

Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial

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Objectives: Avibactam, a novel non- β -lactam β -lactamase inhibitor, restores the *in vitro* activity of ceftazidime against class A, C and some class D β -lactamase-producing pathogens, including those commonly associated with complicated intra-abdominal infections (cIAIs). This randomized, active-controlled, double-blind, Phase II trial (NCT00752219) aimed to evaluate the safety and efficacy of ceftazidime/avibactam plus metronidazole compared with meropenem in hospitalized patients with cIAI.

Methods: Adults with confirmed cIAI requiring surgical intervention and antibiotics were randomized 1:1 to receive intravenously either (i) 2000 mg of ceftazidime plus 500 mg of avibactam plus a separate infusion of 500 mg of metronidazole or (ii) 1000 mg of meropenem plus placebo every 8 h for a minimum of 5 days and a maximum of 14 days. The primary efficacy endpoint was the clinical response in microbiologically evaluable (ME) patients at the test-of-cure (TOC) visit 2 weeks after the last dose of study therapy.

Results: Overall, 101 patients received ceftazidime/avibactam plus metronidazole; 102 received meropenem. The median duration of treatment was 6.0 and 6.5 days, respectively. Favourable clinical response at the TOC visit in the ME population was observed in 91.2% (62/68) and 93.4% (71/76) of patients in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively (observed difference: -2.2%; 95% CI: -20.4%, 12.2%). The incidence of treatment-emergent adverse events was similar for ceftazidime/avibactam plus metronidazole (64.4%) and meropenem (57.8%).

Conclusions: Ceftazidime/avibactam plus metronidazole was effective and generally well tolerated in patients with cIAI, with a favourable clinical response rate in the ME population of >90%, similar to that of meropenem.

Keywords: ceftazidime non-susceptible, appendix, stomach/duodenum, *Escherichia coli*

Introduction

Complicated intra-abdominal infections (cIAIs), defined as those extending into the peritoneal space and associated with peritonitis or abscess formation,¹ are common infections that can be extremely serious and life-threatening, with most patients requiring surgical intervention. The pathogens associated with cIAIs result from perforation of the gastrointestinal tract and, thus, one or more aerobic or facultative anaerobic Gram-negative species is usually involved.

Ongoing surveillance studies have demonstrated an increasing frequency of antibiotic resistance among Gram-negative pathogens,² with one of the most common resistance mechanisms being the production of extended-spectrum β -lactamases (ESBLs).³ Carbapenems are currently the antibiotic group of choice for the treatment of serious infections likely to be caused by ESBL-producing organisms.³ However, resistance to carbapenems involving the production of serine carbapenemases is now emerging in some Gram-negative pathogens [e.g. *Klebsiella pneumoniae* carbapenemase (KPC)]^{4,5} and there

is concern that the widespread use of carbapenems may lead to further emergence of resistant strains.⁶ Currently available β -lactamase inhibitors have poor activity against carbapenemases.⁷ Consequently, options for the treatment of Gram-negative infections are likely to become increasingly limited.³ There is, therefore, a need for more effective drugs or drug combinations to be added to the current treatment options in this area.

Avibactam (formerly known as NX104) is a novel non- β -lactam β -lactamase inhibitor shown to be active *in vitro* against Ambler class A and C β -lactamases, including KPC, and some class D enzymes.⁷ Avibactam alone has little intrinsic antimicrobial activity.^{7,8} However, the addition of avibactam to ceftazidime, a broad-spectrum cephalosporin, has been shown to restore *in vitro* activity against ESBL-producing Enterobacteriaceae and multidrug-resistant *Pseudomonas aeruginosa*.⁷⁻⁹

The objective of the current study was to evaluate the efficacy, safety and tolerability of ceftazidime/avibactam (formerly known as CAZ104) plus metronidazole versus meropenem in the treatment of cIAIs in hospitalized adults.

Patients and methods

This Phase II, prospective, randomized, double-blind, active-controlled trial (ClinicalTrials.gov identifier: NCT00752219) was performed in accordance with International Conference on Harmonization/Good Clinical Practice guidelines and applicable regulatory requirements. A total of 33 sites in eight countries (Bulgaria, France, India, Lebanon, Poland, Romania, Russia and the USA) participated in the trial. The study protocol was approved by each Institutional Review Board and each patient provided written informed consent.

Patients

Male and female patients were eligible for inclusion if they were aged 18–90 years with evidence of cIAI requiring surgical intervention and antibiotics, caused or presumed to be caused by microorganisms susceptible to ceftazidime/avibactam plus metronidazole or meropenem in pre-study cultures. cIAI was confirmed intra-/post-operatively upon visual inspection and specimen culture or diagnosed pre-operatively by clinical examination and confirmed during surgical intervention within 24 h. The acceptable diagnoses were as follows: cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall; diverticular disease with perforation or abscess; appendiceal perforation or peri-appendiceal abscess; acute gastric and duodenal perforation (only if operated on >24 h after perforation occurred); traumatic perforation of the intestines (only if operated on >12 h after perforation occurred); secondary peritonitis (but not spontaneous peritonitis associated with cirrhosis and chronic ascites); or intra-abdominal abscess with evidence of intraperitoneal involvement.

Patients were excluded if they had the following: abdominal wall abscess, small bowel obstruction or ischaemic bowel without perforation; received other systemic antibiotics within 72 h of study therapy (unless the previous therapy was unsuccessful or if <24 h of antibiotic treatment had been received, including pre-operative prophylaxis); concurrent infections that may interfere with the evaluation of the response to study antibiotics; perinephric infections or infections of the female genital tract; infections caused by pathogens known to be resistant to the study agents at study entry or sepsis with shock unresponsive to intravenous (iv) fluid challenge; acute physiological assessment and chronic health evaluation (APACHE) II score >25; anticipated survival less than the study period; abnormal liver function [alanine transaminase and

aspartate transaminase >3 $\times$ upper limit of normal (ULN) or >5 $\times$ ULN if elevations were acute and directly related to the study infection]; chronic hepatitis or cirrhosis; abnormal renal function (creatinine clearance <50 mL/min by the Cockcroft–Gault formula); immunocompromised status (HIV infection with an AIDS-defining illness or CD4+ T lymphocyte count <200 cells/mm³, metastatic/haematological malignancy requiring chemotherapy, splenectomy or maintenance corticosteroid therapy equivalent to >20 mg of prednisolone daily); body mass index >45 kg/m²; haemoglobin level <10 g/dL; absolute neutrophil count <1500 cells/mm³ unless directly related to the infection; or platelet count <100 000 cells/mm³. Patients considered unlikely to respond to 5–14 days of antibiotic treatment were also excluded, as were those who were considered to need effective concomitant systemic antibacterials [other than vancomycin, linezolid or daptomycin for documented methicillin-resistant *Staphylococcus aureus* (MRSA) and/or enterococcal infections] in addition to the study medication.

