REVIEW

Treatment of intra-abdominal and skin and soft tissue infections: The role of the glycylcyclines

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Glycylcyclines; Tigecycline; Complicated skin and soft tissue infections; Intra-abdominal infections

Abstract  The need for new, effective agents to treat multidrug-resistant infections continues to grow as more and more bacteria develop resistance that may result in clinical therapeutic failure. This is particularly true for common surgical infections, such as complicated intra-abdominal infections, which frequently involve multiple pathogens, making therapy with a broad-spectrum antibiotic an important treatment intervention, and also for complicated skin infections, which often involve methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). With treatment options limited, it has become critical to identify antibiotics with novel mechanisms of activity. Several new drugs have emerged as possible therapeutic alternatives: linezolid, quinupristin-dalfopristin and most recently daptomycin have all been FDA-approved for the treatment of skin and skin structure infections. This review examines the potential role of a new class of investigational agents, the glycylcyclines, also recently FDA-approved and currently under review for European licensing, in the treatment of complicated skin infections and intra-abdominal infections. Tigecycline, the first of the glycylcyclines, has shown excellent activity in Phase III studies of these infections, achieving clinical success rates ranging from 70% to 91%. Furthermore, it has a good safety profile, suggesting it will be a clinical useful addition to current therapeutic options for the treatment of complicated skin infections and intra-abdominal infections.

Introduction

There has been an alarming increase in the incidence of Gram-positive infections, including bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and drug-resistant pneumococci. While vancomycin has been considered the drug of last defence against Gram-positive multidrug-resistant bacteria, the late 1980s saw a rise in vancomycin-resistant bacteria, including vancomycin-resistant enterococci (VRE). More recently, strains of vancomycin-intermediate resistant Staphylococcus aureus (VISA) and vancomycin-resistant Staphylococcus aureus (VRSA) have been
isolated. Gram-positive bacteria such as Staphylococcus aureus and Streptococcus pyogenes are often the cause of skin and skin structure infections, ranging from mild pyodermas to complicated infections, including post-surgical wound infections, severe carbunculosis, and erysipelas. Complicated skin and skin structure infections are those involving deep wounds, such as surgical incisions, bites and lacerations, major abscesses, and infected skin ulcers. They include: complicated cellulitis, complex abscesses requiring surgical drainage, perirectal abscesses, surgical and traumatic wound infections, infected diabetic and vascular ischaemic ulcers, and other skin and skin structure infections requiring surgery or intravenous (IV) antibiotic therapy.

Complicated intra-abdominal infection remains a potentially lethal condition. Generally, the diagnosis is relatively straightforward on clinical grounds; however, hospital-acquired or post-operative intra-abdominal infections can prove a much more difficult problem as they are more likely to be multi-resistant. Treatment of these infections is challenging because of their polymicrobial nature, which can include both aerobic and anaerobic species. Unlike complicated skin infections, the predominant pathogens involved in intra-abdominal infections appear to be E. coli among the aerobes and Bacteroides species among anaerobes.

The present paper examines the concerns surrounding the microbiology and diagnosis of complicated skin and skin structure infections and intra-abdominal infections, and also reviews current therapeutic options for the treatment and management of these infections, with an emphasis on the glyyclyclines and their efficacy in clinical studies to date.

**Skin and skin structure infections**

Skin and skin structure infections are commonly seen in surgical practice as they may be either community-acquired or nosocomially acquired as the result of hospitalization or surgical intervention. They are largely caused by Gram-positive bacteria including Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, and group C and G streptococci. Specific skin and soft tissue infections include cellulitis, erysipelas, furuncles, simple abscesses, wound or surgical site infections, necrotizing fasciitis, myositis, and gas gangrene. Complicated skin and soft tissue infections involve the deep tissues such as subcutaneous tissues, fascia and skeletal muscle, and often require surgical intervention and hospitalization. Surgical site infections account for approximately 14–25% of all nosocomial infections among hospitalized patients, which makes them the third most common type of nosocomial infection. S. aureus is considered the most common pathogen involved in community- and hospital-acquired staphylococcal skin and soft tissue infections worldwide, and is particularly prevalent among high-risk populations such as the elderly.

