating syndrome, flatulence, inability to belch or vomit, and dysphagia [15; 53].

Appropriate patient selection is essential for a positive outcome with this procedure, and the strongest predictors include abnormal acidic pH, symptoms of heartburn and regurgitation, and positive PPI trial [15; 211]. In practice, many common indications for NFS (e.g., PPI-refractory GERD symptoms/esophagitis, GERD medication intolerance, desire to discontinue PPIs, large hiatal hernia, PPI non-adherence) deviate from positive outcome predictors [7; 15]. PPI nonresponse is considered a predictor of unfavorable NFS outcomes but remains the most common indication [156]. Antireflux surgery does not lead to significant regression of Barrett esophagus or reduce the risk of esophageal adenocarcinoma [101].

Patients with GERD symptoms who are considered for NFS are recommended to undergo diagnostic confirmation beforehand. pH monitoring rules out functional heartburn, while HRM and barium swallow rule out other possible diagnoses [206].

In GERD with PPI nonresponse, NFS remains the most-studied treatment with the largest data on outcomes after 10 years. NFS can provide symptomatic and physiologic relief of acid reflux, including in patients with NERD and those without symptom/reflux event correlations [156; 212].

Unfortunately, efficacy wanes with time. Ten years after NFS, nearly 35% of patients experience recurrent heartburn and 30% experience regurgitation. Resumption of PPI use increases from 8.8% at 1 year to 18.2% at 10 years, and 9.6% of patients require surgical re-intervention within 10 years [213; 214; 215]. One study concluded as many as 50% patients who underwent NFS resumed PPI use 10 to 15 years post-surgery [216].

Only a minority of patients with GERD are offered a surgical option, mainly due to concerns over potential side effects, variable success rates, and the extreme alteration of gastric anatomy with NFS [210]. The potentially significant side-effect profile of NFS can negatively impact patient quality of life, and this has contributed to the declining popularity of this procedure, with fewer than 20,000 patients undergoing NFS annually. Clinicians may be wary of fundoplication due to significant side effects of dysphagia, gas-bloat syndrome, and inability to vomit [217; 218]. In typical patients with GERD and good symptom control using PPIs, some experts have concluded there appears to be no net benefit over PPI therapy to warrant the use of NFS [219; 220; 221].

MAGNETIC SPHINCTER AUGMENTATION

Magnetic sphincter augmentation (MSA), transoral incisionless fundoplication (TIF), and radiofrequency energy delivery (RFED) are emerging as alternatives to NFS. As with NFS, patient selection remains crucial.

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MSA was designed to obviate many of issues experienced with NFS. The LINX Reflux Management System is a flexible, expandable MSA device laparoscopically placed around the external gastroesophageal junction. The device augments LES function to prevent reflux into the esophagus, while allowing normal LES opening during swallowing, belching, and vomiting often prevented with fundoplication [222]. The LINX is FDA-approved for patients diagnosed with GERD, defined by abnormal pH testing, who continue having chronic GERD symptoms despite maximum PPI therapy [223].

The body of published evidence demonstrates that MSA is an effective alternative to NFS [156]. Compared with NFS, five-year MSA outcomes showed comparable esophageal acid exposure, heartburn, regurgitation, PPI use, quality-of-life scores, and dysphagia, and lower rates of bloating and inability to belch or vomit [156; 219]. MSA has the other advantages of being a less extensive surgical procedure, requiring minimally invasive removal, and less inter-surgeon variability with a standardized device. MSA is not indicated for patients with severe erosive disease, motility disorders, or large hiatal hernia (>3 cm) [156]. Negative predictors of excellent/good outcome with MSA include BMI >35, structurally defective LES, and elevated LES residual pressure [224].

TRANSORAL INCISIONLESS FUNDOPLICATION

TIF and the Medigus endoscopic stapling procedure avoid the risks of laparoscopic fundoplication by creating endoscopic fundoplications to correct anatomical defects of the LES. EsophyX, the only FDA-approved TIF, uses a 270-degree anterior wrap fundoplication. These procedures are limited to patients with normal anatomy, because hiatal hernia repair cannot be performed [54; 156; 219].

In PPI-responsive patients, TIF shows good long-term results up to six years, with lasting symptom relief, decreased reflux on pH-impedance monitoring, and reduced esophageal acid exposure. PPI use is slightly higher in TIF than with NFS or MSA, and symptom remission is lower than with NFS [54]. The longest follow-up in PPI nonresponsive patients is 22 months [156; 219].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Based on existing evidence, the Society of American Gastrointestinal and Endoscopic Surgeons recommends transoral incisionless fundoplication (TIF) can be performed with an acceptable safety risk in appropriately selected patients with GERD.

(https://www.sages.org/publications/guidelines/endoluminal-treatments-for-gastroesophageal-reflux-disease-gerd. Last accessed September 7, 2018.)

Strength of Recommendation: Strong

RADIOFREQUENCY ENERGY DELIVERY

RFED to the LES via the Stretta system was introduced in 2000 as a minimally invasive endoscopic treatment for PPI-nonresponsive GERD [219]. Stretta delivers radiofrequency energy to a broad region of the LES, on the premise that postprocedure ablation scarring and fibrosis will increase LES tone. A systematic review evaluating the efficacy of Stretta in GERD found no difference between Stretta, sham treatment, or PPIs in time spent at pH <4, LES pressure, PPI cessation, or health-related quality of life [225]. Use of RFED has limited evidence support; MSA and TIF are better minimally invasive alternatives [156].

BARIATRIC SURGERY IN PATIENTS WITH GERD AND OBESITY

In obese patients with GERD, what is the recommended bariatric approach?

As discussed, obesity plays a major role in the development of GERD, and treating obesity is an important step in the treatment of GERD. While many studies show comparable outcomes with NFS across weight groups, other surgical options are recommended for obese patients with GERD [15; 48]. For patients with moderate obesity (BMI 35–40), LNF shows good symptom control and moderate weight loss. For patients with BMI >40, bariatric surgery with gastric bypass is preferred [54; 226].

Roux en-Y gastric bypass (RYGB) remains the favored bariatric approach due to its benefit in GERD and long-term weight loss. Performed laparoscopically, RYGB involves creation of a small gastric pouch connected directly to the small intestine to bypass a major portion of the mid/distal stomach and duodenum [48]. A comparative study found laparoscopic RYGB as safe as fundoplication for morbidly obese patients. In-hospital complications were significantly lower in the bypass group, while the mean length of hospitalization, mortality, and treatment costs were comparable [227].

Bariatric surgery options are broadening for obese patients with GERD, including laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy. However, there are growing concerns about side effects induced by these techniques. LAGB is associated with high rates of reoperation or conversion to more definitive bariatric surgery, band erosion, and motor dysfunction of the esophagus, stomach, and small bowel in obese patients with GERD, and is not recommended [16; 54]. Sleeve gastrectomy is considered an effective weight-loss surgery but is consistently associated with new-onset reflux in non-GERD populations and worsening GERD symptoms when reflux is already present, and is not recommended in patients with GERD and obesity as a first-line option [15; 54].

PATIENT-PROCEDURE MATCHING FOR INDIVIDUALS WITH REFRACTORY GERD	
Patient Characteristics	**Indicated Surgical Procedure**
Symptomatic GERD despite twice-daily PPIs	Laparoscopic hernia repair plus magnetic sphincter augmentation (LINX) for hernias <2 cm Laparoscopic hernia repair plus Nissen fundoplication surgery (NFS) for hernias >3 cm Postoperatively, follow patients to ensure lifestyle and dietary adherence, minimize disease recurrence, and detect treatment failure
Incomplete PPI response, ongoing regurgitation, and patient wish for an endoscopic option	Offer transoral incisionless fundoplication (TIF)
Refractory patients with ineffective esophageal motility	TIF or a modified (Toupet) fundoplication to avoid postoperative dysphagia
Patients with good symptom control who want to discontinue PPIs	LINX or NFS
Obese patients (BMI >35) with GERD	Bariatric surgery, with Roux-en-Y bypass preferred over adjustable gastric banding or sleeve gastrectomy
Source: [48; 55]	*Table 3*

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. It is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. 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. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures is being provided, the use of an interpreter should be considered.

CONCLUSION

GERD is a far more complex clinical entity than is often appreciated, with impaired lower esophageal structure and function, not gastric acid over-secretion, the core pathology. Advances in characterizing GERD also show a diverse underlying pathology of symptom presentations and point to the need for a more tailored approach to diagnosis. PPI acid-suppressant medication is the backbone of GERD management, and an empiric PPI trial is a reasonable starting point for most patients. Patients who remain symptomatic require a diagnostic workup to identify the underlying cause of symptom persistence for effective therapeutic targeting. The importance of patient adherence with PPI therapy cannot be overstated. A range of medications and antireflux procedures are available for PPI-refractory patients.

Customer Information/Evaluation insert located between pages 64–65.

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Pathophysiology: The Central Nervous System

Includes 2 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses working in critical care and general and specialty medical-surgical units in which patients with multiple organ system problems are found.

Course Objective
As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing management of their central nervous system disorder.

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

1. Identify the key structures and functional interrelationships in the central nervous system (CNS).
2. Discuss structures and mechanisms in place to protect the CNS.
3. Describe the components and functions of CNS circulation.
4. Discuss the pathophysiologic and environmental influences and effects on the CNS.
5. Outline the role of subjective data in completing a full nursing assessment of the CNS.
6. Describe objective data compiled during a nursing assessment of the CNS.
7. Identify diagnostic tests used in the identification and classification of CNS diseases.
8. Outline the nursing diagnoses, planning, and management of conditions related to CNS dysfunction.
9. Discuss clinical manifestations of congenital diseases of the CNS.
10. Review signs and symptoms of CNS disorders of multifactorial origin and related nursing actions.
11. Describe the common causes, appearances, and treatment of degenerative CNS disorders.
12. Analyze the presentation and nursing management of immunologic CNS disorders.
13. Evaluate pathologic causes and manifestations of infectious and inflammatory disorders of the CNS.
14. Discuss the pathophysiology and clinical manifestations of neoplastic and obstructive CNS disorders.
15. Outline the concepts and information the nurse should provide for the patient who has sustained a traumatic CNS injury.

Faculty
Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. In 1982, she received her PhD in Higher Education Administration from Peabody College of Vanderbilt University. In 1998, Dr. Norman took a position at Tennessee State University. There she has achieved tenure and full professor status. She is a member of Sigma Theta Tau National Nursing Honors Society. In 2005, she began her current position as Director of the Masters of Science in Nursing Program.

Faculty Disclosure
Contributing faculty, Jane C. Norman, RN, MSN, CNE, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner Disclosure
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INTRODUCTION

The nervous system is the body's most organized and complex structural and functional system, and it profoundly affects both psychologic and physiologic function. This course discusses the importance of the central nervous system (CNS) to human function and the major consequences of central neurologic disorders. The onset of neurologic problems may be sudden, as in traumatic spinal cord severance or ruptured aneurysm, or insidious, as in Parkinson disease or multiple sclerosis. Providing care to patients experiencing neurologic disorders is challenging and requires extensive knowledge of neurologic structures and function and neurologic disease processes.

Neurologic problems can be frightening and even devastating to the patient and family involved, especially if the process is irreversible. Many such problems produce varying degrees of physical and/or psychosocial dependency. Physical disabilities may limit self-care, and memory loss and confusion can occur. Subtle or gross changes in consciousness may develop, and patients may not be responsible for their behavior at times. A person's entire way of life may be altered. This course provides the information necessary to plan appropriate nursing care for individuals experiencing CNS problems in both acute and rehabilitative states. An overview of CNS anatomy, physiology, and pathophysiology is detailed, as are assessment, diagnostic tests, pathologic findings, planning, intervention, and evaluation of nursing care provided for these patients.

THE NERVOUS SYSTEM IN HEALTH AND ILLNESS: STRUCTURAL AND FUNCTIONAL INTER-RELATIONSHIPS

Every physical, mental, and emotional aspect of a person's existence is influenced by continually changing internal and external environments. To deal with these changes effectively, the nervous system perceives and interprets the changes and then quickly and continuously initiates, coordinates, and modulates body responses. This job is endless, because the body and the environment are never static. Internal changes include the process of aging, anabolic and catabolic activities, and psychologic states; external changes include ambient temperatures, light, noise levels, and colonies of micro-organisms.

The nervous system not only plays a key role in the management of body functions; it also depends on other body systems. Indeed, the nervous system quickly malfunctions if its sources of nourishment, its waste management systems, or its protective mechanisms are lost or impeded.

The brain is structurally divided into components according to its embryologic development. These components, known as the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon) are further divided according to their location within the adult brain. Knowing these divisions is useful because they are often involved in CNS function or pathology [7; 10].

An understanding of structure and function and the interdependence of body systems is an essential part of the nurse's knowledge base. With this knowledge, nurses can effectively assess and plan care of the patient with CNS dysfunction.

NEURONS

Structure of the Neuron

What are the major types of sensory receptors?

Neurons are the primary components of the nervous system. Working alone or as units, neurons detect environmental changes and initiate body responses needed to maintain homeostasis. Each neuron is composed of a cell body, an axon, and a number of dendrites. Both axons and dendrites vary in size and shape. The axons, ranging in length from miniscule to over a meter, transmit messages throughout the central and peripheral nervous systems. Each cell has only one axon, but axonal branching is common and allows for broader dissemination of neuronal transmissions. Dendrites, the processes of neurons that conduct electrical impulses to the cell body, also have varying branching patterns. These characteristics allow for the efficient transmission and reception of impulses throughout the body [2; 3].

Many central axons are wrapped in insulating sheaths of a white, fatty substance called myelin. The myelin is encased in special cells lying end to end along the axons. Junctures, known as nodes of Ranvier, occur where these cells abut, allowing for more rapid transmission of electrical impulses. Axons often branch at these nodes [2; 3].

Two distinct types of cells cover axons of the nervous system. Those located in the CNS are known as oligodendrocytes. These cells and the neurons they protect cannot be replaced or repaired if damaged. Schwann cells, which surround peripheral nervous system myelinated and unmyelinated axons, form the neurilemma, the outer membrane that supports and protects peripheral nervous system axons and may facilitate the healing of damaged axons [2; 3].

Groups of neurons called nuclei provide routes for the transmission of complex afferent and efferent impulses. Fasciculi are bundles of neurons; groups of fasciculi, encased in a covering called epineurium, are referred to as nerves. Most nerves contain afferent (toward the CNS) and efferent (from the CNS) fibers [2; 3].

Structurally distinct neurons are responsible for receiving and sending specific messages to the brain about the body's internal and external environment. There are five major types of sensory receptors [2; 3]:

- Mechanoreceptors: Receive impulses related to pressure, touch, and mechanical deformation of the receptor
- Thermoreceptors: Respond to heat and cold
- Nociceptors: Receive messages about pain caused specifically by physical or chemical damage
- Electromagnetic receptors: Respond to light on the retina
- Chemoreceptors: Sense flavors, odors, oxygen levels, osmolality of body fluids, and the concentration of carbon dioxide

Each type of receptor is sensitive to the particular stimuli it is designed to receive and almost nonresponsive to other types of stimuli. For example, a nociceptor can be stimulated by electricity, heat, crushing, or other tissue damage that will be experienced as pain. The nociceptor will not, however, respond to light. Each sensory nerve terminates at specific points in the CNS, where the message is interpreted [2; 3].

CNS and peripheral nervous system neurons cannot function independently. Their nutritional and physical support and protection are provided by other cells commonly referred to as glial cells. Glial cells, unlike neurons, are able to undergo mitosis. Astrocytes, star-shaped cells with many projections, are the largest and most numerous glial cells. They provide structural support and nutrition to neurons and maintain a biochemical environment supportive of nerve impulse transmission and synaptic activity. If nervous tissue is destroyed, astrocytes multiply (a process called gliosis) to fill in the area or line a cavity. Microglia, considered the phagocytes of the CNS, are classified as part of the body's reticuloendothelial system. They remove dead tissue and foreign matter. Ependymal cells are involved in cerebrospinal fluid (CSF) system function. They line the choroid plexuses of the ventricular system, the ventricles, and central canal of the spinal cord. Oligodendrocytes and Schwann cells, previously considered for their role in the encasement and protection of axons, are also classified as neuroglia [7; 10].

Neuronal Function

Functionally, neurons are recognized as being motor (efferent) neurons, sensory (afferent) neurons, or internuncial (transmitters of messages) neurons. Neuronal messages are transmitted through electrical impulses, with the necessary voltages created by positive and negative forces produced while ions line up inside and outside the cell's plasma membrane. When a nerve is in a resting state (known as a resting membrane potential), the electrical charge outside the wall is positive and the charge inside is negative [43; 44; 45].

The principal extracellular anion is sodium; the main intercellular anion is potassium. With stimulation of the cell, the charge is reversed, as sodium moves into the cell and potassium moves out. This reversal results in a flow of electric current. With sufficient stimulation, the reversal of polarity travels along the entire axon. This process, known as an action potential, requires only a few milliseconds. Quickly, electrical forces and ion concentration forces re-establish the resting membrane potential. If a stimulus is not sufficient to produce an action potential and another stimulus occurs before the membrane has completely stabilized, depolarization will be facilitated [43; 44; 45].

Information is transmitted from one neuron to another at synapses following the initiation of an action potential. In humans, chemical synapses initiate almost all action potentials. These synapses, located where axons and dendrites meet, employ various neurotransmitters, which are stored in and released from the axon terminal following an action potential. Action potentials are believed to increase the permeability of the axon terminal to calcium, allowing it to move into the axon terminal to stimulate the release of neurotransmitters into the synaptic cleft. The neurotransmitter diffuses across the cleft and attaches to postsynaptic receptors [43; 44; 45].

The influence of neurotransmitters on the postsynaptic receptor depends on the combination of impulses received. This combination is derived from the total number and frequency of impulses received over a period of time from one or multiple synapses. Strong stimuli activate a greater number of neurons. Myelinated fibers speed the transmission of impulses. Inhibitory impulses also influence the postsynaptic receptors' response. Through these combinations, the nervous system "fine tunes" synaptic activity needed to manage the body's complex functions. Nerve impulses are binary (either "on" or "off"), so the CNS must discriminate among stimuli by interpreting variations in strength, frequency, and number of stimuli received [43; 44; 45].

Synapses between neuron effector junctions are similar to chemical synapses between two neurons. A review of the events that produce skeletal muscle contraction serves as a good example of how these synapses work. Following depolarization of the axon terminal and movement of calcium into the terminal, acetylcholine is released. It diffuses across the synaptic cleft at the neuromuscular junction to the plasma membrane of the muscle cell and attaches to the receptor sites, causing an increased permeability of the muscle fiber membrane to sodium and potassium ions. If the impulse, known as an endplate potential, is sufficient to depolarize the muscle-fiber membrane, a propagated action potential leads to contraction of the muscle fiber. At the cleft site, a small portion of acetylcholine diffuses away but most is quickly inactivated by the enzyme cholinesterase, located on the muscle-cell membrane, which prevents continued excitation of the muscle fibers [43; 44; 45].

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There are many other neurotransmitters. About 30 are known or suspected to play a role in nerve-impulse transmission; some have multiple actions. For example, norepinephrine is involved in the maintenance of arousal and dreaming sleep and regulation of moods; dopamine has roles in the regulation of emotional responses and control of complex movements; and endorphins and encephalin are believed to be involved in the perception and integration of pain and emotional experiences [43; 44; 45].

The Cranial Nerves

The functions of cranial nerves (CNs) vary; they may be motor, sensory, or mixed. Motor nerves are innervated with proprioceptive (sensory) branches. The parasympathetic branch of the autonomic nervous system provides a visceral component for some cranial nerves. The 12 pairs of cranial nerves, identified by roman numerals, are ordered by their position within the skull [47].

Cranial Nerve I (Olfactory Nerves)

CN I nerves, made up of sensory receptor cells within the epithelial lining of the nasal mucosa, are responsible for the perception of odors. Nerve impulses originating here are transmitted to the temporal lobes for interpretation [47].

Cranial Nerve II (Optic Nerves)

The optic nerves, which are actually nerve tracts, originate in the retina of the eye and enter the cranium via the optic foramina. Nerve impulses are transmitted to the occipital lobe, where vision is perceived. Optic nerve projections from the orbits meet at the optic chiasm. Here each tract divides, the inner halves joining with fibers from the opposite orbit. From this point, each tract carries fibers from both eyes. Some fibers important for visual reflexes synapse in the midbrain, but most travel to the thalamus to synapse with neurons that form pathways called optic radiations. These fibers terminate in the visual cortex of the occipital lobe [47].

Cranial Nerve III (Oculomotor Nerves)

The oculomotor nerves emerge from the midbrain and enter the orbits through the superior orbital fissures. They are responsible for movement of four of the six extrinsic eye muscles and for opening the eyelid. Parasympathetic innervation supplies the ciliary muscle and the sphincter muscle of the iris to control visual accommodation and adjustment to light intensity [47].

Cranial Nerve IV (Trochlear Nerves)

The trochlear nerves arise from the dorsal side of the midbrain. CN IV is responsible for voluntary movement of the eyeball through its innervation of the superior oblique muscle [47].

Cranial Nerve V (Trigeminal Nerves)

Trigeminal nerve fiber locations are widespread. Both sensory and motor fibers exit from the pons, and some sensory nuclei are located in the medulla. Deep and superficial sensory fibers innervate the face and anterior portion of the head through the ophthalmic, maxillary, and mandibular branches. Sensory fibers for pain, light, touch, and proprioception (i.e., awareness of one's position in space) can be readily identified. The motor components of this nerve are responsible for mastication [47].

Cranial Nerve VI (Abducens Nerves)

CN VI nerves exit from the medulla just below the pons and enter the orbits with CN III and IV. They function to roll the eyes outward [47].

Cranial Nerve VII (Facial Nerves)

CN VII nerves project from the lower edges of the pons. They supply motor neurons for the facial and scalp muscles. Sensory fibers supply the taste buds to detect sweet, sour, and salt on the anterior two-thirds of the tongue. Parasympathetic fibers supply the lacrimal glands and the submandibular and sublingual salivary glands [47].

Cranial Nerve VIII (Vestibulocochlear Nerves)

There are two sensory divisions to the eighth cranial nerves—an auditory division and a vestibular division. Both originate at inner-ear receptors located in the petrous portion of the temporal bones. The two divisions, enclosed in a single sheath, pass to the brain stem just below the pons. Some of the vestibular fibers travel directly to the cerebellum. Auditory impulses are transmitted to the temporal lobes for interpretation [47].

Cranial Nerve IX (Glossopharyngeal Nerves)

The nuclei for CN IX, located in the medulla oblongata, innervate the tongue and pharynx. The motor component is important in swallowing. Sensory responsibilities include perception of bitter taste on the posterior one-third of the tongue; sensory awareness for the mucous membranes of the pharynx, tonsils, and middle ear cavity; carotid body receptor sensitivity to serum oxygen and carbon dioxide levels; and baroreceptor information regarding blood pressure. Parasympathetic neurons innervate the parotid gland [47].

Cranial Nerve X (Vagus Nerves)

The vagus nerve nuclei, also located in the medulla, carry motor impulses to and sensory impulses from the pharynx and larynx. Extensive parasympathetic nerve fibers innervate the pharynx, larynx, and trachea and extend into the thorax and abdomen. Thoracic and abdominal vagal branches influence the function of the esophagus, lungs, aorta, stomach, gallbladder, spleen, small intestine, kidneys, and upper two-thirds of the large intestine. Sensory fibers from the vagus

nerve related to visceral functions generally operate at an unconscious level. An exception is nausea, which is perceived via the vagus nerve [47].

Cranial Nerve XI (Accessory Nerves)

CN XI is formed by two nerves. One projects from the medulla; the other, projecting from the fifth or sixth cervical segment of the spinal cord, is a spinal nerve. Fibers from the cranial portion join with the vagus nerve to supply muscles of the larynx and pharynx. Fibers from the spinal component innervate the trapezius and sternocleidomastoid muscles [47].

Cranial Nerve XII (Hypoglossal Nerves)

The hypoglossal nerves exit from the medulla oblongata and pass through the hypoglossal canals located beneath the tongue. These nerves are responsible for tongue movement [47].

THE BRAIN

The outer area of the cerebral cortex is composed of gray matter in complex folds (gyri) or convolutions separated by deep depressions (fissures) and shallow depressions (sulci). These folds make the surface area much greater. The patterning of gyri and sulci is similar in all individuals. The following well-marked fissures are distinguishable in all brains [7; 10]:

- The longitudinal fissure: Separates the right and left hemispheres of the brain
- The central sulcus (fissure of Rolando): Extends outward and downward over the hemisphere
- The lateral fissure (fissure of Silvius): Begins on the underside of the brain and moves out and around the brain along its side

Each hemisphere of the cerebral cortex is divided into lobes. The frontal lobe is located anterior to the central sulcus and above the lateral fissure. The parietal lobe is positioned behind the central sulcus. The temporal lobe is located below the frontal and parietal lobes (below the lateral fissure) and merges posteriorly with the occipital lobe. The occipital lobe extends from the parieto-occipital sulcus inferiorly abound the base the cerebrum. The insula (island of Reil or central lobe) lies within the lateral cerebral fissure. The cerebellum, which lies below the occipital lobe, is separated by the deep transverse fissure into which a dural fold, called the tentorium cerebelli, extends [7; 10].

Nerve fiber tracts establish connections between areas within the brain. The corpus callosum consists of fibers extending between the right and left hemispheres. The commissural tracts of the corpus callosum located deep in the longitudinal fissure extend from one convolution to a corresponding one in the opposite hemisphere. The internal capsule also allows networking between areas within the brain. The internal capsule is comprised of two distinct sections referred to as anterior and posterior limbs. Here, afferent and efferent fibers extend from an extensive, fanlike radiation of fibers in the cerebrum to link with the brain stem and spinal cord. Short association fibers extend from one convolution to another in the same hemisphere. Long association tracts interconnect cortical regions in different lobes of each hemisphere [7; 10].

The basal ganglia are coated with the white matter of the cerebral hemispheres. This area contains the caudate nucleus, putamen, globus pallidus, thalamus, subthalamus, substantia nigra, and the red nucleus. These structures have many and varied functions, including sensory and motor activities and transmission of afferent and efferent signals to appropriate parts of the nervous system. The hypothalamus, a small but extremely important area of the brain, is situated just below the thalamus. It receives input from all parts of the body, both by neuronal transmission and its blood supply. The hypothalamus, in turn, influences body functions via these same routes [7; 10].

The Cerebellum

The cerebellum lies below the tentorium cerebelli in the posterior inferior portion of the cranial vault. It is made up of two hemispheres connected in the center by a structure called the vermis. The superficial area of the cerebellum is composed of gray matter, which lies in even, horizontal folds forming fissures and sulci. White fiber tracts lying below the gray matter provide extensive afferent and efferent connections with the brain stem, cortex, thalamus, and basal ganglia. Cerebellar efferent signals travel to the brain stem, thalamus, and motor cortex [18].

Cerebellum Function

The cerebellum modulates and coordinates skeletal muscle activity and maintains body posture and muscle tone. It controls movement with both excitatory and inhibitor signals, which modulates fine movements in ways the cerebral cortex is incapable of carrying out. Each hemisphere influences the movement of the ipsilateral side of the body and modifies activity initiated elsewhere in the body. There is no conscious input [48].

