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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, pharmacists, pharmacy technicians, nurses, 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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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.

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.

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.

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.

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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.

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 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

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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.

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*

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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].

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 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.

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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.

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*

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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 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, 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].

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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.

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*

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.

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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*

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].

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].

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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 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

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*

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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 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].

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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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 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.

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.

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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.

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*

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].

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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*

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].

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.

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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.

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 32–33.

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Dizziness and Vertigo

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses and physicians involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.

Course Objective
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.

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

1. Identify models used to describe vertigo and dizziness.
2. Outline anatomy and physiology of structures involved in vestibular disorders.
3. List peripheral etiologies of vertigo.
4. Describe the clinical presentations of central etiologies of vertigo.
5. Discuss the causes and underlying pathophysiology of other dizziness/vertigo etiologies (e.g., trauma).
6. Devise a best practice, cost-effective diagnostic workup for patients presenting with dizziness and/or vertigo.
7. Apply diagnostic reasoning and appropriate clinical evaluation and management strategies to the differential diagnosis of dizziness and vertigo.
8. Compare and contrast pharmacotherapy agents that may be used to manage vertigo and dizziness.
9. Analyze the role of vestibular rehabilitation in the clinical management of dizziness/vertigo.
10. Describe other approaches to the management of specific dizziness etiologies.
11. Outline preventive approaches and safety considerations for patients with dizziness/vertigo.

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
Jane C. Norman, RN, MSN, CNE, PhD

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

What are limitations in the Drachman-Hart dizziness and vertigo paradigm?

Advances in knowledge of pathophysiology and newer imaging techniques have led to a paradigm shift in the classification system and diagnostic algorithm for managing dizziness and vertigo. With this newly identified connectivity between vestibular, balance, and anxiety disorders comes an enhanced ability to identify the stroke mimics of benign dizziness or vertigo. These and other breakthroughs are transforming the clinical care of patients with dizziness and vertigo complaints, connecting clinical syndromes previously considered unrelated, and expanding the range of effective treatment options for patients.

The modern paradigm for the clinical management of dizziness and vertigo was introduced by Drachman and Hart in a seminal 1972 publication [1]. Based on patient response to the question "What do you mean by 'dizzy?'," dizziness was classified into one of four types that best reflected the subjective descriptions of the symptoms [2; 3]:

- Vertigo: Dizziness experienced as a definite sensation of movement or rotation in space
- Presyncope: A sensation of impending faint or loss of consciousness
- Disequilibrium: A sense of unsteadiness or loss of balance without head sensations
- Lightheadedness: Cannot be classed as vertigo, syncope, or disequilibrium

The Drachman-Hart model also suggested that vertigo had a vestibular cause, presyncope a cardiovascular cause, disequilibrium a neurologic cause, and nonspecific dizziness (lightheadedness) a psychiatric or metabolic cause [4]. In accordance with this framework, the character of symptoms reported by the patient determined the type (pathophysiology) of disorder and guided subsequent clinical evaluation, differential diagnosis, testing, and treatment [3].

By current standards, the Drachman-Hart model was based on weak evidence and developed in the absence of modern diagnostic imaging. In reality, patients often have difficulty describing their symptoms and may give conflicting accounts at different times. In one study, an estimated 62% of patients presenting to the emergency department (ED) with past-week dizziness selected more than one type of dizziness on a multi-response questionnaire, and 52% chose a different type when retested six minutes later [5; 6]. As such, the character and quality of symptoms alone does not reliably predict the cause of dizziness or serve as a dependable guide to management.

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Primary care providers see at least 50% of patients who seek medical attention for dizziness or vertigo. The differential diagnosis is large, and each common etiology accounts for 5% to 10% of cases [7]. The central task for providers is to distinguish benign from serious or life-threatening causes of dizziness and vertigo, such as posterior circulation stroke. Misdiagnoses are common and diagnostic testing can be costly, especially if too much reliance is placed on this outdated diagnostic paradigm [8].

These factors can make the medical care of patients with dizziness/vertigo seem daunting. However, a new diagnostic paradigm has replaced the standard symptom-based approach with an algorithm that streamlines the differential diagnosis, increases diagnostic accuracy for benign and dangerous causes alike, and reduces the use of expensive and unhelpful brain imaging [3; 9].

A "timing and triggers" approach to patient history guides the diagnostic workup. The onset (timing), precipitating factors/events (triggers), evolution, associated symptoms and signs, and the context of dizziness episodes can be used to classify cases as triggered or spontaneous forms of episodic, acute, or chronic vestibular syndromes. Placement within one of six vestibular syndromes informs the differential diagnosis, targeted physical exams, and testing. Targeted exams are a range of procedures that assess for peripheral or central causes of dizziness/vertigo without using less accurate, expensive brain imaging [8].

ANATOMY AND PHYSIOLOGY

What structures comprise the vestibular system?

The labyrinth in each inner ear houses the systems that serve the functions of hearing (auditory) and balance (vestibular). The auditory system involves the cochlea, which transmits sound signals to the brainstem via the cochlear branch of the 8th cranial nerve. The vestibular system is comprised of the vestibular end-organs in the labyrinth, the vestibular nuclei in the brainstem and cerebellum, and the vestibular branch of the 8th nerve, which relays labyrinthine input to the vestibular nuclei. The 8th cranial nerve is also called the vestibulo-cochlear nerve [10; 11; 12].

Within each labyrinth are five vestibular end-organs (three semicircular canals and two otolith organs) that help maintain spatial orientation, postural control, and egocentric perception. Changes in angular and linear head acceleration, movement, and orientation to gravity are detected and signaled via the 8th nerve to brainstem and cerebellar circuits, through thalamic and spinal vestibular projections, and finally to the cerebral cortex [13; 14; 15].

This vestibular input, along with visual input from the eyes and proprioceptive input from peripheral sensory nerves (via the spinal cord), is relayed to the cerebral cortex, which integrates the sensory inputs and adjusts outgoing motor responses to maintain balance, posture, and gaze stabilization of retinal images (via the vestibulo-ocular reflex) [11; 14; 16].

Vertigo, dizziness, spatial disorientation, and disequilibrium can result from: asymmetrical vestibular inputs; vestibular hypofunction causing sensory mismatch in brain integration of sensory inputs; pathologies that affect any peripheral (e.g., inner ear, 8th cranial nerve) or central (e.g., vestibular nuclei and brainstem or cerebellar connections) vestibular system component; or a host of systemic, drug-effect, psychiatric, and physical trauma-related factors [14; 16; 17]. Around 80% of dizziness or vertigo cases are peripheral and 20% are central in origin [11; 18].

EPIDEMIOLOGY

Dizziness is a general, umbrella term that encompasses symptoms of impaired spatial perception. Vertigo is often consolidated into the umbrella term dizziness due to highly variable descriptions of the experience. Dizziness/vertigo is the second most common complaint in the ambulatory setting and constitutes 25% of neurology outpatient referrals, 13% of ED neurology consultations, and more than 3 million ED visits annually [9; 19]. The primary complaint of dizziness accounts for 5.6 million clinic visits annually in the United States. Vertigo is roughly two-thirds more common in women than men. Prevalence increases with age but varies depending on the etiology [20].

Benign paroxysmal positional vertigo (BPPV) is the most frequent vestibular disorder and the most common cause of peripheral vertigo, with a lifetime prevalence of 10% [21]. In the general population, the one-year prevalence rate is about 5% for vertigo, 1.6% for BPPV, and <1% for vestibular migraine [20]. An estimated 17% to 42% of vertigo cases are diagnosed as BPPV [22].

Peripheral causes of vertigo are usually, but not always, benign, while central vertigo often indicates a more serious pathology [18]. The negative impact of vertigo should not be underestimated; around 80% of patients report interruption in daily activities, including employment, from symptoms and the need for medical attention [20].

Dizziness, vertigo, and associated symptoms do not always fall easily into either a peripheral or central syndrome or disorder. Patients can have a dominant group of symptoms more closely tied to peripheral or central origin, while others will show a mix of both groups [23].

In the following discussion of pathophysiology, the diagnostic entities associated with dizziness or vertigo are mainly organized by peripheral or central origin and by shared etiologies or clinical features in a few instances. Throughout this course, "benign" is a pathologic and not a clinical descriptor; "benign" vestibular conditions can be intensely distressing for the patient.

PERIPHERAL CAUSES OF DIZZINESS AND VERTIGO

BENIGN PAROXYSMAL POSITIONAL VERTIGO

As indicated by the name, BPPV describes benign (not life-threatening or malignant) paroxysmal (comes in sudden, brief spells) positional (triggered by certain head positions or movements) vertigo [24]. It is characterized by rotational vertigo induced by head position changes, especially when extending or turning the neck, lying down, or rolling over in bed [21].

Epidemiology

As noted, BPPV is the most frequent vestibular disorder and the most common cause of peripheral vertigo, with a lifetime prevalence of 10% [21]. Women are more often affected than men, with a female-to-male ratio of 1.5–2.2 to 1 [22; 25; 26].

The most frequent age of onset is between the fifth and seventh decades of life. BPPV has an overall prevalence of 3.4% in persons older than 60 years of age and is present in 40% of geriatric patients seen for dizziness [27]. The incidence increases with age due to age-related degeneration of otolithic membrane [9]. The adverse impact on health and quality of life is more severe in older individuals, and BPPV is an important health concern in the elderly because it contributes to falls and associated morbidity and mortality [15; 22].

With a 27% to 50% rate of spontaneous resolution, BPPV can be self-limiting or may persist to become a chronic recurrent disorder [15; 22]. An estimated 85% of patients experience interrupted daily activities/lost days at work, 68% reduce their workload, 4% change their job, and 6% quit their job from the disruptive impact of BPPV [28].

The direct and indirect costs of BPPV are significant. Delayed diagnosis and treatment is frequent. It costs an average $2,000 to arrive at the correct diagnosis, and costs related to BPPV diagnosis alone approach $2 billion annually [22].

Only 10% to 20% of patients with BPPV seen by a physician receive recommended repositioning therapy. Before specialist referral, more than 65% of patients receive potentially unnecessary diagnostic testing or treatment, including magnetic resonance imaging (MRI) (70%), computed tomography (CT) (45%), electrocardiogram (41%), and medication therapy (53%). Delayed diagnosis and treatment of BPPV has cost and quality-of-life implications for patients and their caregivers [22; 28].

Across disciplines, the practice variations in BPPV management are considerable, and medication treatment of BPPV varies substantially among primary care providers and across specialties [22].

Pathophysiology

The vestibular system includes three semicircular canals (or simply "canals") and two otolith organs (the saccule and utricle). The canals (posterior, lateral, and anterior) are positioned at right angles to each other to detect angular accelerations of the head. The canals are organized as functional pairs (left and right ear) in the same spatial plane; any rotation in that plane excites one pair member and inhibits the other [29; 30]. The canals are filled with endolymph fluid and lined with sensitive hair cells to act like a gyroscope. Motion from head rotation induces endolymph movement in the canal oriented in the spatial plane, which stimulates hair cells, activates the ampulla (the motion sensor) and cupula, and sends sensory output to the brain via the vestibular nerve [15; 29].

The saccule and utricle contain sensory epithelium and function to detect linear or translational acceleration forces (e.g., gravity, accelerating or braking a car) [15]. Hair cells in the saccule and utricle are embedded in a matrix of calcium carbonate crystals (otoliths). Deflection of otoliths by gravity stimulates or inhibits neuronal output from the attached hair cells [11].

Otoliths that dislodge and migrate into a canal are called otoconia. Endolymph fluid is usually non-reactive to gravity, but otoconia moves with gravity, causing inappropriate endolymph motion and hair cell stimulation and false signaling of head motion to the brain [24].

The brain receives and integrates peripheral sensory inputs. A false vestibular input conflicts with inputs from ocular, proprioceptive, and the unaffected vestibular systems. This causes a sensory mismatch in the brain integration, perceived as a spinning sensation (vertigo) normally lasting less than 60 seconds after cessation of head movement and inappropriate endolymph motion [24; 31].

BPPV is subtyped by afflicted canal and mechanism. Posterior canal BPPV (85% to 95%) is the most common. Lateral canal BPPV (5% to 15%) is less common, likely because it self-resolves sooner. Anterior canal BPPV (<1%) is uncommon due to the orientation. Rare variants include multi-canal and bilateral multi-canal BPPV [15; 22].

Otoconia contact abnormally stimulates the cupula, triggering vertigo and nystagmus. BPPV is subtyped as [21; 32]:

- Canalolithiaisis: Head movements cause free-floating otoconia to stimulate the cupula
- Cupulolithiasis: Otoconia attach to the cupula, rendering it hypersensitive to linear acceleration and gravity

Canalolithiasis is much more common because the otoconia particulate mass required to exceed the symptomatic threshold is much lower than in cupulolithiasis (0.087 ug vs. 0.69 ug) [21; 33].

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Recurrence and Cardiovascular Risk Factors

Cardiovascular comorbidities are significantly associated with, and potentially important risk factors for, recurrent BPPV. In a nationwide study of 2,682 patients with BPPV (mean age: 59.3 years; 61% female), the prevalence of high blood pressure (55.8%), hypercholesterolemia (38.6%), diabetes (17.7%), and family history of cardiovascular disease (49.4%) were significantly higher than the national averages. A high percentage of patients had hearing loss (42.9%), tinnitus (41.2%), or both (26.8%). The presence of hypertension, dyslipidemia, and pre-existing cardiovascular comorbidities were significantly related to recurrent BPPV episodes, and the presence of diabetes or thyroid/autoimmune disease was also relevant [34].

VIRAL OR BACTERIAL INFECTIOUS CAUSES

Vestibular Neuritis

Vestibular neuritis, the second most common cause of vertigo (after BPPV), is a viral or post-viral inflammatory disorder affecting the vestibular portion of the 8th cranial nerve. It most commonly affects persons 30 to 50 years of age, and men and women are equally affected. New cases are more common in the spring and early summer [10; 35]. Histopathologic nerve studies of these patients are consistent with a viral inflammatory etiology [15].

Vestibular neuritis is characterized by the sudden, acute onset of severe vertigo, nausea, vomiting, and gait instability without hearing loss, typically preceded by an upper respiratory tract infection [36]. The course and treatment of vestibular neuritis and viral labyrinthitis are similar; in both, the severity of acute vestibular symptoms can raise concerns of a central etiology, and the severity of vertigo, nausea, and vomiting reflects the severity of vestibular asymmetry [7; 15; 35].

Viral Labyrinthitis

Labyrinthitis is an inflammatory disorder affecting both the vestibular and cochlear components of the 8th cranial nerve, caused by local or systemic viral or bacterial infection resulting in acute loss of vestibular and hearing function [10]. Viral labyrinthitis, the most common form of labyrinthitis, often results from varicella zoster, influenza, or herpes simplex-1 infection [36]. Sudden sensorineural hearing loss in the affected ear is due to pan-labyrinthine inflammation affecting the cochlea. The estimated prevalence of sudden sensorineural hearing loss is 1 case in 10,000 persons; up to 40% of these patients have prominent vertigo or disequilibrium symptoms, and up to 15% of patients presenting with positional vertigo have viral labyrinthitis [36].

The acute onset of sudden sensorineural hearing loss with severe vertigo, nausea, and vomiting can leave patients bedridden until the symptoms subside. Upper respiratory tract infection precedes the onset of vestibulo-cochlear symptoms in up to 50%. Vertigo usually resolves after several days to weeks, due to spontaneous partial recovery of vestibular function and central compensation of residual unilateral vestibular deficits. Unsteadiness and positional vertigo can persist for months, and return of hearing usually coincides with return of vestibular function [35; 36].

Herpes zoster oticus (Ramsay-Hunt syndrome) is labyrinthitis due to reactivation of a latent varicella zoster virus infection. Inflammation of the vestibulo-cochlear nerve causes vertigo and symptoms of deep, burning, auricular pain followed by eruption of a vesicular rash in the external auditory canal and concha. Symptoms usually improve after several weeks, but permanent hearing loss is common [15; 20].

Bacterial Labyrinthitis

What are the common symptoms of bacterial labyrinthitis?

Viral labyrinthitis should be differentiated from the more dangerous disorder of bacterial labyrinthitis, which occurs through direct bacterial invasion (suppurative labyrinthitis) or passage of bacterial toxins and other inflammatory mediators into the inner ear (serous labyrinthitis) [36; 37]. The bacteria that cause labyrinthitis are the same bacteria responsible for meningitis and otitis; potential bacterial causes include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus* species, *Staphylococcus* species, *Escherichia coli*, and *Mycobacterium tuberculosis* [36].

Profound hearing loss, severe vertigo, ataxia, and nausea and vomiting are common symptoms of bacterial labyrinthitis. Suppurative labyrinthitis almost always results in permanent, profound unilateral hearing loss (or bilateral loss with meningitis). Serous labyrinthitis results in unilateral, high-frequency hearing loss in the affected ear. Regardless of etiology, bacterial labyrinthitis accounts for 35% of all adult-onset cases of hearing loss [36].

MÉNIÈRE DISEASE

Ménière disease is a clinical syndrome of cochlear and vestibular symptoms with a prevalence of 34 to 190 per 100,000 population, an age of onset ranging from the third to seventh decades of life, and a slight female predominance. The odds of Ménière disease are greater among older subjects, persons of European descent, and severely obese persons. Common comorbid conditions in Ménière disease include arthritis, psoriasis, gastroesophageal reflux disease, irritable bowel syndrome, and migraine [15; 38].

The clinical features of Ménière disease are characterized by sudden, fluctuating, unilateral low- frequency sensorineural hearing loss with tinnitus and aural fullness and by spontaneous attacks of vertigo with nausea and vomiting, usually lasting hours [15]. Cochlear symptoms can occur between vertigo episodes. Vertigo is often more frequent in the first years of Ménière disease, but the clinical course is variable, with cochlear and vestibular symptoms taking years to develop in some patients. Bilateral sudden sensorineural hearing loss, migraine, BPPV, or systemic autoimmune disease develops in a subgroup of patients [38].

