The incidence of resistant gram-positive bacteria in nosocomial and, more recently, community-acquired infections is increasing. Staphylococci, because of their natural habitat on the skin, have always been the leading cause of peritonitis in patients receiving peritoneal dialysis (PD). These organisms have demonstrated a remarkable ability to develop resistance to antibiotics, first with penicillin, then antistaphylococcal penicillins (methicillin-resistant \textit{Staphylococcus aureus}), and more recently, strains expressing resistance to vancomycin (vancomycin-intermediate and vancomycin-resistant \textit{S. aureus}) have emerged. Enterococci are normal inhabitants of the gastrointestinal tract and occasionally cause PD peritonitis. In the past 15 years, vancomycin-resistant enterococci have emerged as significant pathogens in many areas. In the past 5 years, novel antibiotics that have activity on gram-positive bacteria, including vancomycin-resistant strains, have become available. The problem of resistant gram-positive bacteria in PD peritonitis, their therapy, and the role of these newer agents, quinupristin/dalfopristin, linezolid, and daptomycin, are reviewed.

\textbf{STAPHYLOCOCCI}

\textit{Coagulase-Negative Staphylococci (CoNS)}: \textit{Coagulase-}\textit{negative staphylococci are the most common cause of PD-related peritonitis. These organisms are normal inhabitants of the skin and most often cause peritonitis by contamination of the PD catheter. Compared to other pathogens, CoNS are not as virulent and tend to produce less severe peritoneal and systemic signs and symptoms. On Gram stain of peritoneal fluid, these organisms appear as gram-positive cocci in clusters and can be differentiated from the more virulent \textit{Staphylococcus aureus} on culture.}

Antimicrobial drug resistance has been recognized as a problem since the advent of antimicrobial therapy more than 60 years ago. Pathogenic micro-organisms have shown a remarkable ability to survive in the presence of our antimicrobial drugs. Infection remains the most common complication of patients on peritoneal dialysis (PD), resulting in hospitalizations, catheter loss, and failure of the peritoneal membrane. As in most other types of infections, the most common micro-organisms that cause PD-related peritonitis are becoming more resistant to antimicrobials.

This review will focus on the gram-positive bacteria that most commonly cause PD-related peritonitis, staphylococci and enterococci, the emergence of resistance in these pathogens, and the newer antimicrobial agents that have activity on these resistant pathogens.

\textbf{STAPHYLOCOCCI}

\textit{Coagulase-Negative Staphylococci (CoNS)}: Coagulase-negative staphylococci are the most common cause of PD-related peritonitis. These organisms are normal inhabitants of the skin and most often cause peritonitis by contamination of the PD catheter. Compared to other pathogens, CoNS are not as virulent and tend to produce less severe peritoneal and systemic signs and symptoms. On Gram stain of peritoneal fluid, these organisms appear as gram-positive cocci in clusters and can be differentiated from the more virulent \textit{Staphylococcus aureus} on culture.

Like \textit{S. aureus}, most CoNS produce beta-lactamase and are resistant to penicillin and ampicillin. In the past decade, the incidence of peritonitis caused by methicillin-resistant CoNS has increased significantly (1). The mechanism of methicillin resistance in these organisms is identical to that in methicillin-resistant \textit{S. aureus} (MRSA): expression of a low affinity, penicillin-binding

\textbf{ANTIMICROBIAL-RESISTANT GRAM-POSITIVE BACTERIA IN PD PERITONITIS AND THE NEWER ANTIBIOTICS USED TO TREAT THEM}

\textbf{IN-DEPTH REVIEW}

\textbf{William Salzer}

\textit{University of Missouri–Columbia School of Medicine, Columbia, Missouri, USA}


\textbf{KEY WORDS:} Peritonitis; antibiotic resistance; gram-positive antibiotics.
protein, PBP2a, encoded by the gene mecA (2). Paradoxically, some studies have shown that success rates for methicillin-resistant CoNS peritonitis are comparable with cefazolin or vancomycin treatment when combined with an aminoglycoside (3). Peritonitis caused by methicillin-resistant CoNS probably should be treated with vancomycin to reduce the risk of failure or relapse. Clinical isolates of CoNS with resistance (4) or reduced susceptibility (2,5) to vancomycin have been reported. Currently, vancomycin resistance is not widespread in CoNS. Should this become more prevalent and result in vancomycin failure, alternative antibiotics may be needed.

