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Ertapenem: review of a new carbapenem

George G Zhanel[†], Christel Johanson, John M Embil, Ayman Noreddin, Alfred Gin, Lavern Vercaigne and Daryl J Hoban

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[†]Author for correspondence
Health Sciences Center, Clinical
Microbiology, MS673-820,
Sherbrook Street, Winnipeg,
Manitoba, R3A 1R9, Canada
Tel.: +1 204 787 4902
Fax: +1 204 787 4699
ggzhanel@pcs.mb.ca

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The carbapenems are β -lactam-type antibiotics with an exceptionally broad spectrum of activity. Ertapenem is a new carbapenem developed to address the pharmacokinetic shortcomings (short half-life) of imipenem and meropenem. Ertapenem shares similar structural features with meropenem, including its stability to dehydropeptidase-1, allowing it to be administered without a dehydropeptidase-1 inhibitor. Ertapenem, like imipenem and meropenem, demonstrates broad-spectrum antimicrobial activity against many Gram-positive and -negative aerobes and anaerobes and is resistant to nearly all β -lactamases, including extended-spectrum β -lactamases and AmpCs. However, it differs from both imipenem and meropenem in demonstrating limited activity against *Enterococcus* spp., *Pseudomonas aeruginosa* and other nonfermentative Gram-negative bacteria commonly associated with nosocomial infections. The extensive protein binding of ertapenem extends the half-life and allows for once-daily dosing. Prospective, multicenter, randomized, double-blind, comparative clinical studies demonstrate similar clinical efficacy of ertapenem compared with other agents. Clinical trials of complicated intra-abdominal infection, acute pelvic infection, complicated skin and soft-structure infection, community-acquired pneumonia and complicated urinary tract infections demonstrated that ertapenem has equivalent efficacy and safety compared with ceftriaxone and piperacillin/tazobactam. Ertapenem is a promising new carbapenem with excellent efficacy and safety for the treatment of a variety of community-acquired infections. It also appears to be of great value as an outpatient parenteral antimicrobial therapy.

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The carbapenems are β -lactam-type antibiotics with an exceptionally broad spectrum of activity involving coverage of Gram-positive and -negative aerobes and anaerobes, and are stable to almost all bacterial β -lactamases [1]. The first carbapenem to be identified in the mid 1970s was thienamycin, a compound produced by the soil organism *Streptomyces cattleya* [2,3]. Thienamycin was highly unstable and therefore an N-formimidoyl derivative called imipenem was developed [2]. Although imipenem was stable as a solid and in concentrated solution, it was rapidly degraded by dehydropeptidase (DHP)-1, an enzyme found in the proximal renal tubules of mammals [2,4]. Therefore, imipenem must be coadministered with cilastatin, a DHP-1 inhibitor in order to

be used clinically [2]. This addition of cilastatin is also beneficial in preventing the nephrotoxicity observed in animals when imipenem is administered alone [2,4]. The carbapenems currently available on the market are unstable in gastric acid and require parenteral administration [5]. Imipenem and cilastatin have similar half-lives of approximately 1 h, requiring three to four daily doses [3]. Another disadvantage of the imipenem/cilastatin combination is the increased incidence of seizures observed when it is used at high doses (e.g., 1 g every 6 h) in relation to renal function or body weight and/or in patients with underlying CNS disorders. For this reason imipenem/cilastatin is not suitable for the treatment of meningitis [3,6]. Meropenem was the second carbapenem

released for clinical use. It differs from imipenem in being intrinsically stable to DHP-1 and therefore can be administered as a single entity [7]. It also has the advantage of being less likely to cause seizures and, unlike imipenem, it can be used for infections of the CNS [6]. It has enhanced *in vitro* activity against *Pseudomonas aeruginosa* and other Gram-negative bacilli compared with imipenem, but is slightly less active against Gram-positive cocci [5,7]. Meropenem also requires multiple daily dosing (every 8 h), due to its short half-life [1].

Medical need

Two carbapenems, imipenem and meropenem, have been in clinical use for many years. These agents are both extremely broad spectrum and are primarily used in hospitals as an empiric therapy for the treatment of seriously ill patients [7–9]. The current choices for the treatment of polymicrobial (mixed aerobic and anaerobic) infections include the carbapenems or combination therapies, all of which require multiple daily dosing [10]. A new carbapenem with superior pharmacokinetics was required and ertapenem was developed to fulfil this need. It shares similar structural features with meropenem, including its stability to DHP-1, allowing it to be administered without a DHP-1 inhibitor [11]. Its long half-life, due to extensive protein binding, allows for once-daily dosing [12]. It has broad-spectrum activity, including aerobes and anaerobes, and is resistant to nearly all β -lactamases; however, its limited activity against *Enterococcus* spp., *P. aeruginosa* and other nonfermentative Gram-negative bacteria makes it ideal for the treatment of community-acquired infections, but not optimal for infections caused by nosocomial pathogens [10,13].

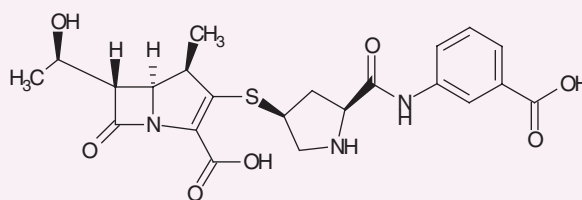
The purpose of this paper is to provide a review of the chemistry, microbiology pharmacokinetics/pharmacodynamics, clinical trials, safety and pharmacoeconomic data currently published on ertapenem. Ertapenem will be compared with imipenem, meropenem, piperacillin/tazobactam, and ceftriaxone where appropriate. Emphasis will be on the most recent data, although older reports will be reviewed and presented as necessary.

Chemistry

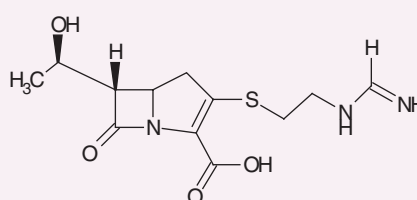
All carbapenems share the basic 4:5 β -lactam ring structure of the penicillins except for a few changes, including a substitution at position 1 of a carbon for the sulfur and the presence of an unsaturated bond between carbons 2 and 3 in the 5-membered thiazolidine ring (FIGURE 1) [2,4,5,14]. The extended antibacterial spectrum of the carbapenems is mainly attributed to their resistance to almost all bacterial β -lactamases. This stability is due to the unique trans- α -1-hydroxyethyl substituent at the 6 position, compared with the side chains in the penicillins and cephalosporins, which have a *cis* configuration [2,5,12,14].

A significant difference between imipenem and meropenem is the presence of the 1- β -methyl substituent on meropenem. This change is responsible for increased stability to DHP-1, permitting the administration of meropenem on its own, without a DHP-1 inhibitor such as cilastatin [4,14,15]. Meropenem

Ertapenem



Imipenem



Meropenem

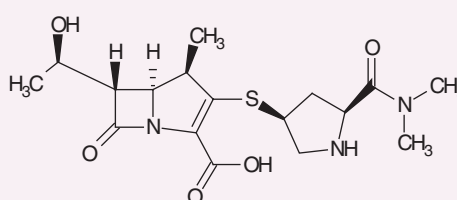


Figure 1. Ertapenem, imipenem and meropenem. Adapted from [10].

also has a pyrrolidinyl-containing side chain at carbon 2, which may be responsible for its superior activity against *P. aeruginosa* and other Gram-negative bacteria compared with imipenem [4].

Similar to meropenem, ertapenem has a methyl group on carbon 1 which confers resistance to DHP-1 [10,12,16]. In actuality, the only difference between meropenem and ertapenem is the presence of a metasubstituted benzoic acid group at position 2 of ertapenem [16]. This substitution is assumed to be the reason for the pharmacokinetics and spectrum of activity displayed by ertapenem [12]. The result of this substitution is an increase in molecular weight and lipophilicity of the molecule [12]. It also imparts an overall negative charge on the molecule due to the ionization of the carboxylic acid on the benzene ring at physiologic pH [10,12]. This ionization accounts for the extensive protein binding of ertapenem, which increases its half-life, thereby allowing once-daily dosing [10,12].

Mechanism of action

All β -lactam antibiotics, including the carbapenems, are bactericidal and act by binding to penicillin binding proteins (PBPs) [1,5,11,12]. This binding inactivates the PBPs, and prevents the transpeptidation (crosslinking) of peptidoglycan strands, which is essential for the synthesis of intact bacterial peptidoglycan [1]. Increased activity against Gram-negative organisms by meropenem and ertapenem compared with imipenem has been associated with differences in PBP binding [17]. Meropenem and ertapenem bind with the highest affinity to PBP2, followed by PBP3, whereas imipenem binds

preferentially to PBP2 and then PBP1a and 1b [5,14,16,18]. Studies of antibiotic binding to PBPs of *Escherichia coli* revealed that ertapenem binds to PBP2 with a similar affinity as imipenem, which is 30 to 40 times stronger than that of ceftriaxone or cefepime [17]. In terms of binding to PBP3, ertapenem, ceftriaxone and cefepime had similar results that were 60 times the binding affinity of imipenem [12,17].

Ertapenem also demonstrates binding to PBPs 1a, 1b, 4 and 5 of *E. coli* [10]. Antibiotic binding to PBP1a/1b and 2 in Gram-negative bacilli leads to the formation of small spheres or ellipsoids, with rapid lysis observed with imipenem without the elongated filament formation observed with third-generation cephalosporins that preferentially bind to PBP3 [1,2,4,16]. This lack of cell growth with filamentation leads to a decrease in endotoxin release [1,16].

Mechanism of resistance

Imipenem and meropenem are known for their activity against multiresistant Gram-negative bacteria due to their stability to almost all bacterial β -lactamases, including the extended-spectrum β -lactamases (ESBLs) and AmpC β -lactamases [7,14]. The incidence of these β -lactamases are increasing and are of considerable interest since they can lead to resistance to, and therefore treatment failure with, third-generation cephalosporins [7,16,17,19]. Studies show that ertapenem retains good activity against those bacteria producing ESBLs or AmpC β -lactamases, although the minimum inhibitory concentration (MIC) values are approximately two to fourfold higher compared with nonproducers [16,17,19–21]. In comparison, the MIC values of imipenem are less likely to be affected when tested against these same bacteria [21]. Even though the MIC values are increased with ertapenem, these isolates are still very susceptible to ertapenem and therefore ertapenem is a potential treatment option for infections caused by ESBLs or AmpC producers [16,17].

Although the spectrum of activity of carbapenems is extremely broad, there are some bacteria that have intrinsic resistance to all the carbapenems, including ertapenem. Poor binding of carbapenems and other β -lactam antibiotics to PBPs found in methicillin-resistant staphylococci, *Enterococcus faecium* and penicillin-resistant streptococci are responsible for the antibiotic resistance observed in these bacteria [4,7,11,16]. Other bacteria, such as *Stenotrophomonas maltophilia* and *Aeromonas* spp. produce metallo- β -lactamases that, unlike most other β -lactamases, are very proficient at hydrolyzing carbapenems [3,4,7,12,14]. These metallo- β -lactamases or 'carbapenemases' are usually chromosomally encoded and contain a zinc atom in their active site, whereas the more commonly found β -lactamases are serine based and do not confer resistance to carbapenems [3,7,12].