Treatment regimens

Patients were enrolled by the clinical investigator and randomized in a 1:1 ratio to receive either ceftazidime/avibactam plus metronidazole or meropenem plus 0.9% saline solution for iv infusion (as a placebo to metronidazole). A central randomization algorithm was used to ensure that the groups were balanced according to the baseline severity of disease (with stratification by APACHE II score ≤ 10 and >10 but ≤ 25), country and site. At each study centre, the study pharmacist obtained the patient's APACHE II score from the clinical investigator's team and contacted the randomization centre using an interactive voice response system (IVRS) to enter data. The IVRS then applied the central randomization algorithm to assign the patient to a treatment arm.

Investigators and patients were blinded to the iv study antibiotic regimen. In order to achieve investigator blinding, preparation of the iv study antibiotics was performed by the study pharmacist (or other designated person), who received the clinical supplies following each patient's randomization. This person was not blinded to the treatments and was not permitted to disclose the treatments to the investigator or the patient. Treatments were supplied to the investigator site in controlled quantities, on a schedule that reflected enrolment at the site.

The approved dose of ceftazidime for the treatment of serious Gram-negative infections is 2000 mg iv every 8 h. Based on *in vitro* susceptibility testing, hollow-fibre experiments and pre-clinical data,¹⁰⁻¹³ a combination of 2000 mg of ceftazidime and 500 mg of avibactam iv every 8 h was selected. This dose was determined as being effective in the restoration of ceftazidime activity against resistant Gram-negative pathogens. A dosing regimen of 2000 mg of ceftazidime plus 500 mg of avibactam given as an iv infusion over 30 min every 8 h was therefore used in this trial, with the addition of an iv infusion of 500 mg of metronidazole given over 1 h every 8 h to provide coverage for anaerobic pathogens. Patients in the comparator group received the standard adult dose of meropenem, 1 g iv every 8 h, with additional placebo infusions given over 1 h to maintain blinding between groups.

Treatment was given for a minimum of 5 days and a maximum of 14 days, depending upon clinical response. No other concomitant systemic antibiotics were permitted except for vancomycin, linezolid or daptomycin, which were permitted for suspected or documented MRSA or enterococcal infections.

Assessments

Blood samples and samples from the site of intra-abdominal infection were taken from all patients at baseline for culture and *in vitro* identification of pathogen(s) and assessment of susceptibility to the study drugs. For the purposes of this study, antibacterial susceptibility to ceftazidime/avibactam was interpreted based on the highest breakpoint for

ceftazidime alone, MIC ≤ 8 mg/L, which is the breakpoint for 2000 mg of ceftazidime every 8 h for *P. aeruginosa*, as defined in the CLSI MIC breakpoints current at the time of the study.¹⁴ Antibacterial susceptibility to the other study drugs (metronidazole, meropenem and ceftazidime alone) was interpreted based on CLSI 2010 MIC breakpoints. For currently registered agents, the categorizations could be 'susceptible' (S), 'intermediate' (I) or 'resistant' (R).

Patients with polymicrobial infections that included one or more pathogens resistant *in vitro* to the study antibiotics, as well as at least one pathogen that was susceptible to both study agents, were considered evaluable if continued in the study at the discretion of the investigator. Cultures were obtained during the study as clinically indicated and, if available, were used in the microbiological determination of outcome. Clinical assessment, including infection-related signs and symptoms, was performed daily throughout the study, at the end of iv therapy, at the test-of-cure (TOC) visit 2 weeks after the last dose of study treatment and at the late follow-up (LFU) visit 4–6 weeks post-therapy.

The primary efficacy endpoint was the clinical response at the TOC visit in the microbiologically evaluable (ME) population, a subset of the clinically evaluable (CE) population. The CE population was defined as those patients having a cIAI confirmed by operative findings and who had received between 80% and 120% of the scheduled study drug, with sufficient information to determine clinical outcome at the TOC visit. The ME population was defined as those patients from the CE population who also had at least one clinically relevant pathogen susceptible to both ceftazidime/avibactam and meropenem isolated in the initial culture. A favourable clinical response was defined as complete resolution or significant improvement of signs/symptoms of infection with no requirement for additional antibiotics or surgery. Clinical response in the ME population was also assessed at the end of iv therapy and at the LFU visit.

Clinical response at the end of iv therapy, at the TOC visit and at the LFU visit was also evaluated in the CE population, the microbiological modified intent-to-treat (mMITT) population (all randomized patients who received at least one dose of a study drug, met the disease definition for intra-abdominal infection and had at least one bacterial pathogen identified at study entry, regardless of susceptibility) and, in a *post hoc* analysis, in all randomized patients who received at least one dose of a study drug (this latter group being equivalent to the safety population). In addition, microbiological response (eradication of the baseline pathogen) was assessed at the end of iv therapy, at the TOC visit and at the LFU visit. If no post-baseline specimen was available for culture, microbiological outcome was based upon clinical assessment.

Safety evaluation

Safety was determined by assessment of treatment-emergent adverse events (AEs), including serious AEs (SAEs), for all patients who received a dose of a study drug [summarized in accordance with the Medical Dictionary for Regulatory Activity (MedDRA, version 12, Chantilly, VA, USA)]. Treatment-emergent AEs were defined as those occurring or worsening after the first dose of the study medication. SAEs were defined as those that resulted in death, were life-threatening, required hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, were a congenital anomaly or birth defect or were considered to be an important medical event. In addition, laboratory tests, vital signs, electrocardiogram and physical examination were performed.

Statistical analysis and sample size calculation

No formal sample size calculation was performed and a sample size of 200 patients was planned for inclusion, based upon currently accepted standards for this type of study, with an assumption that 65% of enrolled

patients would be considered ME. The study was not statistically powered to demonstrate non-inferiority to the comparator, but was intended to provide an estimate of efficacy and safety.