Activities of the cerebellum derive from the multiple inputs from the CNS and peripheral nervous system. Afferent fibers travel to the cerebellum from the cerebral cortex by way of the corticocerebellar tracts and the pons. Peripheral afferent impulses from muscle spindles, Golgi tendon organs, skin, and joint receptors travel to the cerebellum via the ventral and dorsal spinocerebellar tracts. The reticular substance of the brain stem and vestibular tracts also provide the cerebellum with information [48].

Cerebellar efferent impulses are sent to the motor cortex via the thalamus. Additional efferent signals are transmitted to the basal ganglia, red nucleus, reticular formation of the brain stem, and vestibular nuclei. The connections with vestibular nuclei integrate changes in the direction of body movement and posture. The semicircular canals of the inner ear perceive these changes and transmit this information to the cerebellum via the vestibular nerve and the brain stem.

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Balance is maintained through modification of muscle tone. The cerebellum has no direct influence on lower motor neurons [48].

The cerebellum is also involved with predictively coordinating visual cues with bodily motion. For example, the cerebellum is the area of the brain responsible for processing how rapidly an object is approaching. The findings of an experiment on monkeys illustrate the value of this function. In this experiment, when the portion of the cerebellum involved in vision was removed, the monkey could not judge distance from a corridor wall and repeatedly charged into the wall [48].

Frontal Lobes

The frontal lobes of the brain are involved in mental, emotional, and physical functions. Anterior portions have a major role in the control of conscious and unconscious behaviors such as personality, social behavior, judgment, and complex intellectual activity. The central and posterior portions of the frontal lobes control motor function. The primary motor areas, located in precentral gyri, control voluntary movement via the pyramidal tracts. The premotor areas control and coordinate complex, learned movements such as typing, writing, scanning eye movements, conjugate deviation of the eyes, and movement of the head. These activities are affected via the extrapyramidal tracts. Pyramidal and extrapyramidal centers control movements of the opposite side of the body. The dominant frontal lobe also contains Broca's motor speech area [7; 10].

Parietal Lobes

The parietal lobes interpret sensory input. The postcentral convolutions, organized similarly to the major motor strip, receive conscious sensory input. Sensations perceived on one side of the body are interpreted by the contralateral parietal lobe. Somatic sensations perceived include pain, temperature, touch, pressure, and proprioception. The parietal lobes contain the somatesthetic association areas, which lie in the superior portion of the lobes and extend to the medial surface of the hemisphere. Many other connections within the parietal lobe allow for interpretation of sensory input such as stereognosis (i.e., perceiving and understanding an object by touch and relating the sensations to experience and knowledge). Awareness of body parts and establishment of body image also take place here. The angular gyrus, located in the parietal lobe of the dominate hemisphere, is responsible for interpretation of written language [7; 10].

Temporal Lobes

The temporal lobes receive input from three senses—hearing, taste, and smell—and have a role in memory processes. Association fibers, especially in the dominate lobe, allow the comparison of sensory input with past experiences. These fibers, particularly those of the dominant lobe, inter-relate somatesthetic visual and auditory stimuli to give them meaning. Wernicke's area, also located on the dominate side, is involved in the hearing component of speech and in the formulation of language [7; 10].

Occipital Lobes

The occipital lobes contain the primary visual and visual association areas. The primary visual areas receive information and perceive color, while the visual association areas give visual input meaning and have a role in visual reflexes for fixing the eyes on a stationary or moving object. Injury to the medial surface on the dominate side can result in loss of the ability to recognize objects and know their function, although recognition of faces still is possible. A consequence of damage to the nondominant side may be the inability to recognize faces and differentiate various animals, such as horses and elephants [7; 10].

Insula

The insula, thought by some to be a fifth lobe of the brain, lies deep within the lateral fissure, where it is covered by portions of the frontal, temporal, and parietal lobes. It is believed to be involved in visceral activities related to intra-abdominal sensations and visceral motility. Little information is available regarding function [7; 10].

Limbic System

The limbic system consists of a group of structures, including the olfactory bulbs, septum pellucid, fornix, cingulate gyrus, parts of the basal ganglia (including the amygdaloidal nucleus), hippocampus, uncus, mammillary bodies, and various thalamic and hypothalamic nuclei. This system's multiple interconnections with brain structures influence behavior and responses to stimuli. For example, the sensory system, cerebral cortex, and limbic system are involved in the stimulation of visceral and somatic effectors, which results in psychologic expressions of behavior and emotions [7; 10].

The limbic system influences memory, drives, motivation, visceral functions, and interactions with the environment. Emotional expressions believed to evolve from this complex group of structures include rage, placidity, fear, and attack reactions. Animal studies have demonstrated that the limbic system contains centers of reward and punishment, with both serving as important imitators of behavior and affecting memory. The hippocampus is thought to be involved in the transfer of short-term memory into long-term memory, especially with events related to elements perceived in the environment [25; 26].

Amygdala

The amygdala is thought to have major responsibilities for the control of behavior in social and environmental circumstances. It is also believed to influence visceral responses to emotions and various movements related to posturing and eating [25; 26].

Thalamus

The thalamus, a large ovoid gray mass, surrounds the third ventricle. Specific areas within the thalamus receive axons from the cord, brain stem, cerebellum, basal ganglia, and various parts of the cerebellum. These connections allow it to influence motor function and have a role in arousal, alerting mechanisms, and reflex movements [7; 10].

The thalamus influences the motor cortex through its connections with the pyramidal tract neurons. It is involved with the initiation of movement, control of muscle tone, and regulation of cortical reflexes through connections with the cerebellum, globus pallidus, and substantia nigra. The thalamus interprets and relays sensory impulses from all parts of the body, except the olfactory nerve. Recognition of crude sensations, such as pain, temperature, and touch, also take place here. Sensory impulses that the thalamus is unable to interpret are relayed to appropriate primary sensory and association nuclei in the cerebral cortex. The thalamus is even involved in emotional responses—interpreting sensations as pleasant or unpleasant [7; 10].

Hypothalamus

The hypothalamus, a small but important area of brain tissue situated just below the thalamus, plays a major role in the maintenance of many homeostatic functions. Numerous regulatory activities initiated here are affected through the pituitary gland and the autonomic nervous system. The pituitary gland, also known as the hypophysis, lies below the hypothalamus in the sella turcica. Hypothalamic nuclei influence pituitary gland function through neural and endocrine activity [45].

The hypothalamus receives input from all parts of the body. Autonomic nervous system activity is initiated in response to input received from areas within the thalamus, medulla oblongata, spinal cord, and limbic system. The influence of the hypothalamus in autonomic nervous system activity includes regulation of heart rate, blood pressure, and body temperature [45].

The limbic system, important in emotions and behavior, surrounds the hypothalamus and has connections with it. Hypothalamic connections with the thalamus, which interprets feelings of pleasantness and unpleasantness, and with the reticular activating system, which influences wakefulness, provide additional input to which the hypothalamus responds [45].

Many hypothalamic activities are initiated by changes in the perceived composition of its blood supply. For example, specific areas within the hypothalamus are sensitive to changes in water balance, glucose, and insulin levels. The hypothalamic response to an increase in osmotic pressure illustrates this sensitivity. With a loss of body fluid, the hypothalamus detects an increase in osmotic pressure. In response, it initiates the release of antidiuretic hormone by the posterior pituitary gland to concentrate the urine and stimulate the thirst center to increase the oral intake of fluid [45].

Other centers within the hypothalamus regulate appetite. Specific nuclei credited with the initiation of feeding behavior and satiety have been identified. These centers are reciprocal in their inhibition of one another. The hypothalamus also influences gastrointestinal function and sexual activity [45].

Speech Centers and Cerebral Hemisphere Specialization

About 95% of the population has speech centers in the left hemisphere of the cerebral cortex. In the remaining 5%, these centers are in the right hemisphere or (rarely) in both. There is a relation between the dominant hand and the hemisphere controlling speech; most right-handed persons' speech centers are in the left hemisphere, while left-handed person's speech centers tend to be in the right hemisphere. The term "cerebral dominance" refers to the hemisphere containing the speech centers. Two areas within the brain concerned with speech and language are Broca's motor speech area, located in the frontal lobe, and Wernicke's area, located in the superior posterior aspect of the temporal lobe [25; 26].

Research has demonstrated that both hemispheres of the brain have many types of specialization in addition to speech. The dominate hemisphere appears to excel in mathematical calculation and logical analysis of problems, where the other hemisphere appears better able to understand complex visual patterns and spatial relations and to appreciate music. Development and effective use of these special skills require that the fibers connecting the hemisphere be intact [25; 26].

Brain Stem

The brain stem, which lies between the diencephalon and the spinal cord, has three sections: the midbrain (superior portion), the pons (center portion), and the medulla oblongata. The medulla oblongata joins the spinal cord at the foramen magnum, located at the base of the skull. The brain stem contains many fiber tracts that transmit messages to and from the brain. It also serves as a relay station between the cerebellum and brain. Ten of the twelve cranial nerves located here function much like peripheral nerves (spinal nerves). With the exception of CN IV (the trochlear nerve), they are unlike peripheral nerves in that they only innervate tissues ipsilaterally (i.e., on the same side of the body) [7; 10].

Brain Stem Function

Each of the structures of the brain stem has unique responsibilities, but the three function as a unit to serve as a conduit for impulses passing to and from the cerebral cortex and the spinal column. The midbrain, the uppermost portion of the brain stem, contains afferent and efferent nerve tracts that travel to and from the cerebral hemispheres. It also houses the red nucleus, which serves as a relay station for coordination

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of impulses traveling between the cerebellum and cerebral hemispheres, and the corpora quadrigemina, which are involved in reflex responses to visual stimuli and the relay of auditory impulses [25; 26].

The pons sits between the midbrain and the medulla oblongata and anterior to the cerebellum. It contains nerve fiber tracts that provide communication between upper and lower levels of the CNS and the cerebellum. The lower third of the pons contains respiratory reflex centers influenced by the carbon dioxide levels of the blood and spinal fluid. The pons also influences vasomotor activity [25; 26].

The medulla oblongata forms the inferior portion of the brain stem. The pyramids for the motor tracts are located on its ventral surface. Sensory tracts ascend through the medulla to the thalamus. Major reflex centers in the medulla influence respiratory and cardiovascular function [25; 26].

THE SPINAL CORD

The spinal cord is continuous with the brain stem. It begins at the foramen magnum and descends through the vertebral canal to the level of the first or second lumbar vertebrae. Nerve roots known collectively as the cauda equina extend off the base of the spinal cord and travel for some distance before exiting at the appropriate intervertebral foramina [18].

The spinal cord contains neuronal cell bodies, ascending sensory tracts, and descending motor tracts. A cross-section of the cord shows a gray center shaped like an H surrounded by white fibers. The gray area is made up of neuronal cell bodies, internuncial neurons, neuroglial cells, and synapses. In the center of the gray matter lies the differential canal, each is continuous with the fourth ventricle. It may contain CSF but is often filled with cellular debris [18].

The white fiber area of the cord contains myelinated and unmyelinated fiber tracts, which transmit the many messages essential for maintenance of the body's complex functions. Both sensory and motor tracts are located on each side of the cord [18].

There are 31 pairs of spinal nerves, each numbered according to the level of the cord section from which it originates. There are 8 pairs of cervical nerves, 12 pairs of thoracic nerves, 5 pairs of lumbar nerves, 5 pairs of sacral nerves, and 1 pair of coccygeal nerves. The first pair of cervical nerves exits between the occipital bone and the first cervical vertebrae. Because there are eight cervical nerves and only seven cervical vertebrae, spinal lesions are identified according to the cord level rather than the vertebral level. Generally, each cord segment is named for the vertebral body below its exit point. Peripheral nerve trunks extend from anterior and posterior roots, which unite in the intervertebral foramina. Upon emerging from the vertebral foramina, they form mixed nerves, which divide into anterior and posterior branches and extend into the periphery. Also present are white rami, which contain autonomic nervous system fibers. The posterior rami divide into smaller nerves connected to the muscles and skin of the exterior surface of the head, neck, and trunk. Anterior rami (except for the thoracic nerves) divide to supply fibers to the skeletal muscle, skin of the extremities, and the anterior and lateral surfaces. Subdivisions of the anterior rami form three complex networks or plexuses: the cervical plexus, graphical plexus, and lumbosacral plexus. Smaller nerves emerge from these plexuses and continue to subdivide to innervate distal regions of the extremities [18].

Spinal Cord Function

The spinal cord is a conduit for messages to and from the higher levels within the CNS and participates in reflex motor activities. Descending pathways within the cord carry motor instructions to the anterior horn (ventral roots) from the cerebral cortex, brain stem, and cerebellum. Impulses synapse in the anterior horn (motor gray area) just before leaving the cord. This synaptic activity involves upper motor neurons, which are located within the cord, and lower motor neurons, which extend beyond the cord. Ascending (dorsal) roots transmit sensory impulses from the skin and viscera to the cord and CNS. Synaptic activity necessary for transmission for signals occurs at various levels within the cord. Dermatome charts provide a "map" of the area of skin supplied by the dorsal root to each spinal nerve [48].

Specific sensory and motor tracts have been identified within the spinal cord. These tracts, located in the white matter, are anterior, lateral, and posterior funiculi. These funiculi, further divided into tracts called fasciculi, carry similar types of nerve impulses to specific destinations [48].

THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system comprises two efferent subsystems: the sympathetic and parasympathetic subsystems. Organs influenced by the autonomic nervous system are controlled by one of these two subsystems [18].

Sympathetic Nervous System

Sympathetic nervous system impulses are transmitted to the periphery by tracts of sympathetic fibers containing cell bodies and dendrites that extend with the intermediolateral gray horns of the spinal cord from thoracic spinal nerve 1 to lumbar spinal nerve 2. Because of its location, the sympathetic nervous system has been referred to as the thoracolumbar division. Axons leave the cord with the anterior roots of the thoracic and first four lumbar spinal nerves. After exiting, they quickly join the sympathetic trunk via white rami. The sympathetic trunks located on both sides of the cord extend from the second cervical vertebrae to the coccyx. The axons, upon entering the trunks, extend branches up and down the chain. The sympathetic nervous system preganglionic axons terminate on many postsynaptic ganglia present in organs [18].

Parasympathetic Nervous System

Cell bodies of the preganglionic neurons of the parasympathetic nervous system are located in two areas. The nuclei of CN III, VII, and X are located in the brain stem and the lateral gray columns of the sacral cord. In the sacral region, parasympathetic axons are present in spinal nerves. Because of these anatomic locations, the parasympathetic nervous system has been referred to as the craniosacral division [25; 26].

THE RETICULAR ACTIVATING SYSTEM

The reticular activating system is composed of a diffuse system of neurons extending through the medulla, pons, midbrain, diencephalon, and cortex. Afferent and efferent connections also exist between the cerebellum and spinal cord [7; 10].

The reticular activating system regulates spinal motor activity as well as voluntary and reflex muscle activity. Projections to the diencephalon and cortex effect and maintain arousal and alerting states. In addition to maintaining wakefulness, this system also participates in the regulation of sensory input from the periphery, regulation of respiration, and vasomotor activity [25; 26].

MOTOR FUNCTION

Effective skeletal muscle function involves many components of the CNS and peripheral nervous system. Muscle function requires the perception and interpretation of sensory stimuli and an intact motor system to initiate and carry out muscle contraction. Areas of the CNS involved in motor function include the premotor cortex, the primary motor area, pyramidal and extrapyramidal tracts, basal ganglia, thalamus, brain stem, spinal cord, and cerebellum [48].

The premotor cortex (associative cortex), positioned just anterior to the major motor strip, is involved in muscle activities that produce hand skills, voluntary eye movements, eyelid blinking, and vocalization. To appreciate the complexity of the functions carried out by the premotor cortex, consider the many coordinated activities needed to speak. Speaking requires groups of muscles in the tongue, larynx, pharynx, and chest to contract and relax in carefully programmed sequences. Function of the premotor area requires intact connections with the sensory association areas of the parietal lobe, temporal lobe, frontal lobe, occipital lobe, components of the basal ganglia, primary motor cortex, thalamus, brain stem, and spinal cord [48].

The primary motor area is believed responsible for the initiation of movement by individual groups of muscles, such as those involved in the movement of the fingers, toes, and mouth. The cross section of the precentral gyrus illustrates specific areas of the primary motor area identified as initiating willed movement by various muscles. A large amount of gray matter is allocated to muscle groups involved in complex movements of the hands and mouth [48].

Nerve cells of the major motor strip and their conducting fibers make up the pyramidal (corticospinal) motor system. Nerve fibers descend from the motor strip through the internal capsule, midbrain, and pons to the medulla oblongata, where the pyramidal fibers cross. After crossing, the fibers descend in the spinal cord to appropriate levels. Most pyramidal fibers descend via the lateral corticospinal tracts to ventral horns of gray matter in the cord. Some motor fiber travel via ventral corticospinal tracts [48].

Extrapyramidal motor tracts are most complex in their arrangement and synaptic activity in the cerebrum and brain stem. A functional (rather than anatomic) unit, extrapyramidal tracts are involved in maintaining balance and posture by facilitating some muscle movements and inhibiting others. Movements initiated in one hemisphere influence movements on the opposite side of the body. The basal ganglia are part of the extrapyramidal tract. In addition, the thalamus, subthalamus, substantial nigra, and red nucleus have roles in motor function. Multiple connections exist among all of these areas. A second pathway allows for feedback control of extrapyramidal motor activity [48].

The basal ganglia have three motor functions. A major responsibility of the basal ganglia as a whole is believed to be the inhibition of postural muscle tone. The caudate nucleus and putamen, collectively referred to as the striate body, are thought to initiate and regulate gross intention movements such as body posture and major arm movements. This regulation involves pyramidal and extrapyramidal pathways. The globus pallidus is believed to provide background muscle tone for intended movements initiated by the striate body or the cerebral cortex (e.g., the muscle contractions needed to support the arm and trunk while using a tennis racket) [48].

Final pathways for extrapyramidal signals into the cord are the reticulospinal tracts that lie in other ventral and lateral tracts of the cord. Also involved in transmission to a lesser degree are the rubrospinal, tectospinal, vestibulospinal, and possibly olivospinal tracts [48].

PROTECTION AND MAINTENANCE OF THE CNS

What is the middle layer of the meninges?

Understanding the complex capabilities of the nervous system allows for an appreciation of the system's means of protection and maintenance. Recognizing the safeguards of the bony cranial vault and vertebral column is easy. Less obvious but also valuable is the protection provided by the hair, skin, scalp, fascia, muscle, meninges, fluid cushioning, and complex vascular supply. The superficial structures help to limit injuries from external trauma, and the ventricular and vascular systems provide a reinforcement for optimal neuronal function [56].

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The meninges in the cranial vault and vertebral column protect the CNS from physical harm and support the CSF system and circulation. The dura mater, the outermost layer of meninges, forms a double layer over the brain tissue. Its outer layer is an inner periosteal lining for the skull and vertebral canal. In the cranium, the inner layer of dura, for the most part fused with the outer layer, helps to secure the brain to the cranial vault. To provide extra support and protection, the inner layer of dura separates in areas, dipping down between the longitudinal fissures, between the cerebellar hemispheres, and passing over the pituitary glands nestled in the sella turcica. In other areas, dura layers separate to form venous sinuses that collect and carry venous blood away from the brain. Arachnoid processes (villi) project into the dural sinuses [56].

In the spinal cord, the inner layer of dura is continuous with the spinal dura mater. The spinal dura extends to the second sacral vertebrae, where it joins with the external filum terminal and attaches to the back of the first segment of the coccyx. The middle layer of the meninges, the arachnoid, is a thin, fibrous membrane that adheres closely to the inner surface of the dura, allowing only a narrow space between the two. The inner layer of the meninges, the pia mater, adheres so closely to the brain that it follows the contour of the fissures and sulci. The space between the pia mater and arachnoid is bridged with weblike strands of arachnoid called trabeculae. A rich network of pia blood vessels extends into the brain. The area between the arachnoid and pia mater is called the subarachnoid space. Located here are arteries, veins, arachnoid trabeculae, and CSF. Within the spinal cord, fibrous bridges join the pia mater with the arachnoid and dura mater. These bridges, known as denticulate ligaments, help to stabilize the cord within the spinal canal [56].

THE CEREBROSPINAL FLUID SYSTEM

The CSF protects the brain and spinal cord by supporting the tissues, acting as a shock absorber, and serving as a medium for the transfer of elements from the bloodstream to nervous system tissues. CSF flows through the elaborate ventricular system in the brain and through the subarachnoid space surrounding the brain and spinal cord. Two large ventricles are positioned in each cerebral hemisphere. Their central portions extend in the parietal lobes. The anterior horns extend into the temporal lobes, and the posterior horns project into the occipital lobes. A small third ventricle lies below and communicates with each lateral ventricle via a small channel known as the foramen of Monro. The thalamus forms the lateral walls of the third ventricle. The third ventricle is connected via the cerebral aqueduct to the fourth ventricle, which lies below. The pons and medulla are positioned below the fourth ventricle. The cerebellum lies above [56].

CSF flows from the ventricular system to the arachnoid space of the brain and spinal cord by way of the lateral aperture (foramina of Luschka) and the medial aperture (foramen of Magendie). CSF is constantly being produced by capillary tufts called choroid plexuses, located in the ventricles. Arachnoid villi, projecting into the dural sinuses, provide routes for the reabsorption of CSF into the venous circulation [56].

THE BLOOD-BRAIN BARRIER

The blood-brain barrier theory stems from observations that only water, oxygen, carbon dioxide, and alcohol can readily enter or leave the capillaries of the CNS. Large molecules penetrate slowly through special systems or not at all. This protective barrier is believed to prevent sudden, extreme fluctuations in the composition of CNS tissue fluid while allowing nutrients to pass. The blood-brain barrier is thought to be formed within the capillaries by a continuous layer of endothelial cells connected by tight junctions, with a basement membrane surrounding the endothelium. Astrocytes that lie in close apposition are not considered part of this barrier [25; 26].

The blood-brain barrier protects most of the brain and cord tissue. Exceptions include the pineal body and the posterior lobe of the hypophysis, which are believed to be nourished by vessels with fenestrated endothelia that provide specific sites for the transfer of proteins and solutes irrespective of molecular size and lipid solubility. Tight junctions at the intracellular clefts of the choroid epithelium serve as the blood-CSF barrier in the vascular choroid plexuses of the CSF system [25; 26].

CENTRAL NERVOUS SYSTEM CIRCULATION

The viability and functioning of the CNS depends on a rich and continuous blood supply. The brain utilizes approximately 20% of the body's oxygen supply and requires about 400 kcal of glucose per day. The average cerebral blood flow is about 750 mL per minute [56].

The external carotid arteries supply the scalp and parts of the head and neck. Secondary branches of the external carotids (the middle meningeal arteries) supply blood to the meninges of the brain. The right and left internal carotid arteries, after passing through the carotid canals, branch into the anterior cerebral arteries and middle cerebral arteries at the level of the optic chiasm. The right and left anterior cerebral arteries are connected by the small anterior communicating artery to form the anterior portion of the circle of Willis. Anterior cerebral arteries perfuse the caudate and putamen nuclei of the basal ganglia, the corpus callosum, and portions of the internal capsule and frontal and adrenal lobes. The middle cerebral arteries are the major supplier of blood to the precentral and postcentral gyri and feed portions of the temporal, parietal, and frontal lobes [56].

The vertebral arteries, whose source is the subclavian artery, travel to the brain via the foramina of the cervical vertebrae and the foramen magnum. Posterior communicating arteries extending back from the internal carotid arteries complete the anastomosis with the posterior cerebral arteries to form the circle of Willis. This anastomosis, intended to maintain circulation to the brain tissue if one of the vessels closes, is not always functional. Other vessels providing collateral circulation are vessels at the base of the brain; small pial anastomotic branches on the surface; external carotids to the eyes; and anterior, middle, and posterior cerebral anastomoses on the surface of the brain [56].

Passage of venous blood from surface and deep brain tissue takes place via thick veins lacking valves. The blood flows into the dural sinuses and then drains into the internal jugular veins. The superior sagittal sinus serves as a major route for the removal of the constantly forming CSF. The cavernous sinus drains blood from the eye, orbit, and face, while the transverse sinus lies close to the ear [56].

REGULATION OF CEREBRAL BLOOD FLOW

What factors have a direct and potent effect on cerebral blood flow?

Control of blood flow in the CNS is essential for viability and optional function. The body has several built-in mechanisms to maintain effective circulation.

Three major factors that have a direct and potent effect on cerebral blood flow are elevations in concentrations of carbon dioxide, hydrogen ions, and oxygen. The increase in hydrogen ion concentration causes vasodilation of the cerebral vessels. Vasomotor reflex response that affects the body's general vascular perfusion also affects the perfusion of blood in the CNS. Vasomotor centers in the pons and medulla maintain vascular tone through impulses transmitted via the spinal cord to all blood vessels in the body. The reticular areas of the brain stem and hypothalamus have both excitatory and inhibitory effects on vasomotor activity. The hypothalamus also influences vasoconstriction activity through excitatory or inhibitory action on the vasomotor centers. It also helps to regulate total body water (and therefore blood pressure) by increasing or decreasing the release of antidiuretic hormone [56].

A severe drop in blood pressure to 50 mm Hg or less will result in ischemia in the vasomotor center. The resulting local increase in concentration of carbon dioxide causes a profound stimulation of the sympathetic nervous system, which initiates the constriction of blood vessels—some to the point of occlusion. This response, meant to shunt blood to the CNS, is known as the ischemic response [56].

Cushing phenomenon occurs when an increase in pressure in the CSF system equals the pressure in the cerebral vascular bed, hampering the flow of blood to the brain. At this point, the CNS ischemic response is initiated to raise the CNS blood pressure above the CSF pressure and facilitate blood flow to the brain [56].

SPINAL CORD CIRCULATION

As noted, multiple arteries feed the spinal cord. The vessels join, forming a complex network that supplies the vertebrae, periosteum, and dura. Branches supply the ventral and dorsal roots and penetrate deeply into the cord. Anterior and posterior spinal arteries extending the length of the cord originate from the carotid and vertebral arteries [56].

There are no valves in this venous network. As a result, blood flow varies depending on pressure. With elevation of intra-abdominal pressure, venous blood from the pelvic plexus passes into the vertebral venous channels. If the jugular vein is occluded, blood from the skull can drain via the vertebral channels. This venous plexus is believed to provide potential routes for metastasis of neoplasms [56].

PATHOPHYSIOLOGIC INFLUENCES AND EFFECTS

The CNS's complex structure and diverse functions predispose it to a multitude of pathologies, each capable of causing varying types and degrees of dysfunction. The protective structures and mechanisms are obviously not fail-proof. In fact, these structures often produce or contribute to nervous system trauma. The rigid skull and vertebral column allow little room for neuronal swelling, tumor growth, or circulatory congestion. Trauma may also occur when external forces drive the nervous tissue against the inside of the bony structures. Fractures and bony degenerative processes can perforate or crush neurons or supportive tissues [72].

The elaborate CSF system, designed to support and cushion the CNS, is subject to localized or generalized buildup if reabsorption is impeded. This extensive fluid system also provides routes for the spread of infection. Foramina of the skull and vertebral column, serving as avenues for the passage of blood vessels and nerves traveling to and from the periphery, also provide routes for micro-organisms into the CNS [72].