Resistance to imipenem and meropenem in *P. aeruginosa* is caused by a mutation leading to the loss of the OprD (D2) porin, which is the route of entry into the cell for imipenem and meropenem, and increased efflux of the antibiotic (for meropenem only) [4,14,16]. It is hypothesized that the lack of

activity of ertapenem against *P. aeruginosa* is due to a combination of the above mechanisms or an ertapenem specific unidentified mechanism termed MK-X [22,23]. The large anionic side chain on ertapenem may also contribute to decreased entry through the D2 porin of *P. aeruginosa* and through the cell envelope of other nonfermenters, or it may increase its affinity for efflux pumps [12,16]. Resistance to ertapenem has also been reported in β -lactamase-producing *Klebsiella pneumoniae* with concomitant defects in membrane permeability [24].

Microbiology

Like imipenem and meropenem, ertapenem demonstrates *in vitro* activity against Gram-positive and -negative aerobes and anaerobes (TABLES 1–3) [7,25]. It should be stated that the data in TABLES 1–3 are pooled data representing hundreds of isolates. However, unlike the other carbapenems, ertapenem exhibits minimal activity against those pathogens associated with nosocomial infections, including *P. aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Actinobacter* spp., and the enterococci (TABLES 1 & 2) [7,11,25]. In general, carbapenem antibiotics demonstrate more potent *in vitro* activity against Gram-positive, -negative and anaerobic bacteria compared with piperacillin/tazobactam and ceftriaxone, with few exceptions (TABLES 1–3). None of the antibiotics in TABLES 1 & 2 have activity against *S. maltophilia*, which produces metallo- β -lactamases capable of hydrolyzing all β -lactam antibiotics, including the carbapenems [4,7,16]. No values are reported for atypical bacteria since β -lactam antibiotics do not have activity against these bacteria.

Ertapenem demonstrates potent *in vitro* activity against most enterobacteriaceae, exhibiting MIC values between 0.008 and 0.125 mg/l (TABLE 2) [25]. MIC values for ertapenem and meropenem are generally similar and lower than those of imipenem for Gram-negative bacteria [7,16,25]. Imipenem and meropenem are known for their activity against multiresistant Gram-negative bacteria due to their stability to almost all bacterial β -lactamases including the ESBLs and AmpC β -lactamases [7,14]. The incidence of these β -lactamases are increasing and are of considerable interest since they can lead to resistance to and, therefore, treatment failure with, third-generation cephalosporins [7,16,17,19]. Studies show that ertapenem retains good activity against those bacteria producing ESBLs or AmpC β -lactamases, although the MIC values are approximately two- to fourfold higher than nonproducers [16,17,19–21]. In comparison, the MIC values of imipenem are less likely to be affected when tested against these same bacteria [21]. Even though the MIC values are increased with ertapenem, these isolates are still very susceptible to ertapenem and therefore ertapenem is a potential treatment option for infections caused by ESBLs or AmpC producers [16,17].

Nevertheless, ertapenem has good activity against methicillin-susceptible *S. aureus* (MSSA), and streptococci, including *Streptococcus pneumoniae*. Ertapenem has potent activity against most anaerobes (MIC₉₀ $\leq$ 2 mg/l) with the exception of *Clostridium difficile* and *Lactobacillus* spp. (TABLE 3).

Table 1. *In vitro* activity of ertapenem and comparators against Gram-positive aerobes.

Bacteria	Ertapenem [*]			Imipenem [†]		Meropenem [§]		Piperacillin/ tazobactam [¶]		Ceftriaxone [#]	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> (MS)	0.12	0.25	0.008 to >16	0.016	0.03	0.06	0.12	1	2	4	4
<i>Staphylococcus aureus</i> (MR)	4	>16	0.125 to >32	4	32	4	32	16	>32	32	>32
<i>Staphylococcus epidermidis</i>	0.25	4	0.12 to 8	0.03	0.05	0.12	2	0.125	1	0.5	4
<i>Streptococcus pyogenes</i>	0.008	0.03	≤0.008 to 0.25	0.008	0.008	≤0.004	≤0.004	0.06	0.125	0.03	0.06
<i>Streptococcus agalactiae</i>	0.06	0.06	≤0.03 to 0.125	0.016	0.03	0.03	0.03	0.25	0.5	0.03	0.06
<i>Streptococcus pneumoniae</i>	0.03	0.5	≤0.008 to 4	0.008	0.25	0.25	1	0.03	0.12	0.06	0.5
<i>Streptococcus pneumoniae</i> (PS)	0.016	0.03	≤0.008 to 0.25	≤0.008	0.008	0.008	0.016	≤0.06	≤0.06	0.03	0.06
<i>Streptococcus pneumoniae</i> (PI)	0.12	0.5	≤0.008 to 1	0.06	0.12	0.12	0.5	1	2	0.25	1
<i>Streptococcus pneumoniae</i> (PR)	0.5	2	0.12 to 4	0.25	0.5	0.5	1	4	4	1	2
<i>Enterococcus faecalis</i>	8	>16	0.06 to >64	2	4	8	>32	4	8	>64	>64
<i>Enterococcus faecium</i>	>16	>16	0.015 to >64	>16	>16	>32	>32	>128	>128	>32	>32
<i>Listeria monocytogenes</i>	0.25	0.5	0.06 to 1	0.12	0.12	0.12	0.12	NA	NA	64	>64

National Committee for Clinical Laboratory Standards approved and tentative breakpoints [63]: *Staphylococcus* spp.: ertapenem 8 mg/l or more is resistant; imipenem 16 mg/l or over is resistant; meropenem 16 mg/l or more is resistant; piperacillin/tazobactam 16/4 mg/l or more is resistant; ceftriaxone 64 mg/l or over is resistant.

Streptococcus pneumoniae: ertapenem 4 mg/l or more is resistant; imipenem 1 mg/l or over is resistant; meropenem 1 mg/l or more is resistant; ceftriaxone 4 mg/l or over is resistant.

^{*}Data presented are adapted from [39,64–78].

[†]Data presented are adapted from [64,66,70,72–75,78–82].

[§]Data presented are adapted from [64,66,78–82].

[¶]Data presented are adapted from [39,67–69,72,74,76–78,80].

[#]Data presented are adapted from [39,64–69,71,72,75–80].

MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration of 90% of isolates; MS: Methicillin sensitive; MR: Methicillin resistant; NA: Information not available; PI: Penicillin intermediate (penicillin MIC: 0.12–1 mg/l); PR: Penicillin resistant (penicillin MIC ≥ 2.0 mg/l); PS: Penicillin susceptible (penicillin MIC ≤ 0.06 mg/l).

Pharmacokinetics

The pharmacokinetics of ertapenem either alone or against comparators are displayed in TABLES 4 & 5. Single-dose ertapenem studies ranging from 0.4 to 3 g were conducted in healthy young subjects (TABLE 4) [27]. The results illustrated somewhat less than dose proportional increases in plasma concentrations and area under the plasma concentration–time curve (AUC) with increasing dose, due to the nonlinear concentration-dependent protein binding of ertapenem [27,28]. After repeated daily infusions, ertapenem did not show any evidence of accumulation in young or elderly healthy individuals [27,29]. Slight gender differences in pharmacokinetic parameters in both healthy young and elderly women were attributed to the lower body weight of females and are not considered to be clinically relevant; consequently there are no recommendations for dose adjustments based on gender [27].

In the elderly, higher plasma concentrations, an overall decrease in plasma clearance of ertapenem, and a slightly increased half-life were associated with an increase in mean AUC (39% of total ertapenem and 71% of unbound drug) compared with young healthy subjects [29]. Elderly subjects also tend to have a slightly higher percentage of unbound

ertapenem compared with younger subjects (5–11 vs. 5–8%, respectively). Most of these differences are assumed to be related to the decrease in renal function seen in the elderly and there is no suggestion by the manufacturer for any adjustment in dosage based on age [29,30].

Studies of the intramuscular dosage form of ertapenem revealed that the 1 g intramuscular injection has a 92% relative bioavailability compared with 1 g administered by intravenous infusion [28]. The maximum concentration (C_{max}), which occurred approximately 2 h after the intramuscular injection, was 70.6 mg/l, which is lower than that observed after intravenous administration; however, the AUC and half-life of the two administration routes were similar and the time the plasma concentration of ertapenem was above the breakpoint of 4 mg/l was just over 1 hour longer following intramuscular compared with intravenous administration [28]. Similar to the intravenous studies, multiple daily intramuscular dosing showed no evidence of accumulation and had no effect on the pharmacokinetics of ertapenem [28]. Given these results, it has been concluded that the intramuscular and intravenous administration routes could be used interchangeably in clinical practice [28].

Table 2. *In vitro* activity of ertapenem and comparators against Gram-negative aerobes.

Bacteria	Ertapenem*			Imipenem [‡]		Meropenem [§]		Piperacillin/ tazobactam [¶]		Ceftriaxone [#]	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅ 0	MIC 90	MIC ₅₀	MIC ₉ 0	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter</i> spp.	4	>16	0.015 to >32	0.25	0.5	0.5	1	8	32	16	128
<i>Citrobacter freundii</i>	≤0.016	0.03	0.016 to 0.25	1	2	0.03	0.06	2	16	0.25	>32
<i>Enterobacter aerogenes</i>	0.06	0.5	≤0.016 to >16	1	4	0.06	0.06	4	8	0.5	>32
<i>Enterobacter cloacae</i>	0.03	0.125	<0.008 to >16	0.5	2	0.03	0.12	2	64	0.25	32
<i>Escherichia coli</i>	≤0.016	≤0.016	≤0.008 to 0.06	0.12	0.25	≤0.015	0.03	2	8	0.06	0.125
<i>Escherichia coli</i> (ESBL)	0.03	0.05	≤0.015 to 1	0.12	0.5	≤0.015	0.06	16	>128	>64	>64
<i>Haemophilus influenzae</i>	0.06	0.125	≤0.008 to 1	1	2	0.12	0.25	0.06	0.125	0.016	0.016
<i>Klebsiella pneumoniae</i>	≤0.016	0.03	≤0.008 to 8	0.25	0.5	0.03	0.03	2	8	≤0.06	0.06
<i>Klebsiella pneumoniae</i> (ESBL)	0.06	0.5	≤0.015 to 16	0.25	0.5	0.03	0.06	>128	>128	>64	>64
<i>Klebsiella pneumoniae</i> (AmpC)	0.25	1	≤0.015 to 32	0.5	1	≤0.06	0.25	128	>128	32	>32
<i>Klebsiella oxytoca</i>	≤0.016	≤0.03	≤0.008 to 8	0.25	0.5	0.03	0.03	2	4	0.06	0.5
<i>Klebsiella</i> spp.	0.016	0.03	≤0.008 to >16	0.12	0.25	0.03	0.03	2	8	0.06	0.5
<i>Moraxella catarrhalis</i>	0.016	0.016	≤0.008 to 0.25	0.06	0.06	0.008	0.008	≤1	≤1	0.12	0.5
<i>Morganella morganii</i>	0.03	0.12	≤0.008 to 8	2	4	0.25	0.25	0.5	4	0.06	8
<i>Neisseria gonorrhoeae</i>	0.002	0.008	≤0.00025 to 0.031	0.03	0.25	0.008	0.03	0.25	1	0.008	0.015
<i>Proteus mirabilis</i>	≤0.016	≤0.03	<0.008 to 16	1	2	0.06	0.06	0.5	1	≤0.03	0.06
<i>Proteus vulgaris</i>	0.016	0.03	≤0.008 to 2	2	4	0.12	2	0.5	2	0.06	>32
<i>Pseudomonas aeruginosa</i>	8	16	<0.008 to >64	2	8	0.5	8	4	16	32	>32
<i>Salmonella</i> spp.	0.008	0.016	<0.008 to 0.25	0.25	0.5	≤0.06	≤0.06	4	16	0.06	0.25
<i>Serratia marcescens</i>	0.03	0.12	≤0.008 to 16	0.5	2	0.06	0.12	2	8	0.25	0.5
<i>Shigella</i> spp.	0.008	0.015	<0.008 to 0.5	0.25	0.25	≤0.06	≤0.06	1	2	0.03	0.06
<i>Stenotrophomonas maltophilia</i>	>16	>16	1 to >64	>32	>32	32	128	16	16	>64	>64

National Committee for Clinical Laboratory Standards approved and tentative breakpoints [63]: Enterobacteriaceae spp.: ertapenem 8 mg/l or more is resistant; imipenem 16 mg/l or over is resistant; meropenem 16 mg/l or more is resistant; piperacillin/tazobactam 128/4 mg/l or more is resistant; ceftriaxone 64 mg/l or over is resistant.