For the primary and secondary efficacy variables, the response rates with the associated CIs were calculated for each treatment group. The exact 95% Clopper–Pearson CIs for the observed difference in clinical response rates between treatment groups were also calculated for the ME, CE and mMITT populations.

A synopsis of the study protocol is available at ClinicalTrials.gov, NCT00752219.

Results

The study was carried out between 2 March 2009 (first patient enrolled) and 19 December 2009 (after enrolment and last patient follow-up visit was completed). A total of 204 patients were randomized equally between the two study groups. One patient randomized to ceftazidime/avibactam did not receive any study drug. Thus, 101 patients received ceftazidime/avibactam plus metronidazole and 102 patients received meropenem and comprised the safety population (Figure 1). More than 90% of patients in each group completed the LFU assessment 4–6 weeks post-therapy.

The mMITT population comprised 85 patients in the ceftazidime/avibactam plus metronidazole group and 89 patients in the meropenem group. The sole reason for exclusion from the mMITT population in both treatment groups was no valid pathogen isolated at baseline (16 and 13 patients in each group, respectively) (Figure 1).

The CE population comprised 87 patients in the ceftazidime/avibactam plus metronidazole group and 90 patients in the meropenem group. Reasons for exclusion from the CE population were generally similar for the two groups and included violation of the protocol regarding prior or concomitant antibiotics, inadequate surgical control of the infection, incorrect timing of the TOC assessment, inadequate course of therapy and insufficient data to make a clinical assessment (Figure 1). The ME population comprised 68 patients in the ceftazidime/avibactam plus metronidazole group and 76 patients in the meropenem group. Reasons for exclusion from the ME population (in addition to reasons for exclusion from the CE population) were also similar between groups and included no pathogen isolated at baseline ($n=14$ and $n=11$, respectively) or isolation of resistant pathogens at baseline ($n=5$ and $n=3$, respectively) (Figure 1).

Baseline demographics and patient characteristics

The demographics and other patient characteristics were generally similar across the treatment groups (Table 1). Most patients had APACHE II scores ≤ 10 and the percentage of patients with APACHE II scores ≤ 10 or >10 but ≤ 25 was comparable between treatment groups. The most common sites of infection were the appendix and stomach/duodenum. The site of infection, infection processes and surgical procedures were also generally consistent between the groups.

In vitro susceptibility of baseline cultures

The *in vitro* susceptibility of cultures isolated from the source of infection for patients included in the ME population is shown in

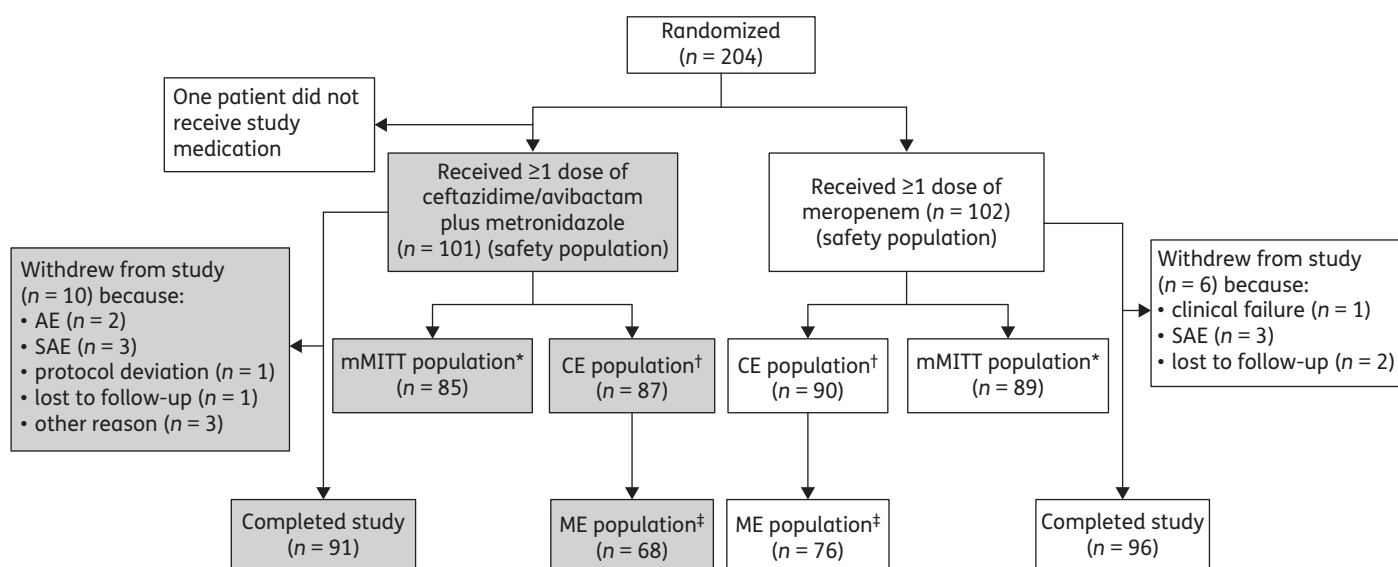


Figure 1. Patient flow and study populations. *Reasons for exclusion from the mMITT population were baseline microbiology—no pathogen isolated ($n=16$ and $n=13$) in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively. †Reasons for exclusion from the CE population were violation of prior or concomitant antibiotics ($n=6$ and $n=2$), inadequate surgical source control ($n=1$ and $n=3$), inappropriate timing of the TOC assessment ($n=1$ in each group), inadequate course of therapy ($n=3$ and $n=4$) and insufficient data for assessment ($n=2$ in each group) in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively. One patient in the ceftazidime/avibactam plus metronidazole group was excluded for a reason classified as ‘other’. ‡Reasons for further exclusion from the ME population (as a subset of the CE population) were no pathogen isolated ($n=14$ and $n=11$) or resistant pathogen ($n=5$ and $n=3$) in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively.

Table 2. As expected, polymicrobial infections were present in a high proportion of patients [28/68 (41.2%) and 27/76 (35.5%) of patients in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively].

Escherichia coli was the most common pathogen isolated from the site of cIAI and all *E. coli* isolates were susceptible to both ceftazidime/avibactam and meropenem. Of the other Gram-negative pathogens isolated, only six had a ceftazidime/avibactam MIC >8 mg/L (i.e. above the susceptibility breakpoint assumed for ceftazidime/avibactam) (Table 2). Two of these isolates were resistant to meropenem (Table 2). Of the six Gram-negative pathogens with a ceftazidime/avibactam MIC >8 mg/L, three were in patients in the ceftazidime/avibactam treatment arm and three were in the meropenem treatment arm. There was one meropenem-resistant Gram-negative pathogen in each treatment arm.