Penicillins and cephalosporins have for many years been the standard care for the treatment of Gram-positive skin and skin structure infections. However, the effectiveness of these traditional antibacterial agents has become increasingly limited as antimicrobial-resistant Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), have become more prevalent. Of even greater concern is the fact that methicillin resistance in S. aureus can be conferred on other β-lactams and antibiotic classes, including macrolides, tetracyclines, lincosamides and aminoglycosides, making the selection of an appropriate antibiotic therapy even more challenging. Multi-drug resistance and cross-resistance among Gram-positive bacteria have been increasing at an alarming rate. Indeed, a methicillin-resistance rate of 34% was reported among S. aureus isolates in the United States between 1997 and 1999, with a methicillin-resistance rate of approximately 30% among skin and skin structure infection isolates. A more recent study by Morgan et al. showed the proportion of skin and soft tissue infections caused by MRSA increased from 29% in 2001–2002 to 64% in 2003–2004.

With bacterial resistance comes an increased probability of treatment failure in patients with complicated skin and soft tissue infections, particularly among those who have polymicrobial infections or those who need to be treated in an ICU setting. Moreover, antibiotics appropriate for MRSA are not always used promptly because physicians are reluctant to use the most potent agents available first and the delay can result in poorer clinical outcomes as well as increased medical resource use and costs. The increased resource use and costs associated with the delayed treatment of methicillin-resistant Gram-positive infections, particularly those caused by MRSA, have been shown to be largely due to increased length of stay (LOS) and/or complications of therapy.

Glycopeptides such as vancomycin have traditionally been the drugs of choice for the treatment
of patients with suspected or proven MRSA infections or multidrug-resistant Gram-positive infections. However, a decrease in vancomycin susceptibility among organisms responsible for skin and skin structure infections, such as enterococci and staphylococci, has been widely observed over the past several years. In addition, vancomycin seems less effective than linezolid in ITU pneumonia, and studies also suggest that the efficacy of vancomycin in methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia and MSSA endocarditis may be lower than that of β-lactam agents.19–22 The combination of increasing resistance to vancomycin, together with the less than optimal efficacy of the drug for methicillin-susceptible Gram-positive bacteria, has increased the need for newer antibiotic agents, particularly for empiric therapy for these infections.

Newly approved options for the treatment of skin and skin structure infections include quinupristin-dalfopristin, linezolid, and most recently daptomycin (see Table 1). Quinupristin-dalfopristin is the first agent in the streptogramin class. It is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant Enterococcus faecium bacteremia and complicated skin and skin structure infections caused by S. aureus and S. pyogenes.23 The approval was based, in part, on a randomized, open-label, controlled clinical trial comparing quinupristin-dalfopristin 7.5 mg/kg q12h IV (n = 221) with cefazolin 1 g q8h IV (n = 222) in the treatment of complicated skin and skin structure infections caused by suspected or confirmed MRSA.23 In the quinupristin-dalfopristin and cefazolin groups, 113 (51%) and 120 patients (54%), respectively, were found to be clinically evaluable. Of these patients, the success rate was 66% in the quinupristin-dalfopristin group and 64% in the cefazolin group. In another trial, quinupristin-dalfopristin 7.5 mg/kg q12h IV (n = 229) was compared with oxacillin 2 g q6h IV (n = 221). 105 patients (46%) in the quinupristin-dalfopristin arm and 106 patients (48%) in the oxacillin arm were found to be clinically evaluable, and of these the success rate was 50% for those taking quinupristin-dalfopristin and 52% for those on oxacillin therapy.23 Of interest is that quinupristin-dalfopristin has activity against vancomycin-resistant E. faecium but not against Enterococcus faecalis. Quinupristindalfopristin has been associated with venous irritation, which can be avoided if the drug is infused through a central line, and also with high rates of injection site reactions and often debilitating myalgias. It cannot be given orally, which may also be considered a disadvantage.

Linezolid is the first drug in the oxazolidinone class and is available in both oral and parenteral formulations. The oral formulation is nearly 100% bioavailable and is thus interchangeable with the parenteral formulation.24 Linezolid is indicated in the treatment of complicated skin and skin structure infections including diabetic foot infections without concomitant osteomyelitis caused by S. aureus, S. pyogenes, and S. agalactiae. In a randomized, multicentre, double-blind, double-dummy trial, 400 patients received linezolid 600 mg IV q12h followed by 600 mg PO q12h, and 419 patients received oxacillin 2 g IV q6h followed by dicloxacillin 500 mg PO q6h.24 Two hundred and forty-five (61%) patients in the linezolid arm and 242 patients (58%) in the oxacillin-dicloxacillin arm were clinically evaluable. Cure rates were 90% in the linezolid group and 85% in the oxacillin-dicloxacillin group. The most common adverse events are nausea, vomiting, diarrhea, and headache, and cases of linezolid resistance to VRE have been reported. In a recently published clinical study of linezolid versus vancomycin in patients with surgical site infections significantly more patients who had MRSA isolated were microbiologically cured (87% vs 48%, p = 0.002) in the linezolid arm of the study.

