Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies

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Objectives: Antimicrobial drug resistance is spreading among Enterobacteriaceae, limiting the utility of traditionally used agents. We sought to systematically review the microbiological activity and clinical effectiveness of tigecycline for multidrug-resistant (MDR) Enterobacteriaceae, including those resistant to broad-spectrum β-lactams due to the expression of extended-spectrum β-lactamases (ESBLs), AmpC enzymes and carbapenemases (including metallo-β-lactamases).

Methods: PubMed was searched for articles including relevant data.

Results: Twenty-six microbiological and 10 clinical studies were identified. Tigecycline was active against more than 99% of 1936 Escherichia coli isolates characterized by any of the above resistance patterns (including 1636 ESBL-producing isolates) using the US Food and Drug Administration (FDA) breakpoint of susceptibility (MIC ≤ 2 mg/L). Findings were not different using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint (≤1 mg/L). Susceptibility rates for Klebsiella spp. with any of the above resistance patterns were 91.2% for 2627 isolates by the FDA criteria and 72.3% for 1504 isolates by the EUCAST criteria (92.3% for 2030 and 72.3% for 1284 ESBL-producing isolates, by the FDA and EUCAST criteria, respectively). The degree of microbiological activity of tigecycline against 576 MDR Enterobacter spp. isolates was moderate. In clinical studies, 69.7% of the 33 reported patients treated with tigecycline achieved resolution of an infection caused by a carbapenem-resistant or ESBL-producing or MDR Enterobacteriaceae.

Conclusions: Tigecycline is microbiologically active against almost all of the ESBL or MDR E. coli isolates and the great majority of ESBL or MDR Klebsiella spp. isolates. Further evaluation of its clinical utility against such resistant Enterobacteriaceae, particularly regarding non-labelled indications, is warranted.

Keywords: glycylcyclines, Citrobacter, Serratia, Proteus, Klebsiella pneumoniae, imipenem

Introduction

The rates of antimicrobial drug resistance and particularly of multiple drug resistance are increasing among Enterobacteriaceae, thus limiting the armamentarium of potentially active antimicrobial agents.1,2 Of particular importance are pathogens of this family that produce β-lactamases with a broad profile of substrate activity such as extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, as well as carbapenemases, including metallo-β-lactamases (MBLs).3 Although the re-evaluation of older agents may be important,4,5 there is clearly a need for the development of new antimicrobial agents to keep in pace with the development and spread of drug resistance mechanisms among Gram-negative bacteria.6

Tigecycline (formerly GAR-936), which is chemically the 9-β-butylglycylamido derivative of minocycline, is a member of
a novel class of antibiotics, the glycylcyclines. Tigecycline
generally has a bacteriostatic mode of action against a broad
spectrum of aerobic and anaerobic Gram-positive (including
methicillin-resistant Staphylococcus aureus and vancomycin-
resistant enterococci) and Gram-negative organisms.7,8 Notably,
resistant enterococci) and Gram-negative organisms.7,8 Notably,
ance determinants and ribosomal protection mechanisms. 9

Regarding Enterobacteriaceae, tigecycline has shown to evade
common mechanisms of acquired tetracycline resistance, such as
those conferred by efflux pumps encoded by the tet(A–D) resist-
ance determinants and ribosomal protection mechanisms. 9
This property can be attributed to the greater affinity of tigecy-
cline in binding with ribosomal sites compared with tetracyclines,
along with the lack of recognition of tigecycline by tetracycline
efflux pumps.10 However, Pseudomonas aeruginosa and Proteae
carry inherently encoded resistance-nodulation-division (RND)
efflux pumps that confer decreased susceptibility to tigecycline.8,11–13

The role of tigecycline for the treatment of infections caused by
Enterobacteriaceae with clinically significant types of antimicrobial
drug resistance has not been adequately evaluated.14 We sought to
assess systematically the microbiological activity of tigecycline
against Enterobacteriaceae exhibiting multidrug resistance (MDR)
and evaluate the clinical evidence regarding the use of tigecycline
for the treatment of infections caused by these pathogens.

Literature review

PubMed was searched applying the terms ‘tigecycline’ and
‘GAR-936’ for articles that evaluated the in vitro activity of tigecy-
cline against Enterobacteriaceae (including Escherichia coli,
Klebsiella spp., Enterobacter spp., Citrobacter spp., Shigella spp.,
Salmonella spp., Serratia spp., Yersinia spp., Proteus spp.,
Morganella spp. and Providencia spp.) with MDR or other clini-
cally significant resistance patterns (1999–November 2007), as
well as the clinical effectiveness of tigecycline against infections
caued by these pathogens (1999–April 2008). Owing to the
considerable respective variabiity observed in biomedical
literature,15 we accepted, for the purposes of this review, an
inclusive definition of MDR in Enterobacteriaceae as resistance
to two or more classes of antibacterial agents among those
considered as potentially effective. We considered those resistance
patterns denoted by the carriage of ESBLs, hyper-production of
AmpC ß-lactamas, carriage of carbapenemases, including
metallo-ß-lactamas (MBLs), and resistance to carbapenems to
be clinically significant.

