Intra-abdominal infections: review of the bacteriology, antimicrobial susceptibility and the role of ertapenem in their therapy

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Complicated intra-abdominal infections require a combination of surgery/drainage and antimicrobial therapy that is active against both the aerobic and the anaerobic bacteria that comprise the intestinal flora. Ertapenem, a parenteral carbapenem, is highly resistant to a wide variety of β-lactamase enzymes, and has a broad spectrum of activity against bacteria associated with community-acquired infections including those of complicated intra-abdominal conditions. This article reviews the bacteriology of complicated intra-abdominal infections, their antimicrobial susceptibility, especially to anaerobes, the utility of animal models in these mixed infections, and the supportive clinical trials and in vitro susceptibility data that show ertapenem to be generally well tolerated and as effective as either piperacillin–tazobactam or ceftriaxone plus metronidazole in the therapy of complicated intra-abdominal infections.

Keywords: Bacteroides fragilis, carbapenems, intra-abdominal abscess, anaerobes, bacteriology

Introduction

Intra-abdominal infections are common causes of hospitalization with approximately 2 million intra-abdominal procedures performed each year in the USA.1 The management of patients with these infections often requires the involvement of multiple medical disciplines. Intra-abdominal infections comprise a wide variety of specific infections, ranging from uncomplicated appendicitis to cholecystitis and florid faecal peritonitis, and are therefore classified as either uncomplicated or complicated. Complicated infections are those that require both surgical or radiological drainage procedures and antimicrobial therapy. Inadequate surgical source control of an intra-abdominal infection with lack of control of the underlying pathological process by resection, closure or drainage, or drainage of existing purulent collections are causes of therapeutic failure. Selection of an ineffective antimicrobial agent is another cause of therapeutic failure. The choice of antimicrobial therapy must take into account the complex normal aerobic and anaerobic flora of the bowel, including a bacterial density of up to 1011 cfu/g of faeces.2 Once peritoneal contamination occurs, the body attempts to defend against this invasion via lymphatic clearance, phagocytosis, sequestration of fibrin and anatomical localization. Anaerobes act synergically with facultative organisms to induce abscess formation more readily than mixtures of either facultative or anaerobic bacteria alone and may protect aerobes from phagocytosis and other body defences. Facultative bacteria also promote the infectious process by lowering the oxidation–reduction potential of the environment and facilitating the growth of anaerobes.

Initial selection of antimicrobial therapy that is active against the broad range of potential aerobic and anaerobic pathogens is associated with therapeutic success and the converse is also true.3 Post-operative peritonitis is a life-threatening form of intra-abdominal infection ‘and carries a higher risk of complications and mortality than does community-acquired disease’.4 If one estimates that there is a 15% infection rate of post-operative peritonitis (following trauma, gun shot or perforated viscus with dirty surgery), including a 4% incidence of abscess formation, then the estimated yearly economic impact of intra-abdominal abscess alone is over US$1 billion.1

Ertapenem, a long-acting parenteral carbapenem, was approved by the US Food and Drug Administration (FDA) in November 2001 for the treatment of several community-acquired and mixed aerobic/anaerobic infections, including moderate to severe complicated intra-abdominal infections due to Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus spp., Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron or Bacteroides uniformis. Ertapenem is highly resistant to a wide variety of β-lactamase enzymes, and has a broad spectrum of activity against many bacteria associated with community-acquired infections, including those of complicated intra-abdominal conditions.5–10 It is more active than imipenem against Enterobacteriaceae and equally active against anaerobic bacteria.5,8 Ertapenem is not considered to be active against enterobacteria.
cocci, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and some non-fermentative aerobic Gram-negative bacilli. This spectrum of activity suggests that ertapenem might be efficacious in the treatment of complicated, community-acquired intra-abdominal infections. This article reviews the bacteriology of intra-abdominal infections, the antimicrobial susceptibility of intra-abdominal isolates with particular attention to ertapenem, with a review of published clinical trials and analysis of microbiological susceptibility data supporting the utility and efficacy of ertapenem in the therapy of community-acquired intra-abdominal infections.

**Bacteriology of intra-abdominal infections**

The specific bacteriology of community-acquired intra-abdominal infections is related to the bacterial inoculum of the numerous normal flora of the organ involved. Infection arising from contamination from the stomach and duodenum is unlikely, and the upper small intestine also contains relatively few organisms. However, the faecal flora of the terminal ileum is a transitional zone to that of the heavily colonized colon, the flora of which can easily establish a florid bacterial peritonitis. A plethora of aerobic, facultative and anaerobic organisms comprise this normal flora, which can act as opportunist pathogens once released from their native habitat through disruption of the mucosal integrity into the peritoneal cavity. These infections are often categorized as 'secondary peritonitis'.