Pseudomonas aeruginosa and other non-Enterobacteriaceae: imipenem 16 mg/l or more is resistant; meropenem 16 mg/l or over is resistant; piperacillin/tazobactam 128/4 mg/ml or more is resistant; ceftriaxone 64 mg/l or over is resistant; no data are available for ertapenem.

*Data presented are adapted from [26,39,65,67–78,83].

‡Data presented are adapted from [70,72–75,77–84].

§Data presented are adapted from [75,77–82,84].

¶Data presented are adapted from [39,67–69,72,74–76,78,80,83,84].

#Data presented are adapted from [39,65,67–69,71,72,75–80,84].

ESBL: Extended-spectrum β-lactamase; MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration of 90% of isolates.

Protein binding

In human serum, ertapenem displays significant plasma protein binding, which is also concentration dependent [27]. Protein binding is between 92 and 95% when total ertapenem concentrations are between 50 and 150 mg/l [27]. At concentrations of

around 300 mg/l (such as those achieved after administration of 2- to 3-g doses of ertapenem), protein binding is decreased to approximately 85% [27]. There are two sites of reversible and saturable binding for ertapenem; the primary site is believed by manufacturers to be serum albumin, although results from

Table 3. *In vitro* activity of ertapenem and comparators against anaerobes.

Bacteria	Ertapenem			Imipenem		Meropenem		Piperacillin/ tazobactam		Ceftriaxone	
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Bacteroides fragilis</i>	0.25	1	0.016 to 32	0.12	0.5	0.12	1	0.5	1	32	64
<i>Bacteroides fragilis</i> group	0.5	2	≤0.008 to 32	0.25	0.5	0.25	0.5	2	16	64	>64
<i>Bacteroides ovatus</i>	0.5	1	0.03 to 8	0.125	0.5	0.25	0.5	4	8	>64	>64
<i>Bacteroides uniformis</i>	0.25	1	0.03 to 4	0.125	0.5	0.12	0.5	0.2	8	32	>128
<i>Bacteroides vulgatus</i>	0.125	0.5	≤0.015–32	0.25	0.5	0.25	0.5	2	8	8	>64
<i>Bacteroides thetaiotaomicron</i>	1	1	0.03 to 4	0.25	0.25	0.25	0.5	8	16	>64	>64
<i>Bacteroides distasonis</i>	0.5	2	0.03 to 4	0.5	2	0.25	0.5	4	8	32	>64
<i>Clostridium difficile</i>	4	8	1–8	4	4	2	2	8	16	32	64
<i>Clostridium perfringens</i>	0.06	0.06	≤0.008 to 0.25	0.06	0.125	0.016	0.03	0.25	0.5	2	4
<i>Fusobacterium</i> spp.	0.015	0.12	≤0.004 to 8	0.25	1	0.125	0.5	≤0.06	0.12	0.125	1
<i>Lactobacillus</i> spp.	2	16	0.03 to >32	0.125	4	8	>8	2	4	64	>64
<i>Peptostreptococcus</i> spp.	0.06	0.5	≤0.004 to 4	0.03	0.12	0.06	0.25	0.125	2	1	8
<i>Prevotella</i> spp.	0.06	0.25	≤0.015 to 2	0.03	0.06	0.06	0.12	≤0.06	0.06	1	16

National Committee for Clinical Laboratory Standards approved and tentative breakpoints [85]: Anaerobes: ertapenem 16 mg/l or more is resistant; imipenem 16 mg/l or more is resistant; meropenem 16 mg/l or more is resistant; piperacillin/tazobactam 128/4 mg/l or more is resistant; ceftriaxone 64 mg/l or more is resistant.

[†]Data presented are adapted from [69,72,73,75,76,86–92].

[‡]Data presented are adapted from [72,73,82,84,87,89–93].

[§]Data presented are adapted from [75,82,86,87,89,91–93].

[¶]Data presented are adapted from [69,72,76,86–91,93].

[#]Data presented are adapted from [69,72,76,90–93].

MIC₅₀: Minimum inhibitory concentration (mg/l) of 50% of isolates; MIC₉₀: Minimum inhibitory concentration of 90% of isolates.

studies do not support this claim [31,32]. The second site contains two subsites, and has a 25-fold lower binding affinity for ertapenem [31]. Although controversial, it is theorized that drug binding to serum proteins should not affect its *in vivo* efficacy since ertapenem can easily dissociate from the plasma proteins and bind to the higher affinity target PBPs in bacteria [30,31]. In this way, the plasma proteins act as a drug reservoir, releasing free drug at the site of action [30,31]. This extensive protein binding results in the increased half-life of ertapenem of 4 h compared with drugs that are less protein bound, such as imipenem and meropenem (TABLE 5), which have half-lives of approximately 1 h and therefore require multiple daily dosing [11,16,30].

Distribution

Studies of ertapenem entry into epidermal blisters have been conducted to assess the ability of ertapenem to distribute into interstitial fluid [33]. Samples were taken on the third day of 1-g intravenous daily administration of ertapenem. The ratio of the AUC_{0–24} of total ertapenem in blister fluid to that in plasma was 61% [33]. A mean C_{max} of approximately 25 mg/l occurred 8 h after administration of the

dose, after which serum drug concentrations in the blister fluid dropped more slowly compared with those in the plasma, to 7.6 mg/l at 24 h [33].

Ertapenem penetration into the cerebrospinal fluid (CSF) of rabbits was 2.4% into noninflamed and 7.1% into inflamed meninges [34]. Ertapenem concentrations were measured in the breast milk of five nursing mothers during the 3 to 6 days of treatment [10,11,35]. Ertapenem concentrations were undetectable after 5 days following the discontinuation of treatment in all but one woman, who had only trace amounts remaining [10,11,35].

Metabolism & elimination

Ertapenem is mainly eliminated through the kidneys by glomerular filtration and secretory processes [30]. Results from metabolic studies have shown that almost 80% of a 1-g dose of ¹⁴C-labeled ertapenem appeared in the urine in approximately equal amounts as unchanged ertapenem and its major metabolite, the open ring β-lactam derivative formed through hydrolysis by DHP-1 (in humans this enzyme is found predominantly in the kidneys) [30,36]. These two compounds make up 95% of the total radioactivity

Table 4. Pharmacokinetic parameters of ertapenem*.

Parameters	Total ertapenem	Unbound ertapenem
Area under the curve ($\mu\text{g}\cdot\text{h/l}$)	572.1 (68.6)	33.2 (5.5)
Apparent plasma clearance (ml/min)	29.5 (3.4)	513.6 (80.8)
Apparent renal clearance (ml/min)	12.9 (4.3)	223.3 (67.8)
Apparent nonrenal clearance (ml/min)	16.1 (5.4)	289.8 (117.8)
Volume of distribution at steady state (l)	8.2 (1.5)	123.1 (37.2)
Concentration at end of infusion ($\mu\text{g/l}$)	154.9 (22.0)	12.9 (3.2)
Concentration at 12 h after infusion ($\mu\text{g/l}$)	9.3 (2.8)	
Concentration at 24 h after infusion ($\mu\text{g/l}$)	1.2 (0.6)	
Plasma half-life (h)	3.8	

Following a 1-g intravenous dose of ertapenem in healthy young volunteers ($n = 16$) (adapted from [27]).

*Mean $\pm$ standard deviation pharmacokinetic parameters for total (protein bound and unbound) and free (unbound) ertapenem.

measured in the urine [30,36]. Radioactivity in the feces was less than 10% of the dose [30,36]. In a recent study, Pletz and colleagues assessed the pharmacokinetics of ertapenem in male and female volunteers and the impact on intestinal flora [37]. These investigators documented that after 1-g doses of ertapenem, fecal ertapenem concentrations were 37.2 and 32.7 mg/kg on days 4 and 8, respectively.

Renal insufficiency

Pharmacokinetic parameters were measured in patients ($n = 26$) with varying degrees of renal insufficiency after administration of a single 1-g intravenous dose of ertapenem. Increases in AUC for patients with mild (creatinine clearance [CL_{cr}]: 60–90 ml/min/ 1.73 m^2), moderate (CL_{cr} : 31–69 ml/min/ 1.73 m^2), advanced (CL_{cr} 5–30 ml/min/ 1.73 m^2) and end-stage ($\text{CL}_{\text{cr}} < 10 \text{ ml/min}/1.73 \text{ m}^2$) renal insufficiency compared with healthy controls were 7, 53, 158 and 192%, respectively [10,11,35]. The half-life of ertapenem was also increased in renal insufficiency to 4.4, 6.1, 10.6 and 14.1 h in mild, moderate, advanced and end-stage disease, respectively [10,11,35]. Based on this study, the recommendation for dosing in advanced and end-stage renal insufficiency ($\text{CL}_{\text{cr}} < 30 \text{ ml/min}/1.73 \text{ m}^2$) is to reduce the normal dose to 500 mg daily [35]. When administered immediately prior to a 4-h hemodialysis session, approximately 30% of the 1-g dose of ertapenem was removed [30,35]. It is therefore recommended that an additional 150-mg dose be given after hemodialysis if the initial 0.5-g dose was given less than 6 h before dialysis [30,35].

Pharmacodynamics

The most important parameter for predicting the *in vivo* efficacy of all β -lactam antibiotics, including the carbapenems is the time that the plasma drug concentration is maintained above the MIC of the infecting organism ($T > \text{MIC}$) [11,14,30,38]. For most β -lactams the $T > \text{MIC}$ should be 50% or more of the dosing interval, whereas for the carbapenems a $T > \text{MIC}$ of 30% or more appears to be sufficient [11,14,30]. Following a 1-g dose of ertapenem administered intravenously, the total and free drug concentrations remain above the MIC_{90} of MSSA, *Streptococci* spp., enterobacteriaceae, *Moraxella catarrhalis*, *Haemophilus influenzae* and most anaerobes ($\leq 1 \text{ mg/l}$) for 24 and 8 h, respectively, which corresponds to 100 and 33% of the dosing interval [16,30,39].

The activity of ertapenem against *S. pneumoniae* isolates (MIC values between 0.015 and 4 mg/l) was assessed in a neutropenic murine thigh-infection model [38]. The overall decrease in bacterial density of the treated animals over 24 h ranged from 0.2 to 4.4 $\log_{10}$ colony-forming units per thigh [38]. The change in bacterial density was highly dependent on the MIC of the infecting isolate. The most pronounced and greatest bactericidal activity was observed against those isolates with MIC values of 2 mg/l or less, whereas the activity against isolates with a MIC of 4 mg/l was inconsistent; nevertheless, the overall survival was 93% during the 4 days of treatment and 3 days after therapy [38]. The results from this study also supported the suggestion that maximal bactericidal activity is observed when the $T > \text{MIC}_{\text{free}}$ is more than 30% of the dosing interval [11,38].