Five of the nine Gram-positive pathogens with a ceftazidime/avibactam MIC >8 mg/L were in patients in the ceftazidime/avibactam treatment group. One of the three meropenem-resistant pathogens was in the meropenem arm. All resistant Gram-positive isolates were from polymicrobial infections that also included susceptible pathogens. All anaerobic pathogens except one were susceptible to metronidazole and meropenem (Table 3).

The most common pathogen in blood was *E. coli*; all had a ceftazidime/avibactam MIC ≤ 8 mg/L and all were susceptible to meropenem (Table 4). Only one Gram-negative blood isolate (*Acinetobacter baumannii*) had a ceftazidime/avibactam MIC >8 mg/L. The same isolate was resistant to meropenem. Of the Gram-positive pathogens isolated from blood, two had a ceftazidime/avibactam MIC >8 mg/L and one was resistant to

meropenem. Only one anaerobic blood pathogen (*Bacteroides caccae*) was isolated, which was susceptible to both metronidazole and meropenem.

Clinical response

Patient exposure to the study treatment was similar between the groups. The median duration of treatment was 6.0 and 6.5 days in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively.

A favourable clinical response in the ME population at the TOC visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime/avibactam plus metronidazole and meropenem patients, respectively. The estimated difference in response rates was -2.2% (95% CI: -20.4% , 12.2%). Reasons for clinical failure at the TOC visit are shown in Table S1 (available as Supplementary data at JAC Online).

At the end of iv therapy, a favourable clinical response was observed in 97.1% (66/68) and 97.4% (74/76) of ME population patients in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively (observed difference: -0.3% ; 95% CI: -17.1% , 15.4%). There was only a small decrease in response rates in both groups between the TOC and LFU visits.

The rate of favourable clinical response at the TOC visit for the CE population was slightly higher than for the ME population: 92.0% (80/87 patients) and 94.4% (85/90) for the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively (observed between group difference: -2.5% ; 95% CI: -19.5% , 10.1%). At the end of iv therapy, a favourable clinical response in the CE population was seen in 96.6% (84/87 patients)

Table 1. Summary of baseline demographics and patient characteristics (safety population)

	Ceftazidime/avibactam plus metronidazole (n=101)	Meropenem (n=102)
Gender, n (%)		
male	70 (69.3)	81 (79.4)
female	31 (30.7)	21 (20.6)
Race, n (%)		
white	56 (55.4)	65 (63.7)
Asian	44 (43.6)	36 (35.3)
American or Alaskan native	1 (1.0)	0
black or African American	0	1 (1.0)
Age (years), mean $\pm$ SD (range)	43.0 $\pm$ 15.9 (18–79)	42.6 $\pm$ 18.1 (18–88)
APACHE II score stratum, n (%)		
≤ 10	84 (83.2)	85 (83.3)
> 10 but ≤ 25	17 (16.8)	17 (16.7)
Body mass index (kg/m ²), mean $\pm$ SD ^a	24.2 $\pm$ 5.2	25.3 $\pm$ 4.9
Site of origin of current infection, n (%) ^b		
appendix	49 (48.5)	47 (46.1)
stomach/duodenum	29 (28.7)	23 (22.5)
colon	12 (11.9)	6 (5.9)
small bowel	4 (4.0)	13 (12.7)
gall bladder	5 (5.0)	9 (8.8)
parenchymal (liver or spleen)	2 (2.0)	3 (2.9)
other	0	2 (2.0)
Infection process, n (%) ^b		
peritonitis (localized or generalized)	84 (83.2)	89 (87.3)
visceral perforation	44 (43.6)	40 (39.2)
abscess (single or multiple)	26 (25.7)	28 (27.5)
Surgical procedure, n (%)		
open laparotomy	91 (90.1)	91 (89.2)
laparoscopic procedure	9 (8.9)	9 (8.8)
percutaneous drainage	1 (1.0)	2 (2.0)
Prior antibiotic therapy (≥ 1 dose), n (%)	53 (52.5)	54 (52.9)

^aData available for n=97 and n=101, respectively.^bPatients could have the origin of current infection in more than one anatomical site and have more than one infection process recorded.

and 97.8% (87/89 patients), respectively, and at the LFU visit in 91.9% (79/86 patients) and 94.4% (84/89 patients), respectively.

In the mMITT population, the favourable clinical response rate at the TOC was 82.4% (70/85 patients) and 88.8%

(79/89 patients) in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively (observed between group difference: –6.4%; 95% CI: –23.8%, 6.0%).

Among all randomized patients who received a study drug (safety population), 84/101 (83.2%; 95% CI: 0.74, 0.90) patients treated with ceftazidime/avibactam plus metronidazole and 91/102 (89.2%; 95% CI: 0.82, 0.94) patients treated with meropenem had a favourable clinical response at the TOC visit. At the end of iv therapy, a favourable clinical response was observed in 93/101 (92.1%) and 93/102 (91.2%) patients, respectively, and at the LFU visit in 84/101 (83.2%) and 89/102 (87.3%), respectively.

There did not appear to be a relationship between the APACHE II score at baseline and clinical response; all patients with APACHE scores of > 10 had a favourable clinical response in both study groups (Table 5), although the number of patients with scores > 10 was limited. Similarly, there did not appear to be a relationship between the site of primary infection and clinical response (Table 5). Moreover, response rates were generally similar between groups, regardless of whether the patient had a monomicrobial [92.5% (37/40) versus 89.8% (44/49) in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively] or polymicrobial [89.3% (25/28) versus 100% (27/27), respectively] infection.

Microbiological outcomes

At the TOC visit, a favourable microbiological response was observed in $> 90\%$ of patients in each treatment group, including most patients with *E. coli* isolates (Table 6). Susceptibility testing showed that the meropenem MIC was 0.0625 mg/L for the *Enterobacter aerogenes* isolate. Most patients with Gram-positive or anaerobic isolates also had favourable microbiological responses, as did all patients with bacteraemia at baseline.

