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CONFERENCIA

MANAGEMENT OF DRUG-RESISTANT GRAM-POSITIVE PATHOGENS

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Drug-resistant Gram-positive pathogens, particularly *Staphylococcus aureus, Streptococcus pneumoniae* and *Enteroccoccus*, have emerged as major problems that have required changes in management and therapy of common infections.

Staphylococcus aureus

S. aureus is a common component of skin flora, and 20% of adults carry this organism in the anterior nares or intertriginous areas. Carriage of *S. aureus* is more common in diabetics, hemodialysis patients, intravenous drug users and persons with chronic dermatologic conditions.

S. aureus is highly pathogenic and causes many infections, the most common ones being wound and soft-tissue infections, pneumonia, catheter infections, bacteremia and endocarditis.

Methicillin-resistant *S. aureus* (MRSA) was first discovered in 1961, and by 1996, 35% of all S. aureus isolates in the United States were MRSA. MRSA is not more virulent than methicillin-susceptible *S. aureus,* but it is more difficult to treat.

Colonization and disease. It is critical to distinguish colonization from disease due to MRSA. Most patients are colonized and do not require therapy, except under unusual circumstances. Only patients with disease require treatment. The separation of colonization from disease depends largely on clinical findings, not on the culture results. Systemic signs indicative of disease include fever and leukocytosis. When MRSA is isolated from sputum, local evidence of infection are increased cough, sputum production and chest x-ray infiltrates. When MRSA is isolated from the skin or from a wound, local pain, erythema, swelling and purulent discharge are indicative of disease.

Treatment. MRSA have altered penicillin-binding proteins and b-lactam drugs are ineffective. Vancomycin is the drug of choice, but it is less effective against MRSA than nafcillin or oxacillin are against methicillin-susceptible S. aureus. Vancomycin's CSF penetration is variable and it is nephrotoxic, especially in combination with aminoglycosides. Gentamicin and rifampin are often used for synergy in patients with serious infection, but should not be used alone.

Other agents that are effective for treatment of MRSA are trimethoprim-sulfamethoxazole, quinolones and doxcycline. However, susceptibility testing should be performed before using these agents. Linezolid, an oxazalidinone, should also be effective, but experience with this agent is limited. One problem with linezolid is that susceptibility testing is not commercially available.

The therapy of MRSA disease depends on its severity. For patients with endocarditis, serious pneumonia, osteomyelitis, or bacteremia, vancomycin and gentamicin, sometimes with rifampin, are used. For less serious infections, such as mild pneumonia, bronchitis and soft-tissue infections, single oral agents can be used, based on drug susceptibility testing.

Infection control. Transmission of MRSA is generally through contact with infected secretions. However, it can be transmitted by aerosolized droplets in patients with respiratory infections or by irrigation of extensive wounds. Most transmission occurs from patient to patient via health care workers. Health care workers who are chronic carriers play a less important role. For hospitalized patients with MRSA colonization or disease, contact isolation is recommended for most cases. In patients with respiratory MRSA disease or with large wounds that require irrigation,droplet isolation is recommended.

In chronic care facilities, the prevalence of MRSA is high but colonized persons and other residents are at minimal risk for disease. Colonized patients should not be isolated as long as they can control infected secretions and attempts to eradicate colonization are unwarranted. Hand washing and wound care precautions are important. Isolation is recommended if there is an outbreak of MRSA disease, if patients have extensive wounds with heavy colonization, if they aerosolize MRSA in infected secretions, and if they are bed-bound with a Foley catheter and an MRSA urinary tract infection.

Eradication of MRSA colonization is only recommended to stop a disease outbreak and to prevent recurrent disease in a patient. In most individuals, eradication is not recommended because it is not cost-effective, may foster resistance, and cause adverse effects. Topical mupirocin is the most active agent to eliminate colonization, and the combination of systemic and topical therapy may be superior. However, colonization often persists or recurs.

The future. Vancomycin-resistant *S. aureus* have been reported, and transmission of resistance via plasmids is a major concern.

Streptococcus pneumoniae

The leading cause of pneumonia, meningitis, otitis media and sinusitis, and a major cause of bacteremia. One third of nasopharyngeal cultures from healthy children yield *S. pneumoniae*. S. pneumoniae is transmitted by respiratory droplets and requires close contact. Nosocomial transmission has not been reported.

The first case of penicillin-resistant pneumococcus was isolated in 1967. By 1997, 25% of U.S. isolates were penicillin-resistant. Resistance does not alter virulence.

Intermediate penicillin susceptibility of pneumococcus is defined as an MIC of 01.-1.0 µg/ml. These organisms are generally susceptible to third-generation cephalosporins. Resistance is defined as an MIC of >1.0 µg/ml. These organisms are susceptible only to vancomycin.

Treatment. For outpatients with pneumococcal pneumonia, azithromycin or a quinolone with enhanced pneumococcal activity can be used. For meningitis, penicillin is no longer adequate empiric therapy. Vancomycin and cefotaxime are used until drug susceptibility is known.

Prevention. Minimize use of antibiotics for viral infections, and use pneumococcal vaccine.

Enterococcus

E. faecalis and *E. faecium* are part of normal intestinal flora, and are much less virulent than S. aureus and S. pneumoniae. It is predominantly a nosocomial pathogen and causes disease primarily in debilitated persons. The most common types of infection are urinary tract infections, pelvic and intra-abdominal infections, endocarditis, surgical wound infections and bacteremia.

Vancomycin-resistant enterococci were first isolated in 1988 and by 1994, 15% of enterococci isolated from ICUs in the U.S. were VRE.

VRE with the vanA phenotype are resistant to teicoplanin, whereas those with the vanB and vanC phenotypes can be susceptible to teicoplanin.

Colonization and disease. As is the case for MRSA, most persons from whom VRE are isolated are colonized with the organism. Only patients with clinical signs of disease should be treated.

Treatment. Enterococci have intrinsic low level resistance to penicillins, cephalosporins, carbapenems and aminoglycosides. E. faecium is more highly resistant than E. faecalis. For VRE, few treatment options are available. High-dose ampicillin (20 mgs/day) can be used if the MIC is < 32 µg/ml, in combination with gentamicin for synergy. Alternatively, vancomycin and ampicillin can be used together. Other antibiotics that may have activity include teicoplanin, chloramphenicol, doxycycline, rifampin, quinolones, novobiocin, quinupristin-dalfopristin and linezolid. Nitrofurantoin can be used to treat urinary tract infections.

Infection control. Generally spread in the same manner as MRSA. Contact isolation and strict handwashing are recommended for hospitalized patients with VRE colonization or disease if infected secretions are present. Roommates should be tested for fecal colonization. In chronic care facilities, patients with diarrhea, incontinence and VRE isolated from stool should be isolated, as well as patients with VRE in large draining wounds Patients with uncomplicated fecal colonization who are continent and those with colonized small wounds that can be covered do not require isolation. No topical or systemic therapy is recommended for colonization.

The future. Vancomycin resistance of the vanA and vanB phenotypes are plasmid-mediated and can be transferred quickly to other Gram-positive bacteria, including S. aureus and S. pneumoniae.

Appropriate use of vancomycin

Vancomycin should only be used for serious infections due to a β-lactam-resistant Gram-positive pathogen, serious infection due to a Gram-positive pathogen in patients with severe β-lactam allergy, empiric therapy of febrile neutropenic patients at high risk for Gram-positive infections, and for treatment of C. difficile colitis when metronidazole therapy has failed.

Vancomycin should not be used to treat single positive blood cultures for coagulase-negative staphylococci without clinical signs of bacteremia, as empiric therapy for all febrile neutropenic patients, MRSA colonization, or prophylaxis for surgery, venous catheters, dialysis or premature infants.

Conclusions

1) Development of antibiotic resistance is inevitable
2) Prevention is much easier than treatment
3) Limit antibiotic use
4) Hand washing is the most effective control measure

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