In vitro studies of the post antibiotic effects (PAEs) of ertapenem, imipenem and ceftriaxone have been conducted against Gram-positive and -negative bacteria [40]. After 2 h of antibiotic exposure to concentrations of ten-times the MIC, imipenem and ertapenem showed similar and longer PAEs against *S. aureus* compared with ceftriaxone (1.3, 1.5 and 0.9 h, respectively), whereas ceftriaxone demonstrated slightly longer PAEs against *S. pneumoniae* compared with the other two antibiotics (2.6 versus 2.4 h). Imipenem and ertapenem also demonstrated a short PAE (0.3 h) against *Enterobacter cloacae* [40]. All the antibiotics tested demonstrated negative or absent PAEs against Gram-negative bacteria. The mean PAE values for ertapenem were: -0.3 h against *E. coli* and no PAEs against *H. influenzae* [40].

Clinical trials

All of the clinical trials carried out have been prospective, multicenter (including USA and international sites), randomized, double-blind, comparative studies designed to show statistical equivalence (noninferiority) between ertapenem and an established comparator, unless otherwise stated. Statistical equivalence is defined by the two-sided 95% confidence interval (CI) for the difference in response rates (ertapenem minus comparator) [11,41–47]. The interval must contain zero and the lower limit can not be less than:

- -10% when the response rate of the comparator is 90% or less

- -15% when the comparator response rate is over 80% but less than 90%
- -20% for comparator response rates 70% or more but less than 80%.

Data from clinical trials are presented in TABLE 6.

Complicated intra-abdominal infection

In a Phase III trial, ertapenem 1 g, once daily was compared with piperacillin/tazobactam 3.375 g administered every 6 h, both infused intravenously for a period of 30 min [44]. The study also permitted the addition of vancomycin, at the discretion of the investigator if *Enterococcus* spp. or MRSA was isolated; this option was exercised in approximately 4% of the microbiologically evaluable patients in each of the treatment groups. The study included patients with a wide range of intra-abdominal infections (IAIs) that required operative or percutaneous procedures in addition to antibiotic therapy. A blinded expert review panel assessed the adequacy of surgical source control to identify failures due to inadequate surgical intervention rather than those due to antibiotic therapy. The patients were stratified based on their diagnosis (complicated appendicitis without generalized peritonitis or all other diagnoses) and the severity of illness (Acute Physiology and Chronic Health Evaluation II score ≥ 15). Approximately 60% of the microbiologically evaluable patients had perforated or abscessed appendicitis. The most common bacteria isolated from all the infections were *E. coli*, *Bacteroides fragilis*, *Bacteroides* spp. and *Clostridium* spp. and 335 out of 396 (84.6%) microbiologically evaluable patients had polymicrobial infections. Of the 633 patients randomized, only 396

(62.6%) were considered to be clinically and microbiologically evaluable. The cure rates (favorable clinical and microbiologic response) of this evaluable group, adjusted for stratum, were 176 out of 203 (86.7%) for the patients treated with ertapenem and 157 out of 193 (81.2%) for patients treated with piperacillin/tazobactam at the test of cure (TOC) assessment, which occurred 4 to 6 weeks after completion of antibiotic therapy. This is a 5.5% difference between the two groups with a 95% CI of -2.2 to 13.1%, indicating equivalence of the two therapies. In the subgroup analysis of the different types of infections in the microbiologically evaluable group, higher efficacy rates were reported for ertapenem versus piperacillin/tazobactam in patients with nonappendiceal infections (83.8 vs. 68.8%), generalized peritonitis (83.3 vs. 73.6%) and postoperative infection (75 vs. 40.9%).

A smaller clinical trial assessed the efficacy of ertapenem 1 or 1.5 g once daily (given intravenously) compared with ceftriaxone 2 g once daily (given intravenously) along with metronidazole 500 mg every 8 h for the treatment of complicated IAIs in adults [48]. An option to switch to oral ciprofloxacin plus metronidazole was allowed after a minimum of 3 full days of intravenous therapy. *E. coli* and *B. fragilis* were the most common bacteria isolated and the study found no significant difference in eradication rates between the patients receiving 1 or 1.5 g of ertapenem. At the TOC visit (4–6 weeks after the completion of intravenous and oral antibiotic therapy), favorable clinical and microbiologic results were reported in 26 out of 31 (84%) of the microbiologically evaluable patients in the 1-g cohort treated with ertapenem, 35 out of 41 (85%) treated with ceftriaxone and metronidazole, and 24 out of 29 (83%) in the 1.5-g cohort treated with ertapenem versus 24 out of 31 (77%) treated with

Table 5. Pharmacokinetic parameters of ertapenem versus comparators.

Drug	Intravenous dose (g)	C _{max} * (mg/l)	AUC* (mg.h/l)	t _{1/2} (h)	Vd* (l/kg)	% protein binding	% excreted unchanged	Dosing interval	Ref.
Ertapenem	1	154.9 (22.0)	572.1 (68.6)	3.8	8.2 (1.5)	92–98 [‡]	44	Once daily	[27]
Imipenem	0.5 1	30–35 60–70	42.2 186	1	0.23–0.31	20	60–70 (with cilastatin)	Three- to four-times daily	[1,94,95]
Meropenem	0.5 1	26 50–60	27.2–32.4 66.9–77.5	1	0.23–0.35	2	70	Three- to four-times daily	[95,96]
Piperacillin/tazobactam	3.375	242/24 [§]	253	0.7–1.2	16–19	30	70	Three- to four-times daily	[97,98]
Ceftriaxone	1	128.7 (14.8)	973.12 (120.61)	7.4	7–13*	83–96**	60	Once daily	[99–101]

*Mean or range with or without $\pm$ standard deviation.

[‡]Concentration dependent.

[§]Values are piperacillin and tazobactam, respectively.

AUC: Area under the concentration–time curve; C_{max}: Peak concentration reached in the plasma/serum; t_{1/2}: Half life; Vd: Volume of distribution.

Table 6. Results of clinical trials.

Author regimen	Number of patients randomized	Duration of parenteral treatment* (days)	Mean (range)	Test of cure (number of days post therapy)	% of patients with a favorable response (number of evaluable patients)			Ref.
					Clinical	Microbiologic	Clinical and microbiologic	
Complicated intra-abdominal infections								
Solomkin <i>et al.</i>	ERT 1 g od iv. P/T 3.375 g q 6 h iv.	633	7.6 (4–17) 7.8 (4–18)	28–42	n.d. n.d.	n.d. n.d.	87 (203) [§] 81 (193) [§]	[44]
Yellin <i>et al.</i>	ERT 1 g od iv. ^{‡§} CTX 2 g od + MTR 500 mg q 8 h iv. [‡]	114	4.9 5.1		n.d. n.d.	90 (31) 85 (41)	84 (31) [§] 85 (41) [§]	[48]
Acute pelvic infections								
Roy <i>et al.</i>	ERT 1 g od iv. P/T 3.375 g q 6 h iv.	412	4 [¶] (2–12) 4 [¶] (3–12)	14–28	94 (163) [§] 92 (153) [§]	94 (128) 94 (129)	n.d. n.d.	[42]
Complicated skin and skin-structure infections								
Graham <i>et al.</i>	ERT 1 g od iv. P/T 3.375 g q 6 h iv.	540	9.1 (3–16) 9.8 (3–18)	10–21	82 (185) [§] 84 (174) [§]	83 (155) 83 (151)	82 (155) 82 (151)	[41]
Complicated urinary tract infections								
Jimenez-Cruz <i>et al.</i>	ERT 1 g od iv. or im. [#] CTX 1 g od iv. or im. [#]	258	4.2 4.4	5–9	n.d. n.d.	86 (97) [§] 85 (53) [§]	86 (97) 85 (53)	[47]
Tomera <i>et al.</i>	ERT 1 g od iv. [#] CTX 1 g od iv. [#]	592	4.4 4.3		n.d. n.d.	92(159) [§] 93 (171) [§]	n.d. n.d.	[45]
Community-acquired pneumonia								
Ortiz-Ruiz <i>et al.</i>	ERT 1 g od iv. ^f CTX 1 g od iv. ^f	502	4 [¶] (2–17) 4 [¶] (2–14)	7–14	92 (182) [§] 91 (201) [§]	93 (96) 95 (113)	n.d. n.d.	[46]
Vetter <i>et al.</i>	ERT 1 g od iv. or im. ^{**} CTX 1 g od iv. or im. ^f	364	5.5 5.6		92 (182) [§] 94 (93) [§]	91 (100) 92 (49)	n.d. n.d.	[43]

*Applies to evaluable patients.

[‡]68% of the microbiologically evaluable patients in the ertapenem group and 61% of patients in the comparator group were switched to oral ciprofloxacin plus metronidazole after 3 days or more of parenteral therapy for a mean total duration of antimicrobial therapy of 8.8 and 8.3 days, respectively.[§]Primary efficacy variable.[¶]Median, not mean is reported.[#]Most microbiologically evaluable were switched to an oral antimicrobial (usually ciprofloxacin) after 3 days or more of parenteral therapy.^{**}Most clinically evaluable patients were switched to an oral antimicrobial (usually amoxicillin-clavulanate) after 3 days or more of parenteral therapy.

CTX: Ceftriaxone; ERT: Ertapenem; im.: Intramuscular; iv.: Intravenous; MTR: Metronidazole; n.d.: No data; od: Once daily; P/T: Piperacillin/tazobactam; q: Every. Adapted from [11].

comparator therapy. The overall microbiologic response rates were 90% for both cohorts treated with ertapenem, and for the patients that received comparator therapy, response rates were 85 and 87% in the 1- and 1.5-g cohorts, respectively. Although the study suggests similar efficacy rates between the two treatment groups, it was not large enough to prove statistical equivalence and only results from the 1-g ertapenem cohort are presented in TABLE 6.

Complicated skin & soft-structure infection

Ertapenem 1 g, administered once daily was compared with piperacillin/tazobactam 3.375 g every 6 h (both administered intravenously) for the treatment of skin and soft-tissue infections in adults [41]. Patients with underlying decubitus ulcers, diabetes mellitus or other neuropathic conditions were stratified from patients with all other infections, which were most commonly

abscesses, cellulitis and surgical-site infections. *S. aureus* was the most common bacterium isolated in the clinically evaluable patients (~40% in each treatment group). Polymicrobial infections accounted for approximately 40% of the clinically evaluable cases and one or more anaerobes were isolated from around 18% of the cases. The primary efficacy end point, a favorable clinical response (based on wound signs and symptoms), was determined at the TOC visit (10 to 21 days post therapy). Success rates in the clinically evaluable patients were reported for 82.4% of those treated with ertapenem and 84.4% of those treated with piperacillin/tazobactam, resulting in a -2.0% difference (95% CI adjusting for strata: -10.2–6.2%), demonstrating statistical equivalence. Bacterial eradication rates and number of patients reporting a favorable microbiologic and clinical response at the TOC visit (TABLE 6) were also similar in both treatment groups.

In an analysis of the subgroup of patients infected with MSSA from the above study, cure rates reported at the TOC visit for the ertapenem and piperacillin/tazobactam treatment groups were almost identical (80.6 vs. 80.9%) [49]. No demographic or clinical characteristics that consistently predicted monomicrobial versus polymicrobial infections could be identified, thereby suggesting the need for a broad-spectrum antibiotic when treating empirically.

Another subgroup analysis was performed for all patients in the original study that were managed by outpatient parenteral antimicrobial treatment (OPAT), which was allowed at the discretion of the investigator after at least 2 days of treatment in the hospital or infusion suite, and presuming the patient was stable [50]. Approximately 40% of all patients treated at the USA test sites received OPAT compared with only two out of 166 (1.2%) patients from Latin America test sites; for this reason, only data from the USA sites were analyzed. Although a larger proportion of patients with severe infection were treated as inpatients, the overall median duration of treatment for all evaluable patients treated as inpatients was shorter than that of those treated as outpatients (8 vs. 11 days, respectively). Cure rates among the evaluable patients treated with OPAT were 45 out of 54 (83.3%) patients treated with ertapenem versus 41 out of 50 (82%) patients treated with piperacillin/tazobactam.