Ménière disease is idiopathic but is also associated with endolymphatic hydrops, a process whereby accumulation of excess pressure within the inner ear endolymphatic system causes fluctuating hearing loss, episodic vertigo, tinnitus, and aural fullness (i.e., pressure and uncomfortable fullness in the ears) [39]. An interaction of genetics and environmental factors is thought to determine the onset of Ménière disease. While associated with the accumulation of endolymph in the cochlear duct and vestibular organs, endolymphatic hydrops per se does not fully account for the frequency of vertigo attacks, progression of hearing loss, and other clinical features of Ménière disease [38].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Bárány Society recommends that familial Ménière disease should be considered if at least one other relative (first- or second-degree) fulfills all the criteria of definite or probable Ménière disease.

(http://www.jvr-web.org/images/55807-Lopez-Escamez.pdf. Last accessed September 18, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

BILATERAL VESTIBULOPATHY

Bilateral vestibulopathy (also called bilateral vestibular loss) has both central and peripheral processes. The cardinal symptoms of bilateral vestibulopathy reflect the pathophysiology, including motion-dependent postural vertigo with unsteady gait and stance that worsens in darkness and on uneven ground (vestibulo-spinal impairment), and oscillopsia with blurred vision when walking or moving the head (vestibulo-ocular reflex impairment). Patients with bilateral vestibulopathy are typically symptom-free when sitting or lying [40; 41].

The prevalence of bilateral vestibulopathy in the U.S. adult population is 28 per 100,000. The age distribution ranges from youth to old age, depending on etiology, and the mean age at diagnosis is 50 to 60 years. About 60% of patients develop bilateral vestibulopathy slowly and progressively; depending on etiology, 40% of patients have a clinical course marked by episodes of dizziness leading incrementally to bilateral loss of vestibular function [41; 42].

Bilateral vestibulopathy involves atrophy of the hippocampus, with associated impairments in spatial memory and navigation. It is the most frequent cause of motion-dependent postural vertigo in older patients. The three most frequently identified causes of bilateral vestibulopathy are ototoxic aminoglycosides, bilateral Ménière disease, and meningitis, but most cases are idiopathic [40; 41].

A connection between bilateral vestibulopathy and degenerative cerebellar diseases has been established. A syndrome comprised of bilateral vestibulopathy, sensory axonal polyneuropathy, cerebellar ataxia, and oculomotor disturbances accounts for around 30% of cases previously considered idiopathic [40; 43]. Bilateral vestibulopathy can be severely debilitating but is partially reversible with vestibular rehabilitation. It is important for clinicians not to overlook this condition when assessing patients with complaints of dizziness/vertigo [44].

VESTIBULAR PAROXYSMIA

Vestibular paroxysmia is characterized by recurrent spontaneous vertigo attacks that are brief (several seconds up to one minute), and frequent (up to 30 per day) [45]. In one study, vestibular paroxysmia accounted for 3.7% of 17,718 consecutive outpatients in a multidisciplinary vertigo and balance disorders center. Men are affected twice as often as women, and the bimodal age of onset peaks in early childhood and again between 40 and 70 years of age [46].

Vestibular paroxysmia symptoms are triggered by neurovascular compression involving the anterior inferior cerebellar artery and the 8th cranial nerve. More than 95% of cases show vessel-nerve contact at the exit point of the 8th nerve from the brainstem, but the finding is nonspecific because it may be seen in healthy, asymptomatic adults as well [47].

CENTRAL CAUSES OF DIZZINESS AND VERTIGO

The vestibular nuclei and its connections to cerebellar, brainstem, spinal cord, and higher cortical structures comprise the central vestibular system. Dizziness, vertigo, ataxia, or disequilibrium can result from pathologies involving central vestibular structures, the most common of which are migraine-related vestibulopathy, brainstem strokes, head trauma, multiple sclerosis, and cerebellar degeneration [48].

Vertigo, vestibular dysfunction, and anxiety disorders are now recognized as co-factors, and the inter-relationship is substantial. Dizziness and vertigo are associated with diverse systemic disorders, trauma, and toxic exposures. Etiologies in psychiatric and systemic disorders are complex and diffuse.

Central abnormalities cause about 20% of dizziness complaints, and patients may present with disequilibrium or ataxia rather than vertigo. Dizziness/vertigo may be the sole presenting symptom of an impending cerebrovascular event origination in the brainstem or cerebellum [7]. In these presentations, distinguishing benign from potentially or imminently dangerous cerebrovascular causes has been the focus of extensive research effort.

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VESTIBULAR MIGRAINE

What is the most common cause of recurrent spontaneous vertigo attacks?

Vestibular migraine is the most common central cause of recurrent spontaneous attacks of vertigo. "Vestibular migraine" is the preferred name for this disorder, because patients may experience a range of vestibular symptoms not limited to vertigo (e.g., dizziness, nausea, vomiting) [19; 49].

Vestibular migraine accounts for 7% of patients seen in dizziness clinics and 9% of patients seen in headache clinics, but it remains underdiagnosed [49]. It is three times more common in women and occurs most often between 20 and 50 years of age. A family history of migraine is a risk factor, and vestibular migraine may involve a genetic susceptibility to enhanced excitability during sensory information processing, which induces interactions of vestibular and pain pathways [7; 49].

Pain and vestibular sensory inputs converge in brainstem structures that modulate pain sensitivity and anxiety responses to pain and vestibular signaling. Vestibular stimulation activates some higher cortical regions involved in pain perception. Vestibular and pain pathways also overlap at brainstem and thalamic levels. This may explain, in part, the frequent clinical overlap of migraine (including vestibular migraine), balance, and anxiety disorders [49; 50].

Vestibular migraine is a clinical diagnosis in which central and peripheral mechanisms arise from genetic and environment interactions. Mechanistic interactions cause excessive sensitivity to pain perception (e.g., headache, allodynia), hearing (e.g., phonophobia), vestibular stimulation (e.g., vertigo, motion sickness, visual vertigo), vision (e.g., photophobia), and sense of smell (e.g., osmophobia) [49; 50; 51].

Vestibular migraine is diagnosed primarily by patient history and exclusion of alternative causes; neurologic exams performed between episodes generally show normal findings [49]. The migraine may occur with episodic vertigo, chronic motion sensitivity, or other vestibular symptoms. Vertigo and motion sickness, with or without headache, is the common presentation, and some patients report mild, transient auditory symptoms of tinnitus, muffled hearing, or ear pressure [15; 19].

CEREBROVASCULAR ETIOLOGIES

Patients with potentially serious or life-threatening stroke may present with vestibular symptoms without other focal neurologic signs. This acute presentation is linked to stroke involving one of several branches that supply the brainstem, cerebellum, or inner ear. Early differentiation is an area of intense research focus. Early recognition of isolated vertigo as a stroke sign allows specific intervention and secondary prevention. Misdiagnosis of stroke-related vertigo as a peripheral cause may result in significant morbidity or mortality, and overdiagnosis of stroke as peripheral vertigo leads to expensive and unnecessary workups, medication, and hospital admissions [52; 53].

Vertebrobasilar Artery Territory (Posterior Circulation) Infarcts or Strokes

Around 20% of all ischemic events occur in the vertebrobasilar artery territory, with dizziness/vertigo the sole presentation in up to 33% of patients. Inferior cerebellar and small brainstem infarctions are an increasingly recognized cause of isolated vertigo, and transient isolated vertigo is a common manifestation of vertebrobasilar artery ischemia. Vertebrobasilar artery transient ischemic attacks (TIAs) typically last eight minutes on average [52; 54]. Several syndromes are associated with TIAs, ischemia, or infarcts in vertebrobasilar artery territories (e.g., the brainstem, cerebellum) [48].

Numerous arteries extend from the posterior inferior cerebellar artery to supply the medial, lateral, and dorsal aspects of the medulla. Vertigo is more frequent in posterior inferior cerebellar artery strokes, and these are the most common cerebellar infarcts [55]. Dizziness/vertigo is one of the most common symptoms of cerebellar ischemic stroke. A large prospective study showed 11% of patients with cerebellar infarction had isolated vertigo, of whom 96% had an infarct in the medial branch of the posterior inferior cerebellar artery [56].

Medial Medullary Infarcts

Medial medullary infarctions usually cause a vertiginous labyrinthian syndrome that mimics peripheral vestibulopathy. Severe vertigo and nystagmus are prominent, and some patients describe feeling as if being pulled to the ipsilateral side by a magnet [53].

Lateral Medullary Infarcts

The vestibular nuclei are more vulnerable to ischemia than other structures in the posterior fossa, and ischemia of the lateral medulla (including the vestibular nuclei) may be a common mechanism of isolated vascular vertigo [52]. Wallenberg syndrome describes a lateral medullary infarction that presents with a range of focal neurologic signs.

Vestibulo-cerebellar symptoms/signs are almost always present, because lateral medullary infarcts involve the vestibular nuclei and their connections. The symptoms/signs include dizziness or disequilibrium; acute vertigo, nausea, or vomiting; ipsilateral facial pain, numbness, and ataxia (falling to the side of the infarct); and decreased contralateral pain and thermal sensitivity. The nystagmus has horizontal and rotational components [48; 53; 54].

Dorsal Medullary Infarcts

Less prevalent than medial or lateral medullary infarction, dorsal medullary infarcts typically cause dizziness/vertigo, imbalance, and ocular motor abnormalities. This is because the dorsal medulla also contains the vestibular nuclei and other structures that relay and process vestibular and ocular motor signals [57].

Anterior Inferior Cerebellar Artery Distribution

The anterior inferior cerebellar artery supplies the lateral pons and branches off to form the internal auditory artery, which irrigates the cochlea and vestibular labyrinth. The labyrinth is especially vulnerable to ischemia, because the internal auditory artery is an end-artery with minimal collaterals. Isolated acute audio-vestibular loss may herald an impending anterior inferior cerebellar artery territory infarction. Auditory artery occlusion causes loss of auditory and vestibular function [48; 52].

Pontine syndrome is a partial pontine ischemia produced by anterior inferior cerebellar artery occlusion, characterized by vertigo, tinnitus, and hearing loss [48; 54].

STRUCTURAL ABNORMALITIES AND LESIONS

Malformations or lesions that affect the vestibular system can cause dizziness or vertigo, as can any process that leads to acute vestibular asymmetry. The brain may adapt to this asymmetry over time to prevent or diminish vertigo, but imbalance may persist when vestibulo-cerebellar pathways are impacted. For example, sudden-onset vertigo is more likely with stroke, but less likely with a slow-growing acoustic neuroma (a vestibular tumor) because central adaptation to the asymmetry is gradual and imperceptible [15].

Superior Canal Dehiscence Syndrome

Superior canal dehiscence syndrome is caused by an abnormal opening (dehiscence) in the thin bony roof of the superior semicircular canal. This is thought to be related to congenital thinning of the temporal bone and occurs in 0.1% of the population. Development of the bony opening renders the membranous labyrinth unusually susceptible to changes in sound and pressure. In addition to dizziness and sensitivity to loud noises, patients with superior canal dehiscence syndrome experience autophony, whereby one's voice, breathing, or bodily sounds are excessively audible [58]. The dizziness/vertigo induced by sound and pressure stimuli can be associated with auditory symptoms of conductive or mixed hearing loss [59].

Chiari Malformation

A Chiari malformation is defined as descent of the cerebellar tonsils ≥5 mm past the foramen magnum [19]. This occurs when the lower part of the cerebellum does not fully migrate rostrally during fetal development. Compression of the cerebellum from this condition may lead to occipital headaches, vertigo, nystagmus, and ataxia in early childhood or later in life [15]. Patients also commonly describe occipital and neck pain provoked by physical activity or maneuvers that increase intracranial pressure [19].

Symptomatic Chiari malformations should be referred for neurosurgical evaluation and considered for posterior fossa decompression. Asymptomatic Chiari malformations can be discovered incidentally during MRI for dizziness from a different etiology. Asymptomatic patients should be spared the risks of surgery [19].

Acoustic Neuroma (Vestibular Schwannoma or Schwann Cell Tumors)

Acoustic neuromas are tumors of the vestibular portion of the 8th cranial nerve, diagnosed in roughly 3,000 cases annually. Acoustic neuromas can expand and compress surrounding structures along the brainstem, potentially leading to sensorineural hearing loss and vertiginous symptoms [20; 60].

DEMYELINATING AND NEURODEGENERATIVE DISORDERS

Multiple Sclerosis

Multiple sclerosis (MS), an idiopathic demyelinating disorder of the central nervous system (CNS), is considered an autoimmune disease most likely caused by an autoantigen to a myelin protein [48]. MS has an annual incidence of 10 to 80 cases per 100,000 individuals in the United States and affects twice as many women than men [60].

CNS demyelinization usually occurs in the white matter, where plaque formation disrupts signal conduction and leads to symptoms [48]. Demyelinating plaques that develop in central vestibular pathways may cause recurrent episodes of vestibular symptoms, especially during illness and with heat exposure (Uhthoff phenomenon). The plaques may be visible on MRI [19; 20].

Vertigo is the presenting symptom at onset in 5% of MS cases, and more than 50% of patients present with vertigo at some point in the disease course. MS can mimic an 8th cranial nerve lesion when plaque develops in the entry of the nerve root in the brainstem to produce vertigo and horizontal nystagmus [48].

MS may present with dizziness, vertigo, or imbalance, especially with brainstem or cerebellum lesions that affect the vestibular system; these lesions may also result in nystagmus, ataxia, slurred speech, and diplopia. Despite the increased risk of CNS vertigo in patients with MS, non-MS (peripheral and central) causes (e.g., BPPV, vestibular migraine) can co-occur [15].

Parkinson Disease and Parkinson-Plus Syndromes

Dizziness may be a manifestation of many neurodegenerative disorders. At presentation, patients with Parkinson disease may describe the shuffling or festinating gait as being "dizzy" or "off balance." Medications such as levodopa or dopamine agonists (e.g., pramipexole, ropinirole) may cause orthostatic hypotension, and hence presyncopal dizziness [19].

The Parkinson-plus syndromes (e.g., multiple system atrophy, dementia with Lewy bodies) often cause many symptoms that are construed as "dizziness." Multiple system atrophy causes dysautonomia (causing orthostatic presyncope or syncope), vertigo, nystagmus (causing oscillopsia), and/or cerebellar findings (leading to gait ataxia). Progressive supranuclear palsy often presents with falls and complaints of imbalance; loss of downgaze often causes imbalance when descending stairs [19].

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Cerebellar Vertigo Syndromes

Neurodegenerative and hereditary diseases of the cerebellum often lead to postural vertigo, gait disorders with ataxia, and cerebellar oculomotor disorders such as saccadic dysmetria, gaze saccades, gaze nystagmus, and downbeat nystagmus [61].

Episodic ataxia type 2 is a rare but important disorder to identify because the random attacks of vertigo, ataxic gait, and slurred speech lasting minutes to days often respond dramatically to acetazolamide. The onset of recurrent episodes may occur in childhood or early adulthood, but the condition is often undiagnosed into late adulthood. This disorder is due to a voltage-sensitive calcium channel mutation [15].

PERSISTENT POSTURAL PERCEPTUAL DIZZINESS

Persistent postural perceptual dizziness (PPPD) develops when a precipitating condition (typically an acute vestibular event, vestibular migraine, panic attacks, or anxiety with prominent dizziness) occurs in individuals with a maladaptive behavioral response to the acute symptoms [62]. In this way, PPPD is a new diagnostic entity that bridges previous knowledge gaps by connecting persistent non-vertiginous dizziness, perceptual hypersensitivity, and chronic anxiety [15; 62].

PPPD may be a highly prevalent cause of chronic non-vertiginous dizziness. The population and primary care prevalence is not yet known, but the female-to-male ratio is 5:1. PPPD symptoms are often worsened by sleep deprivation and stress but not by head motion to the degree seen with most vestibular disorders [15; 62].

The central etiology relates to behavioral factors, neurotransmitter function, and other probable CNS mechanisms [15]. Brain imaging of patients with PPPD shows reduced connectivity in multisensory vestibular processing and spatial cognition, with increased connectivity between visual and emotional processing. Dizziness burden, anxiety, and depression correlate with connectivity in clinically relevant brain regions [63]. PPPD may linger following minor head injury and become entwined with other symptoms of post-concussive syndrome [15].

MAL DE DÉBARQUEMENT SYNDROME

A transient experience of "sea legs" after returning to land from riding on a boat is not uncommon, but in mal de débarquement syndrome it persists for weeks, months, or years. Mal de débarquement syndrome is an uncommon vestibular disorder in which a sense of rocking first appears soon after disembarking and is most common in women. Travel by aircraft or automobile can also trigger the persistent unsteadiness. Symptoms typically abate during passive motion (e.g., a boat or car ride) but resume when motion ceases. The cause is unknown, but it may be a disorder of the vestibular velocity storage mechanism with a limited adaptive ability [15; 62].

SYSTEMIC ETIOLOGIES

Dizziness and vertigo are associated with systemic diseases or conditions as symptoms, comorbidities, risk factors, or shared pathophysiologic pathways. These most commonly involve hemodynamic (orthostatic hypotension), metabolic (diabetes), cigarette smoking, and cardiovascular origins.

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is typically defined by a sustained decline in blood pressure of at least 20 mm Hg systolic or 10 mm Hg diastolic within three minutes of standing, with symptoms of lightheadedness or presyncope on arising. Vertigo is a common and under-appreciated symptom [8].

Orthostatic hypotension is common in older people and a frequent complication of (excessive) hypertensive medication. Such patients experience postural dizziness without documented syncope based on transient reductions in cerebral blood flow. Orthostatic hypotension may occur 5 to 30 minutes after remaining asymptomatic in the upright position, or when orthostatic vital signs have been normal. It may be missed as a cause of periodic syncope or presyncopal dizziness [15].