In addition, the presence of blood in the peritoneal cavity predisposes to, and facilitates the establishment of, infection. The ileum usually contains equal numbers of aerobes and anaerobes. The aerobes isolated include *E. coli*, usually the major isolate, enterococci, viridans streptococci, other Enterobacteriaceae, *Proteus* spp., and occasionally *P. aeruginosa*, *Serratia* spp. and *Acinetobacter* spp. (the latter three are often associated with nosocomial infection). The anaerobes are predominantly the *Bacteroides* species and *Bifidobacterium* species.

Bennion *et al.*11,12 reported the bacteriology of 12 patients with gangrenous, and 18 patients with perforated, appendicitis with associated peritonitis and recovered 21 genera and more than 40 species. They recovered 2.7 aerobes and 7.4 anaerobes per specimen, which is much higher than usually reported in the literature (one survey noted an overall mean of 1.2 aerobes and 0.9 anaerobes per patient specimen11,12). Bennion *et al.*11,12 recovered the following percentage of various bacteria in patients with gangrenous and perforated appendicitis, respectively: *E. coli*, 70%, 77%; viridans streptococci, 19%, 43%; enterococci, 18%, 9%; group D streptococci, 7%, 27%; *Staphylococcus* spp., 15%, 11%; *Klebsiella*/*Enterobacter* spp., 11%, 7%; and *P. aeruginosa*, 11%, 18%. Subsequently, Baron *et al.*13 compared the bacteriology of acute and complicated (perforated and gangrenous) appendicitis and noted that the bacteria isolated were similar to those noted above but that ‘some bacteria traverse the intact appendiceal wall prior to perforation’ and that subsequent perforation allows more bacteria into the peritoneal cavity.

Anaerobic bacteria are also isolated in >80% of cases of complicated appendicitis and in the majority of intra-abdominal infections. *B. fragilis* is the most commonly recognized anaerobic pathogen. It is a member of the *B. fragilis* group of isolates, which includes other virulent pathogens, such as *B. thetaiotaomicron*, *B. distasonis*, *Bacteroides vulgatus*, *B. ovatus* and *B. uniformis*, each of which has its own ecological niche. In a study carried out at two community medical centres, Goldstein & Citron14 noted that the *B. fragilis* group accounted for 34.6% of all anaerobes isolated (relative frequency), of which *B. fragilis* itself was the most common isolate, accounting for 18.9%. *B. fragilis* was more likely to be associated with bacteraemia, accounting for 46% of intra-abdominal isolates. Bennion *et al.*11,12 isolated *B. fragilis* in 7/12 (58%) cases with gangrenous appendicitis and in 15/18 (83%) cases of perforated appendicitis. However, their specimens included appendiceal tissue, although they excluded the lumen, peritoneal fluid and abscess contents. Broek15 found similar results for children with perforated appendicitis. In their studies, Bennion *et al.*11,12 and Baron *et al.*13 isolated a previously undescribed anaerobic bacterium, now named *Bilophila wadsworthia*, in approximately half of the patients. Further, they reported the following percentage of various anaerobic bacteria in patients with gangrenous and perforated appendicitis, respectively: *B. fragilis*, 58%, 83%; *B. thetaiotaomicron*, 50%, 83%; *Peptostreptococcus micros*, 33%, 72%; and *Bacteroides fragilis*, 42%, 39%. This study had excellent microbiology but suffered from the small number of patients studied; hence, broad conclusions should not be drawn from this unique patient population from a single medical facility.

Many university and community hospital laboratories do not attempt to isolate or identify the majority of anaerobes in clinical mixed specimens due to cost and other considerations, which often limits the clinician and forces the selection of agents based on literature reviews.

**Antimicrobial susceptibility of anaerobes**

Susceptibility testing for anaerobic organisms continues to be difficult for most laboratories for a variety of reasons.16

(i) The organisms are slow growing.

(ii) The organisms are often part of a mixed infection and it may take several days to isolate and purify colonies in order to embark on testing.

(iii) Many laboratories do not perform enough testing of anaerobes to be able to maintain expertise.