Acute pelvic infection

In a study by Roy and colleagues, women aged 16 years or older diagnosed with an acute pelvic infection (PI) were stratified based on the type of infection (obstetric/postpartum versus gynecologic/postoperative) and then randomized to receive 1 g (intravenously) of ertapenem once daily or 3.375 g (intravenously) of piperacillin/tazobactam every 6 h [42]. Endomyometritis was the most common diagnosis in both treatment groups, comprising around 75% of patients. Approximately 60% of the bacteria isolated were anaerobes and around 72% of the microbiologically evaluable patients had polymicrobial infection. The primary efficacy end point, the clinical response to treatment, was assessed at the TOC visit (2–4 weeks post therapy). Favorable response rates were reported for 93.9% of

163 clinically evaluable patients treated with ertapenem and 91.5% of 153 evaluable patients treated with piperacillin/tazobactam (95% CI for the difference, adjusted for strata: -4.0–8.8%), indicating the statistical equivalence of the two treatment regimes.

Complicated urinary tract infections

Two large international studies comparing ertapenem and ceftriaxone, each administered as a 1-g dose once daily, for the treatment of complicated urinary tract infections (UTI) were conducted from 1998 to 2000 [45,47]. In a study by Jimenez-Cruz, intramuscular injections were permitted after at least one intravenous dose of the study antibiotic [47]. Both studies allowed a switch to oral therapy (most frequently to ciprofloxacin) after a minimum of 3 days of parenteral therapy, as long as the patient had improved clinically. Patients were stratified into two groups according to their diagnosis; one stratum consisted of patients with acute pyelonephritis and the other comprised patients with all other complicated UTIs without pyelonephritis, which includes diagnoses of UTI in men, or those associated with obstruction, foreign bodies or urologic abnormalities. The most common pathogens isolated were *E. coli* and *K. pneumoniae*. Bacterial eradication rates were assessed at the TOC visit (5–7 days after parenteral and oral treatment was completed) as the primary efficacy end point. In the microbiologically evaluable patients, a favorable microbiologic response was reported in one study for 85.6% of the patients treated with ertapenem versus 84.9% of those treated with ceftriaxone, resulting in a 0.6% difference, adjusting for strata (95% CI: -12.9–14.1%) [47], and in the other study rates of 91.8 versus 93.0% (95% CI, adjusting for strata: -7.6–5.1%) were reported for ertapenem- and ceftriaxone-treated patients, respectively [45]. In a combined analysis of the two studies, recurrence rates at the late follow-up visit (4–6 weeks post therapy) were found to be similar in both treatment groups (8.9% in the ertapenem group and 7.6% in the ceftriaxone group) [51]. Response rates of subgroups based on stratum and severity of disease were also similar between the two treatment groups [51].

Community-acquired pneumonia

In two large, well-designed trials, ertapenem was compared with ceftriaxone (each given as a 1-g dose once daily) for the treatment of community-acquired pneumonia (CAP) in adults [43,46]. Both studies allowed a step down to oral therapy (generally to amoxicillin/clavulanate) if the patient improved clinically after a minimum of 3 days of parenteral therapy. The studies were designed to minimize inclusion of patients with atypical pneumonia by requiring special conditions to be met for patients under 40 years old and excluding patients with a positive urine test for legionella antigen. Patients were stratified into four groups based on age (≤ 65 or > 65) and severity of illness (pneumonia severity index of ≤ 3 or > 3). The first study randomized 502 patients in a 1:1 ratio to receive either ertapenem or ceftriaxone, and all doses of the study antibiotic were

administered intravenously [46]. Clinical and microbiologic cure rates in the evaluable patients at 7 to 14 days post therapy (TOC) in the ertapenem group were 92.3 and 92.7%, respectively, versus 91.0 and 94.7% in patients treated with ceftriaxone. The most frequently isolated pathogens were *S. pneumoniae*, followed by *M. catarrhalis* and *H. influenzae*.

In the second trial, 364 patients were randomized in a 2:1 ratio in favor of ertapenem over ceftriaxone, and investigators had the option of administering either study antibiotic intramuscularly after at least one intravenous dose [43]. At the TOC visit, clinical cure rates reported for the ertapenem and ceftriaxone treatment groups were 92.3 and 93.6%, respectively (95% CI, adjusting for strata: -8.6–5.7%). Favorable microbiologic assessments were reported in 91 versus 91.8% of patients treated with ertapenem and ceftriaxone, respectively. *S. pneumoniae*, followed by *H. influenzae*, *M. catarrhalis* and *S. aureus* were the most frequently isolated pathogens.

A combined analysis of the above two trials demonstrated higher cure rates at the completion of parenteral therapy (95.2 vs. 94.4%) for ertapenem- and ceftriaxone-treated patients, respectively, compared at the TOC visit (92.0 vs. 91.9%) [52]. It was also revealed that approximately 88% of the clinically evaluable patients were switched to oral therapy, which in 92.9% of cases was amoxicillin/clavulanate. A subgroup analysis of data from patients aged 65 years or over who participated in the above two trials found ertapenem and ceftriaxone to be equally effective in the treatment of CAP in the elderly [53]. At the TOC visit, cure rates were reported for 139 out of 148 (93.9%) clinically evaluable patients in the ertapenem group and 113 out of 125 (90.4%) of those in the ceftriaxone group. Favorable microbiologic response rates reported for each treatment group were both more than 90%. In patients aged 75 years or over, ertapenem was actually shown to be superior to ceftriaxone for the treatment of CAP; cure rates at the TOC assessment were 94 versus 87.3% for the ertapenem- and ceftriaxone-treated patients, respectively.

Subgroup & combined analyses

Enterococcus spp.

The impact of the presence or absence of *Enterococcus* spp. on patient outcome was examined in a combined analysis of patients enrolled in three well-designed trials that compared ertapenem and piperacillin/tazobactam for the treatment of various infections [54]. *Enterococcus* spp. was isolated from 223 out of 1558 patients (14.3%) being treated for complicated IAI, acute PI or complicated skin and skin-structure infection (CSSSI); specifically, 125 out of 623 (20%) patients with IAI, 28 out of 529 (5.3%) with CSSSI and 70 out of 406 (17.2%) with PI had enterococcus present in their initial cultures. Piperacillin/tazobactam is considered to have activity against most enterococci, whereas ertapenem has limited activity. Susceptibility testing of enterococci isolated from the clinical trials demonstrated susceptibility of 27% of 220 enterococci isolates to ertapenem, whereas the susceptibility of 218 isolates tested with piperacillin/tazobactam was 90%. Only 60% of

Enterococcus spp. isolates were identified to the level of species, of which 40% were *Enterococcus faecalis* and 8% were *E. faecium*. Polymicrobial infections that included *Enterococcus* spp. were reported in 96% of patients with IAI, and 86% of patients with CSSSI and PI.

In the analysis of microbiologically evaluable patients with and without *Enterococcus* spp., the choice of therapy – ertapenem versus piperacillin/tazobactam – did not have any effect on the cure rates in any of the three trials, but the overall response to both therapies in evaluable patients with IAI was demonstrated to be significantly lower in patients with *Enterococcus* spp. compared with those without. This trend was also seen in patients with CSSSI, but the numbers of evaluable patients with enterococcal infections were too low to be analyzed statistically [54]. In contrast, clinical response rates for patients with PI were slightly higher in the presence versus the absence of *Enterococcus* spp., and patients with moderate infection were more likely than those with severe infection to have *Enterococcus* spp. isolated at enrollment. The authors concluded that:

“these findings suggest that in polymicrobial IAI and PI, enterococci is colonizing the site of infection, rather than causing invasive disease”

Therefore specific therapy directed at *Enterococcus* spp. is unnecessary in immunocompetent hosts [54].

Polymicrobial infections

The efficacy of ertapenem versus piperacillin/tazobactam in the treatment of polymicrobial infections was assessed in a combined subgroup analysis of data from three large clinical trials, which included patients with IAI, PI and CSSSI [55]. Polymicrobial infections were identified in 790 of the 1558 patients (50.7%) treated. *E. coli* and members of the *B. fragilis* group were the most common pathogens isolated from patients with IAI, whereas *S. aureus* and peptostreptococci were predominant in CSSSI, and peptostreptococci, enterococci and *E. coli* in PI. Favorable response rates for evaluable patients with polymicrobial infections treated with ertapenem or piperacillin/tazobactam were similar in all three trials, and the reported cure rates by treatment group were 85.6 and 82.5% in IAI, 80.3 and 78.7% in CSSSI and 95.7 and 92.6% in PI.

Enterobacteriaceae

Gesser and colleagues reviewed the efficacy of ertapenem in the treatment of infections caused by enterobacteriaceae in an analysis of data from seven clinical trials comparing ertapenem with ceftriaxone or piperacillin/tazobactam for the treatment of patients with CSSSI, PI, IAI, complicated UTI and CAP [56]. Infections with enterobacteriaceae accounted for 1167 out of 3255 (35.9%) of all the patients treated in the seven trials and 65.3% of the enterobacteriaceae isolated were *E. coli*. Polymicrobial infections involving enterobacteriaceae accounted for over 75% of infections in evaluable patients with IAI, CSSSI and PI, but were much less common

in patients with CAP and complicated UTI (37 and 3%, respectively). Ertapenem was demonstrated to be equivalent to piperacillin/tazobactam for the treatment of enterobacteriaceae infections in patients with IAI, PI and CSSSI based on clinical response rates of 84.8 and 82.8%, resulting in a 95% CI of -4.9 to 8.9%. Favorable microbiologic outcomes in patients with complicated UTI were reported in 90.5 versus 92% of those treated with ertapenem versus ceftriaxone, respectively (95% CI: -7.1–4.1%).

Overall bacterial eradication rates of enterobacteriaceae were approximately 90% in both ertapenem and comparator groups and none of the 77 patients who had a Gram-negative enteric isolated in their bloodstream had persistent bacteremia at the end of treatment [56]. The development of resistance to ertapenem was not reported in any of the enterobacteriaceae isolated from patients treated with this antibiotic; however, two persistent bacteria (*Citrobacter freundii* and *E. coli*) isolated from patients being treated for a complicated UTI developed resistance to ceftriaxone. Resistance to ciprofloxacin in patients with complicated UTI who were switched to oral therapy was also reported for five *E. coli* and two *K. pneumoniae* isolates in patients originally treated with ertapenem and for three *E. coli* and one *Proteus mirabilis* isolate in patients treated with ceftriaxone. Ertapenem was recently reported to demonstrate excellent clinical utility in treating a variety of infections (bacteremia, pneumonia, soft-tissue abscesses, peritonitis and complicated and uncomplicated UTI) caused by ESBL-producing organisms including *K. pneumoniae*, *E. coli* and *E. cloacae* [57].

Adverse effects

During Phase II and III clinical trials, adverse events (AEs) were monitored daily during treatment and up to 14 days after completion of therapy [41–48,58]. AEs were graded according to their severity and the probability of being related to study therapy. In a pooled analysis of data from Phase II and III trials, the percentage of patients treated with ertapenem, piperacillin/tazobactam and ceftriaxone that experienced one or more clinical AE (possibly, probably or definitely related to antimicrobial therapy) were 23.2, 23.3 and 26.9%, respectively [58]. The most common AEs reported with ertapenem and comparators were diarrhea, infused-vein complications, nausea and headache (TABLE 7) [58]. The incidence of these AEs were similar between ertapenem and the comparators, with most AEs rated mild to moderate [58]. Discontinuation of ertapenem due to a clinical AE occurred in 1.2% of patients due to rash or gastrointestinal disturbances [58].

