Emerging Antimicrobial-Resistant Infections

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Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.

William Osler

The emergence of antimicrobial-resistant bacterial infections has changed the recommendations for the empirical therapy of community- and hospital-acquired meningitis. In the United States, approximately 34% of pneumococcal isolates are penicillin nonsusceptible, and approximately 14% are resistant to ceftriaxone. More than 50% of nosocomial infections in patients in the intensive care unit are due to methicillin-resistant Staphylococcus aureus. The first documented case of vancomycin-resistant S aureus was reported in the United States in 2002.

The National Committee for Clinical Laboratory Standards establishes the standards for determining the susceptibility of bacteria to antibiotics based on the minimum inhibitory concentration (MIC). For pneumococcal meningitis, isolates with an MIC of 0.06 µg/mL or less are considered susceptible to penicillin, those with an MIC of 0.12 to 1.0 µg/mL to be intermediate, and those with an MIC of 2.0 µg/mL or greater to be resistant. A pneumococcal isolate with an MIC for cefotaxime or ceftriaxone of less than 0.5 µg/mL is considered susceptible, 1.0 µg/mL intermediate, and greater than 2.0 µg/mL resistant.

A strain of pneumococci is considered nonsusceptible to an antibiotic when the MIC is in the intermediate or resistant range. Streptococcus pneumoniae develops resistance to penicillins and cephalosporins through alterations of one or more penicillin-binding proteins. Alterations in the penicillin-binding proteins lead to a decrease in the bacteria’s affinity for the antibiotic and thus a decreased susceptibility to the antibiotic. The mechanism of resistance is acquired through a process in which a particular genome encoding the alteration is acquired from other bacteria by pneumococci and incorporated into their own DNA.

Vancomycin-resistant strains of pneumococci have not been seen, but strains of S pneumoniae tolerant to vancomycin have been reported. Tolerance is the ability of a bacterium to survive in the presence of an antibiotic, neither growing nor being eradicated by the antibiotic. Tolerance may be the precursor for the development of antimicrobial resistance because it creates survivors of antibiotic therapy.

To successfully treat an infection, an antibiotic must be selected that will provide a concentration greater than the MIC at the site of infection in the central nervous system for a period adequate to eradicate the organism. Central nervous system infection with an organism that is resistant to an antibiotic can often be successfully treated by using higher doses of the antibiotic for a prolonged period, by using a combination of intravenous and intraventricular therapy, or by using a combination of antibiotics.

Empirical therapy of community-acquired bacterial meningitis is based on the possibility that penicillin- and cephalosporin-resistant pneumococci are the causative organisms of the meningitis. A combination of ceftriaxone (pediatric dose, 100 mg/kg per day in a 12-hour dosing interval; adult dose, 2 g every 12 hours), cefotaxime (pediatric dose, 300 mg/kg per day in a 4- to 6-hour dosing interval; adult dose, 3 g every 4 hours), or cefepime (adult dose, 2 g every 4 hours)
dose, 2 g every 12 hours) plus vancomycin (pediatric dose, 40-60 mg/kg/d in a 6- or 12-hour dosing interval; adult dose, 500 mg every 6 hours or 1 g every 12 hours) is recommended.

Inadequate empirical therapy is associated with increased mortality, but excessive antibiotic use promotes the emergence and spread of antibiotic-resistant bacterial pathogens. To minimize the use of antibiotics for empirical therapy, specific diagnostic tests that differentiate bacterial meningitis from other central nervous system infections need to be readily available. The possibility of bacterial meningitis is considered when the classic triad of fever, headache, and meningismus is present. The classic cerebrospinal fluid (CSF) abnormalities of bacterial meningitis are as follows: (1) elevated protein; (2) 100 to 5000 white blood cells/mm³ with a predominance of polymorphonuclear leukocytes; (3) glucose concentration of 40 mg/dL or less, a CSF:serum glucose ratio of less than 0.31; and (4) gram stain is positive in 70% to 85% of patients and is dependent on the CSF concentration of bacteria. The likelihood of having a positive gram stain also depends on the specific meningeal pathogen. Ninety percent of cases due to S pneumoniae, 75% of cases due to Neisseria meningitidis, and 50% of cases due to gram-negative bacilli have a positive gram stain. Culture is positive in 80% of patients with bacterial meningitis who have not received antibiotic therapy; 48 hours are usually required for accurate identification.

The CSF will appear cloudy or turbid if there are more than 200 white blood cells/mm³, more than 400 red blood cells/mm³, more than 10⁷ bacterial colony forming units/mL, and/or an elevated protein concentration.

A broad-range polymerase chain reaction can detect small numbers of viable and nonviable organisms in the CSF. When the broad-range polymerase chain reaction is positive, a polymerase chain reaction that uses specific bacterial primers to detect the nucleic acid of S pneumoniae, N meningitidis, Escherichia coli, Listeria monocytogenes, Haemophilus influenzae, and Streptococcus agalactiae should then be done. The CSF lactate concentration is nonspecific and therefore not useful in the diagnosis of bacterial meningitis. The serum procalcitonin has a high sensitivity and specificity for bacterial meningitis. Procalcitonin is a polypeptide that increases in patients with severe bacterial infections. It is recommended that lumbar puncture be repeated 36 to 48 hours after the initiation of therapy (unless contraindicated by the neurological examination) to document eradication of the pathogen. This recommendation has become increasingly important to follow with the emergence of antimicrobial-resistant organisms.