(iv) The methods established by the NCCLS have changed over the past decade, and the use of agar dilution versus broth dilution has been somewhat controversial.16-18

The development of the epifluorometer (Etest) testing methodology19 has been helpful in allowing individual clinical laboratories to perform susceptibility testing of individual or selected clinical isolates to a single agent or narrow spectrum of specific agents; nevertheless, most hospital laboratories do not perform such testing.20 Therefore, the use of surveys has been helpful in establishing information on the expected sensitivity of isolates to a panel of antimicrobial agents.21,22

*B. fragilis* and the group of related species remain the most important group of anaerobic organisms since they are the most common anaerobes in bloodstream invasion and the most common anaerobes isolated from abscesses.23 *Bacteroides* bacteraemia is associated with an attributable mortality of 19%, comparable in scope to that of enterococcal bacteraemia as well as bacteraemia from coagulase-negative *staphylococci*.24 In 1981, Tally and co-workers25 initiated a survey of eight hospitals around the USA, with an interest in testing *Bacteroides*, in order to examine susceptibility variations in *Bacteroides* to a variety of antimicrobials. In particular, there was interest in the rate of resistance to clindamycin since there were recent reports of transferable clindamycin resistance in this group of organisms.26 This survey has continued for the past 22 years and has established clear patterns of resistance to a variety of agents, and demonstrated some geographical variation to the resistance patterns. In addition, the survey has recently established the fact that there has been a shift in species from *B. fragilis* to the other species, such as *B. thetaiotaomicron*, *B. vulgatus*, *B. ovatus*, etc.27,28 We now recognize some
Species associations with resistance to certain antimicrobial agents (Table 1). These associations have been established over the past 5 years in surveys conducted on many strains of *Bacteroides* species in surveys by Snydman and colleagues.21,22

One might also ask what is the relevance of *in vitro* activity to outcome for mixed infections in which *Bacteroides* is present? There are both prospective and retrospective data to support the concept that *in vitro* activity has a direct correlation with outcome.28,29 In a prospective, observational study of *Bacteroides* bacteraemia, *in vitro* susceptibility of the isolate to the antimicrobial agent used could be shown to be an independent predictor of clinical utility, even adjusting for severity of illness.29

In the most recent published findings of the survey of *Bacteroides* susceptibility to antimicrobial agents, metronidazole, imipenem, meropenem, ertapenem, ampicillin–sulbactam, piperacillin–tazobactam and ticarcillin–clavulanate have maintained excellent activity.30 Increased resistance to the quinolones, including trovafloxacin and clinafloxacin, has been noted. The newest quinolone, moxifloxacin, has shown resistance rates strikingly similar to those of trovafloxacin for *Bacteroides* species.31 Although imipenem /-lactamase, which can confer resistance to all current carbapenems, has been reported in Japan, its presence in the USA and Europe has been quite limited. In addition, although metronidazole resistance genes have been reported in Europe, they have not been common in the USA, and metronidazole resistance has been very rare in *Bacteroides*.

Current data suggest that ertapenem, the new once-a-day carbapenem, has anaerobic activity comparable to that of imipenem and meropenem.30 In addition, an analysis by Goldstein et al.7 of ertapenem activity against 469 strains of less-frequently identified anaerobes from 11 genera and 52 species from humans demonstrated that ertapenem is uniformly active against nearly all of the strains tested (only a 2% resistance rate). Resistance was seen in a few strains of *Clostridium difficile*, *Clostridium innocuum* and lactobacilli. In addition to these data from the USA, a Spanish study confirms the activity of ertapenem against *Bacteroides* isolated from abdominal sources.32

Current recommendations from the Surgical Infection Society support the use of monotherapy for intra-abdominal infections33 (Table 2). Most of the agents listed under monotherapy have excellent anaerobe activity, although resistance to cefoxitin or cefotetan may be significant for some species of *Bacteroides*. The advent of a once-a-day carbapenem adds to the armamentarium.

### Animal models of mixed infection

The development of animal model systems for the evaluation of agents that might be useful therapeutically in the treatment of mixed aerobic/anaerobic infections and, in particular, intra-abdominal sepsis, was achieved about 30 years ago.24,35 Weinstein, Onderdonk and colleagues34,35 developed a rat model that mimicked the human condition of a ruptured or violated viscus, with spillage of abdominal contents into the peritoneum.