DIABETES

Vestibular dysfunction is a complication of type 2 diabetes, with reported rates 70% higher compared with age-matched controls. Both central and peripheral vestibular dysfunction are observed in type 1 and type 2 diabetes. Hypertension mediates 42% of the association between type 2 diabetes and BPPV, suggesting that hypertension provides the mediating pathway for diabetes' impact on the vestibular system [177].

CIGARETTE SMOKING

In one study, the association between peripheral vestibular disorders and smoking was examined in patients (mean age: 65.3 years) treated for hypertension, dyslipidemia, or diabetes in primary care and followed over one year for new peripheral vestibular disorder events [64]. Compared with never-smokers, the risk of new-onset peripheral vestibular disorder was 2.22 times greater for ever-smokers and 2.70 for all ever-smokers with ≥30 pack-years. Compared with male never-smokers, the risk of new onset peripheral vestibular disorder was 4.41 greater for male ever-smokers with ≥30 pack-years. There were too few female heavy smokers to compare against female never-smokers [64].

VESTIBULAR IMPAIRMENT, ANXIETY, AND PERCEPTION

Clinically relevant vestibular system interactions with traumatic stress, depressive disorders, and other psychiatric disorders have been described. However, vestibular-anxiety interactions are the most extensively studied and compelling and will be the focus of this section.

Anxiety disorders account for 8% to 10% of cases with vestibular symptoms as primary complaints [65]. In patients presenting with dizziness concerns, the rates of panic disorder are 5 to 15 times greater than the general population. Patients with panic disorder frequently experience significant dizziness and often demonstrate vestibular dysfunction [66].

The high co-occurrence of vertigo and anxiety has been described since antiquity [51]. By the late 1800s, dizziness and vertigo, anxiety, autonomic arousal, appraisal of spatial orientation, and threat assessment were appreciated as core contributors to agoraphobia; otologic disease was found to precipitate agoraphobia in patients with anxiety. As otology, neurology, and psychiatry matured into separate specialties in the early 20th century, agoraphobia became a psychiatric disorder and lost its spatial and motion context [62; 67].

While traditional medical teaching describes a narrow range of vestibular system functions (e.g., gaze stability, balance) and dysfunctions (e.g., dizziness, unsteadiness, vertigo), vestibular involvement in brain processes beyond balance, spatial orientation, and gait is established. The inter-relationship of anxiety and balance disorders is being rediscovered more than a century later [68; 69; 70].

Increasingly demonstrated is the extent of multi-directional connectivity and interaction between threat/anxiety, vestibular, visual, and somatosensory systems, and how this helps explain the shared pathophysiology, clinical features, and prevalent comorbidity [71]. As such, it is important to assess for, and treat when present, anxiety disorders, cognitive impairment, and perceptual disturbances in patients with dizziness/vertigo complaints [50; 68; 69]. The suggestion is made that dichotomous thinking (structural disease vs. "emotional issues") should be discarded in order to effectively assess vestibular, psychiatric, and perceptual dysfunction. Each of these domains should be addressed simultaneously for favorable treatment outcomes [72].

SHARED CLINICAL FEATURES

Patients with vestibular or balance disorders often have anxiety symptoms. Likewise, patients with anxiety disorders often show vestibulo-ocular and/or peripheral vestibular dysfunction [73]. Vestibular and balance abnormalities are especially common in panic disorder with agoraphobia [70].

Chronic anxiety and anxiety disorders may be causes or complications of vestibular symptoms or disorders. These psychiatric disorders affect 30% to 50% of patients who seek specialist care for vestibular symptoms, and they adversely affect the treatment outcomes of patients with vestibular disease, especially when unrecognized [62; 71]. Vestibular function is linked to emotional states through complex bidirectional interactions; vertigo worsens emotional symptoms, and emotional states can amplify perceptions of vertigo or disequilibrium [69].

ANXIETY, BALANCE, AND VESTIBULAR INTERACTIONS

Anxiety can impair ocular motor reflexes and gaze control, which may contribute to visual and visual-vestibular syndromes. Anxious states can amplify a normative gaze bias toward potentially threatening stimuli in the visual field, which, in patients with social anxiety disorder, may drive hypervigilance-avoidance gaze patterns. The impairing effect of anxiety on gaze control reduces gaze stability on visual targets, which may underlie dizziness and visual symptoms in PPPD [73; 74].

Exposure to heights reflexively increases body sway in normal subjects by reducing visual feedback to body sway (in the absence of motion). Body sway is more pronounced in subjects with height phobia, and anxiety-related gaze diversion may increase gait instability in patients with fear of falling [74; 75].

Space-motion discomfort describes symptoms of uneasiness over spatial orientation and hyperawareness of motion stimuli. In affected individuals, space-motion discomfort is triggered by movement in visually rich environments and exposure to moving or patterned objects while stationary. It is especially prevalent in patients with panic disorder and agoraphobia; persons with panic symptoms often become destabilized under conflicting sensory conditions. Visual vertigo and other situation-specific interactions between balance and anxiety may be part of a broader space-motion discomfort profile [62; 73; 76].

DISRUPTED MULTISENSORY INTEGRATION

The vestibular system maintains equilibrium through vestibular spinal reflexes, stabilizes visualization through the vestibular-ocular reflex, and contributes to spatial orientation [77]. Accurate perception of gravity and maintenance of spatial orientation, balance, and gait rely on brain integration of visual, vestibular, proprioceptive, and somatosensory signals and cognitive processes [78].

The brain normally resolves mismatched sensory information by updating and realigning the internal spatial representation of the body with the surrounding space. Impairment of one sensory signal is compensated by reweighting of intact sensory inputs [62; 77]. Unsuccessful reweighting impairs multisensory integration, leading to incongruity between visual and vestibular information and visual-vestibular sensory mismatch. This can elicit an erroneous cortical

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representation of the body within the surrounding space, producing spatial disorientation, anxiety, dizziness, balance problems, and increased risk of falls [62; 77; 78; 79].

Visual Dependence

Visual dependence is an over-reliance on visual information to maintain spatial orientation, which compensates for vestibular dysfunction that impairs multisensory integration. Space-motion discomfort, a prominent feature resulting from the visual-vestibular conflict, may cause symptoms of imbalance, discomfort, anxiety, or phobic avoidance in situations where moving, complex, or conflicting visual environments trigger intense dizziness/vertigo symptoms [70; 79].

Depersonalization and Derealization

Depersonalization and derealization are perceptual abnormalities, described primarily from the psychiatric perspective for more than a century. Depersonalization (feeling detached, numb from one's emotions, experiences), derealization (objects, people, and surroundings experienced as unreal, distant, artificial, lifeless), and intact reality testing are symptoms of depersonalization/derealization disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [80; 81]. The DSM-5 also lists derealization and depersonalization as potential panic attack symptoms in the diagnostic criteria for panic disorder [81].

Trauma history and anxiety disorders are prevalent co-factors and antecedents of depersonalization/derealization. Phencyclidine or cannabis use can trigger acute symptoms [82]. Derealization symptoms are particularly distressing, if not profoundly intolerable; an anxious or panic response can amplify depersonalization/derealization symptoms, creating a vicious cycle [80].

Patients diagnosed with depersonalization/derealization disorder have high rates of past-year inpatient hospitalization (25.6%) and ongoing outpatient psychotherapy (40.4%). Depersonalization/derealization disorder has been described as highly chronic, severely underdiagnosed, and often refractory to pharmacotherapy and psychotherapy [83].

The psychiatric perspective is important, but inadequate by failing to consider recent evidence implicating vestibular dysfunction, impaired multisensory integration, and sensory mismatch in depersonalization/derealization [84; 85]. Vestibular inputs provide a frame of reference within which spatial information from other senses is interpreted. Depersonalization/derealization associated with vestibular dysfunction is a consequence of a sensory mismatch between disordered vestibular input and other sensory signals of orientation, creating a misleading frame of reference and impaired bodily representation in the cortex. This leads to a perception of disembodiment and other "unreal" perceptions [84; 85; 86].

Stimulation of semicircular canals or otoliths can provoke depersonalization/derealization symptoms in healthy volunteers without a history of depersonalization/derealization [86]. However, depersonalization/derealization symptoms in vestibular patients with anxiety are more frequent, more severe, and qualitatively distinct from symptoms in patients without anxiety. Anxiety is essential to the appearance and intensity of depersonalization/derealization symptoms in vestibular patients [87].

Out-of-Body Experiences

Out-of-body experiences are states in which the individual experiences the center of awareness as located outside his or her physical body, with the sensation of seeing the environment from this elevated vantage point. Persistent vestibular dysfunction disrupts the integration of visual, somatosensory, and vestibular signals. Perceptual incoherence, a byproduct of the resultant visual-vestibular mismatch, can produce an out-of-body experience, with anxiety a significant co-factor in out-of-body experience etiology. In non-dizzy persons, out-of-body experience is associated with depersonalization or derealization symptoms [88].

COGNITIVE FUNCTION

Vestibular input activates a broad neural network in the cortex for visuospatial processing and memory. Vestibular function is strongly linked to visuospatial ability—how the mind organizes and understands two- and three-dimensional space. Impaired vestibular input can fundamentally change one's mental representation of, and awareness of one's position in, three-dimensional space [69].

Vestibular dysfunction is also implicated in impaired attention, cognitive processing ability, memory, and executive function [69]. This is especially relevant in the elderly, for whom cognitive impairment from vestibular dysfunction is broader and more diffuse. It should be considered in any older patient with dizziness or vertigo [89].

POST-TRAUMA OR TOXIC EXPOSURE

POST-CONCUSSIVE AND CERVICOGENIC VERTIGO

Patients with post-concussive syndrome or cervicogenic dizziness following a whiplash can experience chronic dizziness with headache, insomnia, cognitive symptoms, or mood lability [62].

Post-Concussion Syndrome

In the United States, there are approximately 3.8 million sports-related concussions annually in adolescents and adults. Concussion, the mildest form of traumatic brain injury (TBI), is a transient functional disorder caused by direct trauma, rapid acceleration-deceleration of the head, or blast forces. Post-concussion syndrome persists beyond three months in up to 20% of affected individuals [90].

Headache and dizziness are common symptoms. Other symptoms include light and sound sensitivity, nausea, tinnitus, cognitive dysfunction (mental fog), problems with visual focus, sleep changes, depression, anxiety, and irritability. Dizziness may be due to the direct CNS effects of the trauma (e.g., axonal injury, other microstructural damage), vestibular migraine, or neuropsychiatric disorders (e.g., anxiety, depression, post-traumatic stress disorder). Post-concussion BPPV is not uncommon. A detailed history and examination are crucial when assessing dizziness in these patients, because treatment should address the underlying etiology [91; 92].

Mild TBI

Balance disorders, migraine, and anxiety are also components of mild TBI that appear following exposure to blunt-force or blast trauma, along with symptoms of headache, nausea, vomiting, dizziness/balance problems, fatigue, sleep disturbances, and difficulty with memory or concentration [90; 92]. Dizziness and headache are reported in more than 70% of cases presenting acutely or chronically post-exposure; vertigo emerges sub-acutely. Other significant sequelae are hearing loss, emergent and delayed post-traumatic balance disorders, and chronic migrainous disorders without radiologic evidence of damage, often accompanied by tinnitus and sensitivity to light or sound [50].

Patients with chronic (at least six months) post-traumatic head injury vestibular symptoms (e.g., imbalance, dizziness) show high rates of multiple peripheral and central vestibular disorders. Despite expert neuro-otologic management, 20% of patients have persistent vestibular symptoms at two years. Treatment-resistant vestibular symptoms in these patients may result from brain trauma-induced impairment of brain plasticity-mediated repair mechanisms [93].

Cervicogenic Vertigo

Cervicogenic dizziness is characterized by imbalance, unsteadiness, disorientation, neck pain, limited cervical range of motion, and headache. It is closely related to changes in cervical spine position or cervical joint movement. Common etiologies are post-whiplash injury and inflammatory, degenerative, or mechanical cervical spine dysfunction. The cause of imbalance, unsteadiness, and disorientation symptoms is suggested to involve pain, faulty cervical proprioceptive inputs, and disrupted signaling from upper cervical proprioceptor to vestibular nuclei [94].

Cervicogenic dizziness is diagnosed after mimics are ruled out, including central and peripheral vestibular disorders, vestibular migraine, labyrinthine concussion, cervical arterial dysfunction, and whiplash-associated disorder [94].

EXPOSURE TO TOXINS

Lead or mercury exposure can be ototoxic and may cause vertigo through temporary or permanent damage to the inner ear or auditory nerve [95].

ADVERSE DRUG EFFECTS

Dizziness or vertigo can occur as a direct side effect of medication that resolves after discontinuation without cochleo-vestibular damage, or it may develop (and persist) secondary to cochleo-vestibular damage (ototoxicity).

SIDE EFFECTS

The list of drugs that may cause vertigo or dizziness is extensive and diverse. Medications consistently associated with dizziness include the antihypertensive drugs amlodipine and hydrochlorothiazide; the antibiotics ciprofloxacin, amoxicillin, and clavulanic acid; pantoprazole (a proton pump inhibitor); aripiprazole (an atypical antipsychotic); and atazanavir (a protease inhibitor). Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline can induce vertigo or dizziness as side effects or with abrupt cessation; mirtazapine may cause dizziness side effects [95].

Antiepileptic drugs in particular are linked to adverse effects on auditory or vestibular systems that may be reversible or irreversible. Even at therapeutic dose ranges, long-term treatment with oxcarbazepine, carbamazepine, lamotrigine, phenytoin, valproate, gabapentin, or vigabatrin may result in auditory, central, and/or peripheral vestibular dysfunction [96].

OTOTOXIC DRUGS

What are the most vestibulotoxic of all ototoxic medications?

Ototoxic drugs can damage cochleo-vestibular structures, which may result in hearing loss, tinnitus, dizziness, or disequilibrium [97]. Cochlear damage can present acutely as tinnitus. Early hearing loss, which patients may not recognize, manifests in the highest frequencies (>4,000 Hz). With progression, the lower frequencies are affected, and patients may become profoundly deaf if the drug is continued. Stopping the drug early, before extensive damage, may prevent further loss. Partial recovery of auditory thresholds is possible, but the loss is usually permanent [97; 98].

Vestibular toxicity typically includes imbalance and visual symptoms. As with bilateral vestibulopathy, imbalance is worse in the dark or situations in which footing is uncertain; oscillopsia occurs when the head is moving. Patients do not present with nystagmus or vertigo complaints, because vestibulotoxicity is bilateral [97].

Ototoxicity is linked to more than 100 drug classes. The best-known and most ototoxic are aminoglycosides, amiodarone, macrolides, vancomycin, loop diuretics, antineoplastic agents, salicylates, and antiseptics.

Aminoglycosides

Aminoglycosides are the most vestibulotoxic of all ototoxic drugs. The introduction of streptomycin in 1944 for treat-

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ment of tuberculosis brought ototoxicity to clinical attention, as a substantial number of treated patients developed irreversible cochleo-vestibular dysfunction [97; 98].

The aminoglycosides remain widely used and differ in cochleo-vestibular toxicity. Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially cochleotoxic. Gentamicin affects both cochlear and vestibular systems but is primarily vestibulotoxic, as are streptomycin, tobramycin, and netilmicin [97; 98].

The onset or progression of hearing loss can occur long after cessation of treatment, because aminoglycosides are cleared more slowly from inner ear fluids than from serum. Patients should be monitored for vestibulotoxic effects up to six months after discontinuation [97; 98].

Amiodarone

Amiodarone is a widely used antiarrhythmic drug. Reports of amiodarone-induced vertigo and gait instability followed its introduction in the 1980s, and the drug was first implicated in bilateral vestibulopathy causality in 2017. The prevalence of bilateral vestibulopathy is as high as 81 per 100,000. Most cases are idiopathic, and amiodarone may account for a substantial proportion of bilateral vestibulopathy with unexplained causation [99].

Macrolides

Erythromycin has been sporadically linked to reversible ototoxicity in patients with ototoxic risk factors. Azithromycin and clarithromycin have also been suggested as possibly ototoxic [97].

Vancomycin

Vancomycin is a glycopeptide antibiotic introduced in the 1950s and commonly used for efficacy in methicillin-resistant staphylococcal infections. Ototoxicity is reported in patients with other risk factors, but vancomycin monotherapy at therapeutic doses has not shown ototoxicity [97].

Loop Diuretics

Loop diuretics are used for treating congestive heart failure, renal failure, cirrhosis, and hypertension. The most effective and widely used (i.e., ethacrynic acid, furosemide, and bumetanide) can cause ototoxicity [97].

Antineoplastic Agents

Antineoplastic agents most associated with ototoxicity are the platinum-based compounds cisplatin and (to a lesser extent) carboplatin. Ototoxicity and nephrotoxicity are dose-proportional with both compounds [97].

Salicylates

Salicylate (aspirin) can produce tinnitus and a generally reversible flat sensorineural hearing loss at low doses, especially in elderly patients [97].

Antiseptics

Some antiseptics used for surgical preparation are ototoxic. Povidone-iodine is safe for middle ear surgeries. However, chlorhexidine is toxic if it reaches the inner ear and should not be used, and VoSol and Gentian violet also show ototoxicity [100].

DIAGNOSIS: THE "TIMING AND TRIGGERS" WORKUP

What do targeted examinations emphasize to detect and localize the underlying dizziness/vertigo pathology?

As mentioned, the prevailing clinical model in dizziness and vertigo is being replaced by the "timing and triggers" approach to streamline the differential diagnosis, increase diagnostic accuracy, and reduce unnecessary imaging tests and misdiagnosis.