Meningeal tissues also present hazards as well as protection. With increases in intracranial pressure (ICP), herniation of brain tissue through the tentorial notch formed by the tough dura can seriously injure the brain stem and surrounding tissues. The dura mater, pia mater, and arachnoid fissures also provide extensive, uninterrupted routes for the spread of infection [72].

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The CNS's circulatory bed, so important in providing nourishment, provides routes for migrating micro-organisms and metastases from other parts of the body. Additional risks include an increase in ICP from hemorrhage and/or abnormal vascular structures, such as arteriovenous malformations or reflex vasodilation in response to hypoxia [72].

The neurons, nerves, and nerve tracts, with their long communication chains and multiple connections required for effective afferent and efferent activity, form the most complex part of the nervous system. Because they are present throughout the body, these structures are vulnerable to many pathologic elements, including alternations in the biochemical environmental, structural damage from disease, degeneration of the myelin sheath, trauma, and neurotransmitter abnormality [72].

Various pathologic changes can damage any or many of the components of the nervous system. Diagnosis of the cause or area affected is often difficult because of the inter-relationships of structures and their dependence on nerve fibers and neurotransmitters to carry signals to organs outside the CNS. Each component of a system and its innervated organs may be the cause of a particular symptom or deficit [72].

Nervous system damage often produces complex physical and mental disabilities. A stroke, for example, may produce spasticity rather than flaccid limbs. This spasticity can result in severe positioning problems and contractures. Personality changes can occur from physical deficits produced by the stroke or from psychologic stressors stemming from the disability [72].

INFLAMMATION AND INFECTIOUS PROCESSES

What are possible causes of CNS inflammation?

Inflammatory processes affecting nervous tissue alter the metabolism and thus the tissue's nutritional immune processes. Causes of CNS inflammation include trauma, lumbar punctures, and infectious processes, such as meningitis.

Inflammatory processes are known to attack the spinal cord's gray matter. Inflammation can occur in response to acute infections or can be part of a primary infectious process, such as poliomyelitis. These inflammatory processes can cause necrosis, emboli, or thrombotic complications. Sensory and motor deficits may result [72]. In herpes zoster (shingles), an acute unilateral and segmental inflammation of the dorsal root ganglia produces localized vesicular lesions, confined to one dermatome. Severe pain is experienced in the peripheral areas innervated by the inflamed ganglia [72].

TRAUMA, TUMORS, AND COMPRESSION

Trauma to the nervous system may result from external forces or elements in the nervous system. The skull and vertebral bodies can make it difficult to discover, locate, and assess trauma or physical changes. Symptoms indicating progressing damage may be subtle or lacking until the condition is too advanced to treat effectively [72].

At times, the system's response to the trauma causes more damage than the insult itself. This secondary damage occurs when edema, bleeding, and/or increased ICP destroy nervous tissue by compression or restriction of circulation. Edema results from trauma associated with contusions and lacerations, injury to capillary walls, or hematomas or tumors that obstruct venous blood outflow. Obstruction causes the blood to back up and fluid to move out of the capillaries. Expanding tumors cause an increase in ICP and edema, but they may also cause bleeding by damaging vessels. All of these elements carry the hazard of herniation through the tentorial notch or foramen magnum [72].

Spinal injuries may cause many of the same problems as cranial injuries, but the complexity of the vertebral column's structure and the concentration of neural tracts at all levels of the cord present special concerns. Injuries to the spinal cord are more common in areas of greater mobility, such as at the lower cervical spine (C4 through C7 and T1) and at the lumbar juncture (T12, L1, and L2). Vertebral injuries can cause compression of nerve roots by bone, ligaments, extruded disk material, hematomas, or disruption or overstretching of the neural tissue. Edema caused by trauma can compromise cord function [72].

DEGENERATIVE PROCESSES

Many nervous system diseases can be categorized as degenerative. Their causes vary, as do their severity and influence on lifestyle. For example, progressive muscular atrophy follows degeneration of lower motor neurons in the spinal cord that inhibits impulses that trigger muscle contraction. The upper motor neuron degeneration associated with amyotrophic lateral sclerosis (ALS) leads to impaired speech, chewing, swallowing, and breathing [72].

HEREDITARY AND CONGENITAL DISEASES

Hereditary diseases result from conferred genetic errors that affect development, maturation, and/or aging. These illnesses present varying degrees of risk to offspring both in the threat of developing the disease and carrying it on to another generation. For example, Huntington chorea is transmitted as an autosomal dominate trait, with each child born of a parent with this trait having a 50% chance of developing the disease [72].

Congenital defects causing CNS abnormalities or malfunctions may occur alone or in combination. Causes include a hereditary tendency, intrinsic factors (e.g., inadequate circulation for the embryo), and in-utero exposures to infectious diseases (e.g., rubella) [72].

RELATED SYSTEM INFLUENCES AND EFFECTS

As discussed, the CNS orchestrates activities to maintain body functions and homeostasis. Each major system has a role in maintaining homeostatic activity through the regulation of the body's biochemical environment. Alteration in system functions by disease or trauma can result in abnormal neuronal activity or tissue destruction within the CNS. For example, effective pumping by the heart is essential to nourish the CNS and remove waste. Along with the respiratory system, the cardiovascular system provides the oxygen necessary for function. Failure of these systems quickly results in neuronal death [2; 3].

The kidneys serve several functions to support the nervous system. They participate in the maintenance of blood pressure and in fluid, electrolyte, and acid-base balance. They also contribute to ensuring an adequate oxygen supply through the manufacture of erythropoietin, the hormone that stimulates the production of oxygen-carrying red blood cells [2; 3].

Gastrointestinal absorption maintains an adequate nutritional level of food elements, vitamins, and minerals. The liver also helps by ensuring an effective level of blood glucose and other nutrients and provides detoxification of drugs and other foreign substances [2; 3].

The endocrine system, which has multiple roles in the regulation of body function, influences metabolism, heart rate, water balance, and mental function. Pathology in this system can cause a variety of neurologic abnormalities or deficits [2; 3].

PSYCHOSOCIAL/LIFESTYLE INFLUENCES AND EFFECTS

Bodily changes with aging are the result of alterations in effector tissues, receptor systems, and impairment of the body's homeostatic regulatory system. There is also a gradual decline in activities requiring rapid sensory and motor coordination. Isometric muscle strength usually peaks at about 18 years of age and is maintained through the fifth decade, after which there is a gradual decline related to a decrease in number of muscle fibers and muscle atrophy [4; 27].

Although some changes in muscle mass occur in all aging persons, epidemiologic studies indicate that physical exercise contributes to longevity by decreasing the incidence of heart disease. Exercise may reverse or delay age-related changes in synaptic function and nerve-conduction velocity. Physical training in the elderly has been found to improve heart rate, cardiac output, blood pressure, and joint mobility and to decrease stiffness, although it does not improve pulmonary function [4; 27].

Intellectual performance, as measured by vocabulary and information comprehension, peaks between 20 and 30 years of age and is maintained through life or until the mid-70s, in the absence of disease. As with physical activity, individuals who continue to be active mentally can perform better than those who do not. However, the speed of central processing for mental functioning is impaired with age [4; 27].

The loss of vibratory perception in the lower extremities usually begins at about 50 years of age. Touch becomes significantly diminished due to skin changes and a decrease in the number of sensory receptors. This fact may be particularly significant to nurses during neurologic assessment. Corneal sensitivity, an accurate measurement of sensory perception, shows a decrease with age. Visual, auditory, gustatory, and olfactory senses are also diminished [4; 27].

Cortical size and blood flow decease over time. Brain weight peaks in the early 20s and then slowly declines. Along with the weight loss, the cortical area is reduced, with a broadening of sulci and a flattening of gyri. Cerebral blood flow in healthy adults is about 50–60 mL per minute per 100 g of tissue. (The base requirement for normal cortical function is about 40 mL per minute per 100 g tissue.) Between 30 and 70 years of age, the rate of cerebral blood flow decreases by approximately 20%. Alterations in blood flow from atherosclerosis, structural changes, and heart disease can easily decrease the oxygen supply, compromising neuronal function [4; 27].

Changes in autonomic nervous system function in the elderly can be seen in the deterioration of pupillary, cardiovascular, thermal, and secretory functions. It is not clear whether these changes are the result of peripheral or CNS changes [4; 27].

The elderly face the threat of altered homeostasis due to health problems unrelated to neurologic pathology. If an imbalance occurs in any other system, the nervous system can be affected. Even psychologic reactions to stress can alter neurologic function [4; 27].

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THE NURSING PROCESS FOR PATIENTS WITH CNS DYSFUNCTION

The pervasive influence of the CNS on mental and physical functions often complicates the analysis of neurologic symptoms. Identification of nervous system pathology can be difficult, because symptoms are often far removed from the source. For example, a cerebrovascular accident (CVA) can result in weakness in a lower extremity. Furthermore, similar symptoms and signs among some diseases of the CNS can confound diagnosis; for example, increased ICP can be a symptom of subarachnoid hemorrhage, stroke, or hydrocephalus [30; 40].

SUBJECTIVE DATA

Collection of subjective data from patients with CNS diseases can be difficult, because the disease often compromises the patient's ability to provide reliable information. In some instances, the patient will be unresponsive, unconscious, or unreliable as a historian. In these cases, family members, friends, or persons who were present when the problem arose should be consulted [30; 40].

The fear or apprehension that often accompanies diagnosis of neurologic disease can also limit patient disclosure. A review of the patient's long-term and recent health history is essential, because, as discussed, neurologic problems can result from diseases affecting other systems (e.g., peripheral neuropathy resulting from diabetes). Neurologic problems may also be misdiagnosed as psychiatric diseases. A variety of psychiatric and other health problems should be part of differential diagnosis, and comorbidities should be considered in planning treatment or care. For example, diet, pharmacotherapy, and intravenous therapy are more complex if a patient with neurologic dysfunction also has diabetes, cirrhosis, or renal disease [30; 40].

Head and Neck

Patient symptoms related to the head and neck should be carefully reviewed during the history of the present illness. Headaches are common in a variety of health problems, including stress, tumors, meningitis, or one of the many diseases causing increased ICP. Ear infections can spread into the brain via adjacent blood vessels and the mastoid bone of the skull. Infections of the scalp, paranasal sinuses, and the nasopharynx also present the risk of meningitis or encephalitis because of their proximity to venous sinuses, blood vessels, and foramina [30; 40].

Reported hearing loss may be the result of a conduction problem or of damage to CN VIII or cortical tissue. The patient should be asked about tinnitus (i.e., ringing or buzzing in the ears). Dizziness and vertigo are significant symptoms of tumors or degenerative changes in the vestibular branch of CN VIII, the brain stem, or the cerebellum [30; 40].

Uncontrolled head movements may be indicative of Parkinson disease, other extrapyramidal disease processes, or multiple sclerosis. A partial loss of motor function of the face can be the result of Bell palsy, CVA, or pathology affecting the nuclei of the brain stem. Loss of smell from insult to the olfactory bulbs or tracts can be related to shearing trauma, orbital fractures, or tumors; it may also be an early sign of Parkinson disease. Diseases causing visual changes include multiple sclerosis, myasthenia gravis, stroke, tumors, and trauma [30; 40].

Bowel and Bladder

What are fasciculations?

Bowel and bladder function is controlled by various components of the autonomic nervous system. For patients with known or suspected CNS deficits, it is important to thoroughly review symptoms such as constipation, urinary retention, and fecal and urinary incontinence. Symptoms of ataxia (i.e., lack of muscle coordination) should raise concern about degeneration of the posterior tracts of the spinal cord or cerebellar dysfunction. Spasticity of muscles occurs with CVA and multiple sclerosis. In contrast, flaccidity (i.e., deceased or absent muscle tone) can result from isolation of muscles from neuronal impulses. Fasciculations—fine, rapid, twitching movements originating in small groups of muscle fibers—are often present in patients with ALS [30; 40].

Motor Function

Changes in motor function are often unique to a disease process. Inquiry into changes in motor function should include thorough questioning about localized or generalized weakness. Asking specifically about difficulty arising from or turning in bed; flopping of ankles during walking; difficulty in lifting legs to go up and own steps or lifting objects; or problems keeping eyes open will help patients explain their symptoms better [30; 40].

As noted, ataxia may signal degeneration of the posterior tracts of the spinal cord or cerebellar dysfunction. Plasticity of muscles may occur with CVA or multiple sclerosis, which releases muscles from upper motor neuron control. In contrast, flaccidity can result from isolation of muscles from neuronal impulses [30; 40]. Twitching of the trapezius muscle may occur with lesions in the nucleus of CN XI [30; 40].

Reports of other abnormal movements include spasm of a muscle or muscle groups (myoclonus), as in Creutzfeldt-Jakob disease, dyskinesias, athetosis (i.e., slow, twisting, snakelike movements in the upper extremities), and dystonia (i.e., intense, irregular torsion and muscle spasms). Movement disorders can result from antipsychotic medications, such as chlorpromazine and haloperidol, or from Huntington chorea [30; 40].

Sensory Function

Diseases of the spinal cord's sensory tracts can alter or even prevent transmission of stimuli to the brain for interpretation. Symptoms of this pathology include numbness, tingling, pain, increased or decreased sensitivity to touch, and alteration in perception of cold and heat. Sharp, lightning-like root pain occurs with lesions of the dorsal roots of the spinal nerves. This pain may result from ruptured disks, cord tumors, fractures, inflammatory diseases of the vertebrae, or meningitis [30; 40].

OBJECTIVE DATA

A thorough neurologic assessment of patients with probable CNS disease is important initially and often throughout the nurse-patient interaction. Comprehensive baseline data assist in effective evaluation of the patient's changing status. In addition to the formal assessment, frequent contact with the patient during treatment and activities of daily living allows for closer observation [30; 40].

Physical Assessment

The patient's mental status is an important component of the neurologic assessment, providing valuable insights into the cause of disease and its effect on the body. Determination of level of consciousness is often used to evaluate improvement or decline of health status in patients with traumatic brain injury or tumors [30; 40; 41].

Assessment of level of consciousness begins with noting the degree of alertness. Is the patient awake and alert? If sleeping, is the patient aroused by verbal stimuli or tactile stimulation, such as touch or gentle shaking, or does the patient respond only to anxious stimuli? After arousal, is alertness maintained after the stimulus is removed? Does the patient appear drowsy, restless, irritable, or combative? The patient should be questioned regarding time, place, person, and self. If the patient is becoming disoriented, awareness of time will usually be lost first, then place, then person, and last self. Inappropriate responses to such questioning may not necessarily indicate mental dysfunction. The patient may fail to respond appropriately because of a language barrier, impaired hearing or vision, or some degree of expressive or receptive dysphasia. Patients who have undergone trauma may be confused about time or place because of a period of unconsciousness or the rapidity of events. The patient transferred from another hospital or even from another unit may have trouble keeping up with the changes. This is especially true of the elderly [11; 41].

The patient should also be asked to follow simple commands, such as "squeeze my hand," "hold up your arm," or "wiggle your toes." The response permits assessment of motor and mental function. If the patient does not respond to verbal or tactile stimulation, noxious or painful stimulus may be required. As a general rule, the least invasive/painful but effective stimulus should be used. Even in unconscious patients, noxious stimuli may cause a precipitous rise in blood pressure [11; 41].

Charting should include the stimulus used as well as a description of the patient's response to it. Responses are casually classified as appropriate, inappropriate, or absent. In an appropriate response, the patient localizes the unpleasant stimulus and attempts to withdraw from it or push it away. An inappropriate response involves random or purposeless movements and decerebrate or decorticate posturing. In extreme situations, no response can be elicited and the patient remains flaccid. Because subtle changes in level of consciousness can be significant, precise documentation and clear communication are essential. Avoid words like "confused," "stuporous," and "comatose." Instead, describe the patient's behavior, what is said, and what can or cannot be done. At change of shift, it may be especially beneficial for the nurse coming on duty and the nurse reporting off duty to do an assessment together. In this way, the nurse about to assume responsibility for the patient has a clearer picture of the patient's condition and subtle/minor but significant changes are less likely to be missed or misinterpreted [11; 41].

The Glasgow Coma Scale is an objective measure of level of consciousness that can also be somewhat predictive of recovery. Eye, motor, and verbal responses are measured. Coma is defined as a score of 7 or less. With a score of 3 or 4, there is an 85% chance of dying or remaining vegetative. A score greater than 11 is associated with an 85% chance of moderate disability or good recovery. Response to pain is also significant in determining the prognosis [11; 41].

Station and Gait

What motor response is indicative of cortical damage?

Observation of the patient's station (i.e., manner of standing) and gait can provide useful insight. A decortication response is indicative of cortical damage, and unusual gait, stance, or settling posture can result from motor or sensory deficits. With decorticate posturing, the patient demonstrators hyperflexion of the upper extremities and hyperextension of the lower extremities. With decerebrate posturing, both the upper and lower extremities are hyperextended. This response indicates brain-stem injury [11; 41]. Postures can also be influenced by mental and physical problems.

Meningeal Irritation

Assessment for nuchal rigidity, Kernig sign, and Brudzinski sign aid in diagnosing meningeal irritation associated with meningitis or subarachnoid hemorrhage. In nuchal rigidity, neck flexion is limited by involuntary muscle spasm and the patient is unable to place the chin on the chest [41].

To test for Kernig and Brudzinski signs, the patient is in the supine position. For Kernig sign, one hip is flexed to 90° with the knee also flexed to 90°. If meningeal irritation is present, the patient in this position will be unable to extend the knee

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past 90° without pain. To test for Brudzinski sign, the patient is supine with the legs extended. When the examiner flexes the patient's neck, the hips and knees will spontaneously flex to avoid the accompanying pain if meningeal irritability is present [41].

DIAGNOSTIC STUDIES

As discussed, diagnosis is often complicated because the CNS is contained within the skull and vertebral canal. For this reason, most diagnostic studies for neurologic disease are invasive. Careful patient preparation is necessary for all diagnostic studies. The invasiveness of neurologic tests and the consequences of misdiagnosis increase the importance of patient teaching and nursing care before and after studies are conducted [5; 6; 8].

Most laboratory studies specific for assessment of neurologic function are based on the contents of the CSF or its pressure within the CNS. Other laboratory studies, such as analysis of blood samples, are used to determine whether malfunction of other body systems is compromising CNS function. For example, serum iron and hemoglobin tests can help determine if anemia is reducing the brain's oxygen supply and altering CNS function [5; 6; 8].

X-Rays

X-rays of the skull are used as a basic, noninvasive screening for patients with suspected trauma or neoplasm. They can also reveal pathologic changes, such as pituitary gland tumors, and detect calcified abnormalities or abnormal position of the calcified pineal gland [5; 6; 8].

Spinal radiography may reveal changes in spinal bones resulting from fractures, tumors, or infections. It may also show the bony ridges and spur formations characteristic of osteoarthritis and help to identify congenital defects [5; 6; 8]

Nursing Implications

Before x-rays are taken, the purpose of the procedure and the systems involved should be explained to the patient. Tangled or braided hair is combed, and pins and wigs are removed. Ocular prostheses can produce confusing shadows in a radiograph, so their presence should be noted [17].

Electroencephalography

Electroencephalography (EEG) is essentially a noninvasive test that records a portion of the brain's electrical activity. The EEG is valued for its ability to reveal abnormal brainwave patterns that help in diagnosing seizure disorders, brain tumors, abscesses, and psychiatric disorders. Diagnosis is made by evaluating patterns and characteristics of brain waves recorded, along with the patient's clinical state. An absence of brain waves generally establishes brain death; however, acute drug intoxication or severe hypothermia can also cause a flat EEG [5; 6; 8]

To conduct an EEG, the patient is placed in a bed or on a lounge chair in a quiet, secluded area. Surface electrodes, or occasionally needle electrodes, are positioned on or in the scalp. The patient is instructed to close his or her eyes, relax, and rest quietly. Various stimuli are introduced to determine whether seizure activity can be produced. The patient may be asked to hyperventilate for three minutes, to watch a flashing light, to endure a sensory stimulus (e.g., a minor electrical shock), to observe a back-and-white checkerboard image, and/or to listen to sounds through earphones. The patient is observed carefully and protected if seizure activity occurs. If a sleep EEG is requested, the patient will be instructed to stay awake the night before the test. Medication may be administered to promote sleep [5; 6; 8].

Nursing Implications

Patients scheduled for EEG should be instructed to eat meals as usual, with the exception of coffee, tea, cocoa, and cola, which may be withheld because of their stimulant effects. Medications that may influence the test are often withheld, including anticonvulsants, tranquilizers, barbiturates, or sedatives. Hair should be clean and free from oils, sprays, or pins [17]

An explanation of the procedure and its purpose, the function of the electrodes, and the length of the test will help the patient relax. The test usually takes 40 to 60 minutes, with pretest and post-test care taking another hour. Following test completion, patients may require assistance removing electrode paste from their hair. During this time, it is important to observe for seizures and recovery from sedation, if given during the test. Vital signs and neurologic signs are also assessed, as appropriate [17]. The physician's order for resumption of medications should be reviewed with the patient.

Computed Tomography

Computed tomography (CT) is used to diagnose intracranial locations of hemorrhage and spinal cord lesions. Scans are also used to monitor the effects of surgery, radiotherapy, or chemotherapy and to reveal vascular displacement, hematomas, cerebral atrophy, infarction, edema, and hydrocephalus. An iodinated contrast dye may be administered to make large blood vessels visible or to define lesions. Administered intravenously, the dye increases the blood density and delineates intracranial masses [5; 6; 8].

Nursing Implications

Before a CT is done, the purpose of the procedure should be explained to the patient. If no contrast medium is used, restriction of food and drink is not necessary. If dye is used, the patient should fast for four to six hours to prevent emesis if nausea occurs. Before administering a contrast dye, any allergies to shellfish, iodine, or contrast media should be identified, as dye may be contraindicated in these patients. Skin testing to determine allergy may be indicated [17].

Patients benefit from a knowledge of the details of the procedure, including special positioning, noise emitted by the machine, and length of test. Some machines require the patient to be strapped to the table, which moves into a gantry during the test. Loud clacking or knocking noises are normally emitted during this time. The test takes 15 to 30 minutes if no dye is used; with dye, the time is doubled. Patients receiving the dye should know that it is normal to feel flushed and warm and that sometimes a headache, salty taste, or nausea occurs [17].

Positron Emission Tomography

Positron emission tomography (PET) is a noninvasive nuclear-imaging technique available in large medical centers. It is used to study oxygen uptake, blood flow, and glucose utilization in patients with cerebrovascular disease, seizure disorders, cardiovascular disease, and some degenerative disorders. With PET, viable tissue can be discriminated from nonviable tissue and the amount of nutritional blood flow to an area can be identified. PET is often combined with CT [5; 6; 8].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is possible because hydrogen nuclei in abnormal tissues behave differently in a magnetic field. A computer can manipulate these differences into a detailed picture of the organ under study. This noninvasive study does not require contrast media or exposure to radiation. The patient lies supine in a large magnet. Bone tissue is not visualized with MRI, but soft tissue close to bone is easily viewed, making MRI useful for assessing problems of the skull and spine [5; 6; 8].

Radionuclide Scan of the Brain

A radionuclide scan detects intracranial masses, vascular lesions, and areas of ischemia, infarction, and hemorrhage. A radionuclide, usually administered intravenously, accumulates in affected areas if the blood-brain barrier has been compromised. Oral or intra-arterial administration can also be used. Some scans also include oscilloscope scanning of the carotid and cerebral blood flow. After the radioactive isotope has circulated for at least one hour, a scanner records the accumulation of isotopes. Another scan can be done three to four hours after injection [5; 6; 8].

Nursing Implications

Allergies to the isotope should be assessed prior to a radionuclide scan. No dietary or fluid restrictions are required. Potassium perchlorate may be given to block uptake of the isotope by the thyroid, choroid plexus, and salivary glands. Patient education should include the steps of the procedure, the time requirement, and the fact that the injection will be the only discomfort. All jewelry and metal objects should be removed. To prevent patient apprehension, explain that the radioisotope is harmless to self and others and is quickly excreted from the body. This test is often combined with CT and angiography to help confirm the diagnosis [17].

Cerebral Angiography

Cerebral angiography (also referred to as intra-arterial digital subtraction angiography) is used to diagnose intracranial lesions. With this approach, a radiopaque contrast medium is injected into blood vessels of the head and neck to allow visualization of intracranial and extracranial vessels on x-ray. Cerebral angiography can reveal aneurysms, arteriovenous malformations, and displacement of vessels by masses, edema, or herniation. The test is also used during surgery to check the position and integrity of aneurysm clips [5; 6; 8].

Contrast material used with cerebral angiography can be injected into a variety of sites. The most common are the carotid, brachial, and femoral arteries. Catheters are often used to facilitate access. Injection is done under local or general anesthesia in the operating room or in a special procedures area where resuscitation equipment is available. This test is contraindicated in patients with renal, hepatic, thyroid, or clotting disorders as well as in those who are hypersensitive to iodine or contrast materials [5; 6; 8].

Nursing Implications

Patient education includes a review of the procedure's purpose. The risks of the test should be explained, including CVA, thrombus, allergic reactions, seizures, pulmonary emboli, and visual disturbances. Informed consent forms should be signed. To reduce apprehension, patients should be walked through the procedure and informed that a supine position, with the head secured to prevent movement, will be required throughout the test, which lasts approximately two hours. Periodic assessment of heart function and blood pressure is routine [17].

Careful explanation of sensations expected when the dye is injected is essential to reduce fear; injections of contrast medium into the blood vessels of the head can be painful. Sensations vary from warmth to severe burning behind the eyes and in the jaw, teeth, tongue, and lips. Even fillings in the teeth can feel warm. The sensation of heat lasts four to six seconds after the dye is injected. More than one injection may be necessary [17].

Nursing care also includes collection of baseline data and preparation of the patient. Vital signs and neurologic status should be recorded and pulses distal to the puncture site marked to facilitate assessment after the procedure. If the carotid site is used, documenting neck measurements allows for comparison after the test. Hairpins, nets, and dentures should be removed. The patient should also void before the test begins [17].

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Preprocedure medications may include anti-anxiety agents (to help the patient relax) and atropine sulfate to protect against a reflex response (hypotension, syncope, and bradycardia) by the carotid artery. Patients should be well-hydrated to promote clearance of the dye by the kidneys but otherwise should fast for six to eight hours before the test. The injection site(s) should be shaved and prepared with an antiseptic solution. Local anesthetic is usually given before insertion of the catheter or needle [17].

Immediately following the removal of the needle or catheter from the artery, pressure should be applied to the puncture site for 15 minutes to prevent hemorrhage and development of a hematoma. Vital signs and neurologic checks are conducted and recorded every hour for 4 hours, then every 4 hours for 24 hours. Intake and output should also be noted [17].

The puncture site, surrounding areas, and distal extremities should be carefully monitored. The puncture site should be assessed for redness, swelling, and superficial-to-deep hematoma. A pressure dressing and ice bag may decrease the risk of bleeding and discomfort. When the carotid artery is used, the patient should be monitored for respiratory distress and swallowing difficulty, which may indicate excessive edema or an expanding hematoma. For puncture of the femoral or brachial site, pulses in the distal limb are monitored for 12 hours and the limb is maintained in an extended position and observed for normal temperature, color, and sensation. Blood pressure is not monitored in the involved arm. A physician should be alerted immediately of any untoward effects. The patient should rest quietly in bed for two to four hours after the procedure, with food and medications given as tolerated [17].