This model demonstrated two stages, namely a septic phase with death, and a recovery phase with abscess formation if the animal survived the septic phase.36 This rat model demonstrated the importance of facultative bacteria during the initial phase of disease, which mimics peritonitis. The model also demonstrated the importance of obligate anaerobic microorganisms in the later development of

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**Table 1. Summary of activity/Bacteroides species associations**

<table>
<thead>
<tr>
<th>B. fragilis</th>
<th>B. thetaiotaomicron</th>
<th>B. ovatus</th>
<th>B. vulgatus</th>
<th>B. distasonis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>β-Lactam/ase inhibitors</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Quinolones*</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

+++ : very active, rare resistance; ++ : active but 10–15% resistance; + : moderately active, 15–20% resistance; + : very modest activity, 20–30% resistance; – : inactive, >35% resistance.

*Those with reputed anaerobic activity: trovafloxacin or moxifloxacin.

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**Table 2. Recommended antimicrobial regimens for patients with intra-abdominal infections**

<table>
<thead>
<tr>
<th>Single agents</th>
<th>Combination regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>ampicillin–sulbactam</td>
<td>aminoglycoside (amikacin, gentamicin, netilmicin, tobramycin)</td>
</tr>
<tr>
<td>cefotetan</td>
<td>plus an anti-anaerobic drug</td>
</tr>
<tr>
<td>imipenem</td>
<td>aztreonam plus clindamycin</td>
</tr>
<tr>
<td>ertapenem</td>
<td>cefuroxime plus metronidazole</td>
</tr>
<tr>
<td>imipenem–cilastatin</td>
<td>ciprofloxacin plus metronidazole</td>
</tr>
<tr>
<td>meropenem</td>
<td>third-/fourth-generation cephalosporin (cefepime, cefotaxime,</td>
</tr>
<tr>
<td>piperacillin–tazobactam</td>
<td>cefizidime, cefitzoxime, cefltriaxone) plus an anti-anaerobic drug</td>
</tr>
</tbody>
</table>

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abscess formation. The basic model employs the surgical implantation of intestinal contents into the abdominal cavity of rats. Without the use of antimicrobials, 40–50% of the animals will die within the first 48 h. This phase is characterized by bacteraemia with *E. coli* and peritonitis. Within the peritoneal exudates, *E. coli* predominates, but enterococci, *B. fragilis* and *Fusobacterium* are also present. Those animals that survive almost uniformly develop an abscess at 5–7 days, in which the predominant bacterial species are obligate anaerobes. The model has also been used to understand the immunological response to infection with *Bacteroides* and has also served to demonstrate the critical importance of the capsular polysaccharide in the pathogenesis of *B. fragilis* infection.

The antibiotic dosages administered in the rat model are chosen with a view toward approximating the levels achieved in human serum. The dosing interval is also chosen to simulate the human situation. As might be expected, but is reassuring nevertheless, antibiotics active against facultative aerobic organisms (e.g. amino-glycosides) but which lack anaerobic activity, reduced the incidence of death from sepsis, but almost all the animals that survived developed abscesses. Conversely, the animals that survived following treatment with agents directed primarily against anaerobes (e.g. clindamycin) failed to develop an abscess during the septic phase. A number of agents and studies have confirmed these findings.

This animal model has been used as a probe to test the effectiveness of newer agents in an *in vivo* model system. There have been a number of unexpected findings: for example, agents such as chloramphenicol, which has very good anti-*Bacteroides* activity, did not perform as well as might be expected. However, further examination demonstrated that obligate anaerobes were capable of reducing chloramphenicol to an inactive compound, and this might have accounted for some failures. Conversely, metronidazole, directed only at the anaerobic component, showed some activity against aerobic organisms in this model. Further studies suggested a possible mechanism by which *E. coli*, in the presence of *B. fragilis*, may be inhibited by metronidazole. The hypothesis was that the reduction of metronidazole to its active form could produce activity against aerobic organisms to some degree. The other aspect that the model demonstrates, from these and other data, is that the environment of peritonitis is complex, that bacterial synergy is very important, and that there may be interactions between pathogens and drugs which cannot easily be predicted. Hence, the critical importance of clinical trials in humans.

### Clinical trials

Yellin et al. studied the safety and efficacy of ertapenem (1 g and 1.5 g once daily) versus combination therapy with ceftriaxone (2 g once daily) plus metronidazole (500 mg every 8 h) in the therapy of complicated intra-abdominal infections in adults. The study was conducted in 19 centres in the USA and Latin America, and was prospective, randomized and double-blind. Fifty-nine patients received 1 g of ertapenem once daily, 51 patients received 1.5 g of ertapenem once daily and 55 patients in each comparator group received ceftriaxone plus metronidazole. Patients were allowed to receive follow-up therapy with oral ciprofloxacin plus metronidazole after at least 3 days on intravenous therapy and a satisfactory clinical response.