Ceftazidime-non-susceptible isolates

There were 43 patients in the ME population who had pathogens that were non-susceptible to ceftazidime alone at baseline (MIC > 8 mg/L), 26 in the ceftazidime/avibactam plus metronidazole group and 17 in the meropenem group (one of whom had two non-susceptible pathogens) (Table 7). All but two of the patients with ceftazidime-non-susceptible isolates (one in the ceftazidime/avibactam plus metronidazole group and one in the meropenem group) had a favourable microbiological response.

Safety and tolerability

AEs were observed in 64.4% (65/101) and 57.8% (59/102) of patients in the ceftazidime/avibactam plus metronidazole and meropenem groups, respectively. AEs occurring in $\geq 5\%$ patients in either group are summarized in Table 8. Overall, the types and frequencies of AEs were similar in the two treatment groups, but there were more cases of nausea and vomiting and abdominal pain in the ceftazidime/avibactam plus metronidazole group and more cases of liver enzyme elevations in the meropenem group. In the majority of cases, AEs were mild or moderate in intensity.

SAEs occurred in 9 (8.9%) and 11 (10.8%) patients in the ceftazidime/avibactam plus metronidazole and meropenem groups,

Table 2. Gram-negative and Gram-positive pathogens isolated from the infection site and *in vitro* susceptibility^a to study antibiotics (ME population)

	Agents tested and number of isolates (%)				
	ceftazidime/avibactam		meropenem		
	MIC ≤8 mg/L	MIC >8 mg/L	S	I	R
Gram-negative aerobic pathogens (153 pathogens with susceptibility testing isolated from 127 patients)	147	6	151	0	2
<i>Escherichia coli</i> (105 isolates)	105 (100)	0	105 (100)	0	0
<i>Klebsiella pneumoniae</i> (17 isolates)	14 (82.4)	3 (17.6)	17 (100)	0	0
<i>Pseudomonas aeruginosa</i> (10 isolates)	8 (80)	2 (20)	9 (90)	0	1 (10)
<i>Enterobacter cloacae</i> (5 isolates)	5 (100)	0	5 (100)	0	0
<i>Klebsiella oxytoca</i> (4 isolates)	4 (100)	0	4 (100)	0	0
<i>Acinetobacter baumannii</i> (2 isolates)	1 (50)	1 (50)	1 (50)	0	1 (50)
<i>Proteus mirabilis</i> (2 isolates)	2 (100)	0	2 (100)	0	0
<i>Pseudomonas fluorescens</i> (2 isolates)	2 (100)	0	2 (100)	0	0
other (6 isolates) ^b	6 (100)	0	6 (100)	0	0
Gram-positive pathogens (22 pathogens with susceptibility testing isolated from 19 patients) ^c	13	9	19	0	3
<i>Staphylococcus aureus</i> (11 isolates)	5 (45.5)	6 (54.5)	8 (72.7)	0	3 (27.3)
<i>Streptococcus agalactiae</i> (2 isolates)	2 (100)	0	2 (100)	0	0
<i>Streptococcus constellatus</i> (1 isolate)	0	1 (100)	1 (100)	0	0
<i>Streptococcus intermedius</i> (2 isolates)	1 (50)	1 (50)	2 (100)	0	0
<i>Streptococcus salivarius</i> (1 isolate)	0	1 (100)	1 (100)	0	0
other (5 isolates) ^d	5 (100)	0	5 (100)	0	0

^aThe susceptibility breakpoint for ceftazidime/avibactam was based on the highest breakpoint for ceftazidime (≤8 mg/L). Susceptibility to other study drugs (metronidazole and meropenem) was based on current CLSI MIC breakpoints for the respective pathogens (provided in the Patients and methods section¹⁴).

^bOther Gram-negative pathogens were one isolate each of *Acinetobacter junii*, *Citrobacter braakii*, *Citrobacter freundii*, *Comamonas testosteroni*, *Enterobacter aerogenes* and *Pseudomonas* species.

^cThirty-one patients in the ME population had Gram-positive isolates, but *in vitro* susceptibility interpretation was available for 19 patients.

^dOther Gram-positive pathogens were one isolate each of *Staphylococcus capitis*, *Staphylococcus hominis*, *Streptococcus* group C, *Streptococcus mitis* and *Streptococcus pneumoniae*.

respectively. Three patients died in the ceftazidime/avibactam plus metronidazole group (one case each of multiorgan failure, sepsis and cardiac arrest) and two died in the meropenem group (one case of peritonitis and one of pneumonia and severe decrease in platelet count). None of the deaths was considered to be related to the study drug. One SAE (elevated liver enzymes) in the ceftazidime/avibactam plus metronidazole group was considered by the investigator to be drug related (please see the Supplementary data at JAC Online for details).

Discussion

This randomized, double-blind, multicentre Phase II comparative clinical trial showed ceftazidime/avibactam plus metronidazole to be effective in the treatment of cIAIs in hospitalized adults. Results appeared to be generally consistent with those of the active control, meropenem.

Similar favourable response rates of >90% were seen in both treatment groups for the primary endpoint of clinical response in the ME population at the TOC visit. The response rates were also similar between the two treatment groups at the end of iv therapy and at the LFU visit in the ME population. In the

mMITT population and in all randomized patients who received a study drug, the response rate was numerically slightly lower in the ceftazidime/avibactam plus metronidazole group than in the meropenem group at the TOC and LFU visits. This imbalance was in part due to patients with indeterminate/missing outcomes, which appears to have been an artefact of the relatively small sample size of the study.

Favourable outcomes were observed with both treatment regimens in patients with isolates that were not susceptible to ceftazidime alone at baseline. In total, 25 of 26 patients (96%) in the ceftazidime/avibactam plus metronidazole group and 16 of 17 patients (94%) in the meropenem group with ceftazidime-non-susceptible pathogens *in vitro* demonstrated a favourable microbiological outcome. These results were similar to the response rates in patients with ceftazidime-susceptible pathogens at baseline.

Apart from *E. coli*, the numbers of individual Gram-negative species isolated tended to be small. However, there did not appear to be a relationship between the Gram-negative pathogen and the response to therapy, with all ME patients with *K. pneumoniae* and *P. aeruginosa* isolates demonstrating a favourable microbiological response to either ceftazidime/avibactam or meropenem.