The incidence of drug-related seizures reported with ertapenem, piperacillin/tazobactam and ceftriaxone were 0.2 (three cases), 0.3 (two cases) and 0.0%, respectively. In all five cases, the patients had an underlying neurologic disease or a pre-existing seizure disorder [58]. Pseudomembranous colitis or *C. difficile*-associated diarrhea has been reported in

Table 7. Adverse effects of ertapenem versus comparators.

Adverse effect	Ertapenem* [‡]	Piperacillin/tazobactam*	Ceftriaxone* [§]
Diarrhea	5.0 (10.3)	7.0 (12.1)	5.9 (9.8)
Infused vein complication	4.5 (7.1)	5.5 (7.9)	4.6 (6.7)
Nausea	2.5 (8.5)	3.4 (8.7)	3.3 (7.4)
Headache	1.9 (5.6)	1.2 (5.4)	2.3 (6.9)
Phlebitis/thrombophlebitis	1.6 (1.9)	1.3 (2.7)	1.5 (2.0)
Pruritus	1.2 (2.0)	1.2 (2.6)	1.0 (1.9)
Rash	1.1 (2.5)	1.8 (3.1)	0.6 (1.5)
Abdominal pain	0.7 (3.6)	0.5 (4.8)	1.3 (3.9)
Vomiting	0.9 (3.7)	1.7 (5.3)	1.2 (4.0)
Oral candidiasis	0.1 (0.1)	1.2 (1.3)	1.4 (1.9)
Vaginitis	0.9 (1.4)	0.7 (1.0)	3.5 (3.7)

Incidence (%) of adverse effects reported during study therapy and 14 days follow-up in 1% or more of patients enrolled in Phase II and Phase III trials who received one or more doses of study therapy and were judged by the investigator to be possibly, probably or definitely related to study therapy and in parentheses, those reported "irrespective of relationship to study therapy".

Adapted from [58].

*Includes results from Phase IIb/III complicated intra-abdominal infections, complicated skin and soft-tissue infections and acute pelvic infection trials.

[‡]Includes results from Phase IIa trials, and Phase IIb/III community-acquired pneumonia, complicated urinary tract and im tolerability trials. Most patients in these trials were switched to an oral antimicrobial after 3 days or more (2 days in the intramuscular tolerability trial). The most commonly used oral therapies were amoxicillin-clavulanate and ciprofloxacin (plus metronidazole in the Phase IIa intra-abdominal infection trial).

[§]Patients in the ceftriaxone study group of the Phase IIa IAI trial also received intravenous metronidazole.

0.3% of 1866 patients treated with ertapenem. Overall mortality rates were 1.8% in patients treated with ertapenem, 1.5% in those treated with piperacillin/tazobactam and 1.6% in ceftriaxone-treated patients. None of the deaths that occurred during the clinical trials or during the 14 days following treatment were attributed to drug therapy. In a Phase I study, investigators studied the effects of ertapenem on corrected QT (QTc) intervals. QTc intervals were measured before a single 2-g dose of ertapenem in 20 healthy subjects and 0.5 and 1.5 h after the beginning of the intravenous infusion; these values were then compared with ones obtained from four subjects who received placebo infusions of saline. There were no statistically significant differences observed between pre- and postdose values in the ertapenem group or between the two test groups.

Laboratory adverse effects occurring during study therapy or in the 14-day follow-up period were reported in 13.8, 15 and 11.5% of patients treated with ertapenem,

piperacillin/tazobactam and ceftriaxone, respectively [58]. The most common laboratory AEs observed with ertapenem and comparator agents were transient, mild-to-moderate increases in aminotransferases [58]. Increases in aminotransferase enzymes were more frequently reported for Hispanic patients than white or black patients, which was similar for ertapenem and other comparator studies [58]. In all patients, aminotransferases returned to normal in post-therapy follow-up [58]. Drug-related neutropenia was infrequently reported with ertapenem, piperacillin/tazobactam and ceftriaxone [58]. Discontinuation of therapy due to drug-related laboratory AEs occurred in 0.2, 0.4 and 0.1% of patients, respectively.

In a comparison of intramuscular administration of ertapenem and ceftriaxone, ertapenem was well tolerated [59]. Tolerability and safety profiles were similar between the two agents [59]. The most common local injection site AEs were tenderness and pain. Classification of patients based on gender, age (<65 vs. $\geq$ 65 years), renal function or concomitant therapy did not result in any significant changes in the AE profile of ertapenem [58].

Drug interactions

In vitro studies have shown ertapenem is not a substrate for cytochrome P450 isozymes or P-glycoprotein, and therefore it is not expected to have any drug interactions due to the involvement of these enzymes [35]. To date, the only drug interaction trial performed evaluated the interaction between ertapenem and probenecid [30]. Probenecid was found to decrease the renal clearance of ertapenem by inhibiting active renal tubular secretion with the ertapenem half-life only increasing slightly, from 4.0 to 4.8 h [30,35].

Pharmacoeconomics

Several factors beyond the acquisition cost need to be considered when evaluating the cost of antimicrobial therapy. In addition to the acquisition cost of parenteral antibiotic treatment, the cost of admixture and preparation, ancillary materials and personnel time (e.g., nurse, technician or pharmacist) need to be considered. Other considerations, including the cost associated with maintaining intravenous access, waste disposal and therapeutic monitoring, should also be considered [60]. Antibiotics that are administered once daily, such as ertapenem and ceftriaxone, are advantageous over agents that are given as multiple intermittent doses during the day (e.g., imipenem, meropenem or piperacillin/tazobactam) [60,61]. However, ertapenem, unlike ceftriaxone, has good activity against many clinically important anaerobic bacteria and can therefore be administered as a single entity for the treatment of mixed aerobic/anaerobic infections [61]. Once-daily administration of a single antimicrobial is more convenient for hospital staff and patients, and may decrease the risk of missed doses and other medication errors [48,61,62]. Considering these advantages, as well as the option of intravenous or intramuscular administration, ertapenem is an excellent choice, not only for community-acquired infections

in hospitalized patients, but also for OPAT [61]. Decreasing the length of stay through the use of OPAT may reduce healthcare-associated costs, decrease the risk of nosocomial infections and increase patient satisfaction. The cost-avoidance or savings of OPAT programs have been documented previously [102,103]. When compared with antibiotics used in OPAT programs, ertapenem's safety and efficacy profile is similar [61].

The pharmacokinetic and chemical characteristics allow ertapenem to be delivered by many different OPAT models, but would require same-day preparation of the solution due to stability issues according to the product monograph [61]. Overall, Tice and colleagues concluded that ertapenem would be a good addition to the current arsenal of OPAT antimicrobials, especially as new indications for its use are discovered [61].

Expert opinion & five-year view

Ertapenem is a new carbapenem developed to address the pharmacokinetic shortcomings of imipenem and meropenem. Ertapenem shares similar structural features with meropenem, including its stability to DHP-1, allowing it to be administered without a DHP-1 inhibitor. Ertapenem demonstrates broad-spectrum antimicrobial activity against many Gram-positive and -negative aerobes and anaerobes and is resistant to nearly all β -lactamases including ESBLs and AmpCs. It demonstrates limited activity against *Enterococcus* spp., *P. aeruginosa* and other nonfermentative Gram-negative bacteria commonly associated with nosocomial infections. Extensive protein binding of ertapenem extends the half-life and allows for once-daily dosing. Prospective, multicenter, randomized, double-blind, comparative clinical studies demonstrate similar clinical efficacy of ertapenem compared with other agents. Clinical trials of complicated IAI, acute PI, CSSSI, CAP and complicated UTI, demonstrated that ertapenem has equivalent efficacy and safety compared with ceftriaxone and piperacillin/tazobactam.

Ertapenem appears to be a promising new carbapenem with excellent efficacy and safety for the treatment of a variety of community-acquired infections. It may also prove to be of great value in the emergency-room setting, as well as for outpatient parenteral antimicrobial therapy. Ertapenem represents a new group of carbapenems. Imipenem and meropenem represent carbapenems suitable for nosocomial infections, whereas ertapenem is suitable for community-acquired infections. Ertapenem is challenging the traditional view of carbapenems as agents to be used as a last resort [7]. Limiting the use of ertapenem in this manner precludes its usage in the group of patients most likely to benefit. Ertapenem should not be used for nosocomial infections.

Several key issues with ertapenem need to be resolved including:

- Will the preferential use of ertapenem versus imipenem and meropenem for the treatment of community-acquired infection reduce the selective pressure on *Enterococcus* spp., *P. aeruginosa* and other nonfermentative Gram-negative bacteria commonly associated with nosocomial infections, resulting in reduced superinfections caused by these organisms and/or reductions in resistance of these organisms to imipenem and meropenem?

- Will the equivalent efficacy and safety of ertapenem compared with piperacillin/tazobactam, but with the advantage of once-daily dosing make ertapenem a preferred agent to use for community-acquired infections in place of piperacillin/tazobactam?
 - And will the excellent efficacy and safety of ertapenem make this agent the preferred antibiotic in place of ceftriaxone for outpatient parenteral antimicrobial therapy?
- These questions remain to be answered in the future.