Men accounted for 66% of both ertapenem groups and 64% of the comparator groups. The age of patients in all groups was similar (mean age 38 years in the ertapenem 1 g group, 46 years in the ertapenem 1.5 g group, and 43 years and 49 years in the respective comparator groups). These patients had a variety of intra-abdominal infections. The primary sites of infection were similar for both the 1 g ertapenem group and its comparator group, with 72% and 76% having appendicitis and 17% and 15% having colon-associated infections, respectively. In both the 1.5 g ertapenem group and its comparator group, 53% had appendicitis and 26% had colon-associated infections. The bacteriology of these patients included a wide range of both aerobic and anaerobic Gram-positive andGram-negative bacteria. Seventy patients and 80 patients in the combined ertapenem groups and comparator groups, respectively, were clinically evaluable, and 60 and 72 patients were microbiologically evaluable, respectively. The most common isolates were *E. coli* and *B. fragilis*. Approximately 60% of patients in all groups were switched to oral antimicrobial therapy.

For the microbiologically evaluable patients, response rates were similar for both groups. The following response rates were obtained at the end of study therapy: 84% (1 g ertapenem) versus 85% (comparator) and 83% (1.5 g ertapenem) versus 77% (comparator); and at the 2 week follow-up visit: 70% (1 g ertapenem) versus 73% (comparator) and 89% (1.5 g ertapenem) versus 79% (comparator).

Bacterial eradication rates and adverse reaction rates were similar in all groups. Treatment failures occurred in five of the combined ertapenem group patients and in 10 of the combined comparator group patients. The authors noted that ertapenem had a favourable dosing schedule and was as effective as the combination of ceftriaxone plus metronidazole in the therapy of intra-abdominal infections.

Solomkin et al. enrolled 633 patients with complicated intra-abdominal infections in a worldwide, double-blind, randomized trial of the safety and efficacy of ertapenem (1 g once daily) compared with piperacillin–tazobactam (3.37 g every 6 h). Fifty-seven study centres, including 26 in the USA, participated using a single protocol, which also required evaluation for adequate surgical management. Complicated intra-abdominal infection was defined as an infection requiring surgical intervention (including percutaneous drainage) and which extended ‘beyond the hollow viscus of origin into the peritoneal space’ and was associated with either an abscess or peritonitis. All patients were aged >18 years and had received no prior antimicrobial therapy, unless associated with treatment failure. Patients with traumatic bowel perforation operated upon within 12 h of injury, perforated gastric ulcers operated upon within 24 h of perforation, simple appendicitis, simple cholecystitis, acute suppurative cholangitis, necrotizing pancreatitis, and those with planned staged management or open abdominal technique management were excluded from the study. Also excluded from study were compromised hosts, pregnant or nursing women, patients with a low likelihood of survival, patients with APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of >30 or those seriously allergic to β-lactam antimicrobials, and patients with renal insufficiency (creatinine clearance <30 mL/min) or liver enzymes >6 × normal.

Reported results noted that 323 patients were randomized to the ertapenem group and 310 to the piperacillin–tazobactam group. Demographics and underlying conditions were similar for both groups. More men than women were enrolled (59% of the ertapenem group and 63.5% of the piperacillin–tazobactam group were men). The overall age of both groups was similar, with a range of 17–92 years and a mean age of 46 years in the ertapenem group and 45 years in the piperacillin–tazobactam group. These patients had a variety of intra-abdominal infections. The primary sites of infection were similar for both groups and were as follows for the ertapenem group and piperacillin–tazobactam group, respectively: appendix, 48% versus 61%; colon-associated, both 17%; complicated cholecystitis,
8% versus 6%; small bowel, 9% versus 6%; stomach/duodenum, 9% versus 5%; other, 8% versus 4%. The infectious process was considered to be generalized peritonitis (30% of both groups), localized peritonitis (35% of the ertapenem group versus 37% of the piperacillin–tazobactam group) or abscess(es) (34% in both groups).

Surgical procedures performed in the ertapenem and piperacillin–tazobactam groups, respectively, were as follows: open procedure, 87% versus 91%; laparoscopic procedure, 7% versus 5%; and percutaneous drainage, 5% versus 4%. Primary wound closure occurred in 68% of both treatment groups.