Overall, the types and frequencies of AEs and SAEs were comparable between the two treatments. Although there were more cases of nausea, vomiting and abdominal pain in the ceftazidime/avibactam plus metronidazole group, it should be noted that these are AEs potentially associated with metronidazole.¹⁵

It is recommended that therapy for cIAIs should not be delayed until the results of susceptibility tests are available, as this can increase the rate of failure and even increase the risk

of mortality.¹⁶ However, the choice of empirical antimicrobial therapy is complicated by the diverse species that are implicated in cIAI and the ever-increasing possibility of infection with resistant pathogens.

cIAIs are usually polymicrobial in nature, involving one or more Gram-negative species as well as Gram-positive and anaerobic pathogens. In the current study, Gram-negative species were the most frequent pathogens, with *E. coli* being isolated in 105 (73%) patients. Ongoing monitoring programmes also confirm *E. coli* to be the most common Gram-negative isolate from cIAIs.^{17–19}

Surveillance studies have demonstrated a rise in the proportion of ESBL-producing *E. coli* pathogens isolated from cIAIs.^{18,19} In the USA and Europe, 4.7% and 11.8%, respectively, of *E. coli* isolates from intra-abdominal infections were found to be ESBL positive in 2008,^{2,18} with the rates of ESBL-positive isolates being considerably higher in many Asian countries.^{19,20} Moreover, when compared with ESBL-negative strains, ESBL-producing strains showed significantly reduced susceptibility to a range of antibiotics, with only the carbapenems retaining consistent activity.¹⁹

As the incidence of antibiotic resistance increases, newer carbapenems, such as doripenem, have emerged as treatment options for cIAIs, with previous studies indicating a clinical response achieved with doripenem comparable to the results obtained in the current study.²¹ However, with the emergence of carbapenem resistance,^{4,5} the availability of new treatment options is a key priority in the treatment of serious Gram-negative infections.

A limitation of the present study is that no formal calculation of the sample size was performed and it included a relatively small number of patients, which limits its robustness in terms of comparing the clinical efficacy of the two treatments evaluated. There is also a potential for local practice variability in the 33 centres in the study to be a potential confounder. The analysis of the data did not take this possibility into

Table 3. Anaerobic pathogens isolated from the infection site and *in vitro* susceptibility^a to study antibiotics (ME population)

	Agents tested and number of isolates (%)					
	metronidazole			meropenem		
	S	I	R	S	I	R
Anaerobic pathogens (36 pathogens with susceptibility testing isolated from 19 patients)	35	0	1	36	0	0
<i>Peptostreptococcus micros</i> (2 isolates)	1 (50)	0	1 (50)	2 (100)	0	0
other (34 isolates) ^a	34 (100)	0	0	34 (100)	0	0

^aOther anaerobic pathogens were *Bacteroides fragilis* (nine isolates), *Bacteroides thetaiotaomicron* (three isolates), *Bacteroides uniformis* (three isolates), *Bacteroides caccae* (one isolate), *Bacteroides distasonis* (one isolate), *Bacteroides eggerthii* (one isolate), *Bacteroides vulgatus* (one isolate), *Clostridium ramosum* (four isolates), *Clostridium clostridioforme* (two isolates), *Clostridium perfringens* (two isolates), *Eubacterium lentum* (one isolate), *Fingoldia magna* (one isolate), *Fusobacterium* species (one isolate), *Fusobacterium varium* (one isolate), *Peptostreptococcus prevotii* (one isolate), *Prevotella intermedia* (one isolate) and *Prevotella oris* (one isolate).

Table 4. Gram-negative and Gram-positive pathogens isolated from blood samples and *in vitro* susceptibility^a to study antibiotics (ME population)

	Agents tested and number of isolates (%)				
	ceftazidime/avibactam		meropenem		
	MIC ≤8 mg/L	MIC >8 mg/L	S	I	R
Gram-negative aerobic pathogens (8 pathogens with susceptibility testing isolated from 8 patients)	7	1	7	0	1
<i>Escherichia coli</i> (6 isolates)	6 (100)	0	6 (100)	0	0
<i>Acinetobacter baumannii</i> (1 isolate)	0	1 (100)	0	0	1 (100)
<i>Pseudomonas aeruginosa</i> (1 isolate)	1 (100)	0	1 (100)	0	0
Gram-positive pathogens (4 pathogens with susceptibility testing isolated from 4 patients)	2	2	3	0	1
<i>Staphylococcus aureus</i> (2 isolates)	1 (50)	1 (50)	1 (50)	0	1 (50)
<i>Staphylococcus lugdunensis</i> (1 isolate)	1 (100)	0	1 (100)	0	0
<i>Streptococcus constellatus</i> (1 isolate)	0	1 (100)	1 (100)	0	0

^aThe susceptibility breakpoint for ceftazidime/avibactam was based on the highest breakpoint for ceftazidime (≤8 mg/L). Susceptibility to other study drugs (metronidazole and meropenem) was based on current CLSI MIC breakpoints for the respective pathogens current at the time of the study (provided in the Patients and methods section¹⁴).

Table 5. Favourable clinical response at the TOC visit in patients according to baseline APACHE II score and primary site of infection (ME population)

	Ceftazidime/avibactam and metronidazole (n=68)	Meropenem (n=76)
APACHE II score		
0–5	33/35 (94.3)	39/42 (92.9)
6–10	17/21 (81.0)	21/23 (91.3)
11–15	10/10 (100)	11/11 (100)
16–19	2/2 (100)	0/0
Primary infection site		
stomach/duodenum	17/19 (89.5)	13/13 (100)
gall bladder	2/3 (66.7)	9/9 (100)
appendix	30/32 (93.8)	34/37 (91.9)
small bowel	4/4 (100)	9/10 (90.0)
colon	8/9 (88.9)	4/5 (80.0)
liver/spleen/other	1/1 (100)	2/2 (100)

Results are expressed as number of patients with favourable clinical response/total number of patients in each category (%).

consideration, but the randomization algorithm did make provision for providing balance in treatment assignment across countries and sites. Furthermore, any possible effect was minimized by ensuring that investigators at each study centre followed the pre-defined clinical study protocol for patient enrolment, randomization and management.

A further potential limitation is the inclusion of a relatively large proportion (~50%) of patients with infections relating to the appendix. Furthermore, the majority (~80%) of patients included in our study had a low APACHE II score (≤ 10), which may limit the applicability of the findings in severely ill patients. This was at least partly because the exclusion criteria prevented the inclusion of patients who were very seriously ill or with limited life expectancy, as appropriate for a Phase II study of a novel drug combination.