Key issues

- Ertapenem is a new carbapenem developed to address the pharmacokinetic shortcomings of imipenem and meropenem.
- Ertapenem, like imipenem and meropenem, has very broad-spectrum activity, but demonstrates limited activity against *Enterococcus* spp. and *Pseudomonas aeruginosa*.
- Ertapenem has a long half life, allowing once-daily dosing.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- Norrby SR. Carbapenems. *Med. Clin. North Am.* 79, 745–759 (1995).
- Moellering RC Jr, Eliopoulos GM, Sentochnik DE. The carbapenems: new broad spectrum β -lactam antibiotics. *J. Antimicrob. Chemother.* 24(Suppl. A), 1–7 (1989).
- Balfour JA, Bryson HM, Brogden RN. Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 51, 99–136 (1996).
- Bonfiglio G, Russo G, Nicoletti G. Recent developments in carbapenems. *Expert Opin. Investig. Drugs* 11(4), 529–544 (2002).
- Ayalew K, Nambiar S, Yasinskaya Y, Jantusch BA. Carbapenems in pediatrics. *Ther. Drug Monit.* 25, 593–599 (2003).
- Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Saf.* 15, 87–90 (1996).
- Shah PM, Isaacs RD. Ertapenem, the first of a new group of carbapenems. *J. Antimicrob. Chemother.* 52, 538–542 (2003).
- Thorough review of ertapenem.
- Edwards JR, Turner PJ. Laboratory data which differentiate meropenem and imipenem. *Scand. J. Infect. Dis. Suppl.* 96, 5–10 (1995).
- Edwards JR, Betts MJ. Carbapenems: the pinnacle of the β -lactam antibiotics or room for improvement? *J. Antimicrob. Chemother.* 45, 1–4 (2000).
- Cunha BA. Ertapenem. A review of its microbiologic, pharmacokinetic and clinical aspects. *Drugs Today (Barc)* 38, 195–213 (2002).
- Curran M, Simpson D, Perry C. Ertapenem: a review of its use in the management of bacterial infections. *Drugs* 63, 1855–1878 (2003).
- Hammond ML. Ertapenem: a group 1 carbapenem with distinct antibacterial and pharmacological properties. *J. Antimicrob. Chemother.* 53, II7–II9 (2004).
- Goldstein EJ, Snyderman DR. Intra-abdominal infections: review of the bacteriology, antimicrobial susceptibility and the role of ertapenem in their therapy. *J. Antimicrob. Chemother.* 53, II29–II36 (2004).
- Mouton JW, Touzw DJ, Horrevorts AM, Vinks AA. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin. Pharmacokinet.* 39, 185–201 (2000).
- Fukasawa M, Sumita Y, Harabe ET *et al.* Stability of meropenem and effect of 1 β -methyl substitution on its stability in the presence of renal dehydropeptidase I. *Antimicrob. Agents Chemother.* 36, 1577–1579 (1992).
- Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. *J. Antimicrob. Chemother.* 52, 331–344 (2003).
- Excellent review of the properties of ertapenem.
- Kohler J, Dorso KL, Young K *et al.* *In vitro* activities of the potent, broad-spectrum carbapenem MK-0826 (L-749, 345) against broad-spectrum β -lactamase- and extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli* clinical isolates. *Antimicrob. Agents Chemother.* 43, 1170–1176 (1999).
- Odenholt I. Ertapenem: a new carbapenem. *Expert Opin. Investig. Drugs* 10(6), 1157–1166 (2001).
- Coudron PE, Hanson ND, Climo MW. Occurrence of extended-spectrum and AmpC β -lactamases in bloodstream isolates of *Klebsiella pneumoniae*: isolates harbor plasmid-mediated FOX-5 and ACT-1 AmpC β -lactamases. *J. Clin. Microbiol.* 41, 772–777 (2003).
- Jacoby G, Han P, Tran J. Comparative *in vitro* activities of carbapenem L-749, 345 and other antimicrobials against multiresistant gram-negative clinical pathogens. *Antimicrob. Agents Chemother.* 41, 1830–1831 (1997).
- Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus enterobacteriaceae with potent β -lactamases. *Antimicrob. Agents Chemother.* 45, 2831–2837 (2001).
- Kohler J, Young K, Painter RE, Innumerable JA, Silver LL. Ertapenem resistance selection in *Pseudomonas aeruginosa*. *Proceedings of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Chicago, IL, USA, 16–19 December 2001 (Abstract C1-1518).
- Friedland L, Harm S, Stinson L, Gallagher D. *Pseudomonas aeruginosa* resistance to imipenem (IMI), ertapenem (ETP) and other antibiotics: results of a multicenter ICU study. *Proceedings of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Chicago, IL, USA, 16–19 December 2001 (Abstract E-805).
- Jacoby GA, Mills DM, Chow N. Role of β -lactamases and porins in resistance to ertapenem and other β -lactams in *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* 48, 3203–3206 (2004).
- Wexler HM. *In vitro* activity of ertapenem: review of recent studies. *J. Antimicrob. Chemother.* 53(Suppl. 2), II11–II21 (2004).
- Livermore DM, Alexander S, Marsden B *et al.* Activity of ertapenem against *Neisseria gonorrhoeae*. *J. Antimicrob. Chemother.* 53, 280–281 (2004).

- 27 Majumdar AK, Musson DG, Birk KL *et al.* Pharmacokinetics of ertapenem in healthy young volunteers. *Antimicrob. Agents Chemother.* 46, 3506–3511 (2002).
- 28 Musson DG, Majumdar A, Birk K *et al.* Pharmacokinetics of intramuscularly administered ertapenem. *Antimicrob. Agents Chemother.* 47, 1732–1735 (2003).
- 29 Musson DG, Majumdar A, Holland S *et al.* Pharmacokinetics of total and unbound ertapenem in healthy elderly subjects. *Antimicrob. Agents Chemother.* 48, 521–524 (2004).
- 30 Nix DE, Majumdar AK, DiNubile MJ. Pharmacokinetics and pharmacodynamics of ertapenem: an overview for clinicians. *J. Antimicrob. Chemother.* 53, II23–II28 (2004).
- 31 Sundelof JG, Hajdu R, Gill CJ, Thompson R, Rosen H, Kropp H. Pharmacokinetics of L-749, 345, a long-acting carbapenem antibiotic, in primates. *Antimicrob. Agents Chemother.* 41, 1743–1748 (1997).
- 32 Kiem S, Craig WA. Inhibitory activity of ertapenem in human serum and 5% albumin in broth. *Proceedings of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*. San Diego, CA, USA, 27–30 September 2002 (Abstract A-493).
- 33 Laethem T, De Lepeleire I, McCrea J *et al.* Tissue penetration by ertapenem, a parenteral carbapenem administered once daily, in suction-induced skin blister fluid in healthy young volunteers. *Antimicrob. Agents Chemother.* 47, 1439–1442 (2003).
- 34 Cottagnoud P, Pfister M, Cottagnoud M, Acosta F, Tauber MG. Activities of ertapenem, a new long-acting carbapenem, against penicillin-sensitive or -resistant pneumococci in experimental meningitis. *Antimicrob. Agents Chemother.* 47, 1943–1947 (2003).
- 35 Invanz[®] product monograph. Merck Frosst Canada & Company, Quebec, Canada (2003).
- 36 Wong BK, Sahly Y, Mistry G *et al.* Comparative disposition of [14C] ertapenem, a novel carbapenem antibiotic, in rat, monkey and man. *Xenobiotica* 34, 379–389 (2004).
- 37 Pletz MWR, Rau M, Bulitta J *et al.* Ertapenem pharmacokinetics and impact on intestinal microflora in comparison to those of ceftriaxone after multiple dosing in male and female volunteers. *Antimicrob. Agents Chemother.* 48, 3765–3772 (2004).
- 38 Xuan D, Banevicius M, Capitano B, Kim MK, Nightingale C, Nicolau D. Pharmacodynamic assessment of ertapenem (MK-0826) against *Streptococcus pneumoniae* in a murine neutropenic thigh infection model. *Antimicrob. Agents Chemother.* 46, 2990–2995 (2002).
- 39 Friedland I, Mixson LA, Majumdar A, Motyl M, Woods GL. *In vitro* activity of ertapenem against common clinical isolates in relation to human pharmacokinetics. *J. Chemother.* 14, 483–491 (2002).
- 40 Odenholt I, Lowdin E, Cars O. *In vitro* pharmacodynamic studies of L-749, 345 in comparison with imipenem and ceftriaxone against gram-positive and gram-negative bacteria. *Antimicrob. Agents Chemother.* 42, 2365–2370 (1998).
- 41 Graham DR, Lucasti C, Malafaia O *et al.* Ertapenem once daily versus piperacillin-tazobactam four-times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. *Clin. Infect. Dis.* 34, 1460–1468 (2002).
- 42 Roy S, Higareda I, Angel-Muller E *et al.* Ertapenem once a day versus piperacillin-tazobactam every 6 hours for treatment of acute pelvic infections: a prospective, multicenter, randomized, double-blind study. *Infect. Dis. Obstet. Gynecol.* 11, 27–37 (2003).
- 43 Vetter N, Cambroner-Hernandez E, Rohlf J *et al.* A prospective, randomized, double-blind multicenter comparison of parenteral ertapenem and ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia. *Clin. Ther.* 24, 1770–1785 (2002).
- 44 Solomkin JS, Yellin AE, Rotstein OD *et al.* Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double-blind, randomized comparative phase III trial. *Ann. Surg.* 237, 235–245 (2003).
- Demonstrates the efficacy of ertapenem in complicated intra-abdominal infections.
- 45 Tomera KM, Burdman EA, Reyna OG *et al.* Ertapenem versus ceftriaxone followed by appropriate oral therapy for treatment of complicated urinary tract infections in adults: results of a prospective, randomized, double-blind multicenter study. *Antimicrob. Agents Chemother.* 46, 2895–2900 (2002).
- 46 Ortiz-Ruiz G, Caballero-Lopez J, Friedland IR, Woods GL, Carides A. A study evaluating the efficacy, safety, and tolerability of ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults. *Clin. Infect. Dis.* 34, 1076–1083 (2002).
- 47 Jimenez-Cruz F, Jasovich A, Cajigas J *et al.* A prospective, multicenter, randomized, double-blind study comparing ertapenem and ceftriaxone followed by appropriate oral therapy for complicated urinary tract infections in adults. *Urology* 60, 16–22 (2002).
- 48 Yellin AE, Hassett JM, Fernandez A *et al.* Ertapenem monotherapy versus combination therapy with ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections in adults. *Int. J. Antimicrob. Agents* 20, 165–173 (2002).
- 49 Gesser RM, McCarroll KA, Woods GL. Efficacy of ertapenem against methicillin-susceptible *Staphylococcus aureus* in complicated skin/skin structure infections: results of a double-blind clinical trial versus piperacillin-tazobactam. *Int. J. Antimicrob. Agents* 23, 235–239 (2004).
- 50 Gesser RM, McCarroll KA, Woods GL. Evaluation of outpatient treatment with ertapenem in a double blind controlled clinical trial of complicated skin/skin structure infections. *J. Infect.* 48, 32–38 (2004).
- Demonstrates the efficacy of ertapenem in complicated skin-structure infections.
- 51 Wells WG, Woods GL, Jiang Q, Gesser RM. Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy. *J. Antimicrob. Chemother.* 53(Suppl. 2), II67–II74 (2004).
- 52 Ortiz-Ruiz G, Vetter N, Isaacs R, Carides A, Woods GL, Friedland I. Ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults: combined analysis of two multicentre randomized, double-blind studies. *J. Antimicrob. Chemother.* 53(Suppl. 2), II59–II66 (2004).
- 53 Woods GL, Isaacs RD, McCarroll KA, Friedland IR. Ertapenem therapy for community-acquired pneumonia in the elderly. *J. Am. Geriatr. Soc.* 51, 1526–1532 (2003).
- 54 Teppler H, McCarroll K, Gesser RM, Woods GL. Surgical infections with enterococcus: outcome in patients treated