Of those enrolled in the study, 237 patients were not microbiologically evaluable. In the ertapenem group 52 of 120 (43%) non-evaluable patients had no baseline pathogen isolated, 32 (27%) had an inadequate duration of therapy and 24 (20%) missed their 4–6 week follow-up visit; in the piperacillin–tazobactam group 52 of 117 (44%) non-evaluable patients had no baseline pathogen identified, 22 (19%) had an inadequate duration of therapy and 25 (21%) missed their 4–6 week follow-up visit.

Pathogenic bacteria were isolated in 203 (62.8%) ertapenem-treated patients and 193 (62.2%) piperacillin–tazobactam-treated patients. The bacteriology of these infections was similar to that found in other studies, with *E. coli* being the most common isolate in 147/203 (72%) patients in the ertapenem group and in 132/193 (68%) patients in the piperacillin–tazobactam group. *B. fragilis*, *Clostridium* species and other (non-*fragilis*) *Bacteroides* species were also commonly isolated. Of note, non-USA sites and selected USA sites used a central reference laboratory for anaerobic isolations, which may have impacted on the frequency of anaerobes isolates in the other sites. The susceptibility of 1001 aerobic strains isolated in this study is discussed in the following section on *in vitro* support data and by Goldstein et al. Sixty-five and 37 enterococcal strains, respectively, were isolated from ertapenem- and piperacillin–tazobactam-treated patients.

For the microbiologically evaluable patients response rates were similar for both groups. Ertapenem was slightly, but not statistically significantly, more effective than piperacillin–tazobactam, with the following response rates for ertapenem versus piperacillin–tazobactam groups, respectively: at the end of study therapy, 92% versus 88%; at the 2 week follow-up visit, 89% versus 82%; and at the 4–6 week follow-up, 87% versus 81%. In clinically evaluable patients using a modified intent-to-treat analysis the response rate was 79% in the ertapenem group and 76% in the piperacillin–tazobactam group. Treatment failures occurred in 27 ertapenem- and 36 piperacillin–tazobactam-treated patients and were usually due to persistent or recurrent infection, such as abscess, deep infection or surgical site infection. Of interest, Solomkin et al. noted that in patients with *Pseudomonas* isolated as a baseline pathogen there was a 73% clinical response rate with ertapenem and a response rate of 89% with piperacillin–tazobactam. When enterococci were isolated as baseline pathogens, the clinical response rate was 77% with ertapenem therapy and 65% with piperacillin–tazobactam therapy. The disparity between *in vitro* activity of the compounds against enterococci and the clinical response was not felt to be due to ‘an artifact of vancomycin use’ (~4% in each group). The incidence and type of adverse events encountered were similar in both treatment groups, with mild diarrhoea and vein irritation being most frequently recorded. The authors concluded that ertapenem and piperacillin–tazobactam had ‘equivalent efficacy and comparable safety… in patients with a wide range’ of complicated intra-abdominal infections.

Supportive *in vitro* susceptibility data from trials

The *in vitro* susceptibility of many of the aerobic and anaerobic isolates from the clinical trials of ertapenem in patients with complicated intra-abdominal infections has been reported. However, *in vitro* activity does not imply clinical significance. The NCCLS-approved interpretive breakpoints for ertapenem are: for Enterobacteriaceae and staphylococci, ≤2 mg/L for susceptible, 4 mg/L for intermediate and ≥8 mg/L for resistant organisms; and for anaerobes: ≤4 mg/L for susceptible, 8 mg/L for intermediate and ≥16 mg/L for resistant organisms [Ertapenem package insert (2001) Merck & Co., Rahway, NJ, USA]. Ertapenem MICs for susceptible strains of streptococci (other than pneumococci) and *Haemophilus* spp. are ≤1.0 and ≤0.5 mg/L, respectively; no intermediate or resistant breakpoints have been defined. Friedland et al. studied 11 775 strains of Enterobacteriaceae, 2888 strains of anaerobes and 2206 strains of staphylococci and other isolates to evaluate whether surrogate antimicrobial susceptibility could be used reliably to predict susceptibility to ertapenem. They found that for Enterobacteriaceae and anaerobes, imipenem susceptibility could be used as a surrogate for ertapenem susceptibility; for staphylococci, susceptibility to oxacillin could be used as a reliable surrogate; and for streptococci, penicillin susceptibility was a reliable surrogate.