It should also be noted that a relatively high proportion of the Gram-negative isolates in this study were *E. coli* and only a small proportion of the isolates were identified as being ceftazidime non-susceptible. However, as referred to above, surveillance studies have demonstrated that *E. coli* is the most common Gram-negative pathogen in cIAIs. Furthermore, it was not within the remit of this study to try and select for patients with specific pathogens.

In keeping with the context of a Phase II trial, there are a number of limitations to the present study, as reported above. Nevertheless, the findings provide a positive indication that ceftazidime/avibactam plus metronidazole may be an effective treatment in patients with cIAIs. The results also indicate that ceftazidime/avibactam may be effective in some patients with ceftazidime-non-susceptible pathogens. The results appear to confirm the results of *in vitro* studies, which have shown that the addition of avibactam to ceftazidime restores the *in vitro* activity of this antibiotic against resistant Gram-negative isolates.^{7,8,12,22,23} However, additional clinical studies are required to determine efficacy in a broader range of cIAIs and in more seriously ill patients.

Table 6. Favourable microbiological response^a overall and according to pathogen isolated from the intra-abdominal site at the TOC visit (ME population)^b

Pathogen	Ceftazidime/avibactam plus metronidazole group (n=68)	Meropenem group (n=76)
Overall	62/68 (91.2)	71/76 (93.4)
Gram-positive aerobe		
<i>Enterococcus faecium</i>	3/4 (75)	4/4 (100)
other ^c	13/13 (100)	15/15 (100)
Gram-negative aerobe		
<i>Escherichia coli</i>	47/52 (90.4)	49/53 (92.5)
<i>Klebsiella pneumoniae</i>	6/6 (100)	11/11 (100)
<i>Pseudomonas aeruginosa</i>	5/5 (100)	5/5 (100)
<i>Klebsiella oxytoca</i>	2/2 (100)	2/2 (100)
<i>Acinetobacter baumannii</i>	1/1 (100)	1/1 (100)
<i>Enterobacter aerogenes</i>	0/0	0/1 (0.0)
<i>Enterobacter cloacae</i>	1/1 (100)	4/4 (100)
other	2/2 (100)	7/7 (100)
Anaerobe		
<i>Bacteroides fragilis</i>	3/6 (50.0)	3/3 (100)
other ^d	16/16 (100)	11/11 (100)

Results are expressed as number of patients with favourable microbiological response/total number of patients overall or with each pathogen at baseline (%).

^aIf no post-baseline microbiological specimen was available for culture, microbiological outcome was presumed based on clinical outcome.

^bSome patients had more than one pathogen isolated at baseline.

^cOther Gram-positive aerobes in the ceftazidime/avibactam plus metronidazole group included *Staphylococcus aureus* (4/4), *Enterococcus faecalis* (2/2), *Streptococcus intermedius* (1/1), *Enterococcus avium* (1/1), *Staphylococcus capitis* (1/1), *Streptococcus group C* (1/1), *Streptococcus constellatus* (1/1), *Streptococcus pneumoniae* (1/1) and *Streptococcus salivarius* (1/1). Other Gram-positive aerobes in the meropenem group included *S. aureus* (7/7), *E. faecalis* (2/2), *S. intermedius* (1/1), *Streptococcus agalactiae* (2/2), *Enterococcus durans* (1/1), *Staphylococcus hominis* (1/1) and *Streptococcus mitis* (1/1).

^dOther anaerobes in the ceftazidime/avibactam plus metronidazole group included *Clostridium ramosum* (3/3), *Bacteroides uniformis* (2/2), *Clostridium perfringens* (2/2), *Bacteroides thetaiotaomicron* (1/1), *Clostridium clostridioforme* (1/1), *Peptostreptococcus micros* (1/1), *Bacteroides caccae* (1/1), *Bacteroides distasonis* (1/1), *Bacteroides eggerthii* (1/1), *Finnegalia magna* (1/1), *Fusobacterium varium* (1/1) and *Prevotella intermedia* (1/1). Other anaerobes in the meropenem group included *C. ramosum* (1/1), *B. uniformis* (1/1), *B. thetaiotaomicron* (2/2), *C. clostridioforme* (1/1), *P. micros* (1/1), *Bacteroides vulgatus* (1/1), *Eubacterium lentum* (1/1), *Fusobacterium species* (1/1), *Peptostreptococcus prevotii* (1/1) and *Prevotella oris* (1/1).

Conclusions

Ceftazidime/avibactam plus metronidazole was effective and generally well tolerated for the treatment of hospitalized patients with cIAI. As discussed, there were a number of limitations to this study, including the small patient numbers and a relatively high proportion of less severely ill patients. Nevertheless, the findings suggest that the efficacy of ceftazidime/avibactam plus metronidazole may be similar to that of meropenem, with

Table 7. Favourable microbiological response^a in patients with ceftazidime-intermediate or -resistant^b Gram-negative isolates at baseline (ME population)

Pathogen	Ceftazidime/avibactam plus metronidazole (n=26)	Meropenem (n=17) ^c
<i>Acinetobacter baumannii</i>	1/1	0
<i>Escherichia coli</i>	19/20	13/14
<i>Klebsiella pneumoniae</i>	3/3	3/3
<i>Proteus mirabilis</i>	1/1	0
<i>Pseudomonas aeruginosa</i>	1/1	1/1
Overall response rate	25/26 (96.2%)	16/17 (94.1%)

^aIf no post-baseline microbiological specimen was available for culture, microbiological outcome was presumed based on the clinical outcome.

^bIncludes all baseline isolates within both patient groups that were either resistant or intermediate to ceftazidime based on CLSI 2010 criteria (i.e. Enterobacteriaceae MIC >4 mg/L; and *P. aeruginosa* and *Acinetobacter* spp. MIC >8 mg/L).

^cOne patient in the meropenem group had two ceftazidime-resistant pathogens at baseline.