- with ertapenem versus piperacillin-tazobactam. *Surg. Infect. (Larchmt)* 3, 337-349 (2002).
- 55 Solomkin J, Tepler H, Graham DR et al. Treatment of polymicrobial infections: post hoc analysis of three trials comparing ertapenem and piperacillin-tazobactam. *J. Antimicrob. Chemother.* 53(Suppl. 2), II51-II57 (2004).
- 56 Gesser RM, McCarroll K, Tepler H, Woods GL. Efficacy of ertapenem in the treatment of serious infections caused by enterobacteriaceae: analysis of pooled clinical trial data. *J. Antimicrob. Chemother.* 51, 1253-1260 (2003).
- 57 Munoz LS, Hovsepian M, Snyderman DR et al. Ertapenem for the treatment of extended spectrum β -lactamase (ESBL) producing organisms. *Proceedings of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC, WA, USA, 30 October-2 November 2004 (Abstract K-1591).
- 58 Tepler H, Gesser RM, Friedland IR et al. Safety and tolerability of ertapenem. *J. Antimicrob. Chemother.* 53(Suppl 2), II75-II81 (2004).
- 59 Legua P, Lema J, Moll J, Jiang Q, Woods G, Friedland I. Safety and local tolerability of intramuscularly administered ertapenem diluted in lidocaine: a prospective, randomized, double-blind study versus intramuscular ceftriaxone. *Clin. Ther.* 24, 434-444 (2002).
- 60 Hotchkies L, Grima DT, Hedayati S. The total process cost of parenteral antibiotic therapy: beyond drug acquisition cost. *Clin. Ther.* 18, 716-725 (1996).
- 61 Tice AD. Ertapenem: a new opportunity for outpatient parenteral antimicrobial therapy. *J. Antimicrob. Chemother.* 53, II83-II86 (2004).
- 62 Tellado J, Woods GL, Gesser R, McCarroll K, Tepler H. Ertapenem versus piperacillin-tazobactam for treatment of mixed anaerobic complicated intra-abdominal, complicated skin and skin structure, and acute pelvic infections. *Surg. Infect. (Larchmt)* 3, 303-314 (2002).
- 63 National Committee for Clinical Laboratory Standards. *Methods For Dilution Antimicrobial Susceptibility Tests For Bacteria That Grow Aerobically: MIC Testing Supplemental Tables (6th Edition)*. National Committee for Clinical Laboratory Standards, PA, USA (2003).
- 64 Pankuch GA, Davies TA, Jacobs MR, Appelbaum PC. Antipneumococcal activity of ertapenem (MK-0826) compared with those of other agents. *Antimicrob. Agents Chemother.* 46, 42-46 (2002).
- 65 Hicks PS, Pelak B, Woods GL, Bartizal KE, Motyl M. Comparative *in vitro* activity of ertapenem against bacterial pathogens isolated from patients with lower respiratory tract infections. *Clin. Microbiol. Infect.* 8, 753-757 (2002).
- 66 Hilliard NJ, Johnson CN, Armstrong SH, Quarles S, Waites KB. *In vitro* activity of ertapenem (MK-0826) against multidrug resistant *Streptococcus pneumoniae* compared with 13 other antimicrobials. *Int. J. Antimicrob. Agents* 20, 136-140 (2002).
- 67 Pelak BA, Woods GL, Tepler H, Friedland I, Bartizal K, Motyl M. Comparative *in vitro* activities of ertapenem against aerobic bacterial pathogens isolated from patients with complicated intra-abdominal infections. *J. Chemother.* 14, 227-233 (2002).
- 68 Pelak BA, Bartizal K, Woods GL, Gesser RM, Motyl M. Comparative *in vitro* activities of ertapenem against aerobic and facultative bacterial pathogens from patients with complicated skin and skin structure infections. *Diagn. Microbiol. Infect. Dis.* 43, 129-133 (2002).
- 69 Pelak BA, Citron DM, Motyl M, Goldstein EJ, Woods GL, Tepler H. Comparative *in vitro* activities of ertapenem against bacterial pathogens from patients with acute pelvic infection. *J. Antimicrob. Chemother.* 50, 735-741 (2002).
- 70 Fuchs PC, Barry AL, Brown SD. *In vitro* antimicrobial activity of a carbapenem, MK-0826 (L-749, 345) and provisional interpretive criteria for disc tests. *J. Antimicrob. Chemother.* 43, 703-706 (1999).
- 71 Rolston KV, LeBlanc BM, Streeter H, Ho DH. *In vitro* activity of ertapenem against bacterial isolates from cancer patients. *Diagn. Microbiol. Infect. Dis.* 43, 219-223 (2002).
- 72 Livermore DM, Carter MW, Bagel S et al. *In vitro* activities of ertapenem (MK-0826) against recent clinical bacteria collected in Europe and Australia. *Antimicrob. Agents Chemother.* 45, 1860-1867 (2001).
- 73 Fuchs PC, Barry AL, Brown SD. *In vitro* activities of ertapenem (MK-0826) against clinical bacterial isolates from 11 North American medical centers. *Antimicrob. Agents Chemother.* 45, 1915-1918 (2001).
- 74 Reynolds R, Potz N, Colman M, Williams A, Livermore D, MacGowan A. Antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001-2002: the BSAC Bacteraemia Resistance Surveillance Programme. *J. Antimicrob. Chemother.* 53, 1018-1032 (2004).
- 75 Jones RN, Huynh HK, Biedenbach DJ, Fritsche TR, Sader HS. Doripenem (S-4661), a novel carbapenem: comparative activity against contemporary pathogens including bactericidal action and preliminary *in vitro* methods evaluations. *J. Antimicrob. Chemother.* 54, 144-154 (2004).
- 76 Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell K, Fernandez H. Comparative *in vitro* activity of ertapenem and 11 other antimicrobial agents against aerobic and anaerobic pathogens isolated from skin and soft tissue animal and human bite wound infections. *J. Antimicrob. Chemother.* 48, 641-651 (2001).
- 77 Jones RN. *In vitro* evaluation of ertapenem (MK-0826), a long-acting carbapenem, tested against selected resistant strains. *J. Chemother.* 13, 363-376 (2001).
- Excellent review of ertapenem's *in vivo* activity.
- 78 Ge Y, Wikler MA, Sahm DE, Blosser-Middleton RS, Karlowsky JA. *In vitro* antimicrobial activity of doripenem, a new carbapenem. *Antimicrob. Agents Chemother.* 48, 1384-1396 (2004).
- 79 Thomson KS, Moland ES. CS-023 (R-115685), a novel carbapenem with enhanced *in vitro* activity against oxacillin-resistant staphylococci and *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* 54(2), 557-622 (2004).
- 80 Rhomberg PR, Jones RN. Antimicrobial spectrum of activity for meropenem and nine broad-spectrum antimicrobials: report from the MYSTIC Program (2002) in North America. *Diagn. Microbiol. Infect. Dis.* 47, 365-372 (2003).
- 81 Watanabe A, Tokue Y, Takahashi H et al. Comparative *in vitro* activity of carbapenem antibiotics against respiratory pathogens isolated between 1999 and 2000. *J. Infect. Chemother.* 7, 267-271 (2001).
- 82 Fuchs PC, Barry AL, Brown SD. Comparative *in vitro* antimicrobial activity of a new carbapenem, E1010, and tentative disc diffusion test interpretative criteria. *J. Antimicrob. Chemother.* 48, 23-28 (2001).
- 83 Alhambra A, Cuadros JA, Cacho J, Gomez-Garcés JL, Alos JI. *In vitro* susceptibility of recent antibiotic-resistant urinary pathogens to ertapenem and 12 other antibiotics. *J. Antimicrob. Chemother.* 53, 1090-1094 (2004).
- 84 Rennie RP, Jones RN, Mutnick AH. Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: report from the SENTRY Antimicrobial Surveillance

- Program (United States and Canada, 2000). *Diagn. Microbiol. Infect. Dis.* 45, 287–293 (2003).
- 85 National Committee for Clinical Laboratory Standards. *Methods For Dilution Antimicrobial Susceptibility Tests For Bacteria That Grow Aerobically: Approved Standard, M11-A6 (6th Edition)*. National Committee for Clinical Laboratory Standards, PA, USA (2003).
- 86 Aldridge KE. Ertapenem (MK-0826), a new carbapenem: comparative *in vitro* activity against clinically significant anaerobes. *Diagn. Microbiol. Infect. Dis.* 44, 181–186 (2002).
- 87 Betriu C, Sanchez A, Palau ML, Gomez M, Picazo JJ. *In vitro* activities of MK-0826 and 16 other antimicrobials against *Bacteroides fragilis* group strains. *Antimicrob. Agents Chemother.* 45, 2372–2374 (2001).
- 88 Goldstein EJ, Citron DM, Merriam CV, Warren Y, Tyrrell KL, Gesser RM. General microbiology and *in vitro* susceptibility of anaerobes isolated from complicated skin and skin-structure infections in patients enrolled in a comparative trial of ertapenem versus piperacillin–tazobactam. *Clin. Infect. Dis.* 35, S119–S125 (2002).
- 89 Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez H. Comparative *in vitro* activities of ertapenem (MK-0826) against 469 less frequently identified anaerobes isolated from human infections. *Antimicrob. Agents Chemother.* 46, 1136–1140 (2002).
- 90 Goldstein EJ, Citron DM, Merriam CV, Warren Y, Tyrrell KL. Comparative *in vitro* activities of ertapenem (MK-0826) against 1001 anaerobes isolated from human intra-abdominal infections. *Antimicrob. Agents Chemother.* 44, 2389–2394 (2000).
- 91 Hoellman DB, Kelly LM, Credito K *et al.* *In vitro* antianaerobic activity of ertapenem (MK-0826) compared with seven other compounds. *Antimicrob. Agents Chemother.* 46, 220–204 (2002).
- 92 Wexler HM, Molitoris D, Finegold SM. *In vitro* activities of MK-826 (L-749, 345) against 363 strains of anaerobic bacteria. *Antimicrob. Agents Chemother.* 44, 2222–2224 (2000).
- 93 Hoellman DB, Kelly LM, Jacobs MR, Appelbaum PC. *In vitro* anti-anaerobic activity of the cephalosporin derivative RWJ 54428 compared to seven other compounds. *Clin. Microbiol. Infect.* 8, 814–822 (2002).
- 94 Buckley MM, Brogden RN, Barradell LB, Goa KL. Imipenem/cilastatin. A reappraisal of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 44, 408–444 (1992).
- 95 Zhanel GG, Simor AE, Vercaigne L, Mandell L, and the Canadian Carbapenem Discussion Group. Imipenem and meropenem: comparison of *in vitro* activity, pharmacokinetics, clinical trials and adverse effects. *Can. J. Infect. Dis.* 9, 215–228 (1998).
- 96 Moon YS, Chung KC, Gill MA. Pharmacokinetics of meropenem in animals, healthy volunteers, and patients. *Clin. Infect. Dis.* 24(Suppl. 2), S249–S255 (1997).
- 97 Bush LM, Calmon J, Johnson CC. Newer penicillins and β -lactamase inhibitors. *Infect. Dis. Clin. North Am.* 9, 653–686 (1995).
- 98 Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J. Antimicrob. Chemother.* 31(Suppl. A), 39–60 (1993).
- 99 Chiu LM, Menhinick AM, Johnson PW, Amsden GW. Pharmacokinetics of intravenous azithromycin and ceftriaxone when administered alone and concurrently to healthy volunteers. *J. Antimicrob. Chemother.* 50, 1075–1079 (2002).
- 100 Christ W. Pharmacological properties of cephalosporins. *Infection* 19(Suppl. 5), S244–S252 (1991).
- 101 Zhanel GG, Brunham RC. Third-generation cephalosporins. *Can. J. Hosp. Pharm.* 41, 183–194 (1988).
- 102 Wai AO, Frighetto L, Marra CA, Chan E, Jewesson PJ. Cost analysis of an adult outpatient parenteral antibiotic therapy (OPAT) programme. A Canadian teaching hospital and Ministry of Health perspective. *Pharmacoeconomics* 18(5), 451–457 (2000).
- 103 Bernard L, El-Hajj L, Pron B *et al.* Outpatient parenteral antimicrobial therapy (OPAT) for the treatment of osteomyelitis: evaluation of efficacy, tolerance and cost. *J. Clin. Pharm. Ther.* 26(6), 445–451 (2001).

Affiliations

- George G Zhanel
Health Sciences Center, Clinical Microbiology, MS673-820, Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada
Tel.: +1 204 787 4902
Fax: +1 204 787 4699
ggzhanel@pcs.mb.ca
- Christel Johanson
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, 753 McDermot Avenue, Winnipeg, Manitoba R3T 2N2, Canada
- John M Embil
Health Sciences Center, Departments of Medicine, MS673-820, Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada
- Ayman Noreddin
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, 753 McDermot Avenue, Winnipeg, Manitoba R3T 2N2, Canada
- Alfred Gin
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, 753 McDermot Avenue, Winnipeg, Manitoba R3T 2N2, Canada
- Lavern Vercaigne
University of Manitoba, Department of Medical Microbiology, Faculty of Medicine, 753 McDermot Avenue, Winnipeg, Manitoba R3T 2N2, Canada
- Daryl J Hoban
Health Sciences Center, Clinical Microbiology, MS673-820, Sherbrook Street, Winnipeg, Manitoba, R3A 1R9, Canada