Appelmann et al. used the NCCLS reference agar dilution method with supplemented *Brucella* agar to study the comparative activity of ertapenem against 88 anaerobic isolates obtained from serious intra-abdominal infections associated with the Yellin et al. study. They found ertapenem to have ‘excellent activity’ against 41 *B. fragilis* group strains, with an MIC of ≤4 mg/L. They tested 10 strains of *B. wadsworthia* and found nine had ertapenem MICs of ≤2 mg/L, with one strain being highly resistant.

Pelak et al. reported the comparative *in vitro* activities of ertapenem against 1018 aerobic bacterial pathogens isolated from 531 patients with complicated intra-abdominal infections that were part of USA and international ertapenem trials. The patient isolates were first grown and identified at the local laboratories of participating centres and then isolates on trypticase soy or chocolate agar slants were shipped to Merck Research Laboratories (West Point, PA, USA) where they were stored until study. Susceptibility studies were performed using the broth microtitre dilution method and panels prepared in-house or commercial panels for ampicillin–sulbactam (*Micro-scan*, Dade International Inc., West Sacramento, CA, USA) according to NCCLS guidelines. Enterobacteriaceae accounted for 66.3% of isolates, with *E. coli* being the most common and accounting for 44.8% of isolates. Ertapenem was the most active agent tested and had the lowest MICs with activity against 100% of the 665 Enterobacteriaceae compared with 99% for ceftriaxone, 98% for piperacillin–tazobactam, 80% for amoxicillin–clavulenate and 64% for ampicillin–sulbactam. Pelak et al. noted that 74.6% of the 1018 isolates were inhibited by ≤2 mg/L of ertapenem and 21.9% required ≥8 mg/L for inhibition, which included isolates not expected to be susceptible to ertapenem such as enterococci, meticillin-resistant *S. aureus*, *Acinetobacter baumannii* and *P. aeruginosa*. Despite these microbiological *in vitro* findings, *in vivo* (clinical) efficacy was similar in both groups.

Goldstein et al. isolated 1001 anaerobes from 427 clinical specimens sent to the R. M. Alden Research Laboratory from patients enrolled at 29 sites in 17 countries worldwide involved in an ertapenem complicated intra-abdominal infection study. Operatively obtained specimens of aspirated abdominal pus were placed in anaerobic transport tubes (Anaerobe Systems, Morgan Hill, CA, USA).
USA) and sent via express delivery services to the reference laboratory. Upon receipt, the specimens were placed in an anaerobic chamber and plated onto anaerobic media including supplemented Brucella, Bacteroides bile aesculin, kanamycin–vancomycin laked blood and phenylethyl alcohol blood agars. Growth was obtained in 72.7–100% of submitted specimens per site and yielded an average of three aerobes (range, 0–9) and 2.3 anaerobes (range, 0–13) per specimen. The frequency of isolation and numbers of organisms per specimen were considered consistent with other published studies14–15 and were felt to attest to the ‘quality of the transport system used, since the median time from collection of specimens to processing was 4 days (range, 2–62 days).’4 An earlier study by that laboratory, in which specimens were collected from 17 emergency departments across the USA, found that the research laboratory was able to grow ‘significantly more isolates … than the local laboratories … (P < 0.001).’23 This suggests that reports on the bacteriology of infections that potentially involve anaerobic bacteria processed by laboratories that do not have expertise in anaerobic bacteriology may underestimate the importance and frequency of such infections. The in vitro susceptibility of these isolates was performed by the reference agar dilution method according to the standards of the NCCLS.46

Goldstein et al.7 noted that the B. fragilis group species accounted for 45.5% (455/1001) of all anaerobes isolated, of which B. fragilis accounted for 134 strains (135/1001, 13.4%) and was present in 31.4% of all intra-abdominal specimens. The relative frequency as discerned by the number of strains of B. fragilis group isolates tested were as follows: B. fragilis, 134; B. thetaiotaomicron, 90; B. distasonis and B. uniformis, 50 each; B. ovatus, 46; B. vulgatus, 33; Bacteroides coccaceae, 27; Bacteroides stercoris–Bacteroides merdae group, 16; and B. splanchnicus, nine isolates. Clostridium species accounted for 178 (17.7%) of the anaerobic isolates and included 53 strains of C. clostridiiforme, 40 isolates of C. innocuum, 29 isolates of Clostridium perfringens and 20 isolates of Clostridium ramosum. They noted that etiopathogen was ‘uniformly active against all isolates’, including all B. fragilis group isolates, with the exception of 20% of B. wadsworthia, three strains of lactobacillus and one isolate of Acidaminococcus fermentans. Of the 455 B. fragilis group strains tested by Goldstein et al.,7 three isolates showed some degree of carbapenem resistance, with one strain of B. uniformis having an imipenem MIC of 16 mg/L but susceptible to 2 mg/L of ertapenem, one strain of B. fragilis had an imipenem MIC of 8 mg/L (intermediate); one strain of B. coccaceae had an imipenem MIC of 32 mg/L and an erapenem MIC of 8 mg/L. For isolates of B. fragilis, B. ovatus, B. stercoris–B. merdae group, B. thetaiotaomicron, B. uniformis and B. vulgatus, etapenem MIC90s were ≤1 mg/L. All the 178 clostridia tested were inhibited by ≤4 mg/L of erapenem, with C. perfringens being the most susceptible, requiring only <0.125 mg/L of erapenem for inhibition. Eubacterium species (54 isolates) were susceptible to ≤0.06 mg/L of erapenem whereas almost all P. micros (23 isolates), Porphyromonas (20 isolates) and Prevotella species (41 isolates) were susceptible to ≤1 mg/L of erapenem.