Characteristics of the included microbiological
studies

We reviewed 42 different studies evaluating the in vitro suscepti-
bility of Enterobacteriaceae to tigecycline.8,14,16–55 Twenty-six of
these studies evaluated the in vitro susceptibility to tigecycline
of MDR Enterobacteriaceae or Enterobacteriaceae with other types
of clinically significant resistance patterns and were included in
this review.8,17–44 Eight of the 26 overall included studies involved
isolates originating from North or Latin America,25,26,28,33,37–39,41
7 studies involved isolates originating from Europe,17,18,21,24,32,34,40
while 3 studies involved isolates originating from Asia23,31,36 and
1 study involved isolates originating from Australia.20 Seven
additional studies tested broader collections of pathogens retrieved
in two or more continents.3,9,19,22,27,29,30,35

The microbiological methods used for the determination of the
susceptibility of Enterobacteriaceae isolates to tigecycline
consisted of the broth microdilution method that was used in 19
of the 26 studies included,8,18,19,21–23,26–31,33,35,37–41 the agar
dilution method in 2 studies23,34 the Etest in 4 studies20,21,32,36
and the disc diffusion method also in 4 studies.20,32,36,39 It
should be noted that more than one of the above methods was
used in five of the studies included.20,21,32,36,39

Interpretive criteria

There is discordance between the interpretative MIC breakpoints
of susceptibility of Enterobacteriaceae to tigecycline issued by
the European Committee on Antimicrobial Susceptibility Testing
(EUCAST) (≤1 mg/L) and those approved by the US Food and
Drug Administration (FDA) (≤2 mg/L).56 In this review, 22 of
the 25 included studies used primarily the FDA approved tigecy-
cline MIC breakpoints of susceptibility or corresponding disc
zone diameter breakpoints, whereas 3 studies used the EUCAST
breakpoints of susceptibility17,34,40 and in 1 study susceptibility
data were reported without the application of specific break-
points.26 We additionally extracted susceptibility data from tables
of susceptibilities with regard to both the FDA and the
EUCAST breakpoints, from studies in which relevant information
was available.

For the purposes of this review, we defined as adequate
microbiological activity of tigecycline against a bacterial patho-
gen or a group of pathogens, the susceptibility of at least 90% of
the isolates of the respective pathogens to tigecycline. If specific
susceptibility rates were not reported in a study, we inferred the
degree of the microbiological activity of tigecycline by consider-
ing the relevant MIC data, where applicable.

Susceptibility of Enterobacteriaceae to tigecycline

Cumulative data on the susceptibility to tigecycline extracted
from the included studies and classified according to different
resistance patterns for each pathogen are presented in Table 1.
Detailed relevant data extracted from each of the included
studies are presented in Table S1 available as Supplementary
data at JAC Online (http://jac.oxfordjournals.org/). Summary
data are reported below.

E. coli

We reviewed 35 studies reporting the activity of tigecycline
against E. coli,8,14,16,18,19,21–24,26–30,32,33,35,37–49,51,53–55
Using the FDA approved criteria, almost all of the E. coli isolates
that did not exhibit MDR or other types of clinically significant
resistance patterns, as defined above, were found to be suscepti-
ble to tigecycline. The corresponding MIC90 values were
between 0.25 and 1 mg/L. ESBL production among isolates of
E. coli in the reviewed studies ranged from 1.6% to
16.2%.8,18,21,22,24,26–30,32,33,35,37,49,51,53–55 The rate of MDR among 4014 E. coli
isolates collected in two studies that reported relevant data was
Enterobacter spp.

More than 93% of the non-MDR Enterobacter spp. isolates were susceptible to tigecycline by applying the FDA approved breakpoint of susceptibility. We identified 28 studies that reported data on the activity of tigecycline against Enterobacter spp.

Klebsiella pneumoniae non-MDR

By the FDA approved breakpoint, more than 90% of the non-MDR Klebsiella pneumoniae isolates were found to be susceptible to tigecycline (MIC90 values 0.25–2 mg/L for both species). Adequate microbiological activity of tigecycline was demonstrated in all of the above studies, by either the FDA or the EUCAST criteria. Susceptibility rates were 99.6% for all of the 1936 isolates with the use of the FDA criteria and 99.4% for 795 isolates, for which relevant data were available, with the use of the EUCAST criteria.

Klebsiella spp.