Pneumoencephalography

Pneumoencephalography (PEG) is a radiographic study used to detect small tumors of the cerebral ventricles, cisterns, and intraspinal and intracranial subarachnoid spaces and to visualize the pituitary gland, which is positioned below the ventricles. PEG is seldomly used now, because less painful and less dangerous tests are available. Its use is generally limited to research settings. PEG is contraindicated if there is risk of herniation or if a lumber puncture has been done within the past nine days [5; 6; 8].

PEG is carried out in a special procedures room. The patient is strapped into a motorized chair that can be moved in various directions. A contrast gas (oxygen, room air, or other gas) is injected into the subarachnoid space via a lumbar puncture or via a cisternal or ventricular tap. Patients are normally sedated during the procedure; those who cannot remain still because of anxiety or motor dysfunction are anesthetized [5; 6; 8].

Initially, a small amount of gas is injected and an x-ray taken to make the brain stem visible. Then, small amounts of CSF are removed and gas injected until 25–30 mL of CSF has been replaced. With each injection of gas, the patient's chair is somersaulted to help move gas into the ventricles. (Some institutions do not use a chair but have the patients assume various positions on an examination table.) The needle is removed, and a series of x-rays is taken. The study takes one to two hours [5; 6; 8].

Electromyography and Nerve Conduction Studies

Electromyography (EMG) records electrical activity in muscle at rest and during contraction. Findings allow differentiation of muscle disease from lower motor neuron dysfunction. Recorded electrical patterns can be diagnostic of various diseases, including myositis, dystrophy, and myasthenia gravis. EMG can be used to assess function in the spinal cord, nerve root, nerve plexus, peripheral nerves, and/or myoneural junction, and the test can detect and measure regeneration of nerve and muscle before clinical signs appear. This information can be used to predict recovery [5; 6; 8].

A nerve conduction test is often administered along with an EMG. This test measures the strength and speed of conduction in the sensory and motor fibers of peripheral nerves. Motor conduction studies are valued for assessing nerve damage when minor symptoms of motor weakness or atrophy exist. Sensory fiber conduction rates are especially useful for diagnosing neuropathies in patients with diabetes, alcoholism, metabolic or nutritional disorders, and trauma. Sensory nerve fiber conduction is assessed with a single electrical stimulus. The action potential is recorded by an electrode placed on the skin where the nerve is close to the surface. The recorded conduction time is compared with established norms for healthy nerves [5; 6; 8].

Nursing Implications

Fluid or food intake is not restricted prior to EMG or nerve conduction study. However, in some cases cigarettes, coffee, tea, cola, or medications may be restricted before the test. A written consent is obtained [17].

Patients should be educated about the time EMG takes (one hour or more), steps of the procedure, the need to insert a needle into the muscle, and the changing of needle position, which may cause discomfort. Patients will need to cooperate in flexing and releasing muscles during the test [17].

Residual pain after the test is treated with warm compresses and prescribed analgesics. If medications were withheld for the test, the physician will indicate when they should be resumed [17].

Lumbar Puncture

When a lumbar puncture is done, where does the needle usually enter the subarachnoid space?

Lumbar puncture, also referred to as a spinal tap, is an invasive procedure used to obtain samples of CSF, to measure CSF pressure, and therapeutically to reduce pressure in conditions such as subarachnoid hemorrhage. Lumbar puncture is also done to instill antibiotics, steroids, and/or dye or oxygen for diagnostic studies and to evaluate CSF flow [5; 6; 8].

Lumbar puncture can be done at the bedside or in the diagnostic lab. The procedure is done with the patient positioned to one side (typically the left) with head and knees flexed toward the abdomen. The patient is assisted in maintaining this position, which separates the vertebrae, allowing the needle to enter the subarachnoid space at the level L3-to-L4 or L4-to-L5. Aseptic technique is required [5; 6; 8]. In some patients, particularly those who are overweight, sitting and leaning forward may provide better access.

Contraindications for lumbar puncture include skin lesions in the lumbar area, epidural infection or abscess, and lumbar deformity near the puncture site. Lumbar puncture is also contraindicated with increased ICP because of the heightened risk of brain compression or herniation through the tentorial hiatus when the spinal fluid pressure is lowered. In some circumstances, such as when meningitis is suspected, the need to establish a diagnosis outweighs the dangers of the procedure [5; 6; 8].

Possible complications of lumbar puncture include headache, transitory low back pain and root irritation, and meningitis or abscess. Post-lumbar puncture headache is believed to result from the loss of CSF at the puncture site, which lowers the spinal fluid pressure and places tension on the intracranial structures [5; 6; 8].

Nursing Implications

The purpose of the test and steps of the procedure should be thoroughly explained to the patient, emphasizing the importance of lying still in the flexed position during the lumbar puncture. Patients should be advised of the brief episodes of pain when the anesthetic and spinal needle are inserted. A discussion of postprocedure activity is also helpful [17].

After a lumbar puncture, most physicians require the patient to remain recumbent, but turning should be encouraged. Forcing fluids will help to promote replacement of withdrawn spinal fluid. Headaches, experienced by many, can be treated with hydration, caffeine, and/or prescribed analgesics. Patients should be carefully monitored for signs of meningitis and drainage or discharge at the puncture site. Abnormal findings, such as the presence or absence of glucose and abnormal spinal fluid color, should be reported immediately [17].

Suboccipital Puncture

Suboccipital (cisternal) puncture is an alternative procedure for obtaining CSF when lumbar puncture is contraindicated. For this test, the patient's head should be flexed forward so the chin touches the chest. A short, beveled needle is inserted into the subarachnoid space of the cisternal magna. Suboccipital punctures are hazardous because of the proximity to the brain stem and the risk for subarachnoid hemorrhage [5; 6; 8]. Fluoroscopic guidance can help avoid these complications.

Nursing Implications

Preprocedure care for suboccipital puncture is the same as for lumbar puncture. Bed rest is usually maintained for several hours after the procedure. Respiratory and cardiac function is observed frequently because of the puncture's proximity to medullary centers controlling these functions. Headaches are uncommon [17].

Myelography

In a myelography, fluoroscopy and radiography are combined to study the subarachnoid space, spinal cord, and vertebral bodies. The test reveals spinal cord tumors, herniated or ruptured intervertebral disks, and nerve root injury. In this study, a lumbar puncture is used to replace a small amount of CSF with a radiopaque dye or gas. The patient is positioned on a movable table that tilts to various positions to allow the flow of dye through the subarachnoid space. Abnormalities in flow provide the diagnostic information [5; 6; 8].

Nursing Implications

Prior to myelography, it is important to assess the patient for allergies to iodine, shellfish, or radiographic dye, and to obtain a written consent for the patient. Preprocedure fasting for four to eight hours is necessary, and baseline vital signs and neurologic status should be recorded. An enema may be ordered to reduce x-ray shadows. A sedative (to relax the patient) and atropine (to reduce secretions) may be ordered [17].

Patient education should cover information about the procedure, including the length; the purpose of the lumbar puncture (or suboccipital puncture, if lumbar deformity or skin infection is present); the usual response to the dye, which may include flushing, a warm sensation, a salty taste, headache, nausea, and vomiting; the positioning and strapping to the table; and the need to tilt the table during the study and to remove the dye [17].

After the procedure, the patient's head should be positioned to keep the dye from entering the cranium. Vital signs and neurologic status, including nuchal rigidity, nausea, vomiting, and reports of back pain and spasms, should be monitored for at least 24 hours or as indicated by policy. Headache may be treated by positioning and analgesics. Patients should be encouraged to consume plenty of fluids while their intake, output, and ability to void are monitored [17].

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CSF Analysis

Because CSF is in contact with the components of the CNS, it can be valuable in the diagnosis and evaluation of CNS disease progression or healing process. CSF is colorless and consists of water and traces of protein, glucose, sodium, chloride, and potassium. The average volume in adults ranges from 100–150 mL. CSF pressure in the supine patient ranges from 7–20 cm/H_2O. Fluid that is dark in color or even pink-tinged indicates hemorrhage or a cerebral bleed [5; 6; 8].

The collection and handling of CSF should be carefully controlled to ensure proper analysis. The fluid is collected in sterile tubes and delivered to the laboratory immediately. Some diagnostic evaluations require processing within one hour [5; 6; 8].

Certain analyses of CSF require special considerations. For example, the evaluation of the glucose level requires that a blood glucose level be obtained not more than three hours before the puncture. Because serum glucose levels are reflected in the CSF, an abnormal CSF level may be a reflection of the serum level, rather than a neurologic disease process. Similarly, CSF chloride levels can be affected by serum levels. Because of this influence, CSF chloride levels will not be valid if the patient has received IV therapy with electrolyte solutions prior to or during the lumbar puncture [5; 6; 8].

NURSING DIAGNOSES, PLANNING, AND IMPLEMENTATION

Careful gathering and analysis of patient information, physical findings, and diagnostic data are needed for all patients with suspected CNS dysfunction. Patients who have CNS conditions often require long periods of treatment and time to adapt to the changes in their lives brought on by the disease. These adaptations may involve physical and mental changes, including the reorganization of self-image and the adjustment of expectations of life. Specific nursing interventions depend on when care is sought for the disease process and how the individual responds physically and mentally to the illness [41].

INEFFECTIVE AIRWAY CLEARANCE

Patency of the respiratory tract depends on a person's ability to maintain proper positioning, effective functioning of the muscles of respiration, and healthy respiratory tract mucosa. Neurologic diseases often cause dulled consciousness, confusion, and decreased motor function, all of which can affect respiration. Patients may not be able to assume positions independently that keep the tongue from obstructing the airway. Disease processes that affect cranial nerve function (e.g., myasthenia gravis, ALS) or level of consciousness can make it difficult to swallow or cough to clear the airway of sputum, foreign objects, or vomitus [30; 40].

Ingestion of adequate fluids can be a problem for patients with neurologic problems as well. Those with cognitive impairment may forget to drink, and patients with communication problems may be unable to request fluids. Physical impairments may make drinking difficult or impossible. These situations can result in dehydration and drying and crusting of the mucosal tissue in the oropharyngeal area and respiratory tree, with related damage to mucous cells and cilia. This damage compromises an individual's normal phagocytic action and ability to expel organisms, increasing the risk of respiratory tract infections [30; 40].

Promoting Airway Clearance

What nursing interventions are recommended to promote airway clearance in patients with CNS dysfunction?

For the physically impaired or obtunded patient, careful positioning with pillows and special devices promotes drainage of secretions, maintains a patent airway, and reduces the risk of aspiration. This includes careful positioning during meals, supplemental oral intake, nasogastric feedings, and oral care. A suction machine should be at hand if choking is a risk or secretions are unmanageable. Active or passive range-of-motion exercises and frequent position changes help to promote mobilization of secretions [41].

Steps to ensure adequate hydration support healthy respiratory function both by promoting the elimination of secretions and the destruction of organisms. Careful, ongoing assessment of the oral pharyngeal mucosa, breath sounds, and activity to manage secretions is necessary because the patient's condition may change quickly and the change may not be obvious [41].

ALTERATION IN BOWEL ELIMINATION

Constipation

Many CNS diseases can cause constipation. Neurologic alterations can result in decreased fluid intake, decreased physical activity, impaired communication, inability to monitor bowel patterns, inability to initiate changes in diet to correct constipation, limitations in using toilet facilities, and increased dependence resulting in a lack of privacy [30; 40].

Diseases such as stroke, myasthenia gravis, and ALS may result in paralysis of the lips, tongue, mouth, pharynx, or larynx (bulbar paralysis). The resultant difficulty in swallowing frequently reduces fluid intake, making stools hard and difficult to pass [30; 40].

Immobility from motor neuron damage or deceased level of consciousness limits abdominal muscle contraction and bowel activity slows. Positioning constraints, as with spasticity or contractures, can prevent a patient from assuming positions that facilitate defecation. For example, being confined to bed for treatment of a lumbar disk problem often causes constipation brought about by both immobility and positioning constraints [30; 40].

Loss of toilet privacy frequently accompanies the physical disabilities of weakness, paralysis, and immobility. Embarrassment over exposure during toilet activities and related helplessness can hamper normal defecation [30; 40].

Special nursing techniques for the patient with limited motor function who needs to increase fluid intake to keep stools soft include special positioning and the use of special cups, straws, and other adaptive devices. Recognizing the patient's physical and mental deficits allows for effective planning and assistance. If the patient's communication is limited, family or friends may be able to suggest favored fluids and foods that will increase fluid intake and bulk to relieve or prevent constipation [41].

Incontinence

Bowel incontinence may accompany a wide variety of disease processes. Sphincter control can be lost because of cortical, spinal cord, or peripheral nerve damage; recovery of control may or may not be possible. Following brain trauma, patients may have temporary or chronic loss of bowel continence. Aphasia predisposes some patients to incontinence because they cannot express their need to defecate. Tube feedings and medications may cause diarrhea, which is more difficult to control [30; 40].

INEFFECTIVE BREATHING PATTERN

CNS diseases can interfere with the brain stem's regulation of respiratory function. Related changes in body function—decreased level of consciousness, immobility, obstruction of airway, and aspiration—can result in decreased ventilation, decreased gas exchange, and hypoxia. Hypoxia presents two threats: anoxia in vital neurons and dilation of cerebral vessels leading to an increase in ICP. Signs and symptoms include increased lethargy, rising blood pressure, and depressed respirations [30; 40]

Pathologic conditions producing an increase in ICP can lead to herniation, damaging respiratory centers in the brain stem. This trauma and other pathologies involving the brain stem, such as stoke or tumor, alter the rate, depth, and rhythm of respirations. Diseases, injuries, or infections affecting phrenic innervation of the diaphragm can result in loss of stimulus for breathing [30; 40].

Hyperventilation can result from problems such as encephalitis, drug overdose, and hypoxia. It can also be initiated by psychologic stress or pain, both common in patients with CNS diseases [30; 40].

ALTERATION IN CARDIAC OUTPUT

Impairment of cardiac output can follow injury to the brain stem's vasomotor center, which influences cardiac function via the autonomic nervous system. The brain stem's vasomotor center also controls blood pressure. With sharp elevation in blood pressure initiated to perfuse a severely edematous brain, the vasomotor center initiates a reflex slowing of the heart, reduces contractility, and produces vasodilation. Cardiac output can also be compromised by anoxia stemming from alterations in respiratory function [30; 40].

Decreases in vasomotor tone with various neurologic problems can affect cardiac function due to the decrease in blood returning to the heart. In addition, spinal cord injuries producing spinal shock severely decrease vasomotor tone. Orthostatic hypotension after long periods of bed rest is also the result of a loss of vasomotor tone [30; 40].

IMPAIRED COMMUNICATION

A variety of conditions affecting the CNS, including stroke, gunshot wounds, and carbon monoxide poisoning, can damage speech centers located in the dominant hemisphere. If Broca's area or the nerve fibers connecting Wernicke's area and Broca's area are damaged, speech may be severely limited, but understanding of one's own and others' speech will be intact. If Wernicke's area is damaged, speech may be fluent but nonsensical [30; 40].

Speech can also be impaired if cranial nerves responsible for movement of the lips, tongue, oral pharynx, and larynx are injured. Damage to spinal nerves that control respirations can also affect verbal communication [30; 40].

Destruction or swelling of neuronal tissue in the parietal, occipital, and/or temporal lobes impairs perception and interpretation of stimuli including touch, sight, and hearing. As such, aspects of awareness needed for communication can be altered [30; 40].

Limitations in motor function will impair nonverbal forms of communication, including writing, gesturing, facial expressions, and various postures that add expression to oral communication. Impaired nonverbal communication can influence how information is received, because gestures, facial expressions, and posturing enhance oral communication [30; 40].

IMPAIRED PHYSICAL MOBILITY

Hemiplegia from stroke, tumor, or spinal cord injury, or motor deficits from peripheral nerve injury may be obvious or subtle. Subtle limitations, such as decreases in range of motion, lesser involvement in activities of daily living, or unsteady gait, are often first identified by the nurse, especially in patients with progressive diseases. In extrapyramidal tract diseases, the impairment in mobility may be difficult to detect. Nevertheless, careful analysis may reveal clumsiness and limitations in movement resulting from tremors and rigidity [30; 40].

Mobility may also be compromised by cerebellar dysfunction, alterations in sensory perception, changes in mentation, and changes in mood and energy level. Cerebellar dysfunction can produce ataxia, uncoordinated movements, and limitations in depth perception. Damage to the parietal, temporal, or occipital lobes or to the sensory tract impairs an individual's ability to perceive and interact with the environment to

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varying degrees. Limitations from sensory deficits can often be difficult to determine and measure; careful observation and diagnostic testing are necessary [30; 40].

Activity levels frequently increase or decrease with alterations in mental function. Both states are potentially dangerous. Patients who are restless and confused may also have immobility if restraints are used to ensure safety. Body image changes that accompany neurologic diseases frequently lead to depression, fatigue, decreased participation in daily activities, and fewer interactions with the environment [30; 40].

ALTERATION IN NUTRITION

The physical, psychologic, and social factors accompanying neurologic diseases can have a profound effect on an individual's nutritional status. Common physical problems that may limit intake include lack of exercise, inability or awkwardness in self-feeding, social isolation, difficulty chewing and swallowing, fear of choking, and limited energy for eating [29; 30].

For the individual at home, physical and mental deficits can make buying food and preparing meals challenging. A limited income (because of illness-related unemployment and healthcare costs) can also influence the amount and type of food available. As a result, the quality and quantity of food consumed may be reduced [29; 30].

Sight, smell, taste, and touch—all important to an interest in eating—are altered by many CNS diseases. In addition, mental changes from injury to the cerebral cortex or the psychologic response to disease can diminish interest in eating [29; 30].

SELF-CARE DEFICIT

CNS diseases predispose patients to many types and degrees of self-care deficits. Planning effective care depends on determining how the following factors influence the treatments and activities planned for or by the patient [30; 40]:

- Cause of the illness
- Degree of influence on self-care
- Prognosis and expected outcomes
- The patient's personality and response to deficits
- The family's interest and ability to support the patient mentally and physically

ALTERATION IN SENSORY PERCEPTION

CNS dysfunction can change one's perception of the environment and spatial relations. The parietal, occipital, and temporal lobes all have major roles in the interpretation of messages received from peripheral nerves. The interdependence of these areas within the cerebral cortex and in the cerebellum, subcortical areas, brain stem, and peripheral nerves influences the patient's physical and mental interaction with the environment. Perceptual changes and deficits predispose the patient to injury, depression, confusion, fear, and isolation [30; 40].

SEXUAL DYSFUNCTION

Sexual dysfunction is relatively common in patients with CNS conditions and can result from spinal cord trauma, peripheral nerve trauma, or damage to the nerves necessary for sexual activities. Pharmacotherapy may also produce sexual dysfunction. Mental changes stemming from brain damage may result in inappropriate sexual behaviors [30; 40].

ALTERATION IN URINARY ELIMINATION

Urinary retention or incontinence can result from diseases affecting the cerebral cortex, spinal cord, and/or peripheral nervous system. Patients with CNS dysfunction often experience both a diminished awareness of bladder fullness and a decreased ability to empty the bladder. Alterations in consciousness from trauma, electrolyte imbalance, anoxia, and disease processes can produce temporary or permanent urinary incontinence [30; 40].

CONGENITAL DISORDERS AFFECTING THE CENTRAL NERVOUS SYSTEM

A congenital disorder of the CNS can be defined as a developmental defect. Although the causes of maldevelopments are often unknown, the majority are considered to result from the hereditary transmission of a chromosomal abnormality or are secondary to embryonic damage. The developing CNS in the fetus is particularly vulnerable to radiation effects, anoxia, metabolic diseases, and infections in the mother [14; 15].

CEREBRAL PALSY

Cerebral palsy is not a disease entity per se but a variety of neuromotor disorders resulting from cerebral hypoxia or damage to the nervous system in utero, at birth, or in early life; most cases are the result of damage that occurs before or during birth. Cerebral palsy occurs most often in infants born prematurely or after a difficult labor, at the rate of about 2 cases per 1,000 live births [42; 46]. Causal factors can be divided into four groups:

- Genetic defects associated with chromosomal abnormalities
- Prenatal factors, including:
  - Maternal infections (e.g., rubella, cytomegalovirus, toxoplasmosis)
  - Irradiation
  - Harmful drug intake
  - Malnutrition
  - Toxemia

  - Gestational diabetes
  - Rhesus (Rh) and ABO blood incompatibilities
- Prenatal factors causing anoxia of the brain, such as:
  - Difficult breech and midforceps deliveries
  - Improper anesthesia during labor and delivery
  - Premature birth
  - Low birth weight
- Postnatal factors causing injury to the neonate's brain, including:
  - Cerebral vascular lesions
  - Infections
  - Trauma
  - Malnutrition
  - Prolonged convulsive seizures

Developmental disorders are more frequent in infants of mothers younger than 20 or older than 35 years of age. Data from CT scanning confirm that perinatal and/or postnatal cerebral vascular bleeding is the major cause [42; 46].

Clinical Manifestations

The symptoms and signs of cerebral palsy are variable, ranging from mild muscle incoordination to severe spasticity. Intellectual performance is often hampered by seizures and speech, visual, hearing, and motor impairment. As a result, individuals with cerebral palsy often develop serious emotional and social problems. In addition, at least half have intellectual disability as a primary aspect of the disorder. Patients with cerebral palsy often live into adulthood and develop other health problems [42; 46].

Therapeutic and Nursing Measures

The treatment of cerebral palsy is dependent on the extent of damage and the patient's needs. Although the initial damage in the brain cannot be reversed, earlier and aggressive treatments may help to improve function and adjustments for the young nervous system and musculoskeletal system [1]. Common treatment approaches include physical therapy and rehabilitation, braces and other orthotic devices, assistive technology, pharmacotherapy, and surgery.

MUSCULAR DYSTROPHY

Muscular dystrophy is a hereditary, degenerative neuromuscular disorder characterized by chronic, progressive wasting and weakness of voluntary muscles. Far more common in men than women, the disease affects both children and young adults. The nine different types of muscular dystrophy (i.e., myotonic, Duchenne, Becker, limb-girdle, facioscapulohumeral, congenital, oculopharyngeal, and distal) vary in the age of onset, rate of symptom progression, and clinical manifestations. All types exhibit degenerative changes in the muscle fibers [42; 46].

Clinical Manifestations

Muscular dystrophy is characterized by a progressive weakness and atrophy of all voluntary muscles, with eventual contracture and confinement to a wheelchair. Failure of cardiac or respiratory musculature usually leads to death in the second or third decades of life [42; 46].

Therapeutic Measures

There is no cure for the muscular dystrophies. Accurate diagnosis is essential, however, to rule out similar muscle diseases for which effective treatments are available. Patients with muscular dystrophy are managed with supportive interventions and assistive devices. Physical therapy may enable patients to gain optimal use of affected muscles, and muscle stretching helps prevent contractures. Tendon-lengthening surgeries have varying degrees of success [42; 46].

Specific Nursing Measures

Patients with muscular dystrophy should remain physically active as long as possible. Physical therapy regimens are essential. Stretching and resistive exercises preserve joint range of motion, prevent or minimize contractures, decrease atrophy, and promote mobility. Exercises should be done at least twice every day for the outpatient or four times per day for inpatients. Each joint should be put through its normal arc of motion, as tolerated, while avoiding moving joints beyond the point of resistance. Exercises should be halted whenever the patient has pain [42].

Patients with muscle spasticity experience an increased tonus in a weak muscle. The objective is to promote muscle relaxation and prevent complications, such as contractures, muscle atrophy, pressure injuries, and urinary tract infections. Patients and their families should be taught to avoid stimuli that can increase spasticity, including fatigue, maintaining one position for too long, and cold temperature [42].

Braces may be used to stabilize the lower limbs and trunk, but they should be light enough for weakened muscles to support. Other potentially helpful assistive devices include bed trapezes, handrails, raised toilet seats, and wheelchairs [42].

Management of alteration in nutritional intake is another priority. The physical inactivity of patients with muscular dystrophy may contribute to unnecessary weight gain. Patients can plan meal schedules that permit smaller, more frequent meals. Evaluation of weight patterns and energy requirements can help [46]. The goal is to promote independence as long as possible.

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HUNTINGTON CHOREA

Huntington chorea, also known as Huntington disease, is a rare hereditary disease of the CNS. The disorder is progressive, degenerative, and fatal. It is characterized by severe choreiform movements and mental deterioration. Although the disease was first recognized as a medical entity more than 100 years ago, public awareness has lagged. As noted, Huntington chorea is inherited through the autosomal dominant gene with full penetrance. Therefore, 50% of the children of individuals with the disease eventually inherit it [42; 46].

Clinical Manifestations

What is the most striking characteristic of Huntington chorea?

Huntington chorea usually develops insidiously and runs its course over 15 to 20 years. Onset is typically in middle life (35 to 40 years of age). The earlier the age of onset, the more rapid the deterioration [42].

The choreiform movements are the most striking characteristic of Huntington chorea. They begin slowly, usually first in the face and upper extremities. Facial grimacing and jerking limb movements occur. Over time, movements become frequent, erratic, and violent [42].

As the disease progresses, communication becomes poor, with increasing dysarthria and unintelligible speech. Early behavioral changes include periods of irritability, labile mood swings, and impulsiveness. Periods of apathy, elation, depression, and aggression can be expected. Progressive memory impairment, inattention to personal hygiene, and cognitive impairment accompany the personality changes [46].

Seizures also occur in the end stages of classic Huntington chorea. Death is usually from cardiac or respiratory failure, extreme systemic exhaustion, or suicide [46].

Therapeutic Measures

Treatment of Huntington chorea is difficult. There are no known methods of arresting the disease, and drug regimens have been generally unsuccessful. Exercise, physical therapy, nutritional support, and speech and language therapy can be helpful.

Specific Nursing Measures

The chronic, disabling nature of Huntington chorea requires interventions that are preventive, protective, and supportive. These patients are at high risk for injury, and as the disease progresses, a safe physical environment should be maintained, with precautions similar to those for seizures. As mental and cognitive capacity deteriorate, patients will rely more on caregivers to carry out activities of daily living—daily hygiene, nutrition, and elimination. Genetic counseling is crucial to screen families whose children may later develop the disease, to counsel these families regarding the risks, and to support other family members carrying the gene [42; 46].

NEUROFIBROMATOSIS

Neurofibromatosis is a hereditary disorder characterized by a variety of congenital abnormalities. The skin, CNS, bones, and endocrine glands are most commonly affected. Usually, some form of benign tumor is the typical finding [14; 15].

Neurofibromatosis is one of the most common hereditary disorders. The incidence is approximately one case per 3,000 live births [14; 15]. In the United States, there are an estimated 100,000 cases. The disease is slightly more common in males. Each child of an affected parent has a 50% chance of inheriting the gene and developing neurofibromatosis [14; 15].