Table 8. Most common treatment-emergent AEs occurring in ≥5% of patients in either group, regardless of relationship to study drug (safety population)

	Ceftazidime/avibactam plus metronidazole (n=101)	Meropenem (n=102)
Total number of patients with ≥1 AE	65 (64.4)	59 (57.8)
Nausea	10 (9.9)	6 (5.9)
Vomiting	14 (13.9)	5 (4.9)
Abdominal pain	8 (7.9)	3 (2.9)
Pyrexia	9 (8.9)	11 (10.8)
Wound secretion	3 (3.0)	6 (5.9)
Cough	6 (5.9)	4 (3.9)
Laboratory tests		
alanine aminotransferase increased	8 (7.9)	13 (12.7)
aspartate aminotransferase increased	9 (8.9)	15 (14.7)
blood alkaline phosphatase increased	9 (8.9)	7 (6.9)
platelet count increased	4 (4.0)	7 (6.9)
white blood cell count increased	5 (5.0)	6 (5.9)
haematuria	4 (4.0)	6 (5.9)

Results are expressed as n (%).

favourable clinical responses in >90% of patients with both treatment regimens. Importantly, a favourable microbiological response was observed with ceftazidime/avibactam plus metronidazole in 25 of 26 patients (96%) with pathogens non-susceptible to ceftazidime alone at baseline, a response rate comparable to that observed in patients with ceftazidime-susceptible pathogens. Additional studies are required to determine efficacy in a broader range of cIAIs and in more seriously ill patients.

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J. L. and C. S. were employees of Novexel/AstraZeneca at the time the study was conducted. J. L. is now an employee of Cerexa and C. S. is now an employee of Merck & Co. C. L., I. P. and M. K. R. have no conflicts of interest to declare related to this publication.

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Author contributions

C. S. designed the study, C. L. was International Co-ordinating Investigator and all authors were involved in all diverse phases of the study (including enrolment of patients) and writing and editing the manuscript.

Supplementary data

Table S1 and details of the drug-related SAE in the ceftazidime/avibactam plus metronidazole group (elevated liver enzymes) are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

References

- Solomkin JS, Mazuski JE, Bradley JS et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50**: 133–64.
- Hoban DJ, Bouchillon SK, Hawser SP et al. Susceptibility of Gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother* 2010; **54**: 3031–4.
- Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant Gram-negative organisms: extended-spectrum β -lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clin Proc* 2011; **86**: 250–9.
- Bratu S, Landman D, Haag R et al. A rapid spread of carbapenem resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotics armamentarium. *Arch Intern Med* 2005; **165**: 1430–5.
- Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis* 2009; **9**: 228–36.
- Hawser SP, Bouchillon SK, Lascos C et al. Susceptibility of *Klebsiella pneumoniae* isolates from intra-abdominal infections and molecular characterization of ertapenem-resistant isolates. *Antimicrob Agents Chemother* 2011; **55**: 3917–21.
- Stachyra T, Levasseur P, Pêchereau MC et al. *In vitro* activity of the β -lactamase inhibitor NXL104 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases. *J Antimicrob Chemother* 2009; **64**: 326–9.
- Livermore DM, Mushtaq S, Warner M et al. NXL104 combinations versus Enterobacteriaceae with CTX-M extended-spectrum β -lactamases and carbapenemases. *J Antimicrob Chemother* 2008; **62**: 1053–6.
- Walkty A, DeCorby M, Lagacé-Wiens PR et al. *In vitro* activity of ceftazidime combined with NXL104 versus *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals (CANWARD 2009 study). *Antimicrob Agents Chemother* 2011; **55**: 2992–4.
- Levasseur P, Girard AM, Delachaux C et al. NXL104, a novel β -lactamase inhibitor, restores the bactericidal activity of ceftazidime against ESBL and AmpC producing strains of Enterobacteriaceae. In: *Abstracts of the Forty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2006*. Abstract F127. American Society for Microbiology, Washington, DC, USA. <http://ebookbrowse.com/2006-icaac-nxl-104-levasseur-poster-f-127-pdf-d76709134> (2 November 2011, date last accessed).
- Levasseur P, Girard AM, Lavallade L et al. Use of the hollow fibre infection model in the pharmacodynamic evaluation of the β -lactamase inhibitor NXL104. *Clin Microbiol Infect* 2009; **15** Suppl S4: S410 (Abstract P1463).
- Endimiani A, Choudhary Y, Bonomo RA. *In vitro* activity of NXL104 in combination with β -lactams against *Klebsiella pneumoniae* isolates producing KPC carbapenemases. *Antimicrob Agents Chemother* 2009; **53**: 3599–601.
- Endimiani A, Hujer KM, Hujer AM et al. Evaluation of ceftazidime and NXL104 in two murine models of infection due to KPC-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2011; **55**: 82–5.
- Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement M100-S20*. Wayne, PA, USA, 2010.
- Flagyl (Metronidazole) Solution for Infusion: Summary of Product Characteristics. Winthrop Pharmaceuticals UK Ltd, May 2011. <http://www.medicines.org.uk/EMC/medicine/26714/SPC/Flagyl+Injection/> (9 January 2013, date last accessed).
- Weigelt JA. Empiric treatment options in the management of complicated intra-abdominal infections. *Cleveland Clinic J Med* 2007; **74** Suppl 4: S29–37.
- Hawser SP, Bouchillon SK, Hoban DJ, Badal RE. Epidemiologic trends, occurrence of extended-spectrum β -lactamase production, and performance of ertapenem and comparators in patients with intra-abdominal infections: analysis of global trend data from 2002–2007 from the SMART study. *Surg Infect (Larchmt)* 2010; **11**: 371–8.
- Hawser SP, Bouchillon SK, Hoban DJ et al. Incidence and antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* with extended-spectrum β -lactamases in community- and hospital-associated intra-abdominal infections in Europe: results of the 2008 Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother* 2010; **54**: 3043–6.
- Hawser SP, Badal RE, Bouchillon SK et al. Antibiotic susceptibility of intra-abdominal infection isolates from Indian hospitals during 2008. *J Med Microbiol* 2010; **59**: 1050–4.
- Hsueh PR, Badal RE, Hawser SP et al. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *Int J Antimicrob Agents* 2010; **36**: 408–14.
- Lucasti C, Jasovich A, Umeh O et al. Efficacy and tolerability of iv doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther* 2008; **30**: 868–83.
- Lagacé-Wiens PR, Tailor F, Simner P et al. Activity of NXL104 in combination with β -lactams against genetically characterized *Escherichia coli* and *Klebsiella pneumoniae* isolates producing class A extended-spectrum β -lactamases and class C β -lactamases. *Antimicrob Agents Chemother* 2011; **55**: 2434–7.
- Livermore DM, Mushtaq S, Warner M et al. Activities of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2011; **55**: 390–4.

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