Publications have brought into focus the misdiagnosis of patients with stroke who present with isolated dizziness. The "timing and triggers" approach is shown to reduce this highly concerning problem largely resulting from [8]:

- Over-reliance on the symptom quality approach
- Lack of familiarity with key physical exam findings
- Overweighting traditional stroke risk factors for patient screening (e.g., age, vascular risk factors) and not considering stroke in younger patients
- Over-reliance on CT

The "timing and triggers" approach departs from the Drachman-Hart model by de-emphasizing patient descriptions of symptom quality, dropping presyncope and lightheadedness as dizziness and vertigo classes, and limiting use of the vague term "lightheadedness" [2; 7]. The term "dizziness" is used as a generic descriptor for disturbed balance or spatial orientation, vertigo, lightheaded, spinning, rocking, and others.

Accurate diagnosis is an essential precondition for effective treatment of dizziness and vertigo, best ensured by defining the rapidity of onset, the context, associated symptoms, intermittent or persistent nature of dizziness, and triggers of intermittent symptoms during patient history-taking. This is called the "timing and triggers" diagnostic workup. The workup is structured using the algorithm Triage-TiTrATE-Test [8; 37; 101]:

- Triage: Identify dangerous causes by noting the presence of prominent associated symptoms, abnormal vital signs, altered mental status, or ancillary test results.
- Timing: In the history of presenting illness, classify the pattern of dizziness attacks as episodic, acute, or chronic in duration.

- Triggers: In the history and review of systems, seek an underlying pathophysiologic mechanism by searching for obvious triggers or exposures.
- Targeted exam: Differentiate benign from dangerous causes within a timing-trigger category by using specific exam findings, emphasizing a targeted eye movement exam.
- Test: Choose the best laboratory or imaging test when clinically relevant uncertainty remains about a dangerous cause that has not been ruled out.

The timing and triggers history of the TiTrATE algorithm divides patients into six vestibular syndrome categories [8; 37]:

- Acute vestibular syndrome (AVS)
  - Postexposure (traumatic/toxic) (t-AVS)
  - Spontaneous (s-AVS)
- Episodic vestibular syndrome (EVS)
  - Triggered (t-EVS)
  - Spontaneous (s-EVS)
- Chronic vestibular syndrome (CVS)
  - Context-specific (t-CVS)
  - Spontaneous (s-CVS)

In this context, "vestibular" refers to vestibular symptoms and not etiology. Vestibular symptoms include vertigo, dizziness, nausea, vomiting, and nystagmus [49].

The large differential diagnosis of potential dizziness etiologies is daunting to many clinicians. Triage-TiTrATE-Test greatly streamlines this process such that every forward step eliminates potential etiologies, substantially narrows the range, and by the final step, an accurate diagnosis is already evident or confirmed by referral for specialized testing [8]. This differential diagnosis process has been referred to as a funnel approach [37].

TRIAGE

Some patients with a primary symptom of dizziness have obvious associated symptoms (e.g., gastrointestinal bleeding) or context (e.g., new antihypertensive medications, anticonvulsant toxicity), abnormal vital signs, altered mental status, and/or ancillary test results that usually point to a likely diagnosis. These potential medication, toxicity, metabolic, cardiac, or psychiatric etiologies of dizziness are examined and patients are treated or referred for further evaluation as needed [10; 37].

Other dizziness, medical, and major neurologic etiologies lack prominent associated features, but can be ruled out by assessing [20]:

- Neurologic history
- Recent viral or bacterial infection
- Patient medication list
- Social history for alcohol and substance use
- Psychiatric history

Important associated symptoms to note include headache, hearing loss, tinnitus, nausea and vomiting, impaired vision, focal weakness, and difficulty walking. The severity of impairment should be assessed by asking about impact on work, driving, and recreational and social functioning [11].

Review of systems should seek symptoms of causative disorders, including upper respiratory infection symptoms (inner ear disorders); chest pain and palpitations (cardiovascular disease); dyspnea (pulmonary disease); dark stools (anemia from GI blood loss); and weight change and heat or cold intolerance (thyroid disease) [11]. Past medical history should note recent head trauma (usually obvious by history), migraine, diabetes, heart or lung disease, and regular or daily drug and alcohol use. Identify all current medications, including recent changes in drugs, dosages, or both [11].

After major medical and other etiologies are ruled out, patients with dizziness or vertigo, with or without associated headache, otologic, autonomic, or balance symptoms, should receive a timing and triggers evaluation [37].

TIMING

Timing refers to the onset, duration, and evolution of the dizziness attacks. Narrow the differential diagnosis by classifying the pattern of dizziness attacks as episodic, acute, or chronic in duration by defining the following [102]:

- Onset of dizziness attacks: Sudden or gradual and ill-defined
- Duration of dizziness attacks (minimal and maximal): Seconds to minutes, several minutes to hours, or several hours to days
- Evolution of dizziness attacks:
  - Episodic dizziness lasting seconds to minutes, several minutes to hours, or several hours to days
  - Acute with symptoms lasting days to weeks
  - Persisting symptoms more than three months (chronic)

TRIGGERS

Almost all patients with vertigo feel worse with head movements. The critical distinction is whether head movements trigger (symptoms appear only when provoked by movements) or exacerbate (movements worsen pre-movement vertigo) symptoms [8; 20].

Head movement usually exacerbates dizziness/vertigo of any vestibular cause (benign or dangerous, central or peripheral), but the worsened dizziness is often conflated with a triggered peripheral cause, potentially missing a serious or life-threatening central etiology [6; 8; 37].

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Explicitly assess for the following symptom-triggering circumstances and note whether symptoms are triggered, exacerbated, or improved [15; 102]:

- Rolling over in bed, looking up, changing head position relative to gravity
- Turning the head to the side
- Any head movement
- When standing up or walking
- When supine or recumbent
- Vibration or loud sounds
- Seeing objects in motion

Assessment of triggers establishes the distinctions between positional (change of head orientation with respect to gravity), head motion-induced (head motion regardless of direction), and orthostatic position changes. Obligate triggers are specific triggers that consistently cause dizziness [8].

TARGETED EXAMS

Eye Movement Assessments

At this point in the workup, the patient is placed into one of six vestibular syndromes after some possible etiologies were ruled out during the patient history. The differential diagnosis does not extend beyond possible etiologies within the vestibular syndrome, which substantially narrows the range.

The next task is to differentiate dangerous central mimics from benign causes in acute and episodic vestibular syndromes and to diagnose BPPV by identifying the affected canal. This involves the use of targeted examinations, also called "bedside examinations," which emphasize the assessment of eye movements to detect and localize the underlying pathology of dizziness. The accuracy of eye movement assessment is superior to CT or MRI imaging in differentiating serious CNS from benign causation. Healthcare costs are also reduced by eliminating (in many but not all cases) expensive but unhelpful brain imaging.

Nystagmus is a repetitive, involuntary movement of the eyes, and nystagmus assessment is a core component of the diagnostic workup. Whether spontaneous or triggered, the characteristics of nystagmus help to localize the pathology and suggest a diagnosis. The nystagmus is tested first, because some disorders are diagnosed solely by the nystagmus characteristics [10; 20; 48; 103].

The vestibulo-ocular reflex keeps vision focused on a target during head movement. When looking to one side, the labyrinth on that side signals the head-turn, and the eyes automatically move in the opposite direction to maintain fixed gaze. The vestibulo-ocular reflex maintains gaze for continued reading while turning the head alternately to each side [103; 104]. Vestibulo-ocular reflex assessment is used in the diagnosis of vestibular disorders, because vestibular dysfunction causes inappropriate activation of the vestibulo-ocular reflex that manifests in nystagmus [16].

With vestibular disturbance, when the head is rapidly turned toward the affected side, the eyes move with the head and visual fixed gaze is broken, followed by a refixation ("catch-up") saccade back to the original visual target [104]. This is nystagmus.

In peripheral or central vestibular disorders, understanding the simple "rules" of nystagmus allows rapid, confident diagnoses. With peripheral causes of nystagmus, the fast-phase direction is away from the affected side (of canal/vestibular nerve), and this direction remains constant, regardless of gaze direction. The pattern is primarily horizontal with a torsional component—never purely torsional or vertical. In central nystagmus, the fast-phase varies with the direction with gaze (i.e., right-beating on rightward gaze, then left-beating on leftward gaze). The pattern is any direction, but primarily torsional or vertical.

HINTS is an acronym for three ocular motor tests—the head impulse test (HIT), gaze testing for nystagmus, and alternate cover test for skew deviation—that are combined to differentiate central from peripheral causes of dizziness. Nystagmus is a key observed response. Normal visual fixation can suppress mild nystagmus, but Frenzel lenses worn by the patient block visual fixation and magnify examiner view of eye movements [8; 10; 20]. When conducting the HIT, have the patient fixate his/her gaze on a midline target (e.g., the examiner's nose), then rapidly rotate his/her head 20 degrees to the right or left, bring head back to midline, then rotate to the other side. The presence of a corrective saccade is "positive" for abnormal vestibulo-ocular reflex, which generally indicates a peripheral vestibular process. Gaze that remains locked on the midline target is normal. A normal HIT in patients with AVS is highly suspicious for stroke, but HIT is only useful in patients with AVS and nystagmus. In patients with dizziness (with urosepsis or dehydration) without nystagmus, a normal HIT is a misleading false-positive for stroke.

Gaze testing for nystagmus consists of having the patient look straight ahead ("neutral" or "primary" gaze) and observing for eye movements. Patients whose eyes drift leftward and snap back horizontally to the right have right-beating horizontal nystagmus. Next, look for "gaze-evoked" nystagmus by having the patient look to the right and then to the left, each for several seconds; observe for nystagmus and direction of its fast-beating component. Two patterns suggest stroke or other central cause:

- Dominantly vertical or torsional nystagmus in any gaze position
- Dominantly horizontal nystagmus that changes direction in different gaze positions, termed bilateral or gaze-evoked nystagmus

However, the most common pattern in patients with AVS and stroke is direction-fixed horizontal nystagmus, an acute vestibular neuritis mimic that requires further testing.

Skew deviation is a vertical misalignment of the eyes due to imbalance in gravity-sensing vestibular pathways. Alternate eye cover testing checks for ability to maintain vertical alignment of the eyes. Have the patient gaze directly on a midline target (e.g., the examiner's nose), then cover one eye, and the other, alternating back and forth every one to two seconds.

Skew is shown by slight upward vertical correction on one side, and downward on the other side, appearing the moment the eye is uncovered. Horizontal movements are irrelevant; no vertical misalignment equals no skew. This test is very specific for central etiologies.

The timing-and-trigger syndrome should be identified before targeting the exam, because the same clinical feature can predict a benign condition in one syndrome and a dangerous condition in another syndrome [6; 37].

ACUTE VESTIBULAR SYNDROME

AVS is defined by acute-onset, persistent dizziness lasting days to weeks, sometimes with lingering sequelae. The temporal evolution at onset and progression during the first week is more important diagnostically than total illness duration. Many patients have an early peak in symptom severity, rapid symptom improvement over the first week, and gradual recovery over weeks to months. Unusual cases resolve in less than 48 to 72 hours [37].

Triggered AVS

For diagnostic purposes, AVS is classified into acquired (postexposure/triggered) and spontaneous forms. Triggers in t-AVS refer to behavior or exposures that precipitate dizziness. Patients with AVS typically experience worsening of dizziness (exacerbation) with head movement. This feature can be confusing or misleading, as for example when triggered dizziness in a patient with vestibular neuritis or stroke is misdiagnosed as BPPV [8].

Triggered AVS results from trauma or toxic exposure and is typically diagnosed largely based on exposure history, which is usually obvious. The most common causes are blunt head injury or ingestion of prescribed or illicit drugs affecting the brainstem, cerebellum, or peripheral vestibular apparatus. Carbon monoxide exposure and acute toxicity is a rare but important consideration [37].

Most patients experience a single, acute attack resolving gradually over days to weeks following the exposure. Depending on the nature of trauma or toxin, other symptoms (e.g., headache, altered mental status) may predominate. Rotatory vertigo, spontaneous nystagmus (when looking straight ahead), and head-motion intolerance may be absent or unimpressive if the pathologic effects are bilateral and relatively symmetric (as with most toxins) [37].

Head Injury

Blunt head trauma, blast injuries, whiplash, or barotrauma may lead to direct vestibular nerve injury, labyrinthine concussion, or mechanical disruption of inner ear membranes to result in an AVS presentation. Basal skull fracture and traumatic vertebral artery dissection should always be considered. TBI may cause post-concussion syndrome, typically with a combination of dizziness, headache, fatigue, and minor cognitive impairment, with dizziness the most common symptom in the first two post-injury weeks [37].

Drug Side Effects/Toxicity

Anticonvulsant side effects or toxicity are a frequent cause of dizziness and vertigo seen in the ED. As mentioned, aminoglycoside toxicity is an established cause of acute bilateral vestibular failure. Gentamicin can cause profound, permanent loss of vestibular function with relatively spared hearing; toxicity may occur after just a single antibiotic dose. Patients usually show gait unsteadiness and oscillopsia (bouncing vision) while walking [37].

Spontaneous AVS

Within the first 48 hours of onset, how is posterior circulation stroke most accurately differentiated from a peripheral dizziness cause?

Spontaneous AVS is defined as acute onset of persistent dizziness and vertigo associated with nausea or vomiting, gait instability, nystagmus, or head motion intolerance. A focused physical exam is often diagnostic, because patients are usually symptomatic at presentation [8]. Prototype causes include vestibular neuritis and labyrinthitis [10]. Possible dangerous causes include posterior circulation stroke of the cerebellum or brainstem (the most frequent), bacterial labyrinthitis, and labyrinthine stroke (much less frequent) [8; 37].

Peripheral causes of s-AVS are more common, but central causes are not infrequent and can be fatal if missed, especially with vertebro-basilar ischemia [19]. This would not be as concerning if patients with posterior circulation TIA or stroke presented with classical focal neurologic signs along with the vestibular symptoms of AVS, as the diagnosis would be straightforward [57; 105]. However, this is often not the case.

The 1975 National Institutes of Health (NIH) recommendation that isolated dizziness or vertigo not be considered a TIA persists as a standard teaching [106]. This has contributed to missed diagnoses of TIA and stroke, because many patients with posterior circulation TIA or stroke present with isolated dizziness or vertigo without focal neurologic signs [37; 105; 107]. Patients with s-AVS presenting to the ED with dizziness are at high risk (25%) for stroke. Of nearly 800,000 annual strokes in the United States, 18% are strokes in the posterior fossa (within the brainstem or cerebellum) and up to 70% present with dizziness [8; 19].

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TESTING TO DIFFERENTIATE POSTERIOR CIRCULATION STROKE FROM BENIGN PERIPHERAL VESTIBULAR DISORDER

HINTS is performed in sequence. Test nystagmus first; HINTS is validated only in patients with nystagmus, and gaze testing is non-intrusive (i.e., head movement unnecessary).

- Gaze testing: Is there a central pattern of nystagmus?
- Alternate cover test: Is skew deviation present?
- HIT: Is the head impulse test result negative?

Patients with s-AVS and worrisome nystagmus, skew deviation, or bilateral normal HIT have a presumed stroke and should be admitted to a hospital. If all three tests seem reassuring, perform a targeted neurologic exam to determine if there are any CNS signs. This involves testing for:

- 4D symptoms:
  - Diplopia (double vision)
  - Dysphagia (difficulty swallowing)
  - Dysarthria (difficulty with speech)
  - Dysmetria (lack of coordination)
- The cranial nerves for hearing
- Anisocoria (unequal pupil size)
- Facial loss of pain or temperature sensation
- Cerebellar function for limb ataxia.

The next step is gait testing to determine if the patient can walk unassisted.

If the answer to any of these questions is yes, the cause is presumed central and treated as stroke. If the answer to all questions is no, the cause is presumed peripheral. All answers must be no in order to exclude stroke because none is sufficiently sensitive individually.

Source: [8; 10; 19] *Table 1*

An estimated 45,000 to 75,000 patients with stroke are misdiagnosed annually. Roughly 28% to 59% of cerebellar strokes are misdiagnosed in the ED, and isolated dizziness is a risk factor for this misdiagnosis. Posterior circulation strokes are missed more than twice as often as anterior circulation strokes, and cerebellar strokes are four times more likely to be misdiagnosed than stroke misdiagnosis overall. These misdiagnosed patients suffer higher mortality and disability at follow-up [10; 108; 109; 110].

CT is widely used but ineffective to rule out ischemic stroke in s-AVS; MRI with diffusion-weighted imaging (MRI-DWI) is markedly superior. However, within the first 48 hours of symptom onset, MRI-DWI is falsely negative in 12% to 18% of patients with AVS and 53% of patients with small brainstem strokes. Posterior circulation strokes are five times more likely to be falsely negative than anterior circulation strokes. Indiscriminate CT angiography also has very low utility (1.3%) [8; 52; 111].

In the first 48 hours, physical examination outperforms MRI. If the initial physical examination suggests stroke, a negative MRI result should not be interpreted as excluding stroke. Delayed MRI (three to seven days post-onset) may be required to confirm the presence of a new infarct [8]. Posterior circulation stroke should be differentiated from benign peripheral vestibular disorder (***Table 1***) [8; 10; 19]. Nearly all patients with AVS due to a peripheral cause exhibit nystagmus, which may be inhibited if benzodiazepines/other vestibular suppressants are taken before the exam. When possible, assess for nystagmus before medications to manage symptoms are administered [8; 10].

EPISODIC VESTIBULAR SYNDROME

Whether intermittent dizziness is triggered or spontaneous, the duration of dizziness episodes (seconds, minutes, hours) is more important than total illness duration. EVS excludes relapsing and remitting symptoms lasting weeks at a time [37].