Clinical Manifestations

In the peripheral form of neurofibromatosis, multiple cutaneous and subcutaneous nodules occur. Cutaneous tumors are palpated in the dermis as discrete soft or firm papules varying in size from millimeters to centimeters. If pressed, these soft nodules feel like a seedless grape, which aids in distinguishing lesions of neurofibromatosis from other tumors. Subcutaneous tumors are usually multiple, assuming two forms: discrete or plexiform neuromas. Discrete tumors are firm nodules that attach to the peripheral portion of a nerve. These nodules may cause neurologic or paresthetic pain to pressure and rarely cause weakness, atrophy, or sensory loss in the distribution of the affected nerve. The number of nodules varies from a few to thousands, and the size varies from pea-sized to orange-sized. Plexiform neuromas are an overgrowth of subcutaneous tissue and can reach enormous sizes. The face, scalp, chest, and neck are typically affected with growths that feel like a "bag of worms" when palpated. The hypertrophy is highly disfiguring and often accompanied by underlying bone abnormalities. These tumors, if large enough, can cause increased ICP and brain stem compression [19].

Therapeutic Measures

Neurofibromatosis has no cure. The most promising approach is surgery for removal of symptomatic lesions. In cases of multiple CNS lesions, the decision to have surgery depends on the severity of symptoms, risk for survival, and the quality of life. Some have advocated aggressive plastic surgical treatment for cosmetic reasons or for removing lesions that might degenerate into sarcomas. Radiotherapy is not justified because of unsatisfactory results and the risks associated with radiation exposure [20].

Specific Nursing Measures

Patients with neurofibromatosis should be helped to recognize that there are many variants of the disease and that no two individuals have the same course and prognosis. Patient education should include the current extent of the illness and possible treatment strategies, with emphasis on the patient's right to make decisions regarding treatment choices.

One challenge is helping the patient recognize and cope with the uncertainty of the disease course and prognosis. Lesions can change from asymptomatic to symptomatic at any time, and new lesions can develop spontaneously without warning. Some patients may experience symptom-free periods [42].

ARTERIOVENOUS MALFORMATIONS OF THE BRAIN

An arteriovenous malformation is characterized by the direct shunting of arterial blood into veins. Two-thirds of all patients with intracranial arteriovenous malformations experience symptoms before 30 years of age; most cases are congenital. About 1 in 20 patients with arteriovenous malformation have aneurysms, but only 1 in 75 patients with intracranial aneurysm has an associated arteriovenous malformation [9; 13].

Clinical Manifestations

Clinical manifestations of arteriovenous malformations include seizures, hemorrhage, headaches, motor and sensory deficits, organic mental impairments, visual dysfunction, and syncopal episodes. The most common are seizure activity and hemorrhage [9; 13].

Severe intracerebral bleeds can occur from these malformations. In these cases, presenting symptoms and signs include vomiting, intractable headache, and loss of consciousness. Less severe arteriovenous malformations can cause aphasias and hemiparesis. An estimated 10% to 15% of patients experience sudden, severe paralysis after seizure. An equal percentage develops a progressive rather than sudden hemiparesis. Sizable bleeds in the brain stem can lead to coma and death [9; 13].

Therapeutic Measures

Complete excision of the arteriovenous malformation is the treatment of choice for most patients and eliminates the possibility of rebleeding. Few patients are in the high-risk or inoperable category. Microneurosurgical techniques permit the removal of most lesions, regardless of size and depth. Those with subarachnoid hemorrhage require a recovery period before surgery to permit careful evaluation of neurodiagnostic studies. Angiography is essential to visualize the circulation of the malformation [13].

Specific Nursing Measures

Assessment of initial symptoms and signs (usually related to either seizures or hemorrhage) is one of the most important aspects of care for the patient with intracranial arteriovenous malformation. Although a subarachnoid hemorrhage with an arteriovenous malformation is generally less severe than a ruptured intracranial aneurysm, many of the symptoms will be the same. Intracerebral hemorrhage can occur [39].

Transient episodes of syncope and dizziness increase the patient's risk for injuries from falls. Patients should be instructed to assume a safe position and call for assistance at the initial onset of any of these symptoms. Any episodes should be carefully documented [39].

CNS DISORDERS OF MULTIFACTORIAL ORIGIN

CNS disorders of multifactorial origin can be associated with a combination of lifestyle factors, trauma, environmental toxins, and inherited defects.

STROKE

The two primary types of stroke are ischemic and hemorrhagic. In the United States, approximately 87% of all strokes are ischemic; 10% are hemorrhagic [76]. An ischemic stroke occurs when any artery that supplies the brain with oxygen becomes stenosed or occluded, resulting in infarction. In the case of hemorrhagic stroke, bleeding occurs below the arachnoid, the location of the brain's blood supply, allowing blood to directly contact and damage brain tissue. In addition, TIAs are often a precursor to ischemic stroke.

Hemorrhagic Stroke

Hemorrhagic strokes are categorized by the location of the hemorrhage, either intracerebral or subarachnoid, with the former being more common [76; 77]. Approximately 87% of hemorrhagic strokes are due to intracerebral hemorrhage (ICH), and because of this, the term hemorrhagic stroke often refers to ICH [78]. ICHs are characterized by bleeding directly into the brain parenchyma [78; 79]. Intraventricular hemorrhage describes bleeding that extends into the ventricles [79; 80]. Nontraumatic ICH is categorized as primary (unrelated to congenital or acquired lesions), secondary (caused by a congenital or acquired condition), or spontaneous (unrelated to trauma or surgery) [79].

The signs and symptoms of ICH include headache, vomiting, seizures, depressed consciousness, meningeal irritation, and blood-tainted CSF. The onset of symptoms may occur within seconds to minutes after the start of an ICH. Individuals with this type of stroke often feel more ill than those with an ischemic stroke.

ICH is the least treatable type of stroke [81]. Functional independence is regained within six months in approximately 20% of survivors [82]. The morbidity and mortality depend on the volume and location of the hematoma. The one-year mortality rate varies according to anatomic location, with the highest mortality rate (65%) associated with ICH in the brain stem; the rate is 57% for lobar hemorrhage, 51% for deep hemorrhage, and 42% for cerebellar hemorrhage [83]. Overall, 46% of patients with ICH survive one year and 29% survive five years [84].

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As many as 80% of primary ICHs occur after small vessels are compromised by chronic hypertension [85]. Hypertension is associated with ICH originating in the periventricular deep white matter, deep subcortical structures, pons, and cerebellum [86]. In individuals older than 70 years of age, cerebral amyloid angiopathy, a condition that leads to amyloid protein infiltration into the cortical arterioles, is responsible for approximately 20% of ICHs [87]. Other causes of ICH include anticoagulant and antiplatelet use, drug use (e.g., cocaine, phenylpropanolamine), and other bleeding diathesis [81; 88]. Fewer than 15% of all cases of ICH are secondary to congenital vascular abnormalities and malignant brain lesions [79].

Subarachnoid hemorrhages occur less frequently than ICHs. The hallmark of subarachnoid hemorrhage is the immediate onset of a severe headache with signs of meningeal irritation [89]. Individuals may describe this headache as their "worst ever." Nausea, vomiting, neck pain, and photophobia are also classic symptoms, although they are not always present [89]. Neurologic deficits may be acute or may manifest hours to days after the onset of bleeding.

Nontraumatic subarachnoid hemorrhages are subcategorized as aneurysmal or non-aneurysmal [90]. Aneurysmal subarachnoid hemorrhage is associated with higher rates of morbidity and mortality than non-aneurysmal hemorrhage. Among patients who live 3 months after the event, the risk of death is 8.7% within 5 years and 17.9% within 10 years [91]. In contrast, non-aneurysmal subarachnoid hemorrhages are associated with better outcomes and are less likely to cause death [92].

Most nontraumatic subarachnoid hemorrhages involve rupture of an intracranial aneurysm or cerebral arteriovenous malformation. Congenital arteriovenous anomalies are more likely to cause stroke in adolescents and young adults [93]. The incidence of perimesencephalic subarachnoid hemorrhage, a non-aneurysmal type, is increasing. Although the cause remains unknown, increased use of antithrombotic medications may be a factor [94; 95].

Therapeutic Measures

What are possible signs of hydrocephalus?

The primary focus of medical care after initial aneurysm rupture is to prevent rebleeding. Aminocaproic acid (Amicar) prevents destruction of the clot that has sealed the dome of the aneurysm following initial rupture; it also enables endothelial repair and fibrous tissue development to take pace. Extended use (three weeks or more) has been associated with thrombophlebitis and pulmonary embolism [19; 20].

Communicating hydrocephalus, the third most common complication of subarachnoid hemorrhage, can occur with the bleed or weeks later as a result of a malabsorption or blockage of CSF. Hydrocephalus should be suspected if any of these signs appear:

- Mental status changes
- A decrease in level of consciousness
- Dementias
- Flat affect
- Urinary incontinence
- Disturbances in gait

Hydrocephalus is confirmed by a CT scan that shows an enlargement of the ventricles due to blocked absorption of fluid from the arachnoid space [19].

Surgical repair that includes clipping of the aneurysm neck is the best treatment of a ruptured intracranial aneurysm for patients who are neurologically stable. Early repair (24 to 28 hours after rupture) is sometimes advocated, particularly for those who are asymptomatic. Those who demonstrate more extensive signs of meningeal initiation or neurologic deficit may be at greater risk if repair is attempted during the first week following rupture. One complication of clipping the aneurysm is the potential for the client to develop the syndrome of inappropriate secretion of antidiuretic hormone. Clinical signs include polyuria and increased specific gravity of urine [20].

Specific Nursing Measures

Unfortunately, about 40% to 50% of clients with subarachnoid hemorrhage due to ruptured intracranial aneurysms die from catastrophic bleeds before receiving medical attention [39]. For those who do have medical care, mortality and morbidity rates can be greatly reduced with careful nursing and medical management. Nursing care is aimed at preventing rebleeding, the most life-threatening complication, and other possible complications, including cerebral edema and hydrocephalus [39].

A patient's cardiovascular status may change because of hypothalamic dysfunction; a common cardiac change in a patient with a subarachnoid hemorrhage is sinus bradycardia with ST-segment or T-wave changes. These alterations should be differentiated from those of a myocardial infarction. Electrocardiogram pattern and vital signs should be monitored with the neurologic assessment [39].

Ischemic Stroke

Within minutes of the onset of ischemic stroke, the core of an infarct can begin to form at the least-perfused site. This site is encircled by an area partially altered metabolically and ionically by cytotoxic edema [96]. This area, the ischemic penumbra, is structurally intact and generally salvageable if reperfusion is achieved promptly. Because cerebral function deficits develop rapidly (within minutes to hours) as an ischemic stroke progresses, these brain attacks are a medical emergency. Although irreversible damage occurs, most individuals with stroke have recoverable penumbral tissue for at least three hours following the onset of symptoms [97].

The physical signs, symptoms, and sequelae of ischemic stroke are usually unilateral because of the circulatory anatomy of the brain. In general, ischemic strokes are categorized according to etiology: thrombotic and embolic [98].

Therapeutic Measures

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is the only treatment approved by the U.S. Food and Drug Administration (FDA) for ischemic stroke [97]. Anticoagulant and antiplatelet agents are also used, but their appropriateness is a source of debate and ongoing research. Intra-arterial rt-PA may be beneficial for select patients; however, the drug is not FDA approved for this use [99]. Mechanical thrombectomy is a consideration as both a primary reperfusion strategy and in conjunction with pharmacologic fibrinolysis [97].

With a goal to improve functional outcomes, the American College of Emergency Physicians recommends that intravenous rt-PA should be offered and may be given to selected patients with acute ischemic stroke within three hours after symptom onset at institutions where systems are in place to safely administer the medication. The increased risk of symptomatic intracerebral hemorrhage should be considered when deciding whether to administer rt-PA.

(https://www.annemergmed.com/article/S0196-0644(15)00576-4/fulltext. Last accessed November 9, 2018.)

Strength of Recommendation: B (Recommendation based on moderate clinical certainty)

Although emergent angioplasty and stenting are high-risk procedures, progressing strokes, which occur when patients' moderate neurologic deficits deteriorate significantly within 72 hours after onset, are associated with very poor outcomes and high mortality rates [100]. Therefore, some case studies suggest that emergency angioplasty followed by immediate or delayed stenting is appropriate for patients with a progressing stroke caused by carotid artery occlusion or stenosis, respectively [101; 102].

In the setting of acute ischemic stroke, justification for emergent (within the first 24 hours) or early revascularization with carotid endarterectomy is based on reports of increased risk of recurrent stroke in patients undergoing medical therapy while awaiting revascularization. However, the risk associated with emergency carotid endarterectomy is believed to be high, for several reasons, particularly in patients with an unstable neurologic status [103]. For some patients, however, the benefit of carotid endarterectomy may outweigh the risk.

Specific Nursing Measures

For individuals who have had a stroke and are medically stable, rehabilitation assessment, prevention of medical complications, and secondary prevention become the focal points [97; 104; 105]. To begin, the rehabilitation team's systematic evaluation of the patient addresses various issues, including the need for rehabilitation services; the risk of complications; physical functioning, cognition, and communication; and psychosocial conditions [105]. Next, the team works with the patient and family to implement a rehabilitation plan that includes a detailed exercise program and general as well as tailored strategies for secondary prevention [104]. Throughout, the team should strive to foster a climate of familial support [105].

Medical complications related to illness, being bedridden, or lack of proper care/attention can prolong hospitalization, impede rehabilitation, increase disability, or result in death. Living in an inappropriate post-stroke environment also substantially increases a patient's risk for complications. Complications may develop in as many as 85% of hospitalized patients who have had a stroke [106]. Thus, medical examinations before and during a patient's rehabilitation program should assess the most common risks of complications: skin breakdown, deep vein thrombosis, swallowing dysfunction, bowel and bladder incontinence, falls, and pain [105].

Transient Ischemic Attacks

Transient ischemic attacks (TIAs) are sometimes referred to as "ministrokes" because, like ischemic strokes, they are caused by inadequate cerebral blood flow. TIAs are also called warning strokes, as they often precede an ischemic stroke [107]. The proposed definition states that a TIA is "a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" [108]. This definition was designed to reflect the ischemic pathogenesis of TIA, promote its early management, and support the use of diagnostic imaging techniques to ensure that the patient does not have infarction [108]. The American Heart Association/American Stroke Association guideline defines TIA as, "a transient episode of neurologic dysfunction caused by focal brain, spinal-cord, or retinal ischemia, without acute infarction" [104; 109].

The risk of ischemic stroke is dangerously high in the period following a TIA. Research indicates that one-half of subsequent strokes occur within the first 48 hours, and a meta-analysis showed that approximately 5% of patients who have a TIA will have an ischemic stroke within seven days of that event [107; 110].

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Although the most common focal neurologic signs of TIA are sudden-onset unilateral weakness and numbness or tingling in a limb, a TIA can cause any of the following symptoms [111; 112]:

- Numbness of the face, hand, or leg, with or without weakness
- Paralysis
- Slurred speech
- Dizziness
- Double vision
- Hemianopia
- Transient monocular blindness
- Imbalance
- Aphasia
- Confusion
- Head pain

By the time of evaluation, however, most patients appear asymptomatic because TIAs usually resolve within five minutes [113]. A clinician should highly suspect a TIA if the patient says, "I don't know why I'm here. Whatever it was, it is all better now" [114].

TIAs are caused by conditions similar to those leading to ischemic stroke [104]. Among the common causes are atherosclerosis of large vessels, cardioembolism, and atrial fibrillation. Uncommon causes include hypercoagulable states, arterial dissection, sympathomimetic drugs (e.g., cocaine), and arteritis (caused by noninfectious necrotizing vasculitis, drugs, irradiation, or local trauma) [115].

Therapeutic Measures

The use of certain antiplatelet therapies rather than oral anticoagulation for noncardioembolic ischemic strokes and TIAs has been shown to reduce the overall risk of recurrent stroke and decrease the incidence of fatal recurrent strokes [104]. Clopidogrel is appropriate for patients who are allergic to aspirin or for patients in whom dipyridamole-associated headaches occur.

Aspirin (50–325 mg per day) monotherapy, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, or clopidogrel 75 mg monotherapy are all acceptable options for initial therapy [104]. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.

Because TIA is associated with a significantly increased risk for stroke, secondary prevention strategies mirror those for ischemic stroke.

SEIZURE DISORDERS

Seizures are common neurologic disorders that occur across the entire spectrum of age, gender, race, and socioeconomic background. Rather than a diagnosis focused on location (e.g., "symptomatic temporal lobe epilepsy"), diagnosis should reflect important diagnostic features, such as seizure type, lesion type, localization (e.g., "epilepsy with focal seizures secondary to cortical dysplasia in the temporal lobe"), and possibly other factors, including age at onset, EEG patterns, or other features.

There are many possible etiologies that may lead to the development of seizures or the specific diagnosis of epilepsy. Epileptic seizures have three basic underlying causes: genetic, structural/metabolic, and unknown [65]. Some cases of epilepsy are of a genetic origin, but other forms of epilepsy are caused by structural or metabolic defects, which themselves may or may not have a genetic origin [65; 66]. Other cases of epilepsy do not have any identifiable cause. Similar to structural/metabolic defects, the unidentified causes may have a heritable component.

Some patients with epilepsy experience one type of seizure; others experience several different seizure events. Different syndromes account for the varying patient histories, etiology of seizures, seizure type, clinical presentation, EEG readings, and neuroimaging findings. Common epileptic syndromes include febrile epilepsy, childhood absence epilepsy, juvenile myoclonic epilepsy, primary idiopathic generalized epilepsy, and localization-related epilepsy with complex partial seizures [67]. In total, more than 50 epileptic syndromes have been identified, each with specific associated diagnostic criteria.

Clinical Manifestations

The four generally recognized phases of a seizure are the prodrome (or preictal), ictal, interictal, and postictal stages. Not all patients experience, nor do all seizures include, every phase. The prodromal phase can last several days preceding a seizure. The prodrome is generally characterized as malaise or emotional changes [68]. An aura occurs immediately prior to a seizure, usually lasting a few seconds. Patients often describe an aura as a warning. An aura may be autonomic or it may involve the auditory, olfactory, sensory, or visual senses. The description of an aura can vary and may include weakness, an epigastric sensation, a sense of fear, visual hallucinations, aphasia, headache, feelings of being hot or cold, or sensing unpleasant odors [68; 116]. If a patient experiences auras, the auras are usually fairly consistent in that individual. However, auras may vary in the same patient, and the use of antiepileptic drugs may alter or obscure the aura.

The ictal phase is the duration of the actual seizure activity. The patient experiences a paroxysmal, uncontrolled, abnormal, and excessive discharge of electrical activity in the brain. There are also corresponding EEG changes [116]. The clinical manifestations will coincide with the type of seizure activity that the patient is experiencing.

The interictal phase is the period between seizures. Many people with epilepsy suffer from emotional changes during this phase, including fear, anxiety, and depression [117]. These disturbances can be more troublesome to patients than the seizures themselves.

The postictal period is the interval after the seizure episode. The patient may experience some change in consciousness or behavior. Some patients experience Todd paralysis, a numbness or weakness of an affected extremity or the side of the face. After a tonic-clonic seizure, the postictal phenomena may be more severe. The patient may experience amnesia, confusion, fatigue, and/or coma [116]. Often, neuronal discharges remain abnormal and the EEG may indicate some slowing.

Seizure types are divided broadly into three groups: generalized seizures, focal seizures, and unknown (including epileptic spasms) [65]. Seizures that do not fit any category remain unclassified until further assessment reveals the seizure type; however, this is not a separate classification.

Generalized Seizures

Generalized seizures begin and spread rapidly in bilaterally distributed networks and are followed by a period of postictal phase of continued altered consciousness [65; 118]. They are thought to originate from structures deep within the brain, radiating outward to the cortical surface. The networks may include cortical and subcortical structures, but the entire cortex is not necessarily affected. When a generalized seizure begins, there is synchronous involvement of the entire brain with diffuse EEG abnormalities. Approximately 20% to 25% of seizures are classified as generalized at onset [116]. Generalized seizures may result in a loss of consciousness, convulsions, falls, or muscle spasms. Some generalized seizures may encompass all of these events, while others may involve only one symptom.

Focal Seizures

Focal seizures (sometimes referred to as "partial seizures") are the more common classification and originate in a circumscribed area or areas of the brain (i.e., a localized brain disturbance). This type of seizure occurs in 75% to 80% of patients with epilepsy [117].

A focal ("partial") motor seizure occurs from a focus in the region of the brain's motor cortex. Motor activity occurs in the corresponding part of the body innervated by the motor neurons that are affected. The hands and fingers have a large cortical representation; consequently, seizures are frequently noticed in these areas. The duration of these seizures is usually one to two minutes, although the patient may require additional time to completely recover after the event [119]. The patient will present with twitching/jerking movements in an extremity, the face, the eyes, or another area of the body. The patient remains fully conscious and aware of the seizure but has no control of the event [120]. These seizures usually remain localized, but the involuntary movement may spread centrally and involve an entire limb, one side of the body, or the entire body [117; 121].

Therapeutic Measures

Although prevention of epilepsy is the ultimate goal, this is not always possible. However, there is a variety of treatment options. Comprehensive treatment is an important aspect of care for all patients with epilepsy. Managing the disorder improves the quality of life, and the consequences of not treating may be great. Seizures that go untreated or are poorly controlled have an increased risk of becoming more severe or more difficult to manage. Treatment recommendations tend toward more aggressive management and earlier surgical evaluation for patients with epilepsy.

The utilization of antiepileptic drugs is the mainstay of therapeutic options. The effectiveness of antiepileptic drugs relies on the ability to classify the seizure type by its clinical presentation, history, and diagnostic test findings. It is important to know the correct seizure type, as some antiepileptic drugs will be more effective or will exacerbate certain seizures or seizure syndromes.

Although surgical techniques have improved markedly over the past few years, epilepsy surgery is rarely considered a first-line treatment and is usually considered only after years of medication treatment. A surgical approach may be deliberated sooner if the patient's ability to function is hampered by frequent or severe seizures and a specific epileptogenic focus, such as mesial temporal sclerosis, is identified.

The vagus nerve stimulator, first approved by the FDA in 1997, was the first successful medical device for patients with uncontrolled focal seizures [68]. The stimulator is an implanted device, similar to a cardiac pacemaker, that is connected to the vagus nerve in the neck and stimulates the nerve with electrical impulses. The device is programmed to send electrical discharges at specific intervals automatically and periodically throughout the day [68]. The device is adjusted according to each patient's individual requirements and tolerance.

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Specific Nursing Measures

Epilepsy is a chronic disorder and often requires long-term management. The patient and family should be encouraged to obtain information about epilepsy through self-education. Local epilepsy organizations often provide written materials and information via other media. Frequently, the patient's family or other significant persons require as much education as the patient, because they will be observing the patient during the actual events. These significant persons should be educated to care for the patient during and after a seizure.

Patient education is crucial to obtain medication adherence and provide optimum care. The patient should receive instruction on the type, dose, and potential side effects of each medication [122]. The patient should also understand that the medication is to be taken every day, on time, and as prescribed. Although brand and generic drugs are comprised of the same active compounds, their absorption may vary and patients should be cautioned not to interchange the medications. To avoid undesirable drug interactions, all professionals writing prescriptions should be aware of all medications a patient is taking. The patient should be informed that many medications interact with other CNS depressants, including alcohol. Patients should bring medication bottles with them at each visit.

According to the American Academy of Neurology and the American Epilepsy Society, patients should be advised that their risk for antiepileptic drug adverse events ranges from 7% to 31% and that these adverse events are predominantly mild and reversible.

(https://www.aan.com/Guidelines/home/GetGuidelineContent/688. Last accessed November 9, 2018.)

Strength of Recommendation/Level of Evidence: B (Probably useful based on at least randomized controlled study or two consistent cohort studies.)

Patients with seizure disorders should wear identification wristbands or necklaces. Injuries are the primary complication of seizures. Patients with epilepsy often cause harm to themselves by biting their tongues or falling down and hitting a piece of furniture. The patient should be safeguarded from injuries and falls, and injury prevention is a key aspect of patient education and the maintenance of quality of life. The patient and family should be instructed on constructive methods of safety planning without being overburdened with unnecessary restraints and concern. If possible, the environment should be altered during a seizure rather than restraining the patient.

DYSTONIA

Dystonia is an abnormality of involuntary movement (dyskinesia). The abnormality can involve a single, focal muscle group or can be a diffuse neurologic syndrome in which multiple muscle groups are involved [28].

Clinical Manifestations

Onset of dystonia usually occurs before 15 years of age and is commonly associated with more severe clinical signs. Later onset is rare and more benign. The disease is observed as a slow, sustained, involuntary twisting of affected muscle of the trunk, limbs, neck, and face. Dystonia is not usually present during sleep. During waking periods, dystonic movements can be continuous. Dystonic movements tend to intensify with stress or fatigue and can be alleviated by relaxation or sleep [28].

Therapeutic and Nursing Measures

A primary treatment choice for patients with intractable dystonia has been surgery. More commonly, patients with less severe disease are managed by pharmacotherapy. Anticholinergic drugs have been beneficial in reversing acute symptoms of dystonia induced by antipsychotic drugs [28]. The effect of dystonia on the muscles may be reduced by stretching exercises [38].

HEADACHE

The pathophysiology of headaches is multifactorial and complex. When lesions of the brain cause headache (e.g., mass, fluid, hemorrhage), they do so by involving pain-sensitive structures inside the skull, such as arteries at the base of the brain, the dura area blood vessels, and certain cranial nerves that carry pain fibers. In addition, the external structures of the head are all pain-sensitive and give rise to a variety of headaches.

Headaches may be categorized as either primary or secondary. Primary headaches are pure headache syndromes, meaning they are self-originating and not triggered or produced by other disorders. Primary headaches include migraine, cluster, and tension-type headaches [123]. Secondary headaches, as the name indicates, occur secondary to another cause (i.e., they are a symptom of other diseases). These may include vascular, traumatic, neoplastic, infectious, pressure, and metabolic disorders [123]. Secondary headaches account for only 10% of headaches.

Clinical Manifestations

The various types of headache present with differing symptoms and/or signs. A migraine is a type of neurovascular headache that is initiated by a neurologic event that causes vasodilation, which in turn is interpreted by the brain as pain. Adults with migraine headache describe episodic attacks with pain of moderate-to-severe intensity that are often throbbing in quality, unilateral in position, and aggravated by physi-

cal exertion. Migraines are usually associated with nausea, vomiting, and sensitivity to light and sound. Nausea is the most common characteristic. The duration of these attacks, when not treated, may last anywhere from 4 to 72 hours [124].

Cluster headaches are one of several types of trigeminal autonomic cephalalgias, primary headaches characterized by unilateral pain in the trigeminal nerve region. As defined by the International Headache Society, cluster headaches are attacks of severe unilateral pain in the orbit and/or the surrounding region of the eye that last 15 to 180 minutes [125]. The term "cluster" refers to the headache attacks occurring in daily episodes. The patient is headache-free in between the clusters.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Radiology, the imaging mode of choice for patients who present with sudden onset of severe headache ("worst headache of one's life" or "thunderclap headache") is CT without contrast.

(https://acsearch.acr.org/docs/69482/Narrative. Last accessed November 9, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Tension headaches are among the most common headache type seen in practice today. Episodic tension headaches are usually associated with a stressful event. They are of moderate intensity, typically are self-limited, and usually respond well to over-the-counter headache treatments. They are usually described as soreness, tightness, or a band-like pressure around the entire head. They are often accompanied by stiffness in the neck and shoulders [126]. Chronic tension headaches generally have the same pain characteristics as episodic tension headaches, including phonophobia or photophobia. They occur more frequently, with an incidence of at least 15 headaches per month on average for greater than three months, or greater than 180 days in a given year. The headache may last hours, or it may be continuous [125].