In comparison, all the 455 B. fragilis group isolates studied by Goldstein et al.7 were susceptible to meronidazole but meronidazole MIC90s for B. fragilis, B. thetaiotaomicron and B. coccaceae were 4 mg/L, a value somewhat higher than other reports. The piperacillin–tazobactam MIC90 was 1 mg/L for B. fragilis but MIC90s were higher for all other B. fragilis group species and were as follows: B. stercoris–B. merdae group, B. uniformis and B. vulgatus, 8 mg/L; and B. thetaiotaomicron, B. coccaceae, B. distasonis and B. ovatus, 16 mg/L. Piperacillin–tazobactam MIC90s for strains of B. wadsworthia and C. clostridiiforme were 128 mg/L.

Goldstein et al.7 also reported limited information about variation in the susceptibility of the anaerobic isolates analysed by country of specimen origin. No geographical differences were noted for susceptibility to erapenem or imipenem, but susceptibility to clindamycin varied widely, with those from Canada and Mexico being most susceptible. C. innocuum isolates from Canada and South Africa were noted to be more susceptible to clindamycin than those from Brazil and Guatemala and may have reflected local antimicrobial usage patterns or the presence of clonal dissemination.

Analysis

Clinical trials have shown that erapenem is generally well tolerated and as effective as piperacillin–tazobactam or ceftriaxone plus metronidazole in the therapy of complicated intra-abdominal infections. Based on the clinical efficacy of these trials, the US FDA gave approval for these indications in November 2001 and the European Union gave approval in April 2002. Several microbiological issues remain intriguing and controversial, however, such as the pathogenic role, if any, of Enterococcus species when isolated in mixed culture in intra-abdominal infections. The microbiological response rates of patients with enterococci as part of their baseline cultures and treated with erapenem were relatively high and generally similar to those of patients treated with piperacillin–tazobactam even when vancomycin use was excluded. In addition, surgical management questions regarding what constitutes optimal percutaneous drainage and how to select appropriate patients to achieve maximum efficacy remain to be answered.

Summary

Complicated intra-abdominal infections are commonly encountered in the community. Best results ensue from a combination of adequate surgical source control and the early use of effective antimicrobial therapy. Delay in the institution of either component is associated with complications and/or therapeutic failure. This is especially important in the selection of effective antimicrobial therapy since initially ineffective therapy adjusted after culture data are available (‘escalation therapy’) is associated with complications and increased length of hospital stay. The choice of antimicrobial therapy must take into account the complexity of the potential pathogens that comprise the normal aerobic and anaerobic flora of the bowel (including a bacterial density of up to 1011 cfu/g of faeces). Erapenem, a once-a-day parenteral carbapenem, was shown to be active in vitro against many aerobic and anaerobic bacteria encountered in complicated community-acquired intra-abdominal infections. Review of in vitro data against intra-abdominal isolates, specifically, and the success of erapenem in worldwide comparative clinical trials in the therapy of complicated intra-abdominal infections in adults show that erapenem is generally well tolerated and as effective as either piperacillin–tazobactam or ceftriaxone plus metronidazole in the therapy of community-acquired, complicated intra-abdominal infections.

Transparency declarations

E.J.C.G. has received fees for speaking at symposia organized by Merck & Co., Inc., and has received funds for research from Merck & Co., Inc. E.J.C.G. is a member of the Merck & Co., Inc. erapenem advisory board. D.R.S. has received research funds from Merck &
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