Triggered EVS

Triggered EVS is characterized by brief episodes of dizziness lasting seconds to minutes (depending on etiology), precipitated by an obligate trigger. Common triggers are changes in head position or body posture, as when rising from a seated or lying position, tipping the head back to wash one's hair, or rolling over in bed. Uncommon triggers include loud sounds and the Valsalva maneuver. Patients with nausea or vomiting may overestimate the episode duration, but this can usually be clarified by careful history-taking [8].

As mentioned, clinicians should distinguish triggers from exacerbating features [37]. Prototype t-EVS causes are BPPV and orthostatic hypotension; less commonly, it is caused by superior canal dehiscence syndrome [8]. Possible dangerous

causes include central paroxysmal positional vertigo and serious causes of orthostatic hypotension, such as internal bleeding. Patients with panic or anxiety disorders may also complain of episodic vertigo, lightheadedness, or dizziness during panic attacks that are triggered or spontaneous. Studies show a high prevalence of vestibular dysfunction for these patients [112].

Episodic positional symptoms are common to all causes of t-EVS, differentiated by targeted history and exams. BPPV is identified by maneuvers that reproduce dizziness combined with an observed pattern of nystagmus. Orthostatic hypotension is diagnosed by observing a significant fall in blood pressure upon sitting and standing. Dangerous t-EVS mimics are identified by careful attention to the corresponding signs and symptoms that differentiate these benign conditions from potentially more serious disorders [37]. Positional triggers, such as rolling over in bed or reclining, are common in BPPV but should not occur in orthostatic hypotension [8]. Unlike head position changes in BPPV, the vertigo and oscillopsia attacks in superior canal dehiscence syndrome are triggered by pressure-related changes of the external auditory canals (e.g., loud sounds, Valsalva maneuver) [22].

The nystagmus characteristics of BPPV and central paroxysmal positional vertigo are distinct. Atypical nystagmus (downbeat or horizontal) is suggestive of central paroxysmal positional vertigo, and pure vertical (up- or downbeating) nystagmus should be considered of central origin until proven otherwise [8; 23]. Central mimics of BPPV less often involve strokes and more often involve posterior fossa neoplasm, hemorrhage, or demyelination recognized by association with other abnormalities [104; 113].

Central paroxysmal positional vertigo also includes common, benign causes, such as alcohol or sedative intoxication. Such patients are more apt to complain of continuous, persistent dizziness exacerbated (not triggered) by position change, often readily diagnosed based on context and other signs of intoxication [8; 37].

In general, BPPV is not associated with vertiginous episodes provoked simply by head and body movements in general, but by sudden positional changes relative to gravity. Moreover, unprovoked (spontaneous) episodes while immobile or the constant sensation of unsteadiness also suggest a diagnosis other than BPPV [22].

BPPV

Within any (semicircular) canal, BPPV is caused by abnormal stimulation of the cupula by otoconia that are free-floating (canalolithiasis) or have attached to the cupula (cupulolithiasis) [114]. With head motion in the plane of the affected canal, cupula stimulation produces error signaling that triggers eye movement patterns (nystagmus) specific to the afflicted canal [22]. BPPV should be differentiated from other causes of imbalance, dizziness, and vertigo. Patients should also be assessed for factors that modify management, including impaired mobility or balance, CNS disorders, lack of home support, and increased risk for falling. In patients meeting BPPV diagnostic criteria, it is not necessary to obtain radiography or order vestibular testing in the absence of signs/symptoms inconsistent with BPPV [22].

Provoked nystagmus is used clinically to diagnose BPPV by positioning the head to spatially align the plane of the affected canal with gravity. Gravity challenge moves otolithic debris in the canal, inducing excitation and resultant nystagmus. This identifies the afflicted canal, determines the canal-specific therapy, and distinguishes BPPV from central causes of vertigo [15; 24; 40; 114].

Head movement tests are canal-specific. Because posterior canal BPPV is the most common type, the Dix-Hallpike maneuver is used first. For this maneuver, the patient is moved quickly from sitting upright with head turned 45° in the direction of involved ear, to supine position with head still turned 45° and neck extended 20° off the end of the exam table with the affected ear down [21; 22].

Before initiating physical maneuvers that involve head rotation, the neck should be evaluated to determine if the procedure should be modified or avoided. The Dix-Hallpike maneuver should be performed with caution or avoided in patients with a current or past neck or back injury, surgery, or painful condition [24; 114].

A diagnosis of BPPV affecting the posterior canal (pc-BPPV) is confirmed by vertigo with torsional (rotatory), upbeating (toward the forehead) nystagmus, with onset 5 to 20 seconds after completion of the Dix-Hallpike maneuver (latency) and duration less than 60 seconds. Provoked nystagmus that lasts longer than 60 seconds with no or brief latency identifies cupulolithiasis [21; 22]. If the initial maneuver is negative, it should be repeated with the opposite ear down.

Before performing the Dix-Hallpike maneuver, the patient should be advised that sudden, intense vertigo or nausea is possible but should subside within 60 seconds. The sequential steps and expected results of the maneuver should be explained, orienting the patient to the supine position and location of the head and providing reassurance that the head and body will be supported and guided safely and securely through the maneuver [21; 22].

There are two types of BPPV affecting the lateral canal (lc-BPPV)—geotropic or apogeotropic—with two types of direction-changing positional nystagmus [22; 40]. When BPPV is suspected and the Dix-Hallpike maneuver is negative, the supine roll test should be used to assess for lc-BPPV. The supine roll test provokes a linear, horizontal nystagmus in patients with lc-BPPV. In cases of lc-BPPV caused by canalolithiasis, the nystagmus beats to the ear under the head (i.e., higher intensity on the affected side). If the condition results from cupulolithiasis, the nystagmus beats to the upward ear (i.e., higher intensity on the non-affected side).

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EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Otolaryngology, if the patient has a history compatible with BPPV and the Dix-Hallpike test exhibits horizontal or no nystagmus, the clinician should perform, or refer to a clinician who can perform, a supine roll test to assess for lateral semicircular canal BPPV.

(http://journals.sagepub.com/doi/pdf/10.1177/0194599816689667. Last accessed September 18, 2018.)

Strength of Recommendation: Recommendation (Benefits exceed the harms, but the quality of evidence is not as high)

The Dix-Hallpike maneuver also provokes vertigo and nystagmus in BPPV affecting the anterior canal (ac-BPPV), which shows downbeating nystagmus, sometimes with a torsional component, toward the affected ear. Downbeating positional nystagmus may reflect brainstem or cerebellar lesion, which should be ruled out [21; 40]. BPPV can also mimic orthostatic hypotension by producing dizziness on arising and often goes undiagnosed in the elderly.

Serious Causes of Orthostatic Hypotension

As noted, vertigo is a common but under-appreciated symptom in orthostatic hypotension. Older patients taking antihypertensives can show incidental orthostatic hypotension. Orthostatic dizziness and hypotension are not always related; orthostatic dizziness without systemic orthostatic hypotension may indicate hemodynamic TIA or intracranial hypotension [8].

Serious causes of orthostatic hypotension include fluid loss from bleeding, vomiting, diarrhea, and excessive urination/sweating. Occult internal bleeding is the primary dangerous concern [2]. Concomitant chest, back, abdominal, or pelvic pain suggests an intrathoracic or intra-abdominal emergency [37]. Myocardial infarction, occult sepsis, adrenal insufficiency, or diabetic ketoacidosis may present with severe orthostatic hypotension without other overt signs [8].

Spontaneous EVS

s-EVS is marked by recurrent, spontaneous episodes of dizziness that range in duration from seconds to days, with most lasting minutes to hours. Spells sometimes occur up to several times per day, but they are usually less frequent and can be separated by months or even years, depending on etiology [8].

Unlike t-EVS, dizziness episodes in s-EVS cannot be provoked and diagnostic evaluation relies almost entirely on patient history [37]. Vestibular migraine is the most common cause of s-EVS, with a population prevalence of roughly 1% [37]. The classical Ménière disease symptom triad of episodic vertigo, unilateral tinnitus and aural fullness, and reversible sensorineural hearing loss is initially present in only 25% of patients. Patients with suspected Ménière disease should generally be referred to an otolaryngologist, but care should be taken to avoid missing TIA mimics with audio-vestibular symptoms [37].

Reflex (vasovagal) syncope is also a common cause. In reflex syncope, episodes of near-syncope without loss of consciousness substantially outnumber true syncope. Patients usually have prodromal symptoms for 3 to 30 minutes, most commonly dizziness (70% to 75% of cases) that can manifest in vertigo. Diagnosis is based on clinical history, exclusion of dangerous mimics (especially cardiac arrhythmia), and confirmation (if needed) by formal head-up tilt table testing [8; 37].

s-EVS has been reported in panic attacks; episodes begin rapidly, usually peak within 10 minutes, and are accompanied by additional autonomic, cognitive, and perceptual symptoms. Panic attacks can be precipitated by situational stress, such as airplane travel, but often occur spontaneously [115]. Panic attack mimics include ictal panic attacks from temporal lobe epilepsy that usually last seconds with altered mental status, hypoglycemia, cardiac arrhythmias, and basilar TIA, which can produce dizziness and neurologic and autonomic features [8].

Another cause of s-EVS is vestibular paroxysmia, a condition that should be considered when the patient reports 10 or more spontaneous vertigo attacks per day lasting less than one minute (sometimes mere seconds). These attacks respond to a carbamazepine or oxcarbazepine trial [45].

The most common dangerous causes of s-EVS are vertebrobasilar TIA and cardiac arrhythmias. Less commonly, episodes have been observed with other cerebrovascular (e.g., subarachnoid hemorrhage), cardiorespiratory (e.g., unstable angina, pulmonary embolus), and endocrine (e.g., hypoglycemia) disorders. Carbon monoxide exposure is a rare serious cause [37].

Vestibular symptoms associated with s-EVS cannot be reproduced by bedside examination, and patients may be asymptomatic by the time they present to outpatient care. The history is used to distinguish vestibular migraine from TIA or other causes. Diagnosis of benign s-EVS causes can be clear-cut in typical cases, but as mentioned, classical features of vestibular migraine, vasovagal syncope, Ménière disease, or panic attacks are often absent [37].

Isolated attacks of spontaneous dizziness are the most common symptom of an imminent posterior circulation TIA and are frequent in the days to weeks preceding posterior circulation stroke [8; 37]. TIA presenting with isolated dizziness is easily missed; 90% of patients who seek medical attention for transient dizziness that preceded vertebrobasilar stroke are initially misdiagnosed [107]. Dizziness is the most common presenting symptom of basilar artery occlusion and vertebral artery dissection. Prompt diagnosis is critical; 5% of patients with TIA suffer a stroke within 48 hours, but the

risk is much greater with posterior circulation TIA. Prompt treatment lowers stroke risk after TIA by 80% [8; 116; 117].

The clinical presentation of vestibular migraine is highly variable. The duration of attacks ranges from seconds to days. Nystagmus (peripheral or central), headache, and nausea, vomiting, photophobia, phonophobia or visual auras can be present or absent during an attack. Hearing loss or tinnitus can occur, mimicking Ménière disease [8].

Vestibular migraine is diagnosed by clinical findings of recurrent migraine headache episodes: five or more episodes characterized by moderate-to-severe vestibular symptoms; ≥50% of episodes have pulsating, impairing headache; photo- or phonophobia; and/or visual aura [49].

The prevalence of migraine syndrome is high in patients with Ménière disease, and when such patients present with attacks of s-EVS, the diagnostic attribution may seem difficult. The presence of low frequency hearing loss favors the diagnosis of Ménière disease [19; 49].

Cardiac arrhythmia should be suspected when syncope or exertion is the precipitating factor for the onset of dizziness. Clinical features may increase or decrease the odds of a dangerous cardiac cause, but cardiac specialist testing is often required for diagnostic confirmation [8; 37].

CHRONIC VESTIBULAR SYNDROME

Triggered CVS

Central compensatory mechanisms can ameliorate vestibular symptoms over time, but to an unpredictable extent, and lasting vestibular compensation does not develop or incompletely develops. Thus, some vestibular syndromes become chronic, with persistent dizziness or unsteadiness lasting months to years, with oscillopsia, nystagmus, and/or gait disturbance. CVS develops from poorly compensated unilateral or bilateral vestibulopathy or cerebellar degeneration [118]. Other etiologies include PPPD, autoimmune or neoplastic disease, central vestibular syndromes with downbeat or upbeat nystagmus, and dizziness due to isolated causes [119]. In t-CVS, dizziness or vertigo is provoked by head movement (as in uncompensated vestibular loss), medication side effects, and/or anxiety, depression, or other psychiatric conditions [118].

Bilateral vestibulopathy is a CVS characterized by unsteadiness when walking or standing that worsens in darkness, on uneven ground, or during head motion. Patients may describe head or body movement-induced blurred vision or oscillopsia. Symptoms usually remit when sitting or lying down. Bilateral vestibulo-ocular reflex function is significantly impaired or absent in bilateral vestibulopathy and is assessed using the HIT, video-HIT, or other tests [41].

As discussed, PPPD is a newly defined CVS that unifies key features of chronic subjective dizziness, phobic postural vertigo, and related disorders. Patients with PPPD often develop gait disorder, anxiety, avoidance behaviors, and severe disability [120].

A PPPD diagnosis requires dizziness, unsteadiness, or non-spinning vertigo present on most days for at least three months, exacerbated by posture, movement, and/or moving/complex visual stimuli. Symptoms are precipitated by any condition that causes vertigo, unsteadiness, dizziness, or problems with balance and cause significant distress or impairment [62].

In addition to timing and triggers, the diagnostic approach should also capture the dynamic features of patient history to uncover the nuances of psychologic distress, maladaptive coping, and differential diagnosis. Patients who fulfill diagnostic criteria for PPPD after a TBI or whiplash should receive the diagnosis. The presence of other injury sequelae determines additional diagnoses [62].

According to the Bárány Society, the differential diagnosis of PPPD includes chronic sequelae of acute precipitants, recurrent attacks of episodic precipitants, ongoing manifestations of chronic precipitants, other chronic vestibular syndromes, medical or psychiatric disorders that produce persistent unsteadiness or dizziness, and adverse effects of regularly consumed prescription or non-prescription medications.

(https://content.iospress.com/articles/journal-of-vestibular-research/ves622. Last accessed September 18, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Spontaneous Chronic Vestibular Syndrome

s-CVS conditions include chronic dizziness or vertigo associated with nystagmus, blurred vision, or impaired visual acuity from oscillopsia, originating from cerebellar or brainstem degeneration or atrophy [121]. Other central etiologies of s-CVS include cervical vertigo and Chiari malformations [118]. Several cerebellar syndromes due to neurodegenerative and hereditary diseases can lead to ataxia and postural instability associated with cerebellar oculomotor disorders (e.g., downbeat nystagmus, gaze-evoked nystagmus) [121].

Episodic ataxia type 2, the most frequent inherited cerebellar ataxia syndrome, is characterized by recurrent attacks of dizziness and ataxia lasting several hours, often elicited by physical activity, alcohol consumption, or stress. More than 90% of patients with episodic ataxia type 2 have oculomotor disorders such as downbeat nystagmus [118].

The vertigo symptoms are usually associated with degenerative cervical spine disease and may resemble BPPV due to proprioceptive abnormalities related to cervical spine dysfunction. However, cervical vertigo may be triggered by rotating the head relative to the body while upright, as

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opposed to the vertigo triggered by changes in head position relative to gravity in BPPV [22; 122].

CLINICAL MANAGEMENT

Returning to the funnel analogy, a range of possible dizziness and vertigo etiologies (e.g., orthostatic hypotension, vasovagal syncope, head injury, medication side effects/toxicity, posterior circulation TIA/stroke, central paroxysmal positional vertigo, and cardiac arrhythmias) would be excluded or diagnosed. Certain patients would be treated, and others referred to specialists or admitted to an ED. This would include all etiologies categorized as t-AVS.

After vestibular disorders have been differentiated and diagnosed, treatment selection can be divided into approaches that focus on symptom control, those specific to the underlying vestibular etiology, and those aimed at promoting recovery [123]. Therapeutic approaches broadly used across vestibular etiologies are discussed first, followed by treatments specific to acute, episodic, and chronic vestibular syndromes.

COMMON PHARMACOTHERAPIES

Most pharmacotherapies for dizziness or vertigo related to peripheral or central vestibular, cerebellar, or oculomotor disorders fall into one of seven groups, or the 7 As [61]:

- Antiemetics
- Anti-inflammatory
- Anti-Ménière
- Anti-migraine
- Antidepressants
- Anticonvulsants
- Aminopyridines

Patients with severe nausea or vomiting greatly prefer non-oral administration [123]. As such, vestibular suppressants are usually administered in non-oral routes initially for rapid symptom control, followed by oral medications.

Vestibular Suppressant Medications

Which drug is one of the most effective agents for preventing motion sickness?

As discussed, dizziness, vertigo, disequilibrium, and associated symptoms can arise from diverse central or peripheral disturbances of vestibular function. By suppressing vestibular sensory input, vestibular suppressant medications can reduce conflicting sensory input, control undesirable perceptions, and diminish patient distress [13].

Many distressing vestibular-related symptoms are mediated by the vomiting center in the medulla. The vomiting center is activated through neurotransmitter release involving vestibular and CNS (histamine, acetylcholine), visceral (gut) (dopamine, serotonin), and chemoreceptor trigger zone (dopamine, serotonin) pathways [124]. These pathways are therapeutic targets of most vestibular suppressants, which are effectively used for symptomatic control in nearly all AVS or EVS subtypes, regardless of underlying etiology. These medications are variously effective for controlling dizziness, vertigo, motion sickness, associated symptoms (e.g., nausea, vomiting, diarrhea), and patient distress or anxiety during episodes, which can be severe [22; 178].