Other primary headaches include primary exercise headache, hypnic headache, and headache associated with sexual activity. A secondary headache may be diagnosed when another disorder known to cause headache has been demonstrated; headache occurs in close temporal relation to the other disorder and/or there is other evidence of a causal relationship; and headache is greatly reduced or resolves within three months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder. It is helpful to think of secondary headaches in terms of etiologic categories, such as vascular, traumatic, neoplastic, infectious, pressure, metabolic/toxic ingestions, and medication overuse.

Therapeutic Measures

Treatment of headache focuses on pain relief and prevention of recurrence, in the case of primary headaches, or on amelioration of the underlying cause, in the case of secondary headaches. Nonpharmacologic measures tend to be more effective for tension headaches than for migraines or clusters. These measures include the use of hot or cold packs, ultrasound, electrical stimulation, improvement of posture, trigger point injections, regular exercise, and consistent sleep schedules.

Pharmacotherapy with analgesics (e.g., acetaminophen) and migraine-specific agents (e.g., triptans) is often effective. In general, narcotics should be avoided.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is the most common neurologic disorder to affect the CN V and is also the most frequent of the neuralgias. Paroxysms of recurrent, excruciating, sharp, stabbing pain of short duration along one or more branches of the trigeminal nerve characterize this disorder [69].

Clinical Manifestations

An episode of trigeminal neuralgia is often described as paroxysms of excruciating pain, with a lightening-like stab that burns. The onset is usually abrupt and related to a precipitating event that irritates a "trigger" point. Movements such as speaking, brushing the teeth, washing the face, shaving, laughing, and movements in the maxillary and mandibular divisions of CN V can precipitate an attack [69].

Therapeutic Measures

Standard analgesics are ineffective to address trigeminal neuralgia pain. Morphine provides some relief but is generally contraindicated because of its addictive properties and overdose risk. Phenytoin (Dilantin) may be given intravenously to prevent an acute attack, although long-term use of oral phenytoin is not effective in treating paroxysms of trigeminal neuralgia [64]. Carbamazepine is the usual drug of choice.

Specific Nursing Measures

Preventing attacks of trigeminal neuralgia is the priority of nursing care. Patients should be kept in an environment that avoids exposure to drafts or excessive heat or cold. Patients often lose weight because they fear that chewing movements will precipitate an attack; food choices that avoid excessive chewing can be encouraged. Fearing an episode may also result in patients avoiding washing their faces, performing oral care, or shaving. For patients with loss of corneal sensation, special eye care is necessary to avoid complications [39].

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DEGENERATIVE CNS DISORDERS

Degenerative CNS disorders are those with an unknown etiology that have an insidious onset and involve atrophy of neurons and nerve fibers. It is not uncommon for degenerative diseases to occur after a long period of normal nervous system functioning [69].

ALZHEIMER DISEASE

Alzheimer disease was first identified and named in 1906 by Dr. Alois Alzheimer, a German neuropathologist [127]. Symptoms seen in individuals with Alzheimer disease are partially the result of damage to the hippocampus and the cerebral cortex, reflected in memory loss, impaired cognition, and atypical behaviors.

Alzheimer disease is characterized by insidious, severe, and progressive cognitive impairment that is irreversible and eventually fatal. Alzheimer disease accounts for roughly 60% to 80% of all dementias in the United States [128]. It proceeds relentlessly, gradually destroying all cognitive functions.

There are two types of Alzheimer disease: familial and sporadic. Familial Alzheimer disease follows an autosomal dominant inheritance pattern, while sporadic Alzheimer disease has no known inheritance factor. Familial Alzheimer disease can be further classified as early-onset, when it occurs in individuals younger than 60 years of age, or late-onset, when it affects individuals older than 60 years of age [129].

Clinical Manifestations

The onset of Alzheimer disease is slow and insidious; impaired memory is usually the initial symptom, followed later by deficits in other cognitive domains. Symptoms may be present for several months before the family realizes the severity of the problem. In some situations, a spouse may shelter and cover for the patient so even children and friends are unaware. In other cases, it is the death of the healthy spouse that causes other family members to recognize the changes that have occurred in the living partner. After the diagnosis of Alzheimer disease, most patients will survive for 4 to 6 years; however, this number can vary from 3 to 20 years [130].

The early stages are especially challenging for patients with Alzheimer disease, as they realize that they are slipping away and are unable to do anything about it; each stage brings with it additional mental, emotional, or physical losses. Inevitably, nearly all patients develop amnesia (memory impairment), aphasia (language impairment), agnosia (inability to identify common objects), apraxia (inability to use objects, despite knowing their function), and visuospatial deficit and may exhibit apathy, depression, or psychosis. Afflicted individuals will become dependent on caregivers for meeting even the most basic physical needs. The model of the progressive cognitive and functional decline in Alzheimer disease as "childhood development in reverse" (i.e., from the functional capacity of a child to that of an infant) is one that is easy for nonmedical family members and caregivers to understand [131].

The disease progresses continuously, and it is useful to remember that staging of Alzheimer disease is an artificial construct meant to assist in diagnosis and management. Presentation of the disease is widely varied in patients, with symptoms and deficits affecting every individual differently or not at all.

Therapeutic Measures

There are no treatments that can cure or reverse the effects of Alzheimer disease. However, Alzheimer disease is not a condition for which nothing can be done. Patients and families can be helped with interventions designed to diminish the manifestations of the disease. The disease and its progression are evaluated by the behaviors exhibited by the individual. Care planning is directed toward the management of the identified behaviors. Although there are many common features, each person is unique and requires distinctive approaches based on an assessment that identifies the specific problems of each individual.

In the preclinical stage, the goal of management for susceptible patients is to prevent and/or delay the onset of the disease. Maintaining a healthy diet and lifestyle, with goals including reduction of oxidative stress and blood pressure and improving circulation, may help in preventing dementia or slowing the rate of disease progression [132]. Dietary, exercise, and pharmacologic treatment guidelines for lowering the risk of obesity, diabetes, cardiovascular disease, and particularly hypertension should be followed, as comorbidities complicate Alzheimer disease treatment and exacerbate the disease process. As noted, there is some evidence that certain nutrients, especially omega-3 fatty acids, can reduce the risk of dementia [133]. Engagement in cognitive activities is also highly recommended.

Management of diagnosed Alzheimer disease consists of pharmacologic and nonpharmacologic therapies. Some pharmacologic agents have shown modest benefits in alleviating problems with cognition and behavior in research settings, though these benefits are often not realized in clinical use [133; 134]. These agents include several cholinesterase inhibitors (ChEIs) and memantine, an *N*-methyl-d-aspartate receptor antagonist [135; 136]. The most common adverse effects of ChEIs are nausea, vomiting, and diarrhea, with the most serious being cardiac arrhythmia and other cardiovascular and neurologic effects [133]. Memantine produces fewer adverse effects, and the dropout rate is similar to placebo. Other medications, such as antipsychotic agents and antidepressants, are occasionally necessary, but these agents can cause many unacceptable side effects [135].

Medications for Alzheimer disease may provide temporary improvement in cognition for a subset of patients; however, at present there is no pharmacologic agent or other treatment modality capable of substantially altering the progression of disease. Thus, nonpharmacologic interventions, including social, environmental, and behavioral measures, are the most important elements of a management strategy for patients with Alzheimer disease [137].

Specific Nursing Measures

Patients and family members should be encouraged to make long-term plans after a diagnosis of Alzheimer disease. When the diagnosis is made early in the course of the disease, the patient can and should fully participate. Decisions can be given some thought if they are made before a crisis occurs. The patient and family must be aware of the need for advance planning as a mechanism for protecting the individual's self-determination.

Unmet needs can cause the patient with Alzheimer disease to become agitated and anxious. Patients may be unaware of the source of discomfort or be unable to respond to the cues resulting from unmet needs. A routine should be established that will avoid problems resulting from thirst, hunger, lack of sleep and rest, inadequate exercise, and irregular elimination patterns.

For the patient with Alzheimer disease, palliative care is centered on the alleviation of agitation and anxiety, the prevention of catastrophic reactions, and the management of delusions and hallucinations. Comfort may be extended in a number of ways. Members of the interdisciplinary team work together to develop interventions that will facilitate the individual patient's physical and emotional comfort.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Hartford Institute for Geriatric Nursing asserts that healthcare professionals should maximize the functional capacity of patients with dementia by maintaining mobility and encouraging independence as long as possible; providing graded assistance as needed with activities of daily living; providing scheduled toileting and prompted voiding to reduce urinary incontinence; encouraging an exercise routine that expends energy and promotes fatigue at bedtime; and establishing bedtime routine and rituals.

(https://consultgeri.org/geriatric-topics/dementia. Last accessed November 9, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

PARKINSON DISEASE

Parkinson disease is a neurodegenerative disorder that affects approximately 1% of those older than 60 years of age [138; 139]. This disorder is prominently characterized by the motor symptoms of resting tremor, rigidity, and bradykinesia. The non-motor features are increasingly identified and include sensory, autonomic, and neuropsychiatric symptoms that appear before motor dysfunction is evident. The onset is insidious and often asymmetrical. Numerous, potentially disabling non-motor symptoms are often present, and diagnosis is made clinically.

Clinical Manifestations

What are the cardinal motor features of Parkinson disease?

Parkinson disease is typically diagnosed following the onset of motor features that prompts the patient to seek medical attention. Pre-motor prodromal disease can manifest in non-motor features, such as depression, fatigue, rapid eye movement sleep behavior disorder, anosmia, and constipation, that reflect disease involvement in autonomic, enteric, or somatomotor systems. Visuospatial and cognitive dysfunction, especially mild cognitive impairment with dominant executive dysfunction manifested in diminished multitasking, planning, retrieval, concentration, and attention performance, are increasingly recognized as prevalent in earlier stages [140]. As mentioned, appearance, severity, and progression of pre-motor and motor features corresponds to the nervous system and brain areas afflicted by pathologic infiltration [141; 142; 143; 144].

Motor symptoms can also appear long before diagnosis. In Parkinson disease, the cardinal motor features of bradykinesia, resting tremor, rigidity, and postural/gait impairment reflect parkinsonism [145]. A mnemonic for the core motor features is TRAP [146]:

- **T**remor at rest
- **R**igidity
- **A**kinesia (i.e., bradykinesia and hypokinesia)
- **P**ostural instability

It is important to note that postural instability, while a cardinal motor feature, is seldom present at diagnosis, as it usually appears later in the disease course [147].

Therapeutic Measures

Since curative or disease-modifying agents are not yet available, Parkinson disease is treated symptomatically. Treatment strategies for Parkinson disease are influenced by disease stage, most problematic symptoms, and patient age, and clinical decision-making should balance possible efficacy with potential side-effect risk for each treatment option.

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Initial treatment of early Parkinson disease generally involves monotherapy, and motor control problems can be improved in many patients. Treatment of later Parkinson disease becomes more complicated, with disease progression and prolonged dopaminergic drug administration. Requirements for dopamine replacement therapy become increasingly demanding as motor signs worsen. Patients initially well controlled using dopamine agonists require initiation of levodopa and, over time, increasing amounts given in higher doses with more frequent intervals. Patients initiated on levodopa will require the addition of dopamine agonists and/or other adjuncts that improve response to levodopa [148].

Surgical treatment is considered in patients with advanced Parkinson disease when optimized medical treatment has failed to control motor symptoms. Deep brain stimulation can reduce symptoms of motor fluctuations, dyskinesia, and tremor, but symptoms unresponsive to levodopa in advanced Parkinson disease (e.g., cognitive impairment, gait instability, mood disorders, speech impairment, autonomic dysfunction) are unlikely to improve and may worsen with deep brain stimulation. Guidelines recommend that deep brain stimulation should only be performed in experienced centers [139].

A variety of nonpharmacologic, adjunctive interventions have been evaluated for management of Parkinson disease. These include exercise programs and occupational, physical, and speech therapies. While clinical study design and control group issues have confounded the quality of evidence, clinical experience suggests that these approaches have value. The American Academy of Family Physicians recommends physical therapy, speech therapy, and occupational therapy be offered to patients with Parkinson disease as part of an overall strategy for improving or maintaining function [139].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Occupational Therapy Association recommends engagement of patients with Parkinson disease in exercise and physical activity, specifically multisession, repetitive physical exercise (diachronic) to improve motor and sensory-perceptual performance skills.

(https://www.guidelinecentral.com/summaries/occupational-therapy-practice-guidelines-for-adults-with-neurodegenerative-diseases. Last accessed November 9, 2018.)

Level of Evidence: A or B (There is strong or moderate evidence that occupational therapy practitioners should routinely provide the intervention to eligible clients.)

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a progressive degenerative CNS disease with a relentless, fatal course. The three major aspects of the disease are progressive muscle atrophy, progressive bulbar palsy, and upper motor neuron deficit [23; 24; 57].

The course of ALS varies from one to four years. Men are more frequently affected than women at a ratio of about 2:1. Disease onset typically occurs between 40 and 70 years of age, most frequently in the fifth and sixth decades. The cause of ALS is unknown, but researchers are investigating viral, metabolic, infectious, toxic, immunologic, and specific life events as possible causes [23; 24; 57].

Clinical Manifestations

An EMG of patients with ALS demonstrates muscle wasting, atrophy, fasciculations, and fibrillation. Nerve biopsy is normal; muscle biopsy may demonstrate degenerative fibers interspersed with normal ones. Laboratory tests find normal CSF [23; 24; 57].

Initial symptoms of ALS include skeletal muscle weakness and atrophy that progresses from distal to proximal and unilateral to bilateral involvement in the upper extremities. Damage to CN IX and CN X leads to dysphagia and aphonia. Swallowing problems affect eating, drinking, and swallowing of saliva. Vagus nerve involvement can also cause dyspnea and bradycardia. Damage to CN XII causes difficulty with tongue movements during swallowing and speech [23; 24; 57].

Primary lateral sclerosis results in upper motor neuron signs, including spastic paresis of extremities, positive Babinski's reflex, and hyperactive deep tendon reflexes. Progressive muscle spasm may cause pain because of intact afferent nerve fibers. Most patients remain mentally clear. With total paralysis and lower cranial nerve involvement, a "locked-in" syndrome occurs. Patients are fully conscious of the environment and themselves, but experience a paralyzed body—all movement and ability to verbalize are absent. Some patients may only be able to communicate by eyelid movement and blinking. The immediate cause of death is often respiratory muscle weakness and bulbar palsy causing respiratory failure [23; 24; 57].

Therapeutic Measures

There is no specific or effective treatments for ALS, and it will progress regardless of therapy. Supportive symptomatic therapy is recommended to improve and, in some cases, extend life. Diazepam, baclofen (Lioresal), and dantrolene (Dantrium) may be used to control spasticity. Neostigmine (Prostigmin) is used temporarily to manage bulbar weakness. Analgesics are indicated to control pain.

Efforts should be made to prevent infections, especially of the respiratory tract. In many cases, tracheostomy and mechanical ventilation become mandatory to maintain respiratory function. Regardless of treatment, the prognosis is poor and survival is brief for most patients [23; 24; 57].

Specific Nursing Measures

A common problem for patients with ALS is ineffective communication patterns related to muscular weakness. As such, patients should be supported with alternative methods of communication. Alteration in nutritional status is possible due to swallowing and chewing impairments. This can be addressed with small, frequent feedings to prevent fatigue and choking; a soft diet high in calories, protein, and carbohydrates; and an adequate daily fluid intake. When feeding patients with ALS, the head of the bed should be elevated, with oropharyngeal suction equipment nearby and adequate time allowed for meals. Tube feedings may be necessary for some patients [39].

Alterations in mobility accompany increased motor paresis. To keep patients independent as long as possible, active and passive range-of-motion exercises and physical and occupational therapy are helpful. Assistive devices may be necessary for daily activities. Patients should remain out of bed and up in a chair as long as their condition permits [39].

Management of ineffective breathing patterns related to muscle weakness or aspiration often becomes a nursing priority. Aspiration may occur from dysphagia and excessive salivation. Preventive measures include monitoring the patient during eating, suctioning if necessary, assessing respiratory patterns around meal times, and administering anticholinergic drugs as ordered. Good oral hygiene should be provided [39].

When respiratory involvement progresses, the maintenance of a patent airway and adequate ventilation also become nursing priorities. Respiratory function should be assessed every one to two hours, including observation of rate, depth, and rhythm of respirations and auscultation of breath sounds. Frequent coughing and deep breathing is encouraged. Monitoring of tidal volume, vital capacity, and arterial blood gasses becomes crucial.

Chest physical therapy, including postural drainage, may be required in addition to nasotracheal and oropharyngeal suctioning every hour and as necessary. Intubation and ventilator equipment should be kept on standby. The most difficult nursing task often becomes helping the patient and family members to accept the seriousness of the condition [39].

SPINAL STENOSIS

Spinal stenosis can occur in older persons with a history of osteoarthritis of the spine or chronic disk degeneration, or it can be a congenital problem. The cervical and lumbar spine are most affected [70].

Cervical Stenosis

Patients with cervical stenosis experience spinal cord compression and gradually progress to spastic quadraparesis or paraparesis, often accompanied by fasciculations and atrophy in the upper extremities. Myelography often demonstrates a complete block of the spinal canal when the patient's head is in extension. When the total bony canal is stenotic, posterior decompression laminectomy is indicated [70].

Lumbar Stenosis

Unlike cervical stenosis, lumbar stenosis is manifested mainly by pain. There is no cord damage or spasticity, although there may be considerable numbness and weakness of the lower extremities. More often, the syndrome is manifested by spinal claudication. The patient has rapidly developing severe pain on walking any distance. Unlike vascular claudication, the patient with spinal claudication obtains relief by bending forward, which widens the anterior-posterior diameter of the spinal canal. Diagnosis of lumbar stenosis is confirmed by spinal x-ray, CT scan, and myelography [70].

Patients with lumbar stenosis usually do well following laminectomy. Despite considerable incisional pain, they tend to ambulate on the first post-operative day and are back to their normal activities by the end of one month [70].

IMMUNOLOGIC CNS DISORDERS

MYASTHENIA GRAVIS

Myasthenia gravis is a chronic neuromuscular disorder that affects voluntary (striated) muscles and is characterized by fluctuating muscle weakness that becomes worse with use and shows some improvements with rest. Respiratory infection and emotional stress may briefly exacerbate symptoms. The highest mortality rate is seen in the first year of the disease [23; 24].

Myasthenia gravis is relatively common, with incidence estimated at 1 in 10,000 [23; 24]. Peak incidence is between the second and third decades; onset is rare in the first decade of life or after 70 years of age. Before 40 years of age, women are affected approximately two to three times as often as men. In later life, the incidence is about equal [23; 24].

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This disorder usually persists for life, although there may be periods of spontaneous improvement for weeks or months followed by worsening. This disease is not hereditary, but 15% of infants born to mothers with myasthenia gravis have a transient case of the disease. With treatment, infants recover fully in two to three months [23; 24].

Despite numerous theories and a great deal of research, the cause of myasthenia gravis remains unknown. There is general agreement that the defect occurs at the neuromuscular junction, and myasthenia gravis is now considered an autoimmune disease. In the healthy individual, there are approximately 38 million acetylcholine receptors at each neuromuscular junction. In the patient with myasthenia gravis, acetylcholine receptors are reduced by about 20% [23; 24].

The thymus gland is also considered to be involved in myasthenia gravis. Active from birth until puberty, the gland is thought to initiate the body's immune response and to cease functioning after puberty. In about 85% of patients with myasthenia gravis, however, the thymus gland is abnormal and remains active. An autoimmune reaction is probably triggered by the thymus gland [23; 24].

Clinical Manifestations

The most characteristic finding in myasthenia gravis is an increasing weakness of certain voluntary muscles with activity and some improvement with rest. The muscles of the eyes are often most affected. Unilateral or bilateral ptosis and diplopia are common [24].

Other muscles affected are those of facial expression, chewing, swallowing, and speech. When chewing, patients with myasthenia gravis often become fatigued and must rest. Patients may experience problems with management of saliva, choking, and nasal regurgitation. Speech defects include a weak voice that fades during conversation and diminishes to a whisper. Speech becomes nasal, monotonous, and dysarthric [24].

The shoulder and neck muscles are also often affected. The head tends to fall forward, and patients may have difficulty holding their arms above the head; reaching for an object and fixing the hair are difficult. The muscles for fine hand movement can be affected, resulting in difficulty writing, serving, and moving the hands to the mouth. The most life-threatening situation occurs when the intercostal and/or diaphragm muscle are affected. An early sign of respiratory involvement is breathlessness. Respiratory weakness can develop rapidly [24].

Patients with myasthenia gravis may develop a "cholinergic crisis" as a result of taking too high a dose of their cholinesterase inhibitor medication. Signs of cholinergic crisis are dilated pupils, nausea, and tachycardia. A myasthenic crisis is life-threatening due to the increasing weakness of the respiratory muscles caused by a sudden withdrawal of cholinergic medications. In myasthenia gravis, EMG shows that the amplitude of the evoked muscle's action potential decreases rapidly. This reaction can be diminished or prevented with a single 2-mg IV dose of edrophonium [24; 31].

Therapeutic Measures

Drug therapy is the first line of treatment of myasthenia gravis. The drugs indicated—pyridostigmine bromide (Mestinon), neostigmine bromide (Prostigmin), and occasionally ambenonium chloride (Mytelase)—act by inhibiting anticholinesterase, preventing the rapid destruction of the neurotransmitter acetylcholine. Although this effect does not change the basic abnormality, it increases the amount of acetylcholine available, partially compensating for symptoms of a defective neuromuscular transmission. Drug dosage should be individualized to provide the greatest symptom relief and the fewest side effects [24].

Corticosteroids may be prescribed for patients who do not respond well to anticholinesterase drugs. The recommended approach is prednisone 100 mg every other day for 10 days. Patients may be hospitalized for close observation during the initial treatment period on full-dose therapy. Symptoms intensify after 7 to 10 days of treatment but improve after treatment ends. This treatment is given with anticholinesterase therapy [24].

The surgical removal of the thymus gland (thymectomy) is indicated for patients with hyperplastic thymuses. This procedure is most effective for young women in the first two years of diagnosis and least effective for older men. Even the removal of the thymus gland without an associated tumor produces a high rate of improvement or remission of symptoms in patients with early onset [24].

Specific Nursing Measures

Myasthenia gravis has largely become a treatable condition. Nursing priorities will depend on whether the patient is stable or in crisis. For patients in crisis, ineffective breathing patterns can develop and the patient experiences an abrupt exacerbation of motor weakness, usually from undermedication resulting from an unresponsive neuromuscular junction [39]. In these cases, the nurse's responsibility is to restore and maintain adequate respiration [39].

Breathing patterns are assessed by taking serial vital capacity measurements. Testing can be done at the patient's bedside with a respirometer attached to a mouthpiece, face mask, or tracheostomy or endotracheal tube. The patient should be in an upright position to promote maximum chest expansion, and emergency respiratory equipment should be available [39].

Another important function to evaluate is the patient's ability to swallow. This may be done by gently placing a hand over the anterior neck and instructing the patient to attempt "dry" swallowing. This maneuver is preferable to giving the patient liquids that might induce choking or aspiration. If the swallowing reflex is intact, the gag reflex should also be evaluated [39].

For patients who develop respiratory failure, endotracheal intubation may be necessary, including a planned tracheostomy. A volume-cycled ventilator should be used during periods of acute respiratory insufficiency. During the acute phase, all anticholinesterase medication should be discontinued to allow a "rest period" for the neuromuscular junction. After the patient's condition stabilizes, small doses may be restarted.

During this period, the patient is generally fed by nasogastric tube. To prevent aspiration, check for proper tube placement before each feeding, verify the amount and type of stomach aspiration, and ensure the patient is in the upright position with an inflated tracheal or endotracheal cuff. Aspiration can lead to major complications for patients with bulbar paralysis [39].

Intensive chest physiotherapy should be carried out during crises to prevent respiratory complications. In addition, a bedside physical therapy program should be instituted to prevent muscle atrophy or contractures. Adequate hydration and anti-embolism support stockings should be used to prevent thrombophlebitis [39].

Patients with myasthenia gravis often experience long-term muscle weakness that worsens with activity and fatigue. Anticholinesterase drugs should be taken at the same time every day, usually 30 to 45 minutes before meals. Patients' strength and motor ability with drug administration and side effects should be monitored. Care planning should include rest periods to prevent excessive fatigue [39].

Incomplete eyelid closure can develop, with corneal abrasion or ulceration a potential problem. Routine eye care is necessary, with normal saline every four to six hours and as needed. Protective eye shields may be used [39].

Patients on long-term anticholinesterase drug therapy may have periods of nausea, diarrhea, abdominal cramping, and constipation. These symptoms may indicate anticholinesterase toxicity. Antiemetics and antidiarrheal agents may be necessary. For patients with constipation, enemas should be avoided; mild cathartics or suppositories may be used. Alterations in diet and fluid regimen may be helpful. Patient education should include information about actions of drugs and specific factors that might precipitate an increase in muscle weakness [39].

MULTIPLE SCLEROSIS

Multiple sclerosis is the most common immune-mediated (inflammatory) demyelinating disorder of the CNS. Most cases are diagnosed in persons between 15 and 45 years of age, and it is a common cause of permanent disability in this segment of the population.

The disease is triggered by events that permit autoactivated T-cells to breach the blood-brain barrier and cross-react with myelin components within the white matter of the brain and spinal cord. This precipitates a cascade of immune-mediated inflammatory tissue injury. As seen on radiographic imaging and pathologic examination, the hallmark of the disease is this well-defined, focal zone of injury ("plaque") containing elements of inflammation, demyelination, and axon degeneration [149; 150]. Such lesions may be single or multiple, and over time, they may be partially reparative, relapsing, or recurrent in new locations.

Clinical Manifestations

What is the cause of the primary symptoms of multiple sclerosis?

The early signs and symptoms of multiple sclerosis are typically mild and difficult to detect. They differ in duration and severity from one individual to another and at different times in the same individual. However, at first clinical presentation, most patients report multiple symptoms. Patients generally experience either acute attacks of neurologic compromise or are afflicted by a steadily progressive deterioration in functional capabilities, as will be discussed in detail later in this course [151].

Primary symptoms of multiple sclerosis are caused by the inflammation and demyelination that arises within focal areas of the CNS. The clinical presentation is varied but, in general, consists of some disturbance in vision, sensation, and/or motor function. The most common primary symptoms in patients with multiple sclerosis are:

- Fatigue
- Heat sensitivity
- Muscle spasms

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- Dizziness
- Pain
- Paresthesias
- Ataxia
- Cognitive changes
- Visual complaints
- Bowel or bladder dysfunction
- Sexual dysfunction
- Gait problems
- Nausea/vomiting
- Speech problems
- Tremor
- Weakness

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Federation of Neurological Societies recommends that conventional MRI should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the central nervous system, not only to collect additional evidence for disease dissemination in space, but also to exclude other possible neurologic conditions.

(https://onlinelibrary.wiley.com/doi/pdf/10.1002/9781444328394.ch3. Last accessed November 9, 2018.)