Methicillin-resistant S aureus infections have emerged as an increasing threat owing to the easy transmissibility of this pathogen. One of the most significant risk factors associated with nosocomial-acquired methicillin-resistant S aureus is the close proximity of physicians and nurses who are colonized with methicillin-resistant S aureus, spreading it to patients who are sick and who subsequently become colonized and infected. Similar to how antimicrobial-resistant isolates of S pneumoniae develop, S aureus acquires one particular gene from another bacterium that alters one particular penicillin-binding protein, resulting in absolute resistance to methicillin. The enterococci are part of the normal flora of the gastrointestinal tract. Some isolates of vancomycin-resistant S aureus contain the vanA vancomycin-resistant gene. This gene is acquired from vancomycin-resistant enterococci by conjugative transfer.

Staphylococci are the most common causative organisms of craniootomy bone flap infections, osteomyelitis as a complication of craniootomy, postoperative epidural abscess, and CSF shunt infections. The majority of cases of postoperative meningitis are caused by S aureus, coagulase-negative staphylococci, aerobic gram-negative bacilli, and streptococci. Empirical therapy for postoperative meningitis should include a combination of vancomycin and either cefazidime or cefepime, based on the possibility that methicillin-resistant S aureus is the causative organism. Effective therapy of methicillin-resistant staphylococcal meningitis may require intraventricular vancomycin, especially in those patients who are unable to mount an inflammatory response in the subarachnoid space. Vancomycin penetrates inflamed meninges more readily than it penetrates noninflamed meninges. The toxicity of intraventricular vancomycin is fairly minimal and primarily based on anecdotal reports that include fever, headache, tinnitus, and mental status changes. The intraventricular dose of vancomycin is 20 mg per day in adults and 10 mg per day in children.

To prevent the iatrogenic transmission of methicillin- or vancomycin-resistant S aureus, (1) infected patients should be in a private room, (2) gloves must be worn whenever there is direct contact with the patient, (3) masks should be worn when there will be contact with oropharyngeal secretions, (4) gowns should be worn if any soiling of clothes is anticipated, (5) strict hand-washing procedures should be followed before leaving the patient’s room, and (6) stethoscopes and reflex hammers should be cleaned. To examine the fundi when looking for brainstem reflexes in a ventilator-dependent patient in the intensive care unit, a mask, gloves, and a gown should be worn.

Enterococci are part of the normal flora in the gastrointestinal tract and the second most common pathogenic cause of bloodstream infections in patients in the intensive care unit but a relatively uncommon cause of central nervous system infections. The most common conditions associated with enterococcal meningitis are external ventricular drains, epidural catheters, neurosurgical procedures, immunosuppression therapy, and gastrointestinal disease and Strongyloides species hyperinfection. Most cases of enterococcal meningitis are caused by Enterococcus faecalis. Vancomycin-resistant enterococcal infections are a major problem. Enterococci are naturally resistant to several antibiotics and have the ability to acquire resistance through the exchange of genetic material. Optimal therapy for vancomycin-resistant enterococcal central nervous system infections has not been established, and recommendations are based on case reports and small series. Vancomycin-resistant Enterococcus faecalis meningitis has been successfully treated with linezolid. Linezolid has good CSF penetration and is generally well tolerated. Unfortunately, there are already case reports of patients with linezolid-
resistant *E. faecium* infections. Chloramphenicol can be used to treat vancomycin-resistant enterococcal meningitis; however, an increasing number of vancomycin-resistant enterococci are either immediately susceptible or resistant to chloramphenicol in vitro. Quinupristin/dalfopristin are 2 semisynthetic streptogramin antibiotics that are bacteriostatic against enterococcus. Intravenous quinupristin/dalfopristin penetrates poorly into the subarachnoid space. The administration of quinupristin/dalfopristin by both the intravenous route (7.5 mg/kg every 8 hours) and the intraventricular route (2 mg daily) was successful in eradicating vancomycin-resistant *E. faecium* ventriculostomy-related meningitis.

In summary, recommendations for empirical therapy of community- and hospital-acquired meningitis are constantly changing because of increasing antimicrobial-resistant bacterial infections. Empirical therapy of community-acquired bacterial meningitis is based on the possibility that penicillin- and cephalosporin-resistant pneumococci are the causative organisms of the meningitis. Empirical therapy for postoperative meningitis should include a combination of vancomycin and cefazidime or cefepime, based on the possibility that methicillin-resistant *S. aureus* is the causative organism. Inadequate empirical therapy is associated with increased mortality, but excessive antibiotic use promotes the emergence and spread of antibiotic-resistant pathogens. Empirical therapy should be modified when culture results are available. The need for broad-spectrum antimicrobial therapy should be reevaluated on a daily basis. Physicians should take the necessary precautions to limit the iatrogenic spread of antimicrobial organisms.

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REFERENCES