Drug classes and agents commonly used as vestibular suppressants include antihistamines, benzodiazepines, scopolamine, dopamine antagonists, and ondansetron (***Table 2***). Antihistamines (e.g., meclizine, diphenhydramine, dimenhydrinate) block the release of histamine and acetylcholine and are especially beneficial in vestibular-mediated nausea, vomiting, and motion sickness. Side effects include sedation, confusion, dry mouth, and urinary retention. Meclizine is preferred because it has minimal anticholinergic effects, causes less sedation, and is effective in the treatment of vertigo due to labyrinth dysfunction. It is also the drug of choice in pregnancy [123].

Benzodiazepines (e.g., diazepam, clonazepam, lorazepam) potentiate the inhibitory effects of the gamma-amino butyric acid system to produce anxiolytic, sedative, muscle-relaxant, and anticonvulsant effects. Benzodiazepines can be highly effective in vertigo unresponsive to antihistamines and for calming intensely distressed patients, but they are sedating and mainly used when antihistamines are inadequate [123].

Scopolamine is a belladonna alkaloid that blocks CNS neurotransmission of acetylcholine and is one of the most effective agents for preventing motion sickness. Scopolamine is also effective for vestibular-mediated nausea/vomiting and is better tolerated as a transdermal patch than when taken orally. Common side effects are sedation, constipation, dry mouth, and urinary retention [114; 124].

Dopamine antagonists (e.g., metoclopramide, domperidone, promethazine, prochlorperazine) block dopamine stimulation in the intestines and chemoreceptor trigger zone, limiting emetic input to the medullary vomiting center. Promethazine and prochlorperazine also inhibit central muscarinic and histamine receptors, which contributes to their antiemetic and sedative properties [124].

Ondansetron inhibits serotonin-5HT3 receptors in the small bowel, vagal nerve, and chemoreceptor trigger zone, suppressing serotonergic activation of the vomiting center to alleviate nausea and vomiting. Adverse effects are uncommon but can include headache, diarrhea, and fatigue [124].

Extrapyramidal symptoms, including irreversible tardive dyskinesia (an involuntary movement disorder), are a potential risk with all central dopamine antagonists. Extended use (duration of 12 or more weeks) increases the risk of tardive dyskinesia [126]. However, dopamine antagonists are considered safe for use as acute therapy and are usually reserved for patients with severe vomiting [123].

VESTIBULAR SUPPRESSANT MEDICATIONS	
Medication	**Dosage and Route**
Antihistamine Agents	
Diphenhydramine	50 mg PO twice daily 10–50 mg IM or IV
Meclizine	25–50 mg PO three to four times per day
Promethazine	12.5–50 mg PO every four to six hours 50 mg RS four times per day 10–50 mg IM or IV
Benzodiazepines	
Lorazepam	0.5–2 mg PO two to three times per day
Diazepam	2–5 mg PO three to four times per day
Clonazepam	0.25–1 mg PO two to three times per day
Antiemetic Agents	
Metoclopramide	10–20 mg PO every four to six hours 10–20 mg IM or IV
Prochlorperazine	10–20 mg PO every four to six hours 25 mg RS every six hours 5–10 mg IM or IV
Domperidone	10–20 mg PO every six to eight hours
Ondansetron	8 mg PO every 6 to 12 hours 4 mg SL, IM, or IV
Anti-Motion Sickness	
Scopolamine	1 TD patch (1.5 mg) every three days
IM = intramuscular; IV = intravenous; PO = oral; RS = rectal suppository; SL = sublingual; TD = transdermal.	
Source: [15; 22; 119; 123; 125]	*Table 2*

In peripheral vestibular disorders, all vestibular suppressants can interfere with central compensation, and their use is recommended to not exceed three days [15; 22; 125]. The goal is for patients to rapidly receive specialist care, but patients may not get an immediate appointment and remain highly symptomatic. In this context, vestibular suppressants should continue for symptom control until optimized treatment is initiated by a specialist [119].

Vestibular suppressants can cause drowsiness and interfere with driving. In particular, the use of benzodiazepines is a significant risk factor for falls; this risk increases with polypharmacy, common in the elderly [15; 22]. Antihistamines carry added risks of impaired cognitive functioning, gastrointestinal motility, and vision in elderly patients [22]. Some patients can develop psychologic dependence to benzodiazepines and have difficulty discontinuing the medication [119].

Betahistine

First approved for use in Europe in the 1970s, betahistine has been prescribed to more than 100 million patients with vestibular disorders and is the first-line treatment of Ménière disease in Germany. Betahistine is not approved by the U.S. Food and Drug Administration, but it may be obtained through compounding pharmacies in the United States with a prescription [15; 127]. It reduces vestibular symptoms but seems to differ from vestibular suppressants by promoting vestibular compensation. Histamine regulates sensory coding in the peripheral vestibular system. Betahistine (dihydrochloride or dimesylate), a structural analogue of histamine, is a potent histamine H3 receptor antagonist and a weak histamine H1 receptor agonist [15]. Betahistine reduces the frequency and severity of vertigo, nausea, and vomiting in diverse unilateral vestibular etiologies. Central and peripheral histamine receptor activity is a presumed mechanism [127; 128; 129].

Betahistine dose-dependently increases vestibulo-cochlear blood flow, increases central and vestibular system histamine turnover, decreases peripheral vestibular system input, and reduces histamine-induced excitation in vestibular cells through local H3 receptor blockade. These mechanisms are thought to improve vestibular compensation, reduce functional asymmetry of vestibular organs, and improve labyrinth microcirculation by rebalancing the production and resorption of endolymphatic fluid [127; 128; 129]. In this course, all discussions of betahistine refer to betahistine dihydrochloride, unless otherwise stated.

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Antidepressant Drugs

Monoamines are the neurochemicals serotonin, norepinephrine, and dopamine. Dysregulated monoamine neurotransmission is implicated in anxiety disorders and depression. A bi-directional relationship between impaired monoamine neurotransmission and vestibular signaling dysfunction is suggested, with asymmetric vestibular system release of serotonin, norepinephrine, or dopamine linked to vestibular migraine and other dizziness/vertigo etiologies [51; 61; 119].

Antidepressant drugs include SSRIs (e.g., fluoxetine, escitalopram), serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine), and tricyclic antidepressants (e.g., nortriptyline, imipramine, amitriptyline). They modulate serotonin, norepinephrine, and dopamine neural pathways (with varying specificities) and are first-line treatments for anxiety disorders and depression. These agents are increasingly recommended for use in some vestibular-related disorders [51; 119; 130].

Aminopyridines

Aminopyridines are potassium-channel blockers, established as pharmacotherapy for cerebellar diseases that include downbeat nystagmus, upbeat nystagmus, central positional nystagmus, episodic ataxia type 2, and gait disorders in cerebellar ataxia [61].

Aminopyridines used in these disorders are 3,4-diaminopyridine (3,4-DAP) and 4-aminopyridine (4-AP). 4-AP crosses the blood-brain barrier more easily and is superior to 3,4-DAP in some cases. Both drugs are well-tolerated and without major side effects apart from nausea, transient paresthesia, or headache [121].

QT Interval Prolongation

Some vestibular disorder pharmacotherapies may interact with other medications to risk QT interval prolongation [119]. A prolonged QT interval is a symptom of disordered myocardial repolarization that increases the risk of potentially life-threatening ventricular tachycardia (i.e., torsades de pointes) [131]. A complete list of medications that prolong the QT interval is available at https://www.crediblemeds.org.

VESTIBULAR REHABILITATION

Vestibular rehabilitation, another therapeutic modality broadly used across dizziness and vertigo etiologies, is a specific physical therapy for patients with peripheral or central vestibular disorders. Vestibular rehabilitation reduces symptoms and improves functioning by promoting CNS compensation through exercise-based strategies [132; 133].

Following an acute peripheral vestibular event, clinical recovery occurs in advance of improved peripheral vestibular function. This suggests that most of the early recovery and a substantial portion of total recovery derives from central compensation (long-term changes in neuronal responses to head movements) that is multisensory and is the primary target of vestibular rehabilitation. Early rehabilitation (during a critical period of adaptation and compensation) may be more effective than late intervention. As such, vestibular rehabilitation should begin shortly after symptom onset [132; 134].

Patients typically receive supervised therapy one to two times per week and are taught daily home exercises. The average duration of therapy is 6 to 12 weeks for patients with peripheral vestibular disorder and longer for patients with central vestibular disorder or mobility-impairing comorbidities [44; 133].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Physical Therapy Association concludes that clinicians may prescribe a home exercise program of gaze stability exercises consisting of a minimum of three times per day for a total of at least 12 minutes per day for patients with acute/subacute vestibular hypofunction and at least 20 minutes per day for patients with chronic vestibular hypofunction.

(https://www.asha.org/articlesummary.aspx?id=8589969232. Last accessed September 18, 2018.)

Strength of Recommendation: D (Expert opinion from the clinical experience of the guideline development team)

General Components

What do habituation exercises work to reduce?

Vestibular rehabilitation uses several approaches to reduce symptoms and impairment and to promote function in patients with dizziness, postural instability, and gaze instability. Visual-vestibular interaction (adaptation) exercises strengthen the vestibulo-ocular reflex and gaze stability to promote central compensation for reduced vestibular input, improving gaze instability, balance, and dizziness [44; 132].

Strategic substitution exercises promote the use of sensory stimuli and spatial cues from vision and proprioception to substitute for loss of vestibular inputs. Cervico-ocular reflex input is strengthened to reduce spatial uncertainty, and alternative spatial cues can improve balance and walking [44; 132].

Balance and gait training under challenging sensory and dynamic conditions facilitates visual and somatosensory cues to offset vestibular hypofunction. Equipment to augment training includes gaming technology, optokinetic drums, and virtual reality [44].

Habituation exercises reduce visual motion sensitivity (e.g., visual vertigo, space and motion discomfort) through systematic exposure to noxious stimuli evoking mild, temporary symptoms. Approaches include optokinetic stimuli and virtual reality for immersion in repetitive moving and visually challenging environments [44; 132].

Vestibular rehabilitation can help counteract the negative effects of deconditioning, common in vestibular patients, to avoid symptom provocation [44]. Psychologic deconditioning can progress to PPPD (phobic postural vertigo) to become the greatest obstacle to recovery. After a vestibular event, elderly patients can develop fear of falling, avoidance behavior, and indefinite mobility limitation without vestibular rehabilitation [74].

Based on strong evidence and a preponderance of benefit over harm, patients with acute, subacute, or chronic unilateral or bilateral vestibular hypofunction should be offered vestibular rehabilitation [44]. Without head movements, saccadic or smooth-pursuit exercises should not be used alone as gaze stability exercises.

Acute Peripheral Vertigo

For cases of acute peripheral vertigo, vestibular rehabilitation begins with the patient focusing on an object with a blank background, then moving the head slowly (to avoid severe nausea) to the right and left, and then up/down. This is done two to three times per day for several minutes, and the patient is encouraged to increase the speed as tolerated [132].

Chronic Peripheral Vestibular Hypofunction

The vestibular rehabilitation approach for chronic peripheral vestibular hypofunction is more aggressive, with increasingly more difficult tasks while keeping symptoms manageable. Tasks include eye and head movements while standing, walking forward, walking backward, and standing or walking on compliant or uneven surfaces [132].

Bilateral Vestibular Loss

Central adaptation is much less likely with bilateral vestibular loss than in unilateral loss, but vestibular rehabilitation can promote strategic substitution through strengthening saccadic eye movements and optimizing the efficacy of neck stretch receptors. Vestibulo-ocular exercises are initiated when residual vestibular function is a possibility. Improved balance and gait speed help offset the bilateral loss [135]. Education on fall prevention is critical, because these patients have an especially high fall risk, compounded by darkness and uneven surfaces [132].

Central Vertigo

Recovery of vestibular function in patients with central vertigo is limited because pathologic involvement of central vestibular structures restricts compensation, and improvement takes longer than with peripheral vestibular dysfunction [133]. For these patients, vestibular rehabilitation emphasizes gait and balance activities, along with eye and head movements. Adaptive methods to perform activities of daily function are often taught. If nausea is limiting, antiemetic medications used in conjunction with vestibular rehabilitation may improve participation and final outcomes [132].

ANXIETY AND DIZZINESS

The demonstrable interconnectivity between threat/anxiety, vestibular, visual, and somatosensory systems, and the interactions between anxiety disorders and vestibular morbidity point to the importance of a multimodality treatment approach for patients with anxiety and dizziness [71].

Studies have followed patients with dizziness over time and made several important findings [62; 71]. A highly anxious response to the acute dizziness/vertigo of new-onset vestibular neuritis or BPPV predicts continued dizziness 3, 6, and 12 months later. This initial psychologic response has a far greater impact on long-term outcomes than measurable vestibular dysfunction at baseline or follow-up. Patients with emerging symptoms of PPPD who receive cognitive-behavioral therapy within eight weeks of onset have marked reductions in dizziness and avoidance of provocative situations six months later. A highly anxious response to a precipitating event may be the pivotal initiating pathophysiologic process in PPPD (the leading cause of long-term vestibular disability), and early symptom-specific interventions might counter this effect.

Patients with poor recovery from acute vestibular neuritis have higher rates of visual dependence, autonomic arousal, anxiety, and fear of vestibular symptoms [136; 137]. Poor recovery is also unrelated to vestibular function, but significantly related to acute visual dependence and failure of sensory integration mechanisms to down-regulate visual contribution to central compensation processes. These data highlight the importance of [136; 137]:

- Early identification of abnormal visual dependence and concurrent anxiety
- Early treatment to improve long-term outcomes by reducing visual dependence with sensory re-weighting strategies
- Combining pharmacotherapy and cognitive therapies to reduce anxiety and autonomic arousal

In vestibular patients, successful treatment outcomes require the simultaneous assessment of vestibular, psychiatric (anxiety), and functional (phobic vertigo) disorders. Only when identified can they be addressed by systematically applied treatment that incorporates patient education, vestibular rehabilitation, cognitive-behavioral therapies, and medications to control morbidity and increase the potential for sustained remission [72].

SPONTANEOUS ACUTE VESTIBULAR SYNDROMES

Acute Unilateral Vestibulopathy/Vestibular Neuritis

This acute, spontaneous, peripheral vestibular disorder is characterized by the rapid onset of severe vertigo with nausea, vomiting, and gait instability. The symptoms can be severe and disabling in the short term; patients may need to be hospitalized for intravenous fluids and medications [125; 138].

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Panic disorder has been found to develop in 10% of patients followed for two years after the initial acute vestibular neuritis episode [139].

Vertigo, nausea, and vomiting can be treated with a combination of vestibular suppressants, not exceeding seven days to avoid disrupting CNS adaptation and compensation [15; 125]. The vestibular nerve is selectively vulnerable to inflammation-related swelling and entrapment by its pathway in a narrow, bony canal [35]. Oral corticosteroids may help reduce the severity of vestibular neuritis if initiated in the first few days. The recommended agents are [15; 119]:

- Methylprednisolone initiated at 100 mg/day and then reduced by 20 mg every fourth day, OR
- Prednisone 60 mg/day for one week

When acute symptoms subside, patients should begin vestibular rehabilitation to promote CNS adaptation and sensory re-weighting [15; 125].

Labyrinthitis

A presumed viral acute labyrinthitis is reasonable to treat with corticosteroid therapy, such as a 10-day course of prednisone with 60 mg/daily on days 1 through 5, reduced to 10 mg/daily on days 6 through 9, and 5 mg on day 10. Some evidence suggests corticosteroid therapy may hasten recovery but does not change the long-term prognosis [138]. Patients with bacterial labyrinthitis should be referred to an ENT specialist.

Herpes Zoster Oticus

Patients with herpes zoster oticus should be treated with corticosteroids and a high-dose oral antiviral (acyclovir, famciclovir, or valacyclovir) when reactivation of latent varicella zoster virus is suspected. Carefully look for painful vesicles on the external ear and within the back of the external ear canal. Even in the absence of visible vesicles, treatment with an antiviral agent is probably prudent with significant localized ear pain and normal tympanic membrane [15].

TRIGGERED EPISODIC VESTIBULAR SYNDROMES

Benign Paroxysmal Positional Vertigo

Canalith repositioning procedures (CRPs) are the first-line therapy option and the most effective treatment for BPPV for patients with prolonged symptoms and/or frequent recurrences. Vestibular suppressants are generally avoided, though a brief course of an antihistamine (e.g., meclazine) may be indicated for initial symptom control. This may be all that is needed for patients with mild, self-limited symptoms and infrequent recurrences. Rarely, BPPV can be refractory to CRPs and require surgical occlusion of the affected semicircular canal [15].

Outcome assessment within one month of initial observation or treatment is necessary to document symptom resolution or persistence. Patients with persistent symptoms should be evaluated for treatment failure. Referral to a specialist is recommended to identify unresolved BPPV and/or an underlying peripheral or central vestibular disorder.

In general, CRPs move the patient through a sequence of head position changes that use gravity to move otolith debris (including the pathologic trigger) out of the affected canal and back into the vestibule [22]. CRPs used in canalolithiasis or cupulolithiasis appear similar [22]. These procedures should only be performed after the affected canal is identified by diagnostic positioning techniques. Patients should be informed that dizziness, vertigo, or a sense of falling can develop during a CRP. Patients who had severe nausea or vomiting with the Dix-Hallpike should receive antiemetics 30 to 60 minutes before the procedure [22; 119].

Posterior Canal BPPV

What is the preferred canalith repositioning procedure in posterior canal BPPV?

CRP is strongly recommended as initial therapy for pc-BPPV [22]. The Epley maneuver is the preferred CRP for pc-BPPV and has more than 20 years of evidential support. Meta-analyses have found that, compared with sham or control groups, the Epley led to significantly greater rates of complete vertigo resolution and conversion from a positive to a negative Dix-Hallpike. After 12 months, the Epley was superior to sham maneuver in conversion to negative Dix-Hallpike and perceived disability [22; 140].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Academy of Otolaryngology recommends clinicians should treat, or refer to a clinician who can treat, patients with posterior canal BPPV with a canalith repositioning procedure.