Strength of Recommendation: A (Established as useful/predictive based on at least one convincing broad, blinded prospective study or at least two narrow prospective studies)

Secondary symptoms arise as a result of the presence of certain primary symptoms. For example, pressure ulcers may form as a complication of paralysis, a primary symptom. Bladder problems or urinary incontinence can cause frequent, recurring urinary tract infections. These symptoms are treatable, but ideally they should be avoided by treating the primary symptoms.

Tertiary symptoms may be described as the "trickle down" effects of multiple sclerosis and include the social, psychologic, and vocational complications associated with the primary and secondary symptoms [152]. Depression is a frequent tertiary symptom present among people with multiple sclerosis. Social isolation, job loss, marital or interpersonal conflict, and anxiety may all develop as a result of various primary and secondary symptoms of multiple sclerosis.

Therapeutic Measures

There is no cure for multiple sclerosis. However, effective treatment strategies are available to modify the disease course, treat or reduce exacerbations, prevent relapses, manage signs and symptoms, improve overall function and safety, and provide psychologic support. The treatment strategy depends on the patient's clinical condition and disease course. In cases of mild multiple sclerosis without relapses, usually no treatment is necessary. If a patient experiences relapses or if symptoms become more severe, treatment should be initiated as soon as possible.

Treatment of the acute exacerbations seen with relapsing types of multiple sclerosis relies primarily on corticosteroids and adrenocorticotropic hormone (ACTH). These agents have been found to promote speedier resolution of the neurologic deficits, lessen the severity of an attack, and effectively reduce the risk of permanent residual deficits. Both corticosteroids and ACTH are capable of restoring the breakdown of the blood-brain barrier, reducing inflammation, and immunomodulating mononuclear trafficking mechanisms. Corticosteroids also promote quick recovery from disability [153; 154].

It is now known that B-cell immunity also plays a key role in the pathogenesis of multiple sclerosis. Plasma exchange may be beneficial for relapsing forms of multiple sclerosis in which severe neurologic exacerbations prove refractory to parenteral corticosteroid therapy. It may also be beneficial for some patients with severe, rapidly progressive multiple sclerosis and similar disorders.

The use of disease-modifying drugs has been shown to decrease the relapse rate, reduce progression of disability, and slow the accumulation of lesions for patients with relapsing-remitting multiple sclerosis [63; 71; 155]. The exact mechanism of action of these drugs is still not clear, but it is believed to be the result of immunomodulation regulating the activation of impaired immune cells. Additionally, the blood-brain barrier becomes less permeable with immunomodulation, allowing fewer immune cells to enter the brain and reducing the autoimmune reaction between the immune cells and neuronal tissue.

Specific Nursing Measures

The primary goal of symptomatic multiple sclerosis therapy is to improve quality of life by eliminating or reducing symptoms affecting patients' functional abilities. The approaches to symptomatic treatment focus on controlling the symptom rather than the underlying disease process. Neurorehabilitation together with occupational therapy is the best approach.

INFECTIOUS AND INFLAMMATORY CNS DISORDERS

There are four major routes by which pathogens gain access to the CNS. The most common route is via the bloodstream (hematogenous) from septicemia or a septic embolus from endocarditis, lung infection, or pelvic abscess. Pathogens may also enter after trauma, including skull fracture, penetrating wounds, and operative procedures. Non-traumatic infections can occur from otitis media, mastoiditis, sinusitis, and osteomyelitis. Finally, pathogens may enter in a retrograde manner via nerve trunks (e.g., rabies) or thorough the cerebrospinal route from lumbar or ventricular puncture [13].

MENINGITIS

Meningitis is an inflammation of the meninges caused by a viral, bacterial, or fungal organism. There are three major types of meningitis: aseptic, septic, and tuberculous. Aseptic meningitis is thought to occur from viral inflammation or meningeal irritation. Septic meningitis is caused by infection from pus-forming bacteria (e.g., *Neisseria meningitidis*). Tuberculosis meningitis occurs when the chance location, progression, and rupture of a tubercle (developed following active infection with *Mycobacterium tuberculosis*) enters the subarachnoid space [23; 24].

After a pathogen enters the subarachnoid space, the infection spreads because of the open communication over the brain's convexity along the blood vessels of the pia and then penetrates the sulci. It is not uncommon for affected blood vessels to become engorged, leading to thrombosis or rupture. The accumulation of exudate over the convexities, in the cisterns or the ventricles, can cause obstruction of CSF flow. The exudate may ascend to involve the spinal cord. If the brain surface adjacent to the meninges becomes involved, secondary encephalitis and neuron degeneration can occur [23; 24].

Clinical Manifestations

The clinical course of meningitis can be acute, subacute, chronic, or recurrent. Headache, fever, meningeal irritation, and mental status changes are the most common symptoms. Patients often complain of severe headaches, the worst they have ever experienced. Meningeal signs include nuchal rigidity; photophobia; pain down the back and limbs; alterations in mental status and level of consciousness; restlessness; confusion; hallucinations; and delirium. There may be generalized seizures and increased ICP due to cerebral edema and communicating hydrocephalus. Opisthotonos, a sign of meningeal irritation, is manifested by arching of the neck and back. There also may be medullary signs, such as vomiting, respiratory difficulties, and a weak, rapid pulse. Cranial nerve involvement causes visual disturbances, ptosis, pupil abnormalities, strabismus, deafness, nystagmus, and vertigo. In cases of meningococcal meningitis, a skin rash may be present [23; 24].

Diagnosis is based on history of prior infection or exposure, symptoms and signs of an existing infection, clinical neurologic signs, and diagnostic tests. Skull x-rays are ordered to evaluate for possible fracture and/or infected sinuses or mastoids. Chest x-rays are ordered to assess for pneumonia and lung abscesses. CSF pressure is often increased to 700 mm/H_2O. The appearance of the CSF, as evaluated by lumbar puncture, varies according to the infecting organism. In bacterial infection, the CSF is turbid to purulent. In tubercular infection, the CSF is clear, xanthochromic, or like ground glass. In viral infection, the CSF is usually clear. Glucose levels are low in bacterial and tubercular infections, but normal in viral infections [23; 24].

Therapeutic Measures

In bacterial meningitis, culture confirms the type of bacteria and results of sensitivity tests indicate appropriate drug therapy [24]. Prognosis is good with antibiotic therapy.

In the acute phase of meningococcal meningitis, it is possible to infect others by exposure to nasopharyngeal and droplet secretions from the respiratory tract. Isolation procedures to protect others should be maintained until cultures are negative [24].

Specific Nursing Measures

What is the best measure to prevent meningitis?

The major burden of care of patients with meningitis occurs in the acute phase of infection. During this period, level of consciousness and neurologic signs should be frequently assessed. As noted, appropriate infection control precautions are important. Patients with meningococcal meningitis or meningitis of unknown etiology are kept in isolation [33].

Patients will have a febrile period during which temperature is monitored every one to two hours if higher than 101°F (38°C). Tepid sponge baths, frequent skin care, axillary and groin compresses, and antipyretic drugs may be ordered. If shivering develops, chlorpromazine (Thorazine) may be administered [33].

Fluid volume deficits can occur due to fever and inadequate intake. As such, serum electrolytes should be monitored daily during febrile periods. Oral fluids, intravenous fluids, and/or tube feedings are given as needed. Intermittent or in-dwelling bladder catheterization may be necessary for patients with impaired levels of consciousness [33].

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Sensory perceptual deficits can occur because of photophobia, hyperalgesia, and hyperirritability. A quiet, dark, nonstimulating environment and limited visiting hours can help reduce photophobia. The potential impact of hypoxia or bladder distention on irritability should be ruled out before considering it a neurologic problem. For headache management, keep the head of the bed elevated, unless contraindicated, with good body alignment and repositioning every two hours [33; 64]. Pneumococcal and influenza immunizations are the best preventive measures [33].

ENCEPHALITIS

Encephalitis is an infection of brain tissue caused by a virus (most common), pyogenic bacteria, fungi, or parasite. Epidemic encephalitis begins in a reservoir and is transmitted to humans. For example, equine encephalitis begins in squirrels, horses, wild birds, chickens, frogs, or garter snakes; a mosquito or tick bites the reservoir animal and transmits the virus when it bites a human host. Incubation periods vary according to the host's susceptibility to, reaction to, and strength of the pathogen [23; 24].

Encephalitis begins with the pathogen gaining access to the CNS. This is followed by degeneration and destruction of cortical neurons with demyelination. Patches of hemorrhage, necrosis, and cavitation can occur, depending on the type of pathogen involved. Diffuse cerebral edema results [23; 24].

Viruses are the most common pathogens. Herpes simplex virus has the potential to cause acute encephalitis in the adult and neonatal encephalitis from exposure during vaginal delivery or in the first days of life. Other latent viruses that can cause encephalitis include herpes zoster virus, cytomegalovirus, Epstein-Barr virus, mumps, rabies, and measles [23; 24].

Clinical Manifestations

A prodromal illness often precedes the neurologic signs associated with encephalitis. Usual initial symptoms are headache, fever, malaise, sore throat, and myalgia. This is often followed by marked alteration in level of consciousness ranging from lethargy to coma. Confusion and disorientation with abrupt behavioral disturbances may occur. Objective signs include motor and sensory deficits, tremor, and ataxia. Hyperirritability, meningeal signs, and seizures are possible [23; 24].

Therapeutic Measures

Clinical management of encephalitis is mainly symptomatic and supportive. There is no curative drug therapy, but steroids such as dexamethasone (Decadron) may be used to combat cerebral edema. Not all patients recover completely. Those surviving an acute episode can have residual neurologic deficits, including seizures, dysphasia, memory loss, and/or personality changes [24].

Specific Nursing Measures

Nursing priorities for patients with encephalitis are similar to those for patients with meningitis, with several major differences. Patients with acute encephalitis have more marked alterations in level of consciousness and behavioral manifestations; restlessness, agitation, and dementia are more severe [33].

Neurologic deficits may increase rapidly due to cerebral edema and necrosis. Neurologic signs are monitored frequently during the acute stage, with any changes reported promptly. There is potential for fluid volume overload related to intravenous antiviral administration. To combat this, drugs are administered on a strict schedule and intake and output are maintained. Patients should be observed for other possible drug side effects, including nausea, vomiting, diarrhea, weight loss, and transient alterations in blood cell and liver function tests. Other nursing measures include elevating the head of the bed and monitoring electrolyte levels and respiratory and cardiac status [33].

MYELITIS

Myelitis is an inflammation of the spinal cord. The most common viral diseases causing myelitis are poliomyelitis and herpes zoster [70].

Clinical Manifestations

The viruses that cause myelitis usually have an affinity for motor and sensory neurons rather than spinal tracts. Clinical findings in patients experiencing spinal cord involvement include paresis, numbness of the feet and legs (more than upper extremities), dysuria, and sometimes headache and stiff neck. Neurologic involvement can extend to the brain stem, cerebellum, cerebrum, and optic nerves in some patients [70].

Therapeutic and Nursing Measures

Treatment is supportive. Nursing care is aimed at preventing hazards of immobility and alterations in comfort. Bed rest is usually indicated during the acute phase of the illness. It is important that rehabilitation measures be instituted early [33].

INTRACRANIAL ABSCESS

An abscess may form around or within the brain as a result of a local or systemic foci of infection. Intracranial abscesses are purulent, usually encapsulated collections. Although abscesses can form anywhere in the brain, the most common sites are the temporal lobes, the frontal lobe, and the cerebellum [13].

Most brain abscesses develop secondary to a primary source of infection. Of these, at least 40% are caused by mastoiditis, otitis media, or sinusitis. A smaller percentage result from direct invasion by traumatic injury, such as gunshot wound, basilar skull fractures, or compound skull fractures with dural tears [13].

Clinical Manifestations

During the initial stage of organism invasion of the brain, the patient experiences chills, fever, malaise, and appetite loss. The almost common presenting symptom of an intracranial abscess is headache, which may be associated with vomiting and papilledema. Other common presenting symptoms are alterations in level of consciousness (especially drowsiness and confusion) and partial or generalized seizures. Focal neurologic deficits vary according to the anatomic location of the abscess. These include various motor, sensory, and speech disturbances [13].

In contrast, a subdural abscess tends to produce even more profound symptoms than brain abscesses. A subdural abscess affects the cortical blood vessels, causing thrombosis, arteritis, and eventually ischemia. The abscess usually arises from sinusitis. Headache occurs, with rapid deterioration in neuralgic status including seizures, hemiplegia, and dysphasia. Without treatment, brain compression or abscess rupture into the ventricle or subarachnoid space can be fatal [13].

Diagnosis is usually made by history of a previous infection, neurologic exam, and CT scan. A lumbar puncture is not recommended, because a brain abscess acts as a mass lesion and the negative pressure created by the procedure can lead to a brain shift and herniation. The most important diagnostic test is CT scan, which can demonstrate displacement of the lateral ventricles and locate the abscess, which is observed as an area of decreased density [13].

Therapeutic Measures

Interventions are aimed at diagnosing and managing the primary infection source, providing for abscess drainage, and administering an effective antibiotic regimen. Most intracranial abscesses can be drained via bur hole aspiration. Some may require more than one aspiration. If the abscess has ruptured into the ventricles, ventricular drainage is used. Antibiotic therapy is given for at least six weeks to reduce virulence of the organism, eliminate the pathogen, and penetrate the cavity. Prognosis is usually good after an effective regimen of antibiotics and/or surgery [13].

Specific Nursing Measures

Management of the acute infection is a priority of nursing care for patients with intracranial abscess. Intravenous drug administration sites should be inspected and rotated every 48 to 72 hours to prevent thrombosis phlebitis. During antibiotic therapy, patients are at risk and should be assessed for the development of opportunistic infections, especially in the mouth and gastrointestinal tract [39].

Sudden increases in ICP can result from cerebral edema that may surround an acute abscess. Frequent assessment of neurologic and vital signs, head of bed elevation to 30°, restricted fluid intake, and avoiding any stimulants that can raise ICP are necessary components of care [39].

Seizures are also a concern. Anticonvulsants may be ordered, with periodic checking of serum blood levels. During actual seizures, the patient should be protected from self-injury and helped to maintain a patent airway. Interventions for headache include providing a quiet environment, changing position to promote comfort, and administering mild analgesics, as ordered. Patient education should focus on preparing patients psychologically and physically for surgery (to aspirate the abscess and to provide intrathecal medication). Discharge teaching should include methods of preventing future abscesses if caused by an infected tooth, otitis media, or sinus problem [39].

HERPES ZOSTER

Herpes zoster (also known as shingles) is a viral disorder that affects the posterior root ganglia. It is characterized by cutaneous eruptions of vesicles along the distribution of involved spinal or cranial nerve roots. The highest percentage of cases involve spinal ganglia. Outbreaks occur mainly in adults and are more common in women than men and during the spring and fall [8; 32; 34].

Herpes zoster develops from reactivation of varicella virus, which is responsible for chickenpox. Children without immunization can develop chickenpox if exposed to an adult with shingles [8; 32; 34].

Clinical Manifestations

Mild-to-severe neuralgic pain in the affected nerve root distribution is the most common presenting symptom of shingles. The pain may be burning, tingling, sharp, or dull. Pain may be concurrent with or followed by skin reddening and an eruption of vesicles. Over the next one to two weeks, these lesions become pustules and then develop a crust. After healing, a pigmented scar may appear. If an infection or ulceration accompanies the vesicles, the scarring may be permanent [8; 32; 34].

Diagnosis is usually based on the sudden onset of root pain followed by the characteristic distribution of shingles. The lesions are unilateral and do not cross the midline of the body [8; 32; 34].

There are potential complications from a herpes zoster outbreak, most commonly scarring of the skin, facial palsies, and postherpetic neuralgia. In elderly or immunocompromised patients, the neuralgia can persist for months or years. The skin may also be hypersensitive to touch. Unfortunately, this variant does not respond well to treatment. Less commonly, some individuals develop Guillain-Barré syndrome following a herpes zoster outbreak [8; 32; 34].

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Therapeutic Measures

Most treatment of herpes zoster outbreaks is aimed at giving local care to the vesicles. Topical corticosteroids can alleviate local pain and itching and may shorten the stage of vesicle eruption. Antibiotics may be administered to prevent or treat secondary infections. During the acute phase, bed rest and analgesics can be supportive [8; 14].

Antiviral medications (e.g., acyclovir) may be used to limit duration of outbreaks and help prevent postherpetic neuralgia [21]. Early treatment (within 72 hours of symptom onset) is most effective. Antiviral therapy should continue for 7 to 21 days.

Postherpetic neuralgia is a difficult condition to treat. Intractable cases may require neurosurgical sectioning of affected nerve roots or occasionally irradiation to the site. Treatment results are variable [8; 14].

Specific Nursing Measures

The primary objective of nursing management of patients with shingles is symptom management (to minimize discomfort) and care of interruptions in skin integrity. Patients should be instructed to avoid scratching vesicles to prevent spreading the virus and promoting infection. Open vesicles should be dressed with moist occlusive dressings. If systemic steroid therapy is used, it is important to monitor for side effects. Comfort measures to address localized pain and itching include positioning techniques (especially during bed rest), skin treatment, and analgesics as ordered [33].

NEOPLASTIC AND OBSTRUCTIVE CNS DISORDERS

Where are metastatic tumors of the CNS usually found?

Tumors within the cranium can be either primary or metastatic. Metastatic tumors are found predominantly within the substance of the brain, which they reach through the systemic circulation.

Tumors produce symptoms by invasion or compression of surrounding neural structures. The neurologic symptoms and signs of any tumor affecting the brain depend on the location of the tumor and its rate of growth. Disruption of neural structures can cause an insidious deterioration of neurologic function or an acute neurologic disturbance. Spinal cord tumors can cause spinal cord compression and related pain and other symptoms [27].

TRAUMATIC DISORDERS

Craniocerebral trauma is a major cause of death in persons between 1 and 44 years of age and contributes to more deaths than stroke in persons 45 to 64 years of age [60; 62]. Nearly 6.5 million head injuries occur yearly in the United States. The highest incidence occurs in young, previously healthy men. Serious injury leads to permanent disability and emotional devastation for the patient, and the cost of long-term rehabilitation and maintenance programs have a tremendous impact on the healthcare system [60; 62].

HEAD TRAUMA

Serious cerebral injury can result from a number of factors, including motor vehicle, sports, and industrial accidents a well as assaults and falls. The skull is a rigid sphere filled to capacity with contents that are basically noncompressible. These components include CSF, the vascular system, and brain tissue. All maintain a fairly constant volume; an increase in the volume of one intracranial component occurs at the expense of the others or results in an increase in ICP. Early signs of increasing ICP include restlessness, irritability, and a gradual decrease in the level of consciousness. Lumbar punctures are contraindicated during periods of increasing ICP because herniation of brain structures into the foramen magnum may cause depression of vital centers in the brain [60; 62].

Among the methods for classifying head injuries are mechanism and severity of injury. Mechanisms include direct (acceleration or deceleration) and indirect causes. A direct acceleration injury occurs when the stationary head is struck by a moving object, such as a baseball. A direct deceleration injury occurs when the head in motion strikes an immovable object, such as when a person falls from a bicycle onto the pavement. In an indirect injury, the traumatic force is not directly applied to the head but is usually the result of shaking or slamming the body to the extent that the brain hits the skull [60; 62].

Another major classification is closed or open head injury, referring to whether the skull and the dura mater are intact. A closed head injury is a non-penetrating, blunt injury with no break in the integrity of the skull and dura mater. Brain concussions, contusions, and lacerations may occur with either type of injury. Brain stem compression from increasing ICP occurs late and can cause herniation and death [60; 62]

An important phenomenon in closed head injury is coup-contrecoup. A coup injury is bruising of the brain directly below the point of injury resulting from impact to the skull; there are visible signs of injury. Contrecoup refers to the rebound effect of injury—the mass movement of the brain opposite to the site of impact. For example, a blow to the frontal region (coup) causes damage to the occipital region (countercoup) of the brain [60; 62].

In open head trauma, a penetrating injury breaks the integrity of the skull or dura. Cerebral contusions or lacerations occur. The most frequent fractures are linear, at the base of the skull. Depressed and comminuted fractures are less frequent, but more serious, because of dural tears and lacerations of brain tissue. Infection is a high risk in open head injuries. Cerebral edema develops with any head injury and should be treated as early as possible [60; 62].

Clinical Manifestations

The location of a skull fracture is most crucial for determining damage to the underlying structure: the meninges, blood vessels, and the brain itself. Fractures are classified as linear, diastatic, depressed, compound, growing, or basilar [60; 62].

Linear skull fractures are usually simple breaks in bone continuity anywhere in the skull. These fractures are typically less complicated. Depressed skull fractures are caused by trauma from sharper, penetrating injuries that commonly result in brain lacerations and infection. A compound skull fracture is a scalp laceration along with a depressed skull fracture. Debris (e.g., hair, dirt, foreign material) penetrates into the wound. The dura may or may not be torn. A basilar skull fracture involves injury to the base of the skull. Basilar skull fractures can indicate severe trauma and should be suspected in any significant head injury [60; 62]. Diastatic and growing fractures occur more often in children whose cranial sutures are not yet fused.

Traumatic brain injury is classified as a concussion, contusion, or laceration that may or may not be associated with vascular rupture and cardinal nerve damage. A concussion is considered the most benign form of brain injury. It is characterized by a loss of consciousness for five minutes or less and memory loss of events preceding and following trauma. Other symptoms may include dizziness, spots before the eyes, and a dazed state [60; 62].

A cerebral contusion is a bruising of the brain. There may be petechial hemorrhage of cortical tissue and white matter, with tearing of the pia mater. Contusions cause unconsciousness that persists for longer than five minutes. An initial period of shock is followed by signs of cerebral irritability [60; 62].

A cerebral laceration is a tearing of the brain tissue followed by intracerebral bleeding. Prolonged unconsciousness, immediate neurologic deficits, and a deterioration in condition can be expected [60; 62].

The major vascular hemorrhages from trauma include epidural, subdural, and intracerebral hematomas. Most epidural hematomas are from arterial bleeds. Classically, the trauma causes an initial loss of consciousness, followed by a lucid interval. Rapid and often unexpected unconsciousness follows. Epidural hematomas require prompt surgical intervention [60; 62].

Subdural hematomas are collections of blood from clots in the subdural space between the arachnoid and dura that usually involve venous bleeding. Acute hematoma occurs within 48 hours; subacute occurs within two weeks; and chronic types have an onset more than two weeks after injury. Subdural hematomas can develop over an entire hemisphere. Chronic subdural hematomas can increase in size over time, probably due to rebleeding [60; 62].

Acute subdural hematomas are often associated with massive cerebral or brain-stem injury. Although bleeding is mostly venous, it develops quickly, with a rapid onset of symptoms. Common clinical symptoms and signs include worsening headache, drowsiness, confusion, slow responses, and restlessness. A critical sign of deterioration is an ipsilateral dilation of the pupil that becomes unreactive [60; 62].

An intracerebral hematoma, a collection of blood in brain tissue, is a complication in a small percentage of all head traumas. The hematoma may accompany the contrecoup phenomenon [60; 62].

Therapeutic Measures

The treatment of head trauma often involves both medical and surgical approaches. The initial management of patients with head trauma includes diagnosis of injury and assessment for potential respiratory problems or injury to other systems. The primary focus is on maintenance of a patent airway and appropriate blood pressure, monitoring of ICP, and appropriate antibiotic therapy, as necessary. Hyperventilation therapy is employed in patients with severe head trauma to decrease PCO_2, reducing cerebral vasodilation and ICP [60; 62]. Treatment of cerebral edema includes use of dehydrating agents, such as mannitol, that withdraw water from intracranial tissue. The presence of mental clarity and appropriate behavior indicates a positive response to therapy [60; 62].

Specific Nursing Measures

In patients with decreased levels of consciousness, it is most important to assess which reflex?

As noted, the initial nursing priority for the care of the patient with acute head injury is maintenance of effective airway clearance and breathing pattern. Compromised respiration leads to increased ICP, which causes ischemia. Patients with alterations in level of consciousness are at greatest risk for hypoventilation, and these patients should be monitored for airway patency and adequate pulmonary toilet. When transferring patients from one area to another, a bag-valve mask should be available if needed [39].

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Patients who have sustained a traumatic head injury should be immobilized and not manipulated until cervical injury is ruled out by x-ray or CT scan. Neck hyperextension, flexion, and rotation should be avoided; manipulation can cause airway obstruction or can seriously complicate a cervical injury. If respiratory resuscitation is required, the jaw-thrust maneuver can be used. The mouth and oropharynx should be cleared of foreign bodies, and gentle oropharyngeal suctioning can be done to maintain an effective airway. Nasal suctioning is contraindicated. If the airway is not patent, endotracheal intubation or a tracheostomy will be indicted [39].

Patients with potential for respiratory complications may be repositioned after the cervical spine is stabilized and/or injury is ruled out. The semiprone lateral position facilitates drainage of secretions. Position should be changed at least every two hours. Chest excursions, breath sounds, and respiratory rate, rhythm, and pattern are assessed every one to two hours (or as necessary). Arterial blood gases are monitored initially, after four hours, and subsequently as necessary. Neurologic dysfunction can cause specific changes in respiratory patterns, such as Cheyne-Stokes respirations, and ataxic breathing patterns can indicate an impending respiratory arrest [39].

The neurologic status of the patient with acute head trauma should be assessed immediately after respiratory airway patency is established. Level of consciousness is the single most important aspect of the clinical nursing observation. Consciousness is assessed on a continuum from full reaction to no reaction to various kinds of stimuli. The bilateral corneal reflex should also be assessed on schedule [39].

Care of patients with basal skull fractures includes assessment for bilateral periorbital ecchymosis hemorrhages, Battle sign (an ecchymosis of the mastoid region), and hemotympanum (blood behind the eardrum). CSF leaks may present as rhinorrhea or otorrhea. The nose or ear should not be probed or irrigated if a CSF leak is suspected. If drainage occurs, collect the fluid to test for the presence of glucose. A glucose-positive result can confirm a CSF leak, as glucose is present in CSF but not in mucus. If drainage cannot be collected for testing, carefully inspect the patient's gown and linen. The "halo" sign, a combination of bloody or darker drainage encircled by a lighter yellowish stain, signifies a bloody leakage of CSF from the nose or ears. Basal skull fractures are considered serious head injurers due to the proximity of the fracture site to vital brain stem areas, damage to which can result in severe respiratory and cardiac dysfunction. Patients should be assessed frequently for alterations in urologic, respiratory, or cardiac status [39].

SPINAL CORD INJURY

The vast majority of spinal pathology results from traumatic injury. The highest incidence is in young men in the second and third decades of life, and the leading causes are motor vehicle accidents, sports accidents (e.g., football, diving), and penetrating injuries (e.g., gunshot or stab wounds) [70].

Fracture-dislocations can occur anywhere along the spine. Cervical injuries, the most common, are usually related to flexion-extension maneuvers during traumatic injury. Fracture-dislocations in the thoracic and lumbar areas usually arise from compression injuries, as in falls from high paces. Spinal column fracture-dislocations may also result from pathologic bone processes [70].

Dislocation fractures of the high cervical vertebrae (C-1 to C-2) can occur as a result of fractures or congenital defects from arthritic changes that weaken the ligaments in this area. A forward movement of the skull and C-1 and C-2 vertebrae can compress the cervical cord [70].