Staphylococcus aureus: Staphylococcus aureus is also a normal inhabitant of human skin but, unlike CoNS, which colonizes everyone, colonization is increased in certain groups. Patients receiving dialysis, both hemo- and peritoneal, have much higher rates of S. aureus colonization than other patient groups and the general population. Health care workers are also more likely to be colonized than the general population. Persons colonized with S. aureus are more likely to develop invasive infections with S. aureus and these infections tend to be much more severe than those caused by CoNS. Staphylococcus aureus possesses an arsenal of virulence factors that are responsible for the local and systemic manifestations seen in invasive infections (6). Staphylococcus aureus is usually the first or second most common cause of PD-related peritonitis in most series and, relative to CoNS, is more likely to cause fever and more striking peritoneal signs and symptoms. Like CoNS, most cases of PD peritonitis result from contamination of the catheter by a colonized patient or attendant. Staphylococcus aureus is more likely to cause tunnel infections.

Antibiotic Resistance: Most S. aureus produce beta-lactamase, resulting in resistance to penicillin and ampicillin. Methicillin-resistant S. aureus is common in nosocomial and other health care-related infections. All MRSA strains contain the mecA gene, which encodes for a mutated penicillin-binding protein, PBP2a, which has markedly decreased binding affinity for all beta-lactam drugs, including penicillins, cephalosporins, and carbapenems. Nosocomial strains of MRSA typically are resistant to multiple antibiotic classes, usually macrolides and clindamycin, often tetracyclines, trimethoprim/sulfamethoxazole (TMP/SMX), fluoroquinolones, and sometimes aminoglycosides.

In the past decade, community-acquired MRSA (CA-MRSA) became a growing problem in the USA and other parts of the world. These strains circulate in the community and have caused outbreaks and isolated cases of infection, usually deep cutaneous abscesses, but occasionally cases of sepsis and pneumonia in patients who have had no recent contact with hospitals or health care settings (7). These CA-MRSA strains differ from the classic nosocomial MRSA in that the CA-MRSA strains usually possess the type IV chromosomal cassette (SCCmec), which includes the methicillin-resistance genes. The antibiotic susceptibility patterns of CA-MRSA differ from nosocomial strains in that they usually are susceptible to a number of oral antibiotics, including clindamycin, TMP/SMX, and tetracyclines, and often fluoroquinolones. In addition, CA-MRSA stains usually contain genes encoding for certain toxins such as Panton-Valentine leukocidin and enterotoxins. As these strains become more prevalent in the community, it is quite likely they will appear in patients with PD-associated peritonitis.

Of more concern is the emergence of S. aureus strains with reduced susceptibility to vancomycin (8). Vancomycin-intermediate S. aureus (VISA) was first recognized in Japan in 1996. VISA strains have minimum inhibitory concentrations (MIC) of 8 – 16 μg/mL to vancomycin. Thus far, at least nine cases of VISA infection have been reported in the USA, the majority of which occurred in patients with end-stage renal disease (ESRD) being treated with dialysis. The report by Smith et al. (9) describes 2 patients who developed PD-related VISA peritonitis. The common factor for most reported patients with VISA has been colonization or infection with MRSA and prolonged or repeated treatment with vancomycin prior to the identification of a VISA infection. The mechanism of vancomycin resistance in VISA appears to be overproduction of peptidoglycan, resulting in a thickened bacterial cell wall, impeding access of vancomycin to its active site (10). Fortunately, spread of these strains from the index cases has not occurred because of recognition of the resistant strain and stringent infection-control measures (8).

In 2002, the first clinical isolate of vancomycin-resistant S. aureus (VRSA) was reported (11). As of late 2004, three cases of human VRSA infection have been reported, all from the USA. VRSA strains have MICs to vancomycin of 32 μg/mL or greater. These three VRSA isolates have all been classic nosocomial MRSA strains containing the mecA gene and have acquired the vanA gene from co-colonizing vancomycin-resistant enterococci (VRE), resulting in high-level resistance to vancomycin and many other drugs. The patient reported by Chang had ESRD, diabetes, and peripheral vascular disease with leg ulcers and open wounds. His wounds ultimately became colonized with both MRSA and VRE; he had received several courses of vancomycin before developing VRSA infection of his hemodialysis access catheter. Interestingly, 1 of the 3 patients infected with VRSA had not received vancomycin (12). As in the VISA cases, none of these VRSA strains have spread to other patients...
or close contacts, and all three were epidemiologically unrelated.

Prompt and accurate detection of these isolates is important so that appropriate therapy and infection control measures can be instituted. *Staphylococcus aureus* strains with reduced susceptibility to vancomycin may be difficult for microbiology labs to detect. These organisms often appear vancomycin susceptible when tested by disc diffusion and some automated susceptibility testing systems (8). Broth microdilution, agar dilution, and agar gradient diffusion are recommended for detecting these strains.

Infections with *S. aureus* strains having vancomycin MICs >4 μg/mL do not respond to therapy with vancomycin. Reported cases have been treated successfully with TMP/SMX, tetracyclines, and linezolid. Combination therapy with one of these agents and rifampin has also been used.

Other important aspects of therapy for these organisms are removal of catheters and other indwelling devices and good local wound care. Strict contact isolation is recommended to prevent spread of these strains to other patients. In addition, persons who are colonized or infected with these strains should undergo decolonization with intranasal mupirocin ointment and other measures.

Several studies have shown that topical application of mupirocin to the PD catheter exit site and nares can reduce the incidence of exit-site infection, tunnel infection, and peritonitis caused by staphylococcal species (13). Mupirocin is a topical antimicrobial derived from pseudomonic acid. The drug inhibits bacterial growth by binding to isoleucyl-transfer RNA synthase and blocking RNA and protein synthesis in susceptible bacteria. It is active against most staphylococci and streptococci but inactive against enterococci, enteric bacteria. It is active against most staphylococci and is moderately resistant to vancomycin. Strains containing vanA are highly resistant to teicoplanin and are moderately resistant to vancomycin. Strains containing vanB are susceptible to teicoplanin and are moderately resistant to vancomycin. Because of their inherent resistance to penicillin and other classes of antibiotics, *E. faecium* strains of VRE were particularly difficult to treat until the introduction of new drugs for gram-positive bacterial infections (described below).

TREATMENT OF RESISTANT GRAM-POSITIVE INFECTIONS

Vancomycin: Vancomycin is a glycopeptide antibiotic that has been in clinical use since 1958. Vancomycin is active against most gram-positive organisms, binding to the terminal d-alanine-d-alanine in the cell wall peptidoglycan and inhibiting cell wall synthesis. The drug is not absorbed orally and is excreted almost entirely by glomerular filtration. Vancomycin has been the mainstay of treatment for beta-lactam-resistant gram-positive organisms and for serious gram-positive infections in patients with significant beta-lactam allergies.

Vancomycin remains the drug of choice for the treatment of methicillin-resistant staphylococcal infections and beta-lactam-resistant enterococci and diphtheroid species. In treating PD-related peritonitis, it can be given intraperitoneally, where it is well tolerated, or...
intravenously. By itself, vancomycin has very little nephrotoxicity but may synergistically enhance the nephrotoxicity of aminoglycosides. The “red man syndrome” is a transient erythematous pruritic rash that typically appears on the upper body during intravenous infusion of vancomycin and resolves shortly after stopping the infusion. This is not a true allergic reaction and can usually be prevented by increasing the duration of the infusion or using smaller doses at a shorter interval. True allergic reactions like drug rash and drug fever occur in 2% – 3%, and drug-induced neutropenia in 1% – 2%, which resolve upon stopping the drug.

Resistance to vancomycin occurs by one of two mechanisms. Strains of VISA are thought to be resistant to vancomycin because of an overly thick peptidoglycan layer in the cell wall preventing vancomycin from reaching its site of action. Vancomycin resistance in VRE and VRSA is the result of acquisition of the transmissible genetic elements vanA or vanB, which alter the target depsipeptide from d-alanine-d-alanine to d-alanine-d-lactate. This change in the terminal depsipeptide makes these strains highly resistant to vancomycin.

Quinupristin/Dalfopristin (Q/P): In 1999, quinupristin and dalfopristin, combined in a 30:70 ratio, became the first streptogramin antibiotic released for use in the USA. The two compounds bind to the 50S subunit of the bacterial ribosome and synergistically inhibit the elongation phase of bacterial protein synthesis. Streptogramins bind to a site on the bacterial ribosome that is shared with macrolides and lincosamides. Quinupristin/dalfopristin is active on most gram-positive organisms, including staphylococci, streptococci, and E. faecium, the most common VRE species. One important exception is that E. faecalis is completely resistant to Q/P by means of a gene-encoded efflux pump that reduces the intracellular concentration of the dalfopristin component in this species. Isolates of E. faecium and Staphylococcus species with resistance to Q/P have been identified in <5% of hospital isolates (17). Quinupristin/dalfopristin resistance in these species is most often the result of acquisition of genetic elements containing erm genes. The erm gene encodes an enzyme that methyllates adenine residues at the binding site on the bacterial ribosome for Q/P, macrolides, and lincosamides, resulting in high-level resistance (MLSb) to all three classes of drugs.

Quinupristin/dalfopristin is administered intravenously in a dose of 7.5 mg/kg every 8 hours for VRE infection. The drug is excreted almost entirely by hepatic metabolism. Its half-life is not affected by glomerular filtration rate and no dose adjustment is needed for renal dysfunction. Following intravenous administration, the concentration of Q/P and its metabolites in peritoneal fluid of patients undergoing continuous ambulatory PD was subtherapeutic for most species of bacteria (18). Quinupristin/dalfopristin has been used successfully to treat PD-related peritonitis caused by VRE in 3 patients, 2 of whom were given Q/P intraperitoneally (25 mg/L) in addition to intravenous Q/P (15).

Quinupristin/dalfopristin is given intravenously and causes significant irritation when infused through a peripheral vein (19). An adverse event peculiar to Q/P is the development of significant myalgias and arthralgias in a variable number (5% – 50% in different series) of patients receiving the drug. These symptoms occur without elevation of serum creatine kinase (CK) levels, are often severe enough to require stopping the drug, and resolve rapidly upon discontinuation. Quinupristin/dalfopristin causes elevated total serum bilirubin and occasional elevation in liver enzymes. The drug inhibits the cytochrome P450 3A4 isoenzyme and can cause significant elevation in serum levels of other drugs metabolized by this isoenzyme.

Quinupristin/dalfopristin is approved in the USA for treatment of vancomycin-resistant E. faecium and complicated skin and soft tissue infections caused by staphylococci and streptococci. Given intravenously it is expensive, costing about US$450 per day for a 70-kg person, and probably should be administered via central venous access. It has been used successfully to treat PD-related peritonitis caused by VRE (15). Given its poor peritoneal penetration after systemic administration, it probably should be given intraperitoneally. Quinupristin/dalfopristin could also be used to treat infection caused by VISA or VRSA and considered for patients with MRSA or methicillin-resistant S. epidermidis (MRSE) who are intolerant of vancomycin.

Linezolid: Linezolid is the first in a new class of synthetic antimicrobials called oxazolidinones (19–21). The drug was approved in the USA in 2000. Linezolid binds to the bacterial 50S ribosome and inhibits the early stages of bacterial protein synthesis. It does not exhibit cross-resistance with any other drug classes, but chloramphenicol and lincomycin inhibit linezolid binding to the ribosome. The antibacterial spectrum of linezolid is very similar to vancomycin in that it is active on all gram-positive bacteria, including beta-lactam- and vancomycin-resistant strains. Linezolid is bacteriostatic against staphylococci and enterococci. Linezolid resistance has been reported in patients with VRE who have received the drug; nosocomial spread of these strains has been reported (22). Linezolid-resistant strains of MRSA have also been reported, including a patient with PD-related peritonitis caused by MRSA who...
developed linezolid-resistant MRSA while being treated with linezolid (23). These linezolid-resistant bacteria typically have a mutation in the 23S ribosome that prevents binding of the drug.

Linezolid is available in both oral and parenteral forms and the usual dose is 600 mg two times per day. The bioavailability of the oral form is nearly 100%, resulting in serum levels following oral dosing that are equivalent to intravenous administration. Linezolid is metabolized by oxidation and its metabolites are excreted in urine and feces. The drug does not affect cytochrome P450 enzymes. The dose of linezolid does not have to be adjusted for renal dysfunction, even in patients with ESRD (24). After oral (25) or intravenous (26) administration of 600 mg every 12 hours, linezolid achieves and maintains therapeutic concentrations in PD fluid and has been used successfully to treat VRE peritonitis.

Linezolid may cause minor side effects, including nausea, vomiting, diarrhea, and headache, in a minority of patients. The most commonly reported serious toxicity has been myelosuppression, usually thrombocytopenia, but also anemia and pancytopenia. The risk of linezolid-induced thrombocytopenia and anemia is related to duration of therapy and patients receiving the drug for more than 2 weeks should have blood counts monitored. The abnormalities resolve upon discontinuing the drug. A single case of linezolid-induced lactic acidosis has been reported (27). Peripheral neuropathy and optic neuritis have been reported in a number of patients receiving long courses of linezolid (28).

Linezolid is metabolized, but not by the cytochrome P450 system, and does not affect the activity of any P450 isoenzymes. Linezolid is a weak inhibitor of monoamine oxidase and may produce drug–drug interactions when administered with compounds metabolized by this enzyme. In patients receiving linezolid, administration of tyramine, pseudoephedrine, or phenylpropanolamine results in systolic blood pressure elevation. The serotonin syndrome has been reported in patients receiving linezolid along with selective serotonin reuptake inhibitors (SSRIs) (29). Linezolid should be used with caution in patients who have recently received SSRIs and patients should avoid sympathomimetic decongestants.

Linezolid is approved for VRE infections, pneumonia, and complicated skin infections. The drug’s excellent penetration into PD fluid after oral or intravenous dosing makes it an attractive choice for the treatment of PD-related peritonitis caused by a vancomycin-resistant organism and in patients with MRSA or MRSE who are intolerant of vancomycin. Compared to Q/P, it is easier to administer and less expensive. In patients who can take oral medications there is no reason to use the intravenous form, although the tablets are expensive at about $60 each or $120 per day.

**Daptomycin:** Daptomycin is the only drug from a unique class of antimicrobials called cyclic lipopeptides (30). It was approved for use in the USA in 2003. Daptomycin is active against virtually all gram-positive bacteria, including strains resistant to beta-lactams, vancomycin, linezolid, and Q/P. The drug has a unique mechanism of action, binding to the bacterial cell membrane through calcium-dependent insertion of its lipid tail resulting in the formation of an ion channel. Formation of this channel causes loss of intracellular potassium and disruption of membrane potential in the bacteria. Daptomycin is bactericidal and has a prolonged post-antibiotic effect. Its mode of action is similar to that of amphotericin B in fungi. Daptomycin resistance has occurred infrequently in trials thus far.

Daptomycin is given intravenously in a dose of 4 mg/kg/day in patients with normal renal function. It is not metabolized and is largely excreted by the kidney. The recommended dosing for patients with a creatinine clearance <30 mL/minute is 4 mg/kg every 48 hours. The drug is highly protein bound and has a low volume of distribution. Roughly 15% of the drug is removed during a 4-hour hemodialysis session and only 11% is cleared over 48 hours of PD. This low clearance of daptomycin during PD suggests that systemically administered drug probably would not achieve therapeutic concentrations in PD fluid. Intraperitoneal administration would likely be required to treat peritonitis but such use has not yet been reported.

In clinical trials with daptomycin, the only notable adverse effect has been elevation of serum CK levels. Elevations of CK were seen in preclinical dose-finding studies and are dose related, reversible, and appear to arise from skeletal muscle only. Drug–drug interactions have not been reported and other adverse effects have been mild and infrequent.

Daptomycin is currently approved for the treatment of complicated skin infections at a dose of 4 mg/kg/day. Its potent bactericidal activity against gram-positive bacteria, including resistant strains, and lack of cross-resistance with other antibiotic classes makes it an attractive drug. For parenteral therapy, daptomycin is less expensive than linezolid or Q/P. At this time, there are no published data for the treatment of PD-related peritonitis with daptomycin. Given its extensive protein binding and apparent lack of diffusion into PD fluid after systemic administration, it will probably need to be given intraperitoneally. The tolerability and efficacy of intraperitoneal daptomycin has not been determined at this time.
CONCLUSIONS AND SUMMARY

Antibiotic-resistant gram-positive bacteria seem to be increasingly common causes of PD-related peritonitis. They can cause primary peritonitis which fails to respond to initial empiric therapy or appear as superinfection after or during initial therapy. Antibiotic therapy, if appropriate or inappropriate, increases the risk of resistant gram-positive bacteria by suppressing susceptible strains and increasing the incidence and density of colonization resistant strains.

Empiric therapy with cefazolin and ceftazidime or an aminoglycoside effectively treats most cases. Failure to respond to these regimens suggests possible infection with MRSA, MRSE, enterococci, resistant gram negatives, or Candida. Relapse or re-infection after these regimens should also raise suspicion for these organisms.

There seems to be a move toward using vancomycin as initial empiric therapy for PD peritonitis. Compared to a cefazolin-based regimen, vancomycin effectively treats MRSA, MRSE, and enterococci and would be appropriate in settings with a high prevalence of these organisms. Unfortunately, increased use of vancomycin may result in superinfections or increases in infection with VRE, gram negatives, Candida, and perhaps VISA and VRSA.

The newer antibiotics, Q/P, linezolid, and daptomycin, show promise for treatment of resistant gram-positive PD peritonitis, but published data are sparse at this time. Because of their cost and the potential for development of resistance with excessive use, they should be reserved for patients with documented vancomycin-resistant gram-positive bacteria or patients with serious adverse reactions to vancomycin.

As in most infections, prevention is more desirable than new cures. Good catheter care and infection control measures are essential. Topical mupirocin applied to the catheter exit site may reduce staphylococcal infection, but the emergence and spread of mupirocin-resistant strains may occur with widespread use.

Culture and antibiotic susceptibility data on isolates from patients with PD peritonitis are important for two reasons: First, such information may allow more focused, often less broad-spectrum therapy for the individual patient. For example, empiric vancomycin could be changed to cefazolin to complete the therapy if a susceptible organism is identified. Second, collection of such data over time provides important surveillance information in an institution or practice that could guide the choice of initial empiric therapy. For example, if the incidence of MRSA, MRSE, and enterococci is low in your practice, cefazolin may be appropriate for initial therapy. Attention to these issues may reduce the risk for infection with resistant organisms in your patients.

REFERENCES

14. Perez-Fontan M, Rosales M, Rodriguez-Carmona A, Falcon...