(http://journals.sagepub.com/doi/pdf/10.1177/0194599816689667. Last accessed September 18, 2018.)

Strength of Recommendation: Strong recommendation (Benefits of the recommended approach clearly exceed the harms and that the quality of the supporting evidence is high)

The Semont maneuver uses inertial and gravitational forces to move patients briskly down into a side-lying position and then through a rapid 180° arc. In this manner, the Semont repositions free-floating debris from the posterior canal into the vestibule or breaks off canalith from adherence to the cupula [119].

The Semont and Epley maneuvers are comparably effective in pc-BPPV [22]. With speed of rotation critical for a successful Semont, and adequate neck extension and flexibility required for a successful Epley, patient features such as obesity and neck mobility can guide CRP selection [21]. The Semont is a suggested alternative to the Epley for patients with back problems [119].

Lateral Canal BPPV

Compared with apogeotropic lc-BPPV, the geotropic form is the best-researched and most clinically responsive form. The most frequently used repositioning approaches in lc-BPPV are [21; 22; 40]:

- Gradual rotations around the longitudinal axis of the body toward the nonaffected ear
- Lying for 12 hours overnight on the nonaffected ear (for geotropic) or on the affected ear (for apogeotropic)
- The Gufoni maneuver, which moves the patient from sitting to lying sideways with the head turned downward, holding, and repeating

The Gufoni maneuver can effectively treat canalolithiasis or cupulolithiasis lc-BPPV and has the advantage of eliminating the need to determine the involved form [40; 141]. An alternative is to first convert cupulolithiasis of the lateral canal to canalolithiasis by shaking the head after bending it 90° forward into the vertical plane [40].

Anterior Canal BPPV

The Gufoni maneuver or a reverse Epley maneuver has demonstrated symptom resolution in more than 75% of patients with ac-BPPV [142].

Vestibular Suppressant Treatment

Routine use of vestibular suppressants is not recommended in BPPV, as they may interfere with central compensation and obscure Dix-Hallpike findings. None are as effective as CRPs and cannot be used as CRP substitutes [15; 22].

In some patients, acute/short-term pharmacotherapy can be indicated. Anxiety and BPPV often co-occur; anxiety levels of patients with panic disorder and agoraphobia diagnosed with BPPV remained significantly elevated 14 days after CRP [143]. Thus, benzodiazepines have a role in patients with significant anxiety or who are too anxious to proceed with CRP [15; 22].

Dimenhydrinate, scopolamine, or diazepam may be required in severely symptomatic patients before CRP, patients who become severely symptomatic after CRP, or those who refuse CRP. Patients exceptionally prone to motion sickness should receive meclizine [15; 22; 114]. CRP plus betahistine more effectively reduced vertigo symptoms than CRP alone [144]. If prescribed, clinicians should educate patients that vestibular suppressants can increase risks of cognitive impairment, falls, drug interactions, and machinery or driving accidents [22].

BPPV and CNS Disorders

Aside from migraine, BPPV in patients with pre-existing central neurologic disorders is rarely addressed in the literature. In one study of 93 patients with BPPV, 31.2% had a central neurologic disorder, with cerebrovascular disease and migraine the most common. The efficacy of repositioning therapy was excellent for BPPV with or without a pre-existing central neurologic disorder [145].

Post-CRP Residual Dizziness

Residual dizziness following successful repositioning is common in patients with BPPV, described as continuous or intermittent imbalance, lightheadedness, or unsteadiness without positional vertigo. The duration of vertigo before CRP is linked to residual dizziness and incomplete central adaptation. Residual dizziness is significantly associated with anxiety disorders, and subjects with high anxiety show more durable and disabling dizziness even after the resolution of acute vertigo in absence of otolithic or vestibular dysfunction [128; 146].

Anxiety is highly prevalent in elderly patients with BPPV, and the adverse impact of residual dizziness on psychologic, social, and daily functioning can be severe. Early recognition and treatment of BPPV and comorbid anxiety is recommended to decrease the incidence of residual dizziness [128].

Refractory BPPV

If BPPV remains refractory despite a correct diagnosis and competently performed repositioning maneuvers, surgery may be indicated. The two surgical options are partial neurectomy of the vestibular nerve (singular nerve) or occlusion of the affected (mainly posterior) semicircular canal. Of the two, posterior canal occlusion is favored based on symptom reduction and complications [147].

Superior Canal Dehiscence Syndrome

In superior canal dehiscence syndrome, sound- or pressure-induced dizziness with auditory symptoms of autophony, hyperacusis, or tinnitus results from a bony dehiscence of the superior semicircular canal. Surgical repair of the canal is the recommended treatment [119].

SPONTANEOUS EPISODIC VESTIBULAR SYNDROMES

For patients with vestibular migraine or Ménière disease, vertigo attacks are unpredictable and difficult to control or avoid. The unpredictable, distressing experience may elevate patient anxiety over the next attack sufficiently to induce a secondary panic-like disorder, substantially adding to the psychologic burden [51].

Migraine and anxiety disorders share common genetic and environmental risk factors, and an interaction between migraine and anxiety is established. Auditory center, limbic system, and vestibular system interconnections may account for high rates of anxiety in patients with persistent tinnitus, fluctuating hearing loss, and vertigo symptoms in vestibular migraine or Ménière disease [51; 148].

Ménière Disease and Endolymphatic Hydrops

The episodic vertigo, hearing loss, and tinnitus in Ménière disease is associated with endolymphatic hydrops in the labyrinthine system of the affected ear [125]. Ménière dis-

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ease should be viewed and managed as a chronic condition, and treatment is tiered by disease stage and severity [149]. Acute symptomatic relief does not address the underlying pathophysiology, and the clinical goal is to minimize recurrent vertigo attacks and hearing symptoms to prevent new or additional damage to vestibular structures [150].

First Tier

Patients with Ménière disease are vulnerable to dietary and environmental factors that can impact hearing and balance. Triggers for Ménière disease may include high salt intake, caffeine, alcohol, nicotine, stress, monosodium glutamate, and allergies. Patients who identify and avoid triggers may greatly reduce their Ménière disease symptoms [150]. Therefore, lifestyle modification is the cornerstone of first-tier treatment.

Caffeine and nicotine are vasoconstrictors that may reduce microvascular flow in the labyrinthine system. Alcohol also causes fluid and electrolyte shifts that can stress a fragile ear. Smoking cessation and limiting daily intake to one caffeinated or alcoholic beverage are typically recommended [150].

When dietary and environmental changes fail to control the episodes, combinations of diuretic and as-needed vestibular suppressant/antiemetic agents are effective to control vertigo episodes in many patients, but do not protect hearing loss. Off-label use of sublingual lorazepam (0.5–1 mg up to four times per day) is anecdotally effective in achieving relief from acute vertigo attacks [150].

Betahistine is a conservative treatment option widely used in Europe for Ménière disease. It is believed to decrease symptoms by improving microcirculation in the inner ear and re-balancing endolymph production with resorption [151]. In one study, patients with mixed vestibular etiologies including Ménière disease received betahistine 48 mg/day. The decrease in average vertigo attacks per month from baseline to 60 days on betahistine persisted unchanged at 60 days off betahistine, which may suggest durable vestibular compensation [129]. As mentioned, demonstrating a treatment effect separate from spontaneous remission is difficult in Ménière disease and other s-EVS disorders.

Based on clinical experience with long-term treatment in patients with Ménière disease, long-term, high-dose betahistine is the recommended therapy, initiated at 48 mg three times per day [40; 61]. If symptom alleviation is insufficient after three months, the dose can be increased up to 480 mg/day [119; 152]. As noted, betahistine can be obtained at compounding pharmacies in the United States with a prescription [15].

Second Tier

Intratympanic injection (ITI) of corticosteroids is suggested for patients with Ménière disease-related disabling vertigo attacks despite conservative treatments, as the complication rates are low and side effects minimal. ITI of 0.4–1.0 mL high-dose dexamethasone solution (12 mg/mL) can improve vertigo symptoms and patient functioning, which may remain durable over 6 to 24 months [119]. However, patients may require repeated injections to maintain efficacy that can wane over time, and intratympanic gentamicin may be more effective [150].

Third Tier

Intratympanic gentamicin, a vestibulotoxic antibiotic, is a favored approach for Ménière disease refractory to less invasive options. Gentamicin induces unilateral vestibular loss to facilitate central compensation, reduce Ménière disease symptoms, and improve overall function [97; 153]. Meta-analyses of published clinical trials found 92.7% of patients achieved complete or substantial vertigo control and 74.7% achieved complete vertigo control with intratympanic gentamicin [98; 154].

ITI of gentamicin is ototoxic in some patients and has mainly been reserved for patients with Ménière disease and pre-existing hearing loss. To offset this limitation, a newer technique injects a minimal dose of gentamicin (0.5–0.75 mL of a 40 mg/mL solution) into the middle ear. A single injection provided good vertigo control over four years in 76% of patients; 15% to 20% required a second injection [150].

ITI gentamicin (2.0 mL of 40.0 mg/mL solution; up to two injections) was superior to ITI dexamethasone (4 mg/mL, three injections over seven days) in achieving complete vertigo control (81.0% vs. 43%) and complete or substantial vertigo control (93.5% vs. 61%). Significant hearing loss (>10 dB) developed in 13% of patients taking gentamicin [150; 155].

Intractable Bilateral Ménière Disease

Ménière disease may become bilateral in 15% to 20% of patients, usually within the first several years of onset. Bilateral involvement limits some vestibular ablation options, because treating both ears can result in bilateral vestibular loss [15]. Treating one side may not relieve vertigo, and interventional treatment can cause permanent hearing loss in a patient already at risk of hearing loss in both ears [125].

Options for intractable Ménière disease include endolymphatic mastoid shunt procedures, vestibular neurectomy, or labyrinthectomy, the latter used only in patients already deaf in the affected ear. Ablative surgical procedures are mainly reserved for ITI gentamicin failure. Because the development of Ménière disease is multifactorial, no single approach to therapy is expected to become the standard for all patients [147].

Vestibular Migraine

Treatment efficacy for vestibular migraine is not well-studied, partially because the disorder was only defined in 2013 [156]. Established treatments for migraine and/or vertigo are primarily recommended as abortive or prophylactic therapies for migraine symptoms in vestibular migraine. These medications may improve both headache and vertigo symptoms but can be hit or miss, and patients may need several different trials to find an individualized therapy [156; 157].

PROPHYLACTIC PHARMACOTHERAPY FOR VESTIBULAR MIGRAINE	
Characteristic	**Recommended Agent(s)**
By Available Evidence	
High-quality evidence of efficacy	Topiramate 25–100 mg/day Valproate 300–900 mg/day Metoprolol sustained-release 50–200 mg/day
Moderate-quality evidence of efficacy	Propranolol 40–240 mg/day Flunarizine 5–10 mg/day
Low-to-moderate-quality evidence of efficacy	Amitriptyline 50–100 mg/day Verapamil extended-release 120–360 mg/day Cinnarizine 37.5–75 mg/day
Lowest-quality evidence of efficacy	Acetazolamide 250–750 mg/day
By Attack Frequency	
Three or more attacks per month or long-lasting/disabling attacks	First-line: Propranolol 80–240 mg/day, metoprolol 50–200 mg/day, or bisoprolol 5–10 mg/day Second-line: Flunarizine 5–10 mg/day Third-line: Topiramate 25–100 mg/day or valproic acid 500–600 mg/day
Fifteen migraine attacks or more than eight migraine headaches per month for longer than three months	First-line: Topiramate 25–100 mg/day Second-line: A trial of onabotulinum toxin type A (155 MU) is reasonable but unlikely to improve vestibular symptoms
By Clinical Profile	
Prominent nausea and/or headaches and less prominent or minimal anxiety	Verapamil 120–240 mg/day (well-tolerated medication with good efficacy) Alternative: Topiramate 50–200 mg/day (often effective)
Prominent vertigo or dizziness, less frequent migraine headache	Lamotrigine 25–100 mg/day to reduce the frequency of vertigo episodes; less effective in reducing headache frequency
Severe vestibular migraine	Combination of two or three migraine prophylactic medications from different drug classes Consider zonisamide or acetazolamide
Source: [15; 119; 158; 159; 160; 161]	*Table 3*

Symptomatic Treatment of Acute Episodes

Acute attacks of vestibular migraine are treated with vestibular suppressants that include benzodiazepines (e.g., clonazepam, lorazepam), antiemetics (e.g., promethazine), antihistamines (e.g., meclizine, dimenhydrinate), and anticholinergic agents (e.g., scopolamine) [157]. Patients with excessive nausea or vomiting may prefer non-oral (e.g., IV, nasal spray, suppositories, subcutaneous injections) routes [158].

Abortive Treatment

Acute migraine treatment with triptans may offer benefit for patients with vestibular migraine. Sumatriptan was particularly efficacious in improving vertigo; rizatriptan helped prevent motion sickness symptoms. Zolmitriptan probably has little benefit in vestibular migraine [157].

Prophylactic Treatment

Treatment with migraine prophylactic medication may be needed when symptoms are frequent or severe and interfere with quality of life [15]. The indications for prophylactic therapy in vestibular migraine mirror those in migraine, which consider the frequency, duration, and disabling nature of attacks [119]. If caffeine and other triggers play a role in inciting episodes, they should be avoided when possible, as avoidance may enhance the efficacy of prophylactic therapy in vestibular migraine [49; 157].

Medications evaluated for prophylactic efficacy in vestibular migraine include antiepileptic drugs (e.g., topiramate, valproate/valproic acid, lamotrigine), beta-adrenergic blockers (e.g., propranolol, metoprolol sustained-release, bisoprolol), calcium channel blockers (e.g., flunarizine, verapamil extended-release, cinnarizine), and antidepressants (e.g., venlafaxine, nortriptyline, imipramine, amitriptyline). Prophylactic recommendations have been based on available evidence, attack frequency, and clinical profile (***Table 3***).

Vestibular Migraine and Anxiety

Patients with vestibular migraine are more anxious than patients with non-vestibular migraine [162]. Anxiety is so prevalent in vestibular migraine, migraine, and vestibular disorders that a new disorder—migraine-anxiety-related dizziness—was proposed to define the association [49].

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The recommended pharmacotherapy for vestibular patients with prominent anxiety, panic attacks, or depression and less prominent nausea is [15]:

- Venlafaxine 75 mg/day, OR
- A tricyclic antidepressant (e.g., nortriptyline, imipramine, amitriptyline) 50–75 mg/day

The established efficacy of venlafaxine in anxiety disorder treatment suggests a potential advantage over other vestibular migraine prophylaxis. One study evaluated patients with vestibular migraine randomized to venlafaxine (37.5 mg/day), flunarizine (10 mg/day), or valproic acid (1,000 mg/day) for three months [163]. Significant decreases in precipitating physical factors and functional consequences of vestibular migraine were noted with all three medications. Improvements in emotional consequences of vestibular migraine (with venlafaxine only), vertigo attack severity (with venlafaxine and flunarizine but not valproic acid), and vertigo attack frequency (with venlafaxine and valproic acid but not flunarizine) were also noted. This suggests venlafaxine more effectively reduced emotional distress and anticipatory anxiety related to vestibular migraine attacks, as well as attack frequency and severity [163].

Other Treatment Options

Betahistine plus flunarizine leads to greater improvements in vertigo frequency and severity than betahistine alone. Decreases in headache frequency and severity are comparable [164].

Vestibular rehabilitation is effective, with improved symptoms and disability in patients with vestibular migraine as add-on treatment to medical therapy or as stand-alone treatment [49; 157].

Vestibular Paroxysmia

With vestibular paroxysmia, the characteristic brevity (seconds up to a few minutes, very seldom many hours) and frequently of recurring vertigo attacks makes the differential diagnosis generally straightforward [46]. The frequent vertigo attacks respond to carbamazepine (200–800 mg/day) or oxcarbazepine (300–900 mg/day), even in the lower dose range. Both drugs are recommended to start with a low dose, slowly progressing to higher doses as necessary [119].

Second-Line Therapies for Carbamazepine/ Oxcarbazepine Intolerance

Alternative drug options include phenytoin, gabapentin, valproate, lamotrigine, topiramate, and baclofen or other non-antiepileptic drugs used in trigeminal neuralgia [46]. Treatment should start with low doses. Options include [119]:

- Phenytoin 100 mg once daily, increased up to three times per day
- Gabapentin 300 mg once daily, increased to three times daily over four to seven days and further increased with insufficient symptom relief (up to a maximum 1,800 mg)
- Valproate dosing proportional to body weight (start with 10 mg per kg body weight, increasing the dose every three days up to 20 mg/kg)

Antiepileptic medications can themselves elicit dizziness and should be prescribed cautiously, ideally by specialists who can differentiate possible side effects from dizziness or vertigo sensations per se [119].

Refractory Vestibular Paroxysmia

Surgical microvascular decompression of the 8th cranial nerve is used for medically intractable cases or in rare cases with non-vascular compression of the 8th nerve by a tumor or cyst [46].

CHRONIC VESTIBULAR SYNDROMES

Context-Specific (Triggered) CVS

Most t-CVS syndromes have been defined too recently for consistently effective therapies to surface. There is some evidence for the treatment of bilateral vestibulopathy, PPPD, depersonalization and derealization disorder, and mal de débarquement syndrome.

Bilateral Vestibulopathy

The primary cause of bilateral vestibulopathy is aminoglycoside ototoxicity, typically gentamicin or streptomycin. In these cases, the ototoxic medication should be stopped or switched to a non-ototoxic drug. Other underlying causes of bilateral vestibulopathy include autoimmune processes, local or systemic infectious/inflammatory processes, bacterial or viral meningitis, bilateral Ménière disease, head trauma, neoplasms, or malformations. The cause should be identified and resolved or symptomatically managed [119].

Vestibular rehabilitation improves dynamic visual acuity, diminishes oscillopsia, and lessens asymmetry of vestibulo-ocular function by promoting adaptation and substitution using vision and proprioceptive cues to stabilize gait and mobility [165]. Vestibular rehabilitation is strongly recommended for patients with bilateral vestibulopathy [15; 119].

Persistent Postural Perceptual Dizziness

Cognitive-behavioral therapy, possibly combined with an SNRI such as venlafaxine or duloxetine, is strongly recommended for patients with PPPD. Patients should be encouraged to not stop taking the antidepressant too early; four to five weeks is required to assess effectiveness [15; 119]. Vestibular rehabilitation can help address phobic avoidance behavior.

Depersonalization and Derealization Disorder

Patients with depersonalization and derealization disorder have benefited from SSRIs, benzodiazepines, lamotrigine, opioid antagonists, and CNS stimulants, probably from targeting other mental disorders commonly associated with or precipitated by the disorder [80].

Mal de Débarquement Syndrome

There is no established treatment for mal de débarquement syndrome, but an uncontrolled trial suggests that inducement of re-adaptation of the vestibulo-ocular reflex may result in improvement. In this approach, patients are exposed periodically to a rocking that mimics the pace and direction of their perceived sway while in a full-field optokinetic stimulus [15; 166].

Spontaneous CVS

Central Vestibular and Cerebellar Syndromes

The American Academy of Neurology has made the following treatment recommendations for cerebellar syndromes associated with nystagmus, vertigo, and ataxia [167]:

- Episodic ataxia type 2: 4-AP 15 mg/day
- Spinocerebellar ataxia or ataxia of mixed etiology: Riluzole
- Spinocerebellar ataxia type 3: Valproic acid 1,200 mg/day
- Spinocerebellar degeneration: Thyrotropin-releasing hormone over 14 days
- Degenerative ataxias: Inpatient rehabilitation (four weeks) to improve ataxia and function, transcranial magnetic stimulation to improve cerebellar motor signs

In episodic ataxia type 2, other treatment recommendations include [15; 119]:

- Acetazolamide 375–1,500 mg/day
- Dalfampridine sustained-release 10 mg PO once or twice per day

Cervicogenic Vertigo

With cervical vertigo, treatment options include manual therapy, muscle relaxant or anti-inflammatory medication, and tailored vestibular rehabilitation. With significant nerve compression that cannot be treated conservatively, interventional approaches remain a therapeutic option [119].

Post-Traumatic Vertigo

In patients with post-traumatic vertigo, the primary diagnosis should be treated. With BPPV present, CRP plus vestibular rehabilitation is the recommended approach. For patients with brainstem or labyrinthine concussion, use vestibular rehabilitation. Vestibular suppressants may be added in cases of labyrinthine concussion [22].

DIZZINESS AND FALLS PREVENTION IN OLDER PATIENTS

Vestibular dysfunction in older adults places them at substantially increased risk for what?

Dizziness and imbalance in older adults deserves specific attention. Among older adults (i.e., age older than 65 years), falls are the leading cause of disability, institutionalization, and premature mortality from injury and the fifth leading cause of death. Fear of falling, also called post-fall anxiety syndrome, is a well-recognized syndrome in older adults [168; 169; 170]. In 2015, the estimated cost of fall-related injuries in older adults in the United States was $50 billion [171].

As such, vestibular dysfunction is critical to identify in older adults. Dizziness is highly prevalent (up to 38%) in older patients, and symptomatic dizziness or vertigo substantially increases the risk for falls [172; 173].

During 2001–2004, an estimated 35.4% of adult Americans had vestibular dysfunction requiring medical attention. The prevalence of balance impairment and vestibular dysfunction increases with age—the rate is 75% among persons older than 70 years and 85% among persons 80 years of age or older. Persons with vestibular disorders have an eight-fold increase in risk of falling and resultant morbidity/mortality. Uncompensated vestibular hypofunction results in postural instability, visual blurring with head movement, and subjective complaints of dizziness and/or imbalance [44].

RISK FACTORS FOR FALLS IN THE ELDERLY

Falls typically result when age-related and environmental (e.g., unfamiliar surroundings, unsafe walking surface) risk factors intersect. Gait and balance impairment are the most consistent risk factors, followed by medications (e.g., benzodiazepines, antidepressants) and polypharmacy [174]. Older patients may have multiple risk factors, including vestibular dysfunction, cerebrovascular disease, cervical spine disorders, physical deconditioning, and postural hypotension. Visual impairment is common and promotes multisensory deficit [173; 175].

Postural control and balance rely on sensory input from proprioceptive and vestibular systems. Age-related changes in these systems impair postural control and increase the risk of falls; they include loss of proprioceptive sensitivity in the lower extremities and loss of labyrinthine hair cells, vestibular ganglion cells, and nerve fibers in the vestibular system [174]. Compounding the loss of proprioceptive and vestibular function are age-related changes in the CNS, including neuronal loss and neurotransmitter depletion, causing further impairments in postural control [174].

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ASSESSMENT OF FALLS RISK

A targeted history and physical exam can identify patients at risk for falling. All older patients, especially patients with a dizziness/vertigo diagnosis, should be asked at least once yearly about falls [174]. Questions for initial screening of falls risk include [22]:

- Have you had a fall in the past year? How many times? Were you injured?
- Do you feel unsteady when standing or walking?
- Do you worry about falling?

With positive response, the clinician can perform a more detailed assessment or refer the patient to a specialist [22]. Treatment should be directed at the most readily modifiable fall risk factor(s) [173].

Clinicians should counsel patients and their families on the risk of falls with any balance, dizziness, or vestibular disorder, especially the frail elderly, who are more susceptible to serious injury from falling. Counseling should occur during the initial diagnosis and can include assessment of home safety, activity restrictions, and the need for home supervision until symptoms resolve. Healthcare providers should also ask about dizziness while driving, which may require intervention to prevent patient and public injury or fatality [22; 173; 176].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with dizziness/vertigo, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient or caregiver understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. 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 are being provided, the use of an interpreter should be considered.

CONCLUSION

Knowledge advances are transforming the clinical care of patients with dizziness and vertigo. A paradigm-changing classification system and diagnostic algorithm for dizziness and vertigo affords greater diagnostic ease and accuracy for clinicians. An expanded understanding of the vestibular system highlights the relationship of anxiety to vestibular dysfunction. The differentiation of potentially dangerous cerebrovascular mimics of benign vertigo and dizziness enhances early detection and rapid intervention. The important contribution of vestibular dysfunction to risk for falls in the elderly has been clarified, as falls are a leading cause of disability and death from injury in this population. Despite the demonstrated efficacy of repositioning therapy for the management of BPPV and the ease with which this can be used in the primary care setting, patients with BPPV frequently experience delayed diagnosis, unnecessary testing, and non-recommended treatment. Thus, continuing education has an important role in helping to ensure that clinicians and their patients benefit from current concepts, tools of evaluation, and strategies for managing dizziness and vertigo.

RESOURCES

Vestibular Disorders Association (VeDA)
https://vestibular.org

Fall Prevention Center of Excellence
http://stopfalls.org

David E. Newman-Toker, MD, PhD
Johns Hopkins Medicine

HINTS Video
https://collections.lib.utah.edu/details?id=177180

Dix-Hallpike Maneuver Video
https://collections.lib.utah.edu/details?id=177177

Supine Head Roll Video
https://collections.lib.utah.edu/details?id=177185

Customer Information/Evaluation insert located between pages 32–33.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 32–33.
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MODERATE SEDATION/ANALGESIA

#30462 • 15 ANCC / 15 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide nurses with the knowledge required for safe drug delivery based on standardized operational guidelines. Preprocedural, intraprocedural, and postprocedural patient care are presented, as well as a thorough review of the drugs used, their advantages and disadvantages, and the safe administration of these agents.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses, especially those in procedural and diagnostic areas, such as radiology, endoscopy, cardiac cath, outpatient surgery, intensive care, and emergency departments.
Additional Approval: AACN Synergy CERP Category A, CCMC

BURNOUT: IMPACT ON NURSING AND QUALITY OF CARE

#31432 • 5 ANCC Hours

By Mail – $26 • Online/eBook – $20

Purpose: Given the integral relationship between work-related stress, job dissatisfaction, burnout, and patient care, properly addressing nursing burnout is essential. The purpose of this course is to provide nurses with information to identify burnout and with effective strategies to manage work-related stress and prevent burnout.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for nurses and nurse practitioners at all levels and in all settings, especially oncology, palliative care, mental health, and critical care.
Additional Approval: AACN Synergy CERP Category C

WOMEN AND HEART DISEASE

#33222 • 15 ANCC / 5 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to identify the unique challenges that face women with heart disease, including prevention, diagnosis, and treatment.
Faculty: Margo A. Halm, RN, PhD, NEA-BC
Audience: This course is designed for all nurses in family practice or medical/surgical areas, especially critical care or cardiac units..
Additional Approval: AACN Synergy CERP Category A, CCMC

PATHOPHYSIOLOGY: THE CENTRAL NERVOUS SYSTEM

NEW!

#38920 • 15 ANCC / 2 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: 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.
Faculty: Jane C. Norman, RN, MSN, CNE, PhD
Audience: This course is designed for nurses working in both critical care and general and specialty medical-surgical units in which patients with multiple system problems are found.
Additional Approval: AACN Synergy CERP Category A, CCMC

CARING FOR THE GERIATRIC PATIENT

NEW!

#39100 • 3 ANCC Hours

By Mail – $21 • Online/eBook – $15

Purpose: The purpose of this course is to provide nurses with an overview of the physical and psychosocial considerations necessary when providing care to geriatric patients.
Faculty: Alice Yick Flanagan, PhD, MSW; Allan G. Hedberg, PhD
Audience: This course is designed for nurses in a variety of practice settings who work with older patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIAGNOSING AND MANAGING HEADACHES

#90212 • 10 ANCC / 8 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: Given the common and difficult diagnoses associated with headaches, the purpose of this course is to educate the healthcare professional about the epidemiology and treatment of the various types of headaches so they may make early and accurate diagnoses, begin effective treatment, and/or refer patients to a specialist when necessary.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for physicians and will be of interest to nurses and other medical personnel who may encounter patients who complain of headaches.
Additional Approval: AACN Synergy CERP Category A, CCMC

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ISCHEMIC STROKE

#90282 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.

Faculty: Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.

Additional Approval: AACN Synergy CERP Category A, CCMC

CLINICAL MANAGEMENT OF VENTRICULAR ARRHYTHMIAS

#90372 • 15 ANCC / 4 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals with up-to-date knowledge of risk factors for development of ventricular arrhythmias, recommended therapies for the immediate and long-term management of arrhythmias, and indications of complications or side effects of therapy necessary to facilitate effective patient management, early identification of problems, and appropriate patient and family education.

Faculty: Karen Majorowicz, RN, ARNP

Audience: This course is designed for physicians, physician assistants, nurse practitioners, and nurses seeking to enhance their knowledge of foodborne illness. The course is of particular importance for clinicians in the primary care and emergency settings.

Additional Approval: AACN Synergy CERP Category A, CCMC

HYPERLIPIDEMIAS AND CARDIOVASCULAR DISEASE

#90842 • 10 ANCC / 7 Pharm Hours

By Mail – $46 • Online/eBook – $40

Purpose: The purpose of this course is to increase awareness of the crucial role of hyperlipidemias in the development of cardiovascular disease, evaluate the therapeutic benefits of pharmacological and nonpharmacological approaches to lipid control, and contribute to a more positive interaction between the healthcare professional and the patient, through fostering patient awareness, implementation of lifestyle changes, and compliance to therapy.

Faculty: A. José Lança, MD, PhD

Audience: This course is designed for physicians, physician assistants, nurses, and nurse practitioners who may intervene to limit the effects of hyperlipidemias in their patients, promoting better long-term health and preventing cardiovascular disease.

Additional Approval: AACN Synergy CERP Category A

PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

WV Mandate

#91601 • 3 ANCC / 3 Pharm Hours

By Mail – $21 • Online/eBook – $15

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, physician assistants, and nurses in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approval: AACN Synergy CERP Category A

Special Approvals: This course fulfills the West Virginia Board of Examiners for Registered Professional Nurses requirement for 3 hours of education related to Drug Diversion and Best Practice Prescribing of Controlled Substances.

This course fulfills the West Virginia State Board of Examiners for Licensed Professional Nurses requirement for 3 hours of education related to Chemical Dependency/Substance Abuse.

CARE OF THE PEDIATRIC TRAUMA PATIENT

#92072 • 15 ANCC Hours

By Mail – $66 • Online/eBook – $60

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

AUTISM SPECTRUM DISORDER

#92202 • 5 ANCC Hours

By Mail – $26 • Online/eBook – $20

Purpose: The purpose of this course is to provide healthcare professionals with a basic understanding of the very complex, misunderstood, often puzzling, and sometimes disabling condition, enabling them to provide more thorough patient care, recognize symptomatology, and educate patients, families, teachers and communities about autism spectrum disorder.

Faculty: Sharon M. Griffin, RN, PhD

Audience: This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.

Additional Approval: AACN Synergy CERP Category A

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Course Availability List *(Cont'd)*

SEPSIS: DIAGNOSIS AND MANAGEMENT

#94342 • 4 ANCC / 3 Pharm Hours

By Mail – $22 • Online/eBook – $16

UPDATE

Purpose: The purpose of this course is to provide healthcare professionals with a current review and updated, evidence-based guidance for the diagnosis and management of sepsis and septic shock. The objective is to address knowledge gaps, enhance clinical skill, and enable effective strategies of collaborative care to improve patient outcomes.
Faculty: Patricia Lea, RN, DNP, MSEd, CCRN; John M. Leonard, MD
Audience: This course is designed for all healthcare professionals who work with patients who present with sepsis, including nurses and physicians.
Additional Approval: AACN Synergy CERP Category A, CCMC

AUTOIMMUNE DISEASES

#94452 • 15 ANCC / 10 Pharm Hours

By Mail – $66 • Online/eBook – $60

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune disorders according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.
Additional Approval: AACN Synergy CERP Category A, CCMC

GASTROESOPHAGEAL REFLUX DISEASE IN ADULTS

#94900 • 10 ANCC / 5 Pharm Hours

By Mail – $46 • Online/eBook – $40

NEW!

Purpose: 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.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for physicians, nurses, and members of the interprofessional healthcare team involved in the diagnosis, treatment, and care of patients with gastroesophageal reflux disease (GERD).
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/ Controlled Substances & Pain Mgmt

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 Approvals: This course is designed to meet the requirement for opioid/controlled substance education.

FRONTOTEMPORAL DEGENERATION

#96101 • 2 ANCC / 1 Pharm Hour

By Mail – $21 • Online/eBook – $15

MA Mandate

Purpose: The purpose of this course is to provide healthcare professionals with current information on frontotemporal degeneration (FTD). Providing a foundation for the care of patients with FTD and support for their families.
Faculty: Ellen Steinbart, RN, MA
Audience: This course is designed for physicians, nurses, and allied health and mental health professionals who may intervene to support patients with frontotemporal degeneration and their families.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approvals: This course meets the one-time Massachusetts requirement for education in the diagnosis, treatment, and care of patients with cognitive impairments.

ANXIETY DISORDERS

#96181 • 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

MENTAL HEALTH ISSUES COMMON TO VETERANS AND THEIR FAMILIES

#96340 • 2 ANCC Hours

By Mail – $21 • Online/eBook – $15

WV Mandate

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of military service on patient health as well as the skills necessary to effectively identify and intervene for these patients.
Faculty: Alice Yick Flanagan, PhD, MSW; Mark Rose, BS, MA
Audience: This course is designed for nurses and other healthcare professionals who may treat veterans or their family members.
Additional Approval: AACN Synergy CERP Category A
Special Approvals: This course is designed to meet the West Virginia requirement for 2 hours of education on mental health conditions common to veterans and family members of veterans.

DOMESTIC AND SEXUAL VIOLENCE

#97790 • 5 ANCC Hours

By Mail – $26 • Online/eBook – $20

KY Mandate

Purpose: The purpose of this course is to provide healthcare professionals with the skills and confidence necessary to identify victims of sexual or domestic violence and to intervene appropriately and effectively.
Faculty: Alice Yick Flanagan, PhD, MSW; John M. Leonard, MD
Audience: This course is designed for a wide range of healthcare and mental health professionals, including physicians, physician assistants, nurses, social workers, mental health/rehabilitation counselors, and marriage and family therapists.
Additional Approval: AACN Synergy CERP Category B
Special Approvals: This course meets the Kentucky requirement for domestic violence continuing education.

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	95072	Antibiotics Review / 5 Contact Hours	$20
	98400	Dizziness and Vertigo / 10 Contact Hours	$40

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☐	33222	Women and Heart Disease / 15	$66
☐	38920	Pathophysiology: The Central Nervous System / 15	$66
☐	39100	Caring for the Geriatric Patient / 3	$21
☐	90212	Diagnosing and Managing Headaches / 10	$46
☐	90282	Ischemic Stroke / 10	$46
☐	90372	Clinical Management of Ventricular Arrhythmias / 15	$66
☐	90842	Hyperlipidemias and Cardiovascular Disease / 10	$46
☐	91601	Prescribing Opioids: The WV Requirement / 3	$21
☐	92072	Care of the Pediatric Trauma Patient / 15	$66
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☐	95150	Responsible and Effective Opioid Prescribing / 3	$21
☐	96101	Frontotemporal Degeneration / 2	$21
☐	96181	Anxiety Disorders / 15	$66
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1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
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

#98400
Dizziness and Vertigo
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

#95072 Antibiotics Review — If you answered yes to question #14, what change(s) do you plan to make in your practice? _____

_____

_____

#98400 Dizziness and Vertigo — If you answered yes to question #14, what change(s) do you plan to make in your practice? _____

_____

_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

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