Clinical Manifestations

The extent of a patient's functional loss following injury depends on the degree of spinal cord injury. Complete spinal cord transection causes a total and irreversible loss of motor and sensory function below the level of injury [70].

In the cervical areas, millimeters can be crucial for spinal nerve-root function. With cervical cord transection, quadriplegia (paralysis of all four extremities) results, with varying degrees of respiratory and arm paralysis, depending on the injury level. Cord transection of the thoracic spine through L-1 and L-2 causes paraplegias (paralysis of both legs). In a complete cord transection, the individual sustains an immediate flaccid paralysis, loss of sensation, and usually loss of reflexes below the level of injury. Some reflexes may be intact initially and then disappear within a few days. The loss can last for days, weeks, or several months. As paralysis subsides, reflexes usually return and flaccidity changes to involuntary spastic movement. Recovery of any motor or sensory function is rare when there is complete paralysis of these functions for several days after injury [70].

With incomplete spinal-cord injuries, degrees of sensory and motor defect below the level of damage vary, resulting in one of several spinal cord syndromes [70]. A number of factors are examined to assess the degree of spinal cord damage. The first consideration may be the mechanism of injury. A compression of the cord can occur from ligaments, bone, and herniated disk material or hematomas. A contusion causes a bruising of the cord. In transection injuries, the spinal cord is actually or physiologically severed. Hematomyelia can occur within the cord substance [70].

Another important factor influencing the degree of spinal injury is the diameter of the spinal canal, or the amount of space the spinal cord has to move while avoiding compression. This factor is especially crucial in the cervical area. Spinal cord necrosis can result from a number of factors, including disturbances in circulation causing poor cord perfusion, edema, and progressive hemorrhage of central gray matter [70]. Neurons do not regenerate within the cord substance.

Therapeutic Measures

In cases of acute spinal cord injury, the patient's spine should be handled with extreme caution. Patients with spinal cord trauma and neurologic deficits need special attention during transport to prevent further deterioration in neurologic status. Spinal precautions should include the use of a backboard and hard cervical collar. Pressure sore development is a common complication during long transports and care should be taken to pad all bony prominences. Administration of methylprednisolone or similar medication for spinal cord injury is a requisite and should be initiated and subsequently continued throughout transport. Any life-threatening injury to another body system or signs of systemic shock should be treated immediately. For emergency life support, the neck should not be hyperextended. In most trauma units, early fixation and spinal traction have replaced decompression laminectomies [70].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association of Neurological Surgeons recommends expeditious and careful transport of patients with acute cervical spine or spinal cord injuries from the site of injury by the most appropriate mode of transportation available to the nearest capable definitive care medical facility. Whenever possible, the transport of these patients to specialized acute spinal cord injury treatment centers is recommended.

(https://www.cns.org/guidelines/guidelines-management-acute-cervical-spine-and-spinal-cord-injuries. Last accessed November 9, 2018.)

Level of Evidence: III (Strategy for patient management for which the clinical utility is uncertain.)

Another goal of therapy is to reverse the effects of vertebral body fractures. Neurosurgery replaces the injured vertebra with bone, acrylic, or a combination. The advantage of acrylic is early mobilization for the patient, whereas bone fusion requires some internal fixation. For patients who remain unstable, a halo frame and body jacket vest are applied for several months, until stabilization is achieved. In the lower thoracic and lumbar areas, internal fixation can be achieved using rods [70].

Patients with spinal cord injury are at greatest risk in the first 7 to 10 days after trauma. During this time, shock, pulmonary dysfunction, infection, and paralytic ileus can be major problems. Patients who sustain quadriplegic injuries require intensive total medical and nursing management. The posttraumatic care of these patients mainly involves management of bladder and bowel dysfunction, skin care, nutrition maintenance, and physical therapy [70].

Specific Nursing Measures

Continuous monitoring of the patient's neurologic status, including respiratory, motor, and sensory functions, is essential. Level of consciousness and pupillary response should also be assessed. Progression of any neurologic deficit should be reported immediately [39].

With high cervical lesions, there will be ineffective airway clearance and alterations in breathing patterns. Many patients require endotracheal or tracheostomy tubes with ventilator support. Oxygen administration will be ordered by tracheostomy tube, tracheostomy collar, or ventilator [39].

High cervical injuries frequently cause respiratory arrest. During this emergency, the jaw-thrust maneuver is used for resuscitation. The patient then requires careful nasotracheal intubation or an emergency tracheostomy. For patients admitted with respiratory function intact, respiration should be carefully observed. During spinal shock, it is not uncommon for the level of injury to ascend one or two levels above actual damage due to massive spinal cord edema. When this occurs, patients may develop respiratory dysfunction and/or arrest, even if they did not have the problem initially. These patients are at high risk for pulmonary complications such as pneumonia and atelectasis (hypoventilation). Other possible complications include decreased cardiac output, decreased venous pressure, and severe hypotension [39].

To alleviate early cerebral or spinal-cord edema, large doses of intravenous or intramuscular glucocorticoids are often given. This may cause gastric distress or other side effects, such as behavioral changes, elevated glucose levels, and an acne-like rash [39].

Patients who have sustained a spinal injury are also at risk for abdominal distention and paralytic ileus. Nothing should be given by mouth until bowel sounds return. If necessary and not contraindicated, a rectal tube may be used to relieve abdominal distention. For patients with ulcer histories, cimetidine (Tagamet) may be ordered with steroids to prevent gastrointestinal bleeding [39].

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The plan of care should include measures to prevent hazards of immobility, emboli, skin breakdown, and bowel and bladder dysfunction. It may be helpful to begin a bowel management program by administering a cleansing enema. To establish a bowel reflex, a combination of bulk in the diet, stool softeners, prune juice, and daily suppositories is provided. When the patient resumes eating, an oropharyngeal suction machine may be kept at the bedside for safety [39].

Patients should be assessed for symptoms and signs of thrombophlebitis and pulmonary embolism; in many cases, patients are unable to give subjective reports of calf pain [39]. One of the most important steps to prevent pressure ulcers is physically repositioning the patient frequently. Repositioning should be done every one to two hours, depending on the patient's condition. Every time the patient is repositioned, look for areas of redness and make sure that the new position does not put weight on these areas.

Perhaps the most sensitive area of nursing care is the patient's psychologic reaction to paralysis. Body image and the patient's future plans have been suddenly and irrevocably altered. It is vital to assess available support systems and prevent sleep deprivation and sensory overload [39]. The range of emotion the patient experiences should be recognized and validated, with the goal of supporting the patient in progressing toward eventual acceptance and resolution. Patients should be encouraged to make as many decisions about their care as possible to help regain a sense of control over self and environment [39].

The acceptance of permanent disability may take a long time and should not be forced; denial can be beneficial for a time. Nurses can be empathetic listeners who can accurately reflect the patient's comments and feelings [39].

After vertebral fractures fuse, patients can be transferred to stretcher chairs. Hypotension and dizziness may occur during this process, so mobilization should be done progressively. Abdominal binders and anti-embolism stockings can help decrease hypotensive episodes and periods of dizziness [39].

Sexual dysfunction is a major concern that patients may or may not verbalize. Factors that determine future potential for sexual function include the anatomic level of injury, the patient's personality and former sexual experience, and the effectiveness of sexual counseling. The most important fact to convey is that a caring, loving relationship is possible after injury [39].

Autonomic dysreflexia is possible with patients who sustain high thoracic lesions (above the T-6 level). This condition results from abnormal autonomic responses (usually pain or discomfort below the level of injury). Bladder or bowel distention or skin stimulation can trigger the response. Autonomic dysreflexia is an emergency that may lead to increased ICP and severe hypertension. When symptoms occur, the patient's head should be elevated to lower blood pressure, the patency of the indwelling catheter should be assessed, and patients should be evaluated for a possible fecal impaction. Antihypertensive drugs may be necessary. The nurse can help prevent episodes of dysreflexia by preventing conditions that result in stimulus overload, fecal impaction, or bladder distention [39].

CONCLUSION

With knowledge of CNS structure and function and the dynamic pathology that intrudes and impedes normal function, nurses are more prepared to provide quality and often lifesaving care to patients. An awareness of symptoms' precipitating events leads to quicker reporting of changes in the patient's condition, and immediate interventions can be performed based on standing orders and the patient's needs. This changes what could be only technical care to professional care through the use of informed decision-making skills.

CASE STUDIES

CEREBROVASCULAR ACCIDENT

Patient A, 85 years of age, wakes in the morning to paralysis on his whole right side and no sensation in his arm or leg. He tries to get up with help from his wife but cannot. Mrs. A calls their physician and describes the situation. The physician instructs her to call 911 to have her husband taken to the hospital by ambulance, where he will meet them. Patient A protests but ultimately cooperates with emergency medical services when they arrive. He is quickly evaluated upon arrival in the emergency department and is admitted to the critical care unit (CCU).

Past Medical History

Patient A lives with his wife in their own home in a lower-middle class neighborhood. They have four sons who are living in different parts of the country. Until five years ago, Patient A had worked as a house painter.

Patient A's wife provides the patient's medical history. Patient A has not had any significant illness until two years ago, when he began to develop bilateral cataracts. Since then, he has consumed increasing amounts of alcohol as the encroaching cataracts impaired his ability to pursue his hobby of building ship models. Six months ago, the cataracts were successfully removed and lenses implanted. Since then, Patient A's alcohol consumption has decreased and he has resumed work on his models.

Mrs. A reports no knowledge of high blood pressure, heart disease, lung disease, kidney disease, cancer, or any other serious medical illness in the patient. He has no history of surgery or serious injuries during their 65 years of marriage.

Assessment and Diagnosis

Upon admittance to the CCU, a full physical exam is conducted (***Table 1***). Several laboratory tests are ordered, with the following results:

- Complete blood count with differential: Within normal limits
- Serum electrolyte levels: Within normal limits
- Serum glucose level: Mildly elevated

Based on the results of the assessment, Patient A is diagnosed with:

- CVA (thrombosis or aneurysm of left middle cerebral artery), with right hemiparalysis and hemiparesis and questionable aphasia
- Benign prostatic hypertrophy

Management

When Patient A is admitted to the CCU, the nurse orients him and his wife to the physical layout and pertinent policies of the unit. The nurse also completes an initial physical assessment while carrying out the medical and nursing orders for supportive management. Nursing actions include:

- Continue oxygen by mask at 8 L/min and obtain arterial blood gas sample.
- Take vital signs every 15 minutes until stable, then every 30 minutes for two hours, then increasing interval until every four hours.
- Complete neurologic checks every hour.
- Insert IV devices and administer dextrose 5% in water (D5W) at a rate of 100 mL/hour.
- Insert 16F indwelling urinary catheter connected to a urinometer.
- Monitor and record intake and output every hour.
- Suction oropharynx to stimulate coughing and remove secretions.
- Frequent oral care, including Patient A's usual denture care routine.
- Repositioning every two hours, with body kept in functional alignment.
- Skin care and some passive range of motion with each turning so all joints are exercised every eight hours.
- Administer ordered medications:
  - Acetylsalicylic acid (aspirin): 650 mg every six hours
  - Sodium nitroprusside (Nipride) infusion: As needed to maintain systolic arterial pressure between 170 and 180 mm Hg

Twelve hours after admission, the nurse assessing Patient A notes that his eyes are half open, with ptosis of the right eyelid, and eye movements occur when the nurse or his wife speaks his name. Patient A's right cheek is more flaccid than the left. His right arm and leg are limp with no muscle tone. There is some grasp strength in the patient's left hand, although he does not grasp on command. Patient A responds with grunts to painful stimuli but does not attempt to speak, follow commands, or answer questions.

Study Questions

1. Outline a complete neurologic status assessment.
2. How did the physician conclude that Patient A's CVA involved the left side cerebral artery?
3. What signs and symptoms would alert the nursing staff to occlusion of the left anterior or posterior cerebral artery?
4. Why did the physician order sodium nitroprusside to keep Patient A's systolic arterial pressure between 170 and 180 mm Hg?
5. What nursing diagnoses or nursing problems and outcomes assume priority in the acute care period of a CVA?
6. What other disciplines would be expected to assist in rehabilitation of a patient with a CVA? When should disciplines such as physical and occupational therapy be expected to begin working with the patient?

ACUTE PYOGENIC MENINGITIS

Patient B is a white woman, 67 years of age, who felt well until approximately one week ago, when she developed an upper respiratory tract infection. She has improved slowly, but during the past 48 hours she has developed a more severe cough with significant production of rust-colored sputum, fever with occasional shaking chills, and muscle aches. Patient B arrives at the hospital emergency department. She is transported by her husband, who was concerned when the patient woke in the morning mildly confused and complaining of a severe headache.

At the hospital, Patient B informs the physician (with some difficulty concentrating) that she has had a "bad cold" for about a week. She explains that her neck feels stiff, sore, and extremely painful when she tilts her head forward and bright lights hurt her eyes. She also tells the physician that she has had no skin rashes, nausea, or vomiting but has had some severe chills. She does not recall any of her recent contacts being ill, and she denies any difficulty breathing or chest pain.

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PATIENT A'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Semiconscious and aphasic. Made no attempt to respond verbally to questions. Height: 5 feet 9 inches (175 cm) Weight: 163 pounds (74 kg)
Head and eyes	Face flushed Pupils equal, round, reactive to light, accommodation Corneal reflexes present Unable to test extraocular muscle function Nasal passage clear, with septum deviated to the left Edentulous, full dentures not in place, gums without lesions Tongue deviated to the left when protruded spontaneously Facial drooping on left
Ears	Tympanic membranes intact and clear No history of impaired hearing
Chest	Symmetrical excursion while lying in bed Lungs clear to auscultation and percussion Breath sounds diminished in the bases
Abdomen	Flat Bowel sounds present in all quadrants Soft and without masses or organomegaly on palpation
Extremities	Flaccid right arm and leg
Genitourinary system	Normal adult male with smooth, enlarged prostate gland
Neurologic status	Spontaneous respirations with regular variation in depth and rate Deep tendon reflexes in arms and femorals: 2+ Deep tendon reflexes in popliteals, posterior tibials, and dorsalis pedis: 1+ Spontaneous movement and active response to pain in left arm and leg Grimace but no movement with pain in right extremities
Cardiovascular system	Heart sounds consisted of normal S_1, S_2, and S_3 Soft systolic ejection murmur heard at second intercostal space to right of sternum
Vital Signs	
Blood pressure	200/110 mm Hg
Temperature	100° F
Heart rate	86 bpm and regular
Respiratory rate	22 breaths per minute and stertorous Oxygen mask in place with flow at 8 L/min
Source: Author	*Table 1*

Past Medical History

Patient B denies any past history of head trauma, sinus infection, immunodeficiency disorders, or medications that cause immunosuppression. She has smoked a half-pack of cigarettes each day for the last 45 years, was diagnosed with emphysema five years ago, and had several severe episodes of chronic bronchitis and one episode of pneumonia in the past two years. Her emphysema is being managed with ipratropium bromide delivered with a metered-dose inhaler (two to four puffs every six hours). She has never suffered from episodes of angina or symptoms of heart failure. She has an allergy to peanuts but not to any medications. She is taking no medications other than ipratropium and combined estrogen plus progestogen therapy for menopausal symptoms. The patient was vaccinated for influenza six months previously and pneumococcus when she turned 65 years of age.

Assessment and Diagnosis

Upon admittance to the CCU, a full physical exam is conducted (***Table 2***). A blood chemistry panel, chest x-rays, and lumbar puncture are ordered. Chest x-ray finds shadows on the right middle and lower lobe consistent with pneumonia; the left lung is clear but hyperinflated. Several laboratory tests are ordered, with the following results:

- Hematocrit: 41%
- Hemoglobin: 14.8 g/dL
- Red blood cells: 5.2 million/mL
- White blood cells: 14,000/mL (90% neutrophils)
- Platelets: 280,000/mL
- Sodium: 145 meq/L
- Potassium: 5.0 meq/L
- Chloride: 110 meq/L
- Calcium: 9.3 mg/dL
- Bicarbonate: 22 meq/L
- Fasting blood glucose: 123 mg/dL
- Blood urea nitrogen: 12 mg/dL
- Creatinine: 1.0 mg/dL
- CSF white blood cells: 1,100/mL (predominately neutrophils)
- CSF protein: 1,254 mg/dL
- CSF glucose: 40 mg/dL
- CSF gram stain: Positive for encapsulated diplococci
- CSF culture: Positive for *Streptococcus pneumoniae*
- Sputum gram stain: Positive for diplococci

Based on the physical examination and results of diagnostic testing, a preliminary diagnosis of meningitis is made. Patient B is admitted to the hospital for treatment and continued observation.

Study Questions

1. List clinical manifestations that strongly suggest that a patient has developed meningitis.
2. Why is it appropriate for the physician to examine the patient for a head injury?
3. Define papilledema and explain the significance of lack of papilledema in this patient.
4. Explain the pathophysiology behind this patient's lymphadenopathy.
5. Is the patient's rating on the Glasgow Coma Scale normal or abnormal?
6. Based on all of the available test data, what is an appropriate neurologic diagnosis for Patient B?
7. How did this patient's neurologic condition probably develop?
8. Which type of white blood cell predominates in the blood and CSF of patients with acute bacterial meningitis?

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PATIENT B'S PHYSICAL EXAM RESULTS	
Parameter	**Findings**
General appearance	Slight female in acute distress, with headache, intermittent chills, and constant coughing. Appears older than her stated age. Height: 5 feet 0 inches (152.5 cm) Weight: 97 pounds (44 kg)
Head and eyes	Normocephalic with no signs of head injury Pupils equal at 3 mm, round and sluggishly reactive to light Difficult to view fundi due to photophobia, but no papilledema observed Nares slightly flared, purulent discharge visible Pharynx red with purulent postnasal drainage No tonsillar exudates Mucous membranes moist
Ears	Within normal limits
Neck	Stiff and painful with flexion Shows mild anterior cervical lymphadenopathy
Chest	Significant use of accessory muscles Breath sounds markedly decreased in right middle and lower lobes Crackles present at right posterior axillary line Clear left lung, both upper and lower lobes
Abdomen	Flat, soft, non-distended, with no tenderness to palpation Bowel sounds present in all four quadrants and within normal limits No masses, bruits, or organomegaly
Extremities	Peripheral pulses full and symmetric in all extremities No cyanosis, rashes, or edema upon careful inspection Mild clubbing
Genitourinary system	Normal adult female
Neurologic status	Oriented, but conversation is slightly confused Level of consciousness assessed at 14 on Glasgow Coma Scale Cranial nerves intact, including eye movements Strength 5/5 and symmetric throughout Deep tendon reflexes 2+ and symmetric Gait steady Positive Kernig and Brudzinski signs
Cardiovascular system	Distinct S_1 and S_2 with no murmurs or gallops Regular rate and rhythm Skin warm, moist, and pale
Vital Signs	
Blood pressure	160/74 mm Hg (right arm sitting)
Temperature	101.5° F
Heart rate	115 bpm and regular
Respiratory rate	24 breaths per minute and slightly labored Oxygen mask in place with flow at 8 L/min
Source: Author	*Table 2*

Customer Information/Evaluation insert located between pages 64–65.

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POSTOPERATIVE COMPLICATIONS

UPDATE

#30762 • 15 ANCC / 1 Pharm Hour
By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIABETES PHARMACOLOGY

#35322 • 10 ANCC / 10 Pharm Hours
By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to meet the needs of nursing professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.
Additional Approval: AACN Synergy CERP Category A, CCMC

THYROID DYSFUNCTION

UPDATE

#38502 • 4 ANCC / 1 Pharm Hour
By Mail – $22 • Online/eBook – $16

Purpose: As a result of the high prevalence of thyroid conditions, nurses and other healthcare providers encounter thyroid dysfunctional patients every day. The purpose of this course is to provide the most current information regarding thyroid disease diagnosis, treatment, and management to facilitate early diagnosis and treatment and optimum patient outcomes.
Faculty: Marilyn Fuller Delong, MA, BSN, RN
Audience: This course is designed for nurses, allied surgical professionals, and other healthcare workers in all practice settings who may care for patients with thyroid dysfunction.
Additional Approval: AACN Synergy CERP Category A, CCMC

ORGAN AND TISSUE DONATION AND RECOVERY: THE NEW JERSEY REQUIREMENT

NJ Mandate

#38551 • 1 ANCC Hour
By Mail – $21 • Online/eBook – $15

Purpose: The purpose of this course is to provide nurses with information regarding the clinical aspects of organ and tissue donation and recovery, including strategies to overcome barriers to donation.
Faculty: John M. Leonard, MD
Audience: This course is designed for all nurses licensed in New Jersey who may intervene to improve organ and tissue donation rates and facilitate the donation process.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course fulfills the New Jersey requirement for 1 hour of education on organ and tissue donation and recovery.

BIOTERRORISM: AN UPDATE FOR HEALTHCARE PROFESSIONALS

NV Mandate

#91762 • 5 ANCC / 1 Pharm Hour
By Mail – $26 • Online/eBook – $20

Purpose: The purpose of this course is to address the various components of a bioterrorism attack and the appropriate responses required for a healthcare facility.
Faculty: Elizabeth T. Murane, PHN, BSN, MA; Carol Shenold, RN, CIC
Audience: This course is designed for all hospital and clinic staff, physicians, nurses, behavioral health professionals, and entire medical teams, all of whom are expected to respond in the case of a bioterrorist event.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course fulfills the 4 hour Bioterrorism requirement for Nevada healthcare professionals.

PROMOTING THE HEALTH OF GENDER AND SEXUAL MINORITIES

#91792 • 5 ANCC Hours
By Mail – $26 • Online/eBook – $20

Purpose: More individuals who identify as gender and sexual minorities and their families want culturally appropriate information as well as support and referral. The purpose of this course is to provide healthcare professionals with strategies that promote cultural competency when treating and caring for these patients, supporting the concept of patient-centered care.
Faculty: Leslie Bakker, RN, MSN
Audience: This course is designed for all members of the interdisciplinary team, including physicians and nurses, working in all practice settings.
Additional Approval: AACN Synergy CERP Category B

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Course Availability List *(Cont'd)*

CARE OF THE PEDIATRIC TRAUMA PATIENT

#92072 • 15 ANCC Hours

By Mail – $66 • Online/eBook – $60

UPDATE

Purpose: As injury remains a leading cause of mortality and morbidity among children, the purpose of this course is to allow healthcare professionals to provide timely care to pediatric trauma patients and to assist parents and caregivers in recognizing measures that prevent this type of injury.

Faculty: Susan Engman Lazear, RN, MN

Audience: This course is designed for all healthcare professionals involved in the care of pediatric patients, especially those in trauma care centers.

Additional Approval: AACN Synergy CERP Category A

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES

#94192 • 15 ANCC / 5 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.

Faculty: Susan Semb, MSN, RN, CDE

Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.

Additional Approval: AACN Synergy CERP Category A

HYPERTENSION: STRATEGIES TO IMPROVE OUTCOMES

#94221 • 5 ANCC / 5 Pharm Hours

By Mail – $26 • Online/eBook – $20

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with hypertension.

Faculty: John J. Whyte, MD, MPH

Audience: This course is designed for all physicians, osteopaths, physician assistants, and nurses involved in the care of patients with hypertension.

Additional Approval: AACN Synergy CERP Category A

INFLUENZA: A COMPREHENSIVE REVIEW

#94422 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to help healthcare professionals minimize the burden of influenza on their patients and their communities. Information is included to help healthcare professionals accept the importance of influenza vaccine in lessening the impact of the disease on their patients, preventing complications and hospitalizations, and saving healthcare dollars.

Faculty: Elizabeth T. Murane, PHN, BSN, MA

Audience: This course is designed to help healthcare professionals and allied personnel understand influenza and their role in its prevention.

Additional Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

#94672 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

UPDATE

Purpose: The purpose of this course is to provide primary care clinicians and other members of the healthcare team with the knowledge and skills necessary to appropriately diagnose, treat, and prevent pneumonia. It is designed to enhance clinical skills, improve outcomes, and foster an interprofessional collaborative practice consistent with published guidelines.

Faculty: Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intenstive care units.

Additional Approval: AACN Synergy CERP Category A, CCMC

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

#95150 • 3 ANCC / 3 Pharm Hours

By Mail – $21 • Online/eBook – $15

Opioid/ Substance Abuse

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for all physicians, osteopaths, physician assistants, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approval: AACN Synergy CERP Category A, CCMC

Special Approval: This course is designed to meet the requirement for opioid/substance abuse education. This course meets the New Mexico requirement for 3 hours of non-cancer pain management.

ALZHEIMER DISEASE

#96152 • 15 ANCC Hours

By Mail – $66 • Online/eBook – $60

UPDATE

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

Faculty: Joan Needham, MSEd, RNC

Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.

Additional Approval: AACN Synergy CERP Category A, CCMC

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Course Availability List *(Cont'd)*

ANXIETY DISORDERS

#96180 • 15 ANCC / 10 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Additional Approval: AACN Synergy CERP Category A, CCMC

SUICIDE ASSESSMENT AND PREVENTION

#96440 • 6 ANCC Hours

NV APN Mandate

By Mail – $30 • Online/eBook – $24

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for physicians, nurses, psychologists, social workers, therapists, counselors, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approval: AACN Synergy CERP Category A

Special Approval: This course is approved to fulfill the Nevada requirement for 2 hours of education on suicide prevention and awareness.

ASSESSMENT AND MANAGEMENT OF PAIN AT THE END OF LIFE

#97142 • 2 ANCC / 2 Pharm Hours

NJ APN Mandate

By Mail – $21 • Online/eBook – $15

Purpose: Because pain is frequently encountered in the palliative and hospice care environments, a knowledge of appropriate diagnosis and alleviation is vital to all members of the interdisciplinary team. The purpose of this course is to provide an overview of the assessment and management of pain in the end of life, focusing on the components integral to providing optimum care.

Faculty: Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for physicians, physician assistants, nurses, social workers, and other members of the healthcare team seeking to enhance their knowledge of pain management.

Additional Approval: AACN Synergy CERP Category A

HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW

UPDATE

#98392 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Faculty: A. José Lança, MD, PhD

Audience: This course is primarily designed for physicians and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

Additional Approval: AACN Synergy CERP Category A

DIZZINESS AND VERTIGO

NEW!

#98400 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide clinicians with the information necessary to appropriately diagnose and treat causes of dizziness and vertigo and improve patients' quality of life.

Faculty: Mark Rose, BS, MA

Audience: This course is designed for physicians and nurses involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.

Additional Approval: AACN Synergy CERP Category A, CCMC

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8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
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11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Did the activity strengthen your interest in and commitment to interprofessional team learning and collaborative practice?
14. Do you plan to make changes in your nursing practice as a result of this course content?

#95072
Antibiotics Review
5 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No
14. ☐ Yes ☐ No

#94900
Gastroesophageal Reflux Disease
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No
14. ☐ Yes ☐ No

#38920
Pathophysiology: The Central Nervous System
15 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No
14. ☐ Yes ☐ No

#95072 Antibiotics Review — If you answered yes to question #14, what change(s) do you plan to make in your practice? _____

_____

#94900 Gastroesophageal Reflux Disease in Adults — If you answered yes to question #14, what change(s) do you plan to make in your practice?

_____

#38920 Pathophysiology: The Central Nervous System — If you answered yes to question #14, what change(s) do you plan to make in your practice?

_____

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