We reviewed 37 different studies evaluating the activity of tigecycline against Klebsiella spp. isolates. By the FDA approved breakpoint, more than 90% of the non-MDR Klebsiella pneumoniae isolates and almost all of the non-MDR Klebsiella oxytoca isolates were found to be susceptible to tigecycline (MIC90 values 0.25–2 mg/L for both species). ESBL production among isolates of K. pneumoniae in the reviewed studies ranged from 5.3% to 52.8,27–29,33,35,37,38,44 We identified 23 studies that evaluated the susceptibility to tigecycline of Klebsiella spp. isolates with MDR or other clinically significant resistance pattern, including a total of 3046 isolates.8,17–19,21–31,33–35,37,39–41 By the FDA criteria, adequate microbiological activity of tigecycline was shown in 18 of the 23 studies, and the susceptibility rate to tigecycline was 91.2% for 2627 isolates. By the EUCAST criteria, adequate microbiological activity of tigecycline was shown in 2 of 20 studies that reported specific relevant data;8,17–19,21–23,25,27–29,31,33–39,41 the susceptibility rate to tigecycline was 72.3% for 1504 isolates, for which relevant data were available.

Enterobacter spp.

We reviewed 28 studies reporting the activity of tigecycline against Enterobacter spp. More than 93% of the non-MDR Enterobacter spp. isolates were susceptible to tigecycline applying the FDA approved breakpoint of susceptibility.8,16,26,30,35,39,42,43,46–49,53,55 We identified 11 studies that reported data on the susceptibility to tigecycline of 686 Enterobacter spp. isolates with multiple drug resistance or other types of clinically significant resistance pattern. By the FDA criteria, adequate microbiological activity of tigecycline was noted in 6 of the 11 studies,2,21–24,34,40 and 380/576 (66.0%) of isolates, for which specific relevant data were available, were susceptible to tigecycline.17,20–24,34,37,40,41 By the EUCAST criteria, adequate microbiological activity of tigecycline was noted in only one study, out of seven studies that reported specific relevant data, and the overall susceptibility rate of 278 Enterobacter isolates identified in these studies was 73.4% (compared with 87.8%, using the FDA criteria for these seven studies).17,20–23,34,40

Citrobacter spp.

We reviewed 13 studies reporting the activity of tigecycline against Citrobacter spp.16,22,24,26,28,34,39,42–46 More than 96% of the non-MDR Citrobacter spp. isolates were susceptible to tigecycline by applying the FDA approved breakpoint, with MIC90 values of 0.25–2 mg/L.26,29,39,42,44,46,49 We identified three studies that reported data on the susceptibility to tigecycline of 46 Citrobacter spp. isolates with MDR or other types of clinically significant resistance pattern. The susceptibility rate to tigecycline was 95.7% with the use of the FDA criteria.22,24,34

Serratia spp.

We reviewed 22 studies reporting the activity of tigecycline against Serratia spp.8,16,20–22,26,28,29,33–35,39,41–49,55 More than 90% of the non-MDR Serratia spp. isolates were susceptible to tigecycline, by the FDA breakpoints, in all studies, with MIC90 values of 1–4 mg/L.8,16,26,29,33,35,39,43–49,55 We identified six studies that reported data on the susceptibility to tigecycline of 90 Serratia spp. isolates with multiple drug resistance or other
types of clinically significant resistance patterns.\textsuperscript{20–22,28,34,41} Adequate microbiological activity of tigecycline was noted in three of these six studies, using the FDA criteria,\textsuperscript{21,22,34} and the susceptibility rate to tigecycline was 78.4\% for 51 isolates, for which specific relevant data were available.

**Proteae**

We reviewed 14 studies that evaluated the activity of tigecycline against species of the tribe of Proteae and more specifically against 1890 isolates of *Proteus mirabilis* and 1032 strains of the indole-positive Proteae (including 183 isolates of *Proteus vulgaris*, 264 isolates of *Morganella* spp, and 238 isolates of *Providencia* spp).\textsuperscript{16,26,29,30,34,39,40,42–46,53,55} In the majority of these studies, the MIC\textsubscript{90} values for Proteae was 4–8 mg/L and most of the isolates had intermediate susceptibility to tigecycline, by the FDA breakpoints (MIC of 4 mg/L).\textsuperscript{16,26,39,42–46} We identified two studies that reported specific data on the susceptibility to tigecycline of ESBL- or AmpC-producing isolates (Table S1 available as Supplementary data at JAC Online, http://jac.oxfordjournals.org/).\textsuperscript{34,40}

**Clinical effectiveness of tigecycline for infections caused by MDR Enterobacteriaceae**

Tigecycline has been evaluated for the treatment of complicated intra-abdominal infections, in comparison to imipenem/cilastatin,\textsuperscript{57–59} as well as in complicated skin and skin structure infections in comparison to the combination of vancomycin plus aztreonam.\textsuperscript{9,58,60} The findings regarding the use of tigecycline in these two types of infections were favourable, leading to the approval of this agent by the FDA and the European Medicines Agency for both the above indications. Tigecycline has also been evaluated for the treatment of community-acquired pneumonia\textsuperscript{61} and nosocomial pneumonia, as well as for the diabetic foot infections, including osteomyelitis.\textsuperscript{62}