Daptomycin is the most recently licensed addition to our therapeutic options and also represents

<table>
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<th>Table 1</th>
<th>Antibiotics currently approved for the treatment of skin infections caused by MRSA</th>
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<td><strong>Class</strong></td>
<td><strong>Year approved</strong></td>
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| Vancomycin | Glycopeptide | 1956 | IV | 1 g, q12h | Red man syndrome (infusion rate) Arthralgias/myalgias (>20%); injection site reactions (10–70%)
| Quinupristin–dalfopristin | Streptogramin | 1999 | IV | 7.5 mg/kg, q8-12h | |
| Linezolid | Oxazolidinone | 2000 | IV, PO | 600 mg, q12h | Marrow suppression (dose and duration) Myopathy (dose related)
| Daptomycin | Cyclic lipopeptide | 2003 | IV | 400 mg, qd | |
a new class of antibiotics, the cyclic lipopeptides. Clinical trials showed good results in skin and soft tissue infections. Adult patients with clinically documented complicated skin and skin structure infections were enrolled in two randomized, multinational, multicentre, investigator-blinded studies. One study was conducted primarily in the United States and South Africa and the other was conducted at non-US sites only. A total of 534 patients received daptomycin 4 mg/kg IV q24h and 558 patients received the comparator drug, which consisted of either vancomycin 1 g q12h or a semisynthetic penicillin (i.e. nafcillin, oxacillin, cloxacillin, flucloxacillin; 4–12 g IV per day). In the first study, success rates in the clinically evaluable population were 76% (158/208) in the daptomycin group and 77% (158/206) in the comparator group. In the second study, clinical success rates in the clinically evaluable population were 89% (214/238) in patients taking daptomycin and 91% (226/250) in those treated with comparator drugs. However, the failure rate of daptomycin was excessive in a controlled trial for community-acquired pneumonia. The most common adverse events included gastrointestinal disorders, general disorders (i.e. injection site reactions, fever), and nervous system disorders.

Of the new agents in development, the glycylcyclines and in particular tigecycline show much promise. Tigecycline is the first of a new synthetic class of antibiotics engineered to overcome the bacterial mechanisms of resistance that have rendered the tetracycline class increasingly less effective. It has an extended broad spectrum of activity that includes activity against most methicillin-susceptible and -resistant Gram-positive organisms, as well as activity against key Gram-negative pathogens, with an MIC range of ≤0.015–1 μg/ml. It demonstrated no cross-resistance with tetracycline or with other classes of antimicrobial agents in a study by Biedenbach et al., which suggests this new glycylcycline has potential therapeutic value for infections caused by organisms resistant to tetracycline and tetracycline derivatives. Clinical data with tigecycline in the treatment of complicated skin and skin structure infections and in the treatment of complicated intra-abdominal infections in hospitalized patients are given later in this review.

**Intra-abdominal infections**

Intra-abdominal infection is defined as infection arising from movement of microorganisms from any part of the gastrointestinal (GI) tract to another, usually sterile, area within the abdomen. These infections occur as a result of GI trauma, intrinsic GI disease, or surgical resection of the GI tract—perforated appendices and diverticulitis being among the most common causes. Intra-abdominal infection rarely occurs as a result of upper GI trauma because this region of the GI tract contains few microorganisms. By contrast, the large bowel is densely populated with both aerobic and anaerobic bacteria. Intra-abdominal infection encompasses both bacterial peritonitis and intra-abdominal abscesses. These infections share a common microbial aetiology, and both are treated similarly in terms of antibiotic therapy and the need for surgical intervention. Peritonitis is defined as inflammation of the peritoneum that is due to a bacterial infection. Peritonitis can occur spontaneously, that is, without an obvious source of bacteria. However, this is far less common than secondary peritonitis, which can occur as a result of a lesion (such as a bowel perforation), obstruction, or operative contamination.

Primary (or spontaneous) peritonitis tends to occur in patients who have hepatic ascites, as well as those at risk for nephrotic syndrome. In many cases, the source of infection is thought to be bacteraemia and, in fact, many patients with primary peritonitis have a simultaneous bacteraeemia with the same organism. Translocation of bacteria across the gut wall has also been suggested as a source of primary peritonitis.

Primary peritonitis should be suspected in patients with ascites who present with acute symptoms, including abdomen tenderness, fever, and leucocytosis. Because up to 30% of patients will lack tenderness and have a normal temperature, a culture is needed for a definite diagnosis of primary peritonitis. A white cell count of 500 cells/μl can be a useful indicator to begin empiric antibiotics. The mortality rate associated with primary peritonitis is greater than 50%, which reflects the severe underlying disease that is the backdrop to this syndrome.

Contamination of the peritoneal cavity as a result of damage to the gastrointestinal wall is a cause of secondary peritonitis and intra-abdominal abscess. As bacteria and other gut contents are released into the peritoneum, an inflammatory response is elicited. This response includes the release of humoral inflammatory mediators, as well as the recruitment of macrophages and polymorphonuclear leucocytes to the site of contamination. If the level of contamination is low, the host immune response may be able to clear it in its entirety. If the inflammatory response succeeds in confining the process to the immediate locality of
the contamination, an abscess results. Peritonitis will ensue if the level of contamination is so high that the initial inflammatory response is overwhelmed. In this event, there are immediate systemic consequences, which lead to severe symptoms. The history from patients presenting with peritonitis includes nausea, abdominal pain, diarrhoea or constipation, fever, and chills. Once peritonitis has been diagnosed, surgical intervention is required.33

It can be difficult to diagnose intra-abdominal abscess because it is walled-off and localized. Thankfully, due to advances in modern surgery, the incidence of intra-abdominal abscess as a post-operative complication has been documented to be only 2%.34 As with most intra-abdominal infections, which must be corrected surgically or by percutaneous drainage, all intra-abdominal abscesses must be drained. Approximately 25% of abscesses will require a second procedure regardless of the initial methods employed.

It is not surprising that the microbiology of intra-abdominal infections is complicated given that the contents of the gastrointestinal tract have been shown to contain more than $10^{11}$ organisms per gram, which are made up of more than 400 different bacterial species. It is of interest to note that, of these, only 15 species account for 90% of the isolates cultured.35

In a susceptibility study by Aldridge et al. that focused on clinical anaerobic isolates from four large US medical centres,36 the authors found that piperacillin-tazobactam was the only antibiotic tested to which all 556 isolates were susceptible. The resistance rates among the B. fragilis group to ampicillin-sulbactam and clindamycin were 11% and 29%, respectively, which the authors felt warrant concern.

Because of the large number of potential infecting organisms, and the fact that culture and susceptibility results can take 48 h to become available, all initial antibiotic therapy is empirical. Both facultative aerobes and anaerobes are common causes of infection and, for this reason, complete coverage can be difficult to achieve.

Although the anatomical site of origin of the infection is often a useful predictor of the organisms involved in intra-abdominal infections, this is frequently complicated by concomitant medication. For example, patients undergoing surgery for acid-related disorders are likely to be co-medicated with antisecretory drugs such as H₂-receptor antagonists or proton pump inhibitors. Colonization of the stomach by Gram-negative organisms is pH-dependent, occurring primarily at pH ≥ 4. Consequently, by raising the intragastric pH, antisecretory agents could increase the risk of Gram-negative intra-abdominal infection.37

Because intra-abdominal infections are nearly always polymicrobial in nature, standard antimicrobial regimens generally include combination therapy with an aminoglycoside plus an anti-anaerobic agent (e.g., metronidazole, which has virtually 100% activity against anaerobes or clindamycin), or monotherapy with an agent that has a broad spectrum of activity that includes activity of anaerobes (e.g. imipenem-cilastatin). Updated treatment guidelines from both the IDSA (Infectious Disease Society of America) and the Surgical Infection Society were published in 2003 and 2002, respectively.38,39 Recommended single agents now include second-generation cephalosporins with anaerobic coverage, β-lactam/β-lactamase inhibitor agents, and carbapenems (imipenem/cilastatin, meropenem, and ertapenem). Recommended combination regimens include cefuroxime or a third- or fourth-generation cephalosporin plus an anti-anaerobic agent (either clindamycin or metronidazole), aztreonam plus clindamycin, ciprofloxacin plus metronidazole, or an aminoglycoside plus an anti-anaerobe (Table 2). It is likely that other agents will be added to this list in the future as prospective trials of newer agents are completed and published.

The published literature provides little guidance in selecting a specific regimen. However, the combination of gentamicin with clindamycin or metronidazole is considered by many to be the gold standard empiric intravenous therapy for intra-abdominal infections. Many surgeons also choose to add ampicillin for enterococci coverage.

<table>
<thead>
<tr>
<th>Single agent</th>
<th>Ampicillin/sulbactam</th>
<th>Piperacillin/tazobactam</th>
<th>Ticarcillin/clavulanic acid</th>
<th>Ertapenem</th>
<th>Imipenem/cilastatin</th>
<th>Meropenem</th>
<th>Cefoxitin</th>
<th>Cefotetan</th>
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<tbody>
<tr>
<td>Combination regimen</td>
<td>Gentamicin, tobramycin, netilmicin, or amikacin plus an anti-anaerobe (clindamycin or metronidazole)</td>
<td>Cefuroxime plus metronidazole</td>
<td>Cefotaxime, ceftriaxone or ceftazidime, each in combination with metronidazole</td>
<td>Ciprofloxacin plus metronidazole</td>
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Adapted from Solomkin et al.38
However, aminoglycoside treatment is associated with a relatively high incidence of nephrotoxicity and ototoxicity (10–25% and 12%, respectively). Imipenem/cilastatin IV monotherapy also appears to achieve clinical and bacteriological outcomes similar to those obtained with standard aminoglycoside regimens. However, it should be noted that imipenem/cilastatin is contraindicated in patients who are known to be hypersensitive to \( \beta \)-lactam agents. In addition, this drug has been shown to cause seizures in some patients and should therefore be administered with caution to patients with pre-existing CNS disorders or renal failure.

**Role of glycyclines**

Future antibiotics will need to be active broadly, not just against "the usual suspects", but also against new strains, particularly those with resistance. The glycyclines, in particular tigecycline, the first of the class, are showing promise in this regard. All members of the class circumvent the known tetracycline resistance mechanisms, and tigecycline has exhibited a broad spectrum of antibacterial activity against organisms such as MRSA, VRE and ESBL (extended-spectrum \( \beta \)-lactamase)-producing Enterobacteriaceae. Unlike most of the agents with activity against the multidrug-resistant Gram-positive cocci, tigecycline retains potent in vitro activity against multidrug-resistant Gram-negative bacteria, with most MICs \( \leq 2 \) mg/ml. Unfortunately, in vitro studies suggest *Pseudomonas aeruginosa* and the *Proteus* spp. are not well covered, primarily due to non-specific efflux mechanisms. However, *Acinetobacter* spp. and *Stenotrophomonas maltophilia*, although not common causes of skin infections, are pathogens considered to be some of the most recalcitrant of the Gram-negative spectrum, and are well covered by the tigecycline spectrum of activity.

A study, led by Postier, to assess the clinical efficacy of tigecycline in hospitalized patients with possibly life-threatening, complicated skin and skin structure infections gave promising results. The infections involved deeper soft tissue or required significant surgery and included: infected ulcers (35%), burns, or bites; major abscesses (31%); superficial infections or abscesses with a high risk of infection by anaerobic or Gram-negative bacteria. In the study, 85% of patients who received 50 mg doses of tigecycline were cured at the end of their 7–14-day treatment, and 74% were cured at the test-of-cure visit (the study’s primary outcome measure), about 21 days after their initial dose of tigecycline. Similarly, 78% of patients treated with the 25 mg doses were cured at the end of treatment, and 67% at the test-of-cure visit. The decrease from 78% to 67% is a reflection of patients receiving either additional antibiotics or surgery between the end of treatment and test-of-cure visits. The 50 mg group also had a higher overall bacterial eradication rate at the end of therapy, 74%, compared to 62% for those treated with the 25 mg dose. At the test-of-cure visit, the rates were 70% and 56%, respectively.

Similarly, tigecycline was shown to be safe and efficacious in a randomized, double-blind, controlled study of 546 patients with complicated skin and skin structure infections that compared tigecycline to the combination of vancomycin and aztreonam. Clinical response in the tigecycline and combination vancomycin and aztreonam groups was similar in the clinically evaluable modified intent-to-treat (c-mITT) population (84.3% [95% CI 79.3, 88.5] vs 86.9% [82.1, 90.7], \( p = 0.4755 \)) and the clinically evaluable (CE) population (89.7% [84.9, 93.3] vs 94.4% [90.4, 97.1], \( p = 0.1015 \)). Microbiological eradication occurred in 84.8% [78.3, 89.9] of patients receiving tigecycline and 93.2% [87.9, 96.7] of patients receiving vancomycin and aztreonam. The number of patients reporting adverse events was similar in the two groups, with increased nausea and vomiting rates in the tigecycline group and increased incidence of rash and increases in ALT/AST levels in the combination vancomycin and aztreonam group. Sacchidanand et al. also examined the safety and efficacy of tigecycline compared to that of vancomycin/aztreonam in patients with complicated skin and skin structure infections (cSSSI). Eligible patients were hospitalized adults with cSSSIs that involved deep soft tissue (including extensive cellulites at least 10 cm in width or length), required surgical intervention, or was associated with significant underlying disease (e.g., diabetes mellitus, peripheral vascular disease, peripheral neuropathy, or lower venous insufficiency). In addition to the infection, the patient had to have at least two of the following signs and symptoms: drainage or discharge, fever, erythema, swelling, localized warmth, pain, and/or white cell count of \( > 10,000 \) cells/mm\(^2\). In this study, cure rates were again similar between the two groups (82.9% tigecycline vs 82.3% vancomycin/aztreonam). Microbiological eradication rates were also similar between the two groups (78.3% tigecycline versus 77.0% vancomycin/aztreonam). Tigecycline was shown to have good activity against anaerobic pathogens. All
Gram-positive anaerobic bacteria isolated were inhibited by ≤2 μg/ml tigecycline. The frequency of adverse events was also similar between the two groups. Patients who were treated with tigecycline had a higher incidence of nausea, vomiting, dyspepsia, and anorexia, while increased ALT/SGPT, pruritis and rash occurred significantly more often in vancomycin/aztreonam-treated patients.

Two Phase III clinical studies have been completed to date that compare tigecycline with imipenem/cilastatin for the treatment of intra-abdominal infection. In these trials, patients were stratified by disease severity and randomly assigned to tigecycline or imipenem/cilastatin for 5–14 days. For the microbiologically evaluable patients, the clinical responses at test-of-cure (12–44 days after therapy) were 80.6% (199/247) for tigecycline vs 82.4% (210/255) for imipenem/cilastatin (95% CI –8.4, 5.1; p < 0.001). Corresponding clinical cure rates for the microbiologically modified intent-to-treat (m-mITT) populations were 73.5% (227/309) for tigecycline vs 78.2% (244/312) for imipenem/cilastatin (95% CI –11.0, 2.5; p < 0.001). A similar safety and tolerability profile was apparent for the two groups, with the most commonly reported adverse events for tigecycline and imipenem/cilastatin being nausea (31.0% and 24.8%) and vomiting (25.7% and 19.4%). In the second study, the primary diagnoses were complicated appendicitis (41%), cholecystitis (22%), and intra-abdominal abscess (11%). Clinical cure rates at the test-of-cure were 91.3% for tigecycline and 89.9% for imipenem/cilastatin (95% CI –4.0, 6.8; p < 0.001). The most commonly reported adverse events in this study were nausea (17.6% tigecycline vs 13.3% imipenem/cilastatin; p = 0.100) and vomiting (12.6% tigecycline vs 9.2% imipenem/cilastatin; p = 0.144). Tigecycline has not yet been evaluated as prophylactic therapy for these infections.

**Summary**

Complicated skin and skin structure infections and intra-abdominal infections each present surgeons with a number of severe challenges. These infections occur increasingly as a result of multidrug-resistant Gram-positive pathogens, including MRSA, and new strategies to combat such infections are urgently needed. Complicated intra-abdominal infections are challenging to treat because of their polymicrobial nature and their potential for accompanying complications and for the risk of death. For most episodes, antimicrobial therapy is initially empiric and involves a combination approach to ensure coverage of both aerobic and anaerobic organisms. Tigecycline, the first of a new class of antibacterial agents called glycylcyclines, has shown excellent activity against methicillin-susceptible and -resistant Gram-positive organisms and against key Gram-negative facultative bacteria commonly associated with intra-abdominal infection. Its minimum inhibitory concentration (MIC<sub>90</sub>) values have been shown to be significantly lower than those for vancomycin, quinupristin-dalfopristin and linezolid against clinically important Gram-positive and -negative aerobic bacteria including most Enterobacteriaceae (including ESBL-producing strains), *Staphylococcus aureus* and *Enterococcus* spp. Clinical trial data to date have shown it to be clinically efficacious and to have a good safety profile, so that there is justifiable optimism about its continued clinical use and about the development of other glycyclines.

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