Microbial drug resistance and the roles of the new antibiotics

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ABSTRACT

Physicians should be cautious in prescribing broad-spectrum antibiotics, particularly vancomycin and the fluoroquinolones, because widespread use of these drugs is promoting antibiotic resistance. Resistance is now found in many organisms, including staphylococci, enterococci, streptococci, pneumococci, and *Pseudomonas aeruginosa*. Some resistant strains can be treated with alternative narrower-spectrum antibiotics. In addition, five newly licensed antibiotics are available, but they should be used judiciously because of their side effects, high cost, and ability to promote additional resistance.

Indiscriminate antibiotic use begets drug resistance

FIVE NEW ANTIBIOTICS recently approved by the Food and Drug Administration (FDA) in the United States have a role in fighting resistant infections: quinupristin-dalfopristin (Synercid), linezolid (Zyvox), gatifloxacin (Tequin), moxifloxacin (Avelox), and atovaquone-proguanil (Malarone). Unfortunately, many of these are costly and several may have serious side effects. I recommend reserving them for judicious treatment of infections resistant to traditional medications.

PATTERNS OF BACTERIAL RESISTANCE

Vancomycin resistance in enterococci

The emergence of vancomycin-resistant enterococci (VRE) has long been feared. Fortunately, VRE tend to produce indolent infections; patients often die *with* VRE infection rather than *because* of it. Patients who develop VRE infections are often already hospitalized and have serious underlying illnesses. Most have received prior antibiotic therapy.

A number of studies have linked antibiotic use, especially cephalosporins, to the subsequent emergence of VRE. At the Cleveland Clinic, we have changed our prescribing patterns to use third-generation cephalosporin antibiotics more judiciously, a change that has been accompanied by a reduction in the percentage of resistant enterococcal isolates from 17% in 1999 to 12% in 2000.

There are many options for the treatment of VRE infections. Over 70% of VRE isolates are susceptible to chloramphenicol. In addition, these organisms are usually susceptible to the new drugs quinupristin-dalfopristin and linezolid.

Vancomycin resistance in *Staphylococcus aureus*

In very rare cases, *Staphylococcus aureus* organisms are emerging with partial or near-complete resistance to vancomycin.

Vancomycin-intermediate *S aureus* (VISA) strains are defined as those with a minimum inhibitory concentration (MIC) of 8 to 16 µg/mL of vancomycin, and vancomycin-resistant *S aureus* (VRSA) strains are those with an MIC greater than 32 µg/mL. The mechanism of resistance is not understood.

The first recognized case of VISA occurred in 1995 in France. Subsequent cases were reported in Japan, and the first US case was reported in 1997. Since 1997, mercifully, there have been only six cases of VISA in the United States, although there have been 17

New developments in infectious disease

NEW TREATMENT OF MALARIA

Atovaquone-proguanil (Malarone) has been licensed for prophylaxis and treatment of falciparum malaria, including the drug-resistant strains. It is an attractive alternative to mefloquine, the standard choice, because it can be started as little as 1 to 2 days before departure for the malaria-endemic location. In contrast, mefloquine should be started 2 weeks before departure. Thus, atovaquone-proguanil is particularly useful for people making brief or unexpected trips.

The drug is taken daily while the patient is in the endemic area and for 7 additional days after return. Again, this is preferable to mefloquine, which should ideally be taken for several weeks after return.

In prophylactic doses, side effects are rare; headache and abdominal pain may occur in 3% to 5% of patients, rates similar to those occurring in placebo patients. At the higher doses required for treatment, side effects are more common and include abdominal pain, nausea, vomiting, and headache.

Atovaquone-proguanil does not carry the risk of tremor, which is a rare side effect of mefloquine. Thus it may be better for individuals who require fine motor coordination during their travel abroad.

NEW AGENTS FOR FLU PREVENTION

Two new antivirals have been shown to be effective for prophylaxis and treatment of influenza.

Oseltamivir (Tamiflu) effectively and safely prevented influenza when given in a single daily oral dose during influenza season.[9,10]

Daily inhaled zanamivir (Relenza) was highly effective in preventing influenza in outbreak settings and among family contacts of infected patients.[11] It was also effective in alleviating symptoms in influenza and shortening their duration.[12]

Both oseltamivir and zanamivir are better tolerated than the older compounds amantadine and rimantadine, but they are costly. A 5-day course of oseltamivir costs about $50, and a 5-day course of zanamivir costs about $44.

Although both of these agents are effective, immunization should remain the cornerstone of prevention. The effectiveness of immunization was confirmed once again in a recent study showing that influenza vaccine was highly effective in protecting health care workers against both type A and type B disease during the flu season.[13]

I recommend using oseltamivir and zanamivir for prophylaxis only in unvaccinated high-risk individuals who are exposed to infection, and in situations when, after the development of the vaccine, the prevalent virus changes to a nonvaccine strain.

additional cases of *S aureus* infection with an MIC of 4 μg/mL.

The typical patient with VISA has chronic renal failure and an indwelling vascular catheter and, because of recurrent *S aureus* bacteremia, has been heavily treated with vancomycin. Five of the six US patients with VISA had renal failure, and all were heavily pretreated with vancomycin. Four of the six had recurrent bacteremias, most of them line-related. Although four of the patients died, only two of the deaths were attributable to the VISA infection.

Fortunately, all six of these isolates were susceptible to trimethoprim-sulfamethoxazole, linezolid, and quinupristin-dalfopristin.[1]

One aspect of *S aureus* infection that may pose a problem in the future is heterotypic resistance, which is the presence of slightly different populations of bacteria in the same patient, some of which may be vancomycin-resistant. A disturbing study from Japan in 1997 found that 20% of patients with *S aureus* had heterotypic resistance, that is, they were colonized with a population of bacteria that included some VISA strains.[2] The great fear among infectious disease physicians is that continued widespread indiscriminate vancomycin use could encourage the growth of the VISA strains.

Because VISA is most likely in patients with renal failure, a history of sustained vancomycin use, and recurrent *S aureus* bacteremia, we should be especially careful to avoid indiscriminate vancomycin use in this population.

Drug resistance in *Streptococcus pneumoniae*

In 1999, the Centers for Disease Control and Prevention (CDC) reported that, of 1,600 *Streptococcus pneumoniae* isolates from several medical centers, 30% were partially resistant to penicillin and 12% had high-level resistance. Four percent of the isolates were resistant to ceftriaxone, 13% to tetracycline, and 20% to trimethoprim-sulfamethoxazole. In addition, 5% of the isolates were resistant to multiple antibiotics. The prevalence of resistance varied widely from one location to the next, ranging from as low as 13% to as high as 65%.[3]

The emergence of quinolone resistance in *S pneumoniae* is very recent and may herald a future problem. Between 1988 and 1997, the use of ciprofloxacin and other fluoroquinolones in Canada increased nearly sevenfold, and concurrently, the prevalence of strains with reduced susceptibility to ciprofloxacin rose from zero to 1.7% (or 3% among adults).[4] Clearly, indiscriminate use begets antimicrobial resistance.

Multidrug-resistant strains are also on the rise. The CDC found that among invasive pneumococcal infections in eight US regions, 24% of the isolates in 1998 were penicillin-resistant, including 14% that were highly resistant. Two thirds of the penicillin-resistant isolates were also resistant to all drugs tested, and the penicillin-resistant strains were more likely to display high-level resistance to the other drugs. The proportion of isolates that were resistant to three or more drug classes increased from 9% in 1995 to 14% in 1998. Fewer than 10% were tetracycline-resistant.[5]

Also, in the Atlanta area, macrolide resistance among isolates from invasive pneumococcal disease increased from 16% in 1994 to 32% in 1999. The increase was attributable to the spread of a gene called *mefE*, a macrolide efflux gene.[6]

Treating pneumococcal infections

The emergence of drug-resistant pneumococci poses a temptation for the practicing physician to treat all patients in whom pneumococcal disease is suspected with fluoroquinolones, which have excellent activity against these organisms. However, such a practice runs the risk of promoting the development of fluoroquinolone resistance in these organisms in the future.

Recent guidelines have been published by the Infectious Disease Society of America for empiric and pathogen-specific therapy of community-acquired pneumonia.[7] In addition to fluoroquinolones, recommended agents for oral outpatient empiric therapy and therapy for suspected *S pneumoniae* include amoxicillin, cefuroxime axetil, cefpodoxime, cefprozil, doxycycline, erythromycin, clarithromycin, or azithromycin. In hospitalized patients, pneumococcal isolates susceptible or intermediately resistant to penicillin nevertheless respond to penicillin, ceftriaxone, or cefotaxime. Penicillin-resistant isolates also seem to respond to ceftriaxone. In critically ill patients with suspected or proven pneumococcal pneumonia, vancomycin or a fluoroquinolone are appropriate pending antimicrobial susceptibility data.

Indiscriminate use of fluoroquinolones to treat community-acquired bronchitis or sinusitis should be avoided, as this may breed endemic resistance in the community. In patients with recurrent bronchitis or sinusitis in whom the suspicion of penicillin-resistant pathogens may be higher, especially if heavily pretreated with antibiotics, fluoroquinolones may have a role, but attempts should be made to establish a microbiologic diagnosis in such individuals.

For patients with pneumococcal meningitis with suspected or proven penicillin-resistant strains, ceftriaxone may be ineffective and vancomycin is the treatment of choice. Again, if *S pneumoniae* isolated from the cerebrospinal fluid is susceptible to penicillin, penicillin or ceftriaxone are acceptable alternatives.

Resist the temptation to use quinolones for community-acquired pneumonia

Methicillin resistance in staphylococci

Methicillin resistance is now very common among coagulase-negative staphylococci, which is troubling because coagulase-negative staphylococci are now the leading cause of nosocomial bloodstream infections. They are also an important cause of postoperative surgical site infections, which usually present as indolent wound infections rather than as fulminant septicemic clinical syndromes.

For example, coagulase-negative staphylococci are the most common cause of postoperative sternal wound infection following open heart surgery at the Cleveland Clinic; fortunately they occur in only 1% to 2% of patients.[8] Such coagulase-negative staphylococcal infections often present without fever or bacteremia. Patients may complain of sternal pain and watery drainage; frank purulence is often absent on physical examination or upon wound debridement.

Local resistance patterns in *Pseudomonas aeruginosa*

Resistance patterns vary widely from location to location, so clinicians must inform themselves about local microbial epidemiology and resistance rates. In many major medical centers, this information is available through the microbiology laboratory or the hospital infection control program.

To illustrate the importance of understanding local bacterial epidemiology, I'd like to take the example of *Pseudomonas aeruginosa*. At the Cleveland Clinic, 74% of isolates are susceptible to piperacillin, making this our empiric drug of choice for this infection, pending susceptibility testing of a specific isolate.

Resistance varies by region: Learn about the rates in your area

Unfortunately, the data also show an alarming trend: In 1993, piperacillin covered 93% of isolates, whereas in 1999, the percentage dropped to about 82%. Similarly, we have seen a decline in the percentage of isolates covered by imipenem, ciprofloxacin, and ceftazidime. However, like all tertiary care centers, the Cleveland Clinic sees very sick patients who have been heavily pretreated at other institutions, so bacterial resistance is more frequent here than in the community.

ROLES OF THE NEW ANTIMICROBIAL DRUGS

The five new antimicrobials approved for US use in the past year, although likely to be useful in treating resistant infections, have several potential drawbacks including high cost, adverse effects, and the possibility of further promoting drug resistance. I therefore recommend using them wisely.

Quinupristin-dalfopristin (Synercid)

This intravenous drug is a fixed 30/70 combination of two streptogramin antibiotics that inhibit ribosomal protein synthesis. Available in Europe and Canada for many years, it has been approved by the FDA for treating VRE bloodstream infections and complicated skin and skin structure infections due to methicillin-susceptible *S aureus* and group A streptococci. It is active against staphylococci (including methicillin-resistant strains), enterococcal species (including VRE), and pneumococci (including penicillin-resistant strains).

Unfortunately, up to 10% of patients experience significant side effects that limit the drug's use. Major side effects include nausea, vomiting, diarrhea, arthralgias, myalgias, phlebitis, and abnormalities on liver function tests.

Quinupristin-dalfopristin is a good second-line agent for the treatment of VRE and other gram-positive infections in patients who cannot tolerate more conventional agents such as chloramphenicol. However, this drug will probably remain a niche drug because of its toxicity and high cost (over $1,500 for 1 week of intravenous therapy in the hospital).

Linezolid (Zyvox)

Linezolid has many of the advantages and disadvantages of quinupristin-dalfopristin. Available in both oral and intravenous forms, it is active against enterococci, staphylococci, *Streptococcus viridans*, *S pyogenes*, and *S agalactiae*. Linezolid has a relatively high incidence of side effects, which include diarrhea, headache, and nausea. Thrombocytopenia develops in about 3% of patients. Linezolid is also relatively costly; 7 days of intravenous therapy in the hospital cost nearly $1,000, and oral therapy may cost more than $700 per week.

Linezolid is approved for the following indications: VRE infections; nosocomial pneumonia due to *S pneumoniae* or *S aureus*; complicated skin and skin structure infections due to gram-positive cocci; uncomplicated skin and skin structure infections produced by methicillin-susceptible *S aureus* and group A streptococci; and community-acquired pneumonia due to pneumococcus or *S aureus*.

However, because of the cost and side-

effect profile of this drug, I recommend using linezolid only as a second-line drug for VRE infections or for other gram-positive infections in antibiotic-intolerant patients. For example, I have used it for a patient with a thoracic aortic graft infection due to a methicillin-resistant coagulase-negative staphylococcus who developed severe rashes with both vancomycin and doxycycline.

Gatifloxacin (Tequin) and moxifloxacin (Avelox)

Gatifloxacin is one of the two newly licensed fluoroquinolones. It is active against *S aureus*, penicillin-susceptible pneumococcus, both sensitive and resistant *Escherichia coli*, *Haemophilus influenzae* and *H parainfluenzae*, some gram-negative rods, and legionella and mycoplasma organisms. It is available in oral and intravenous forms, and in its oral form it requires only once-daily dosing. Its safety has not been established in either children or pregnant women.

Gatifloxacin may prolong the QT interval in at-risk patients, and thus should be used with care in patients who are also taking procainamide, quinidine, or amiodarone. Interestingly, unlike many other fluoroquinolones, gatifloxacin is not associated with photosensitivity. Its other major side effects are nausea (8%), vaginitis (6%), diarrhea (4%), headache (3%), and dizziness (3%).

The FDA-approved indications are for acute exacerbation of chronic bronchitis, acute sinusitis, community-acquired pneumonia, uncomplicated and complicated urinary tract infections, and uncomplicated urethral, cervical, and rectal gonococcal infections. A 1-week course of therapy costs about $64.

Moxifloxacin, the other new fluoroquinolone, is available in a once-daily oral form. Its range of activity is similar to that of gatifloxacin, and includes among others *S aureus*, pneumococcus, *E coli*, and *H influenzae* and *parainfluenzae*. Its side-effect profile is also similar to that of gatifloxacin, including the potential prolongation of the QT interval. Approved indications are bacterial sinusitis, exacerbation of chronic bronchitis, and community-acquired pneumonia.

Although both drugs are promoted as first-line therapy for community-acquired respiratory infections, I recommend against their indiscriminate use for this indication. In addition, widespread use of broad-spectrum agents such as gatifloxacin and moxifloxacin has the potential to promote resistance among both pneumococci and gram-negative bacilli. If a fluoroquinolone is indicated, other fluoroquinolones are as effective and may be somewhat cheaper than these two new options.

Quinolone resistance in *S pneumoniae* may be a coming problem

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