We identified 10 studies evaluating the clinical effectiveness of tigecycline for the treatment of patients with infections caused by MDR Enterobacteriaceae or Enterobacteriaceae with other types of clinically significant resistance.\textsuperscript{62–71} Data extracted from these studies are presented in Table 2. The 10 studies included present data on 33 cases of patients with infections caused by MDR Enterobacteriaceae (identified as *K. pneumoniae*, *E. coli* or *Enterobacter* spp.). The types of infections reported were complicated intra-abdominal infections (including complicated pelvic infections) in 16 of the 33 patients (48.5\%), bacteraemia in 8 patients (24.2\%), while 6 other patients had pulmonary infection and 3 patients had a urinary tract infection. Tigecycline was administered as monotherapy in 23 patients and in combination with other microbiologically active agents in 7 cases.\textsuperscript{63,65,66,68} Relevant data were not reported for 3 patients.\textsuperscript{64}

A favourable outcome of the infection was observed in 23 of the overall 33 included patients (69.7\%), while clinical response was deemed uncertain in 3 additional cases. In 1 of the 23 patients with resolution of the infection, two recurrences of empyema occurred along with an associated rise in the tigecycline MIC from 0.75 to 2 mg/L during the course of treatment, but re-treatment was successful.\textsuperscript{65} It should also be mentioned that among the 26 patients with a favourable or uncertain outcome of the infection, prolonged administration of tigecycline (over 21 days) was required in 5 patients. In four of those, delayed (more than 3 days) microbiological clearance or recurrence of the infecting pathogens was observed.\textsuperscript{65,66,68,70} Finally, the tigecycline MIC for the infecting pathogens was more than 2 mg/L (the FDA breakpoint of susceptibility) in 2 of the 10 cases in which specific relevant data were reported.\textsuperscript{68} In both these cases, the clinical outcome was characterized as uncertain.

**Further considerations**

In this review, potent microbiological activity of tigecycline was shown for *E. coli* isolates with MDR or other clinically significant resistance patterns (mostly production of ESBLs) by the use of either the FDA or the EUCAST breakpoints of susceptibility. Regarding ESBL-producing *Klebsiella* spp. isolates with the same as above resistance characteristics, adequate microbiological activity of tigecycline was shown with regard to the FDA criteria, but susceptibility rates fell below 90\% with the use of the more conservative EUCAST criteria. Susceptibility rates to tigecycline for carbapenem-resistant *Klebsiella* spp. isolates were not lower compared with ESBL-producing ones, potentially suggesting that porin loss, which is a common mechanism contributing to carbapenem resistance in this species, may not appreciably affect the activity of tigecycline,\textsuperscript{17} although it may relate to decreased susceptibility to other antibacterial agents apart from β-lactams.\textsuperscript{72} Tigecycline manifested a moderate degree of antimicrobial activity against MDR *Enterobacter* spp. isolates. The small number of isolates of other species of Enterobacteriaceae identified in the included studies (Citrobacter spp., *Serratia* spp. and *Proteus* spp.) does not allow for safe conclusions to be drawn regarding the microbiological activity of tigecycline.

The different methodologies used in the included studies for the determination of microbial susceptibility to tigecycline should be taken into consideration. Specifically, although the majority of the included studies were entirely or partly based on the broth microdilution method for the determination of susceptibility to tigecycline, five studies did not use this method. Specifically, three studies used the Etest along with the disc diffusion method,\textsuperscript{32,36} while two other studies used the agar dilution method.\textsuperscript{33,34} The reproducibility of findings regarding susceptibility to tigecycline of Enterobacteriaceae with the use of different microbiological methods has not been adequately evaluated. Yet, it appears that the Etest provides concordant findings compared with other methods.\textsuperscript{32,54,73} Regarding broth microdilution, it has been shown that the use of aged media (more than 12 h) may result in relative loss of the activity of tigecycline due to oxidation and thus in falsely higher MIC values.\textsuperscript{26,74} It is plausible that some of the earlier studies included in this review (performed prior to 2005) may not have taken this issue into consideration.

Randomized controlled trials have proven the effectiveness of tigecycline for complicated intra-abdominal infections and complicated skin and skin structure infections. Whether the observed microbiological activity of tigecycline against most of the Enterobacteriaceae with the various patterns of resistance evaluated in this review is translated into clinical effectiveness for off-label indications cannot be well established on the basis of the available clinical evidence.\textsuperscript{14} Although some experimental animal data support the above assumption,\textsuperscript{16,75} relevant clinical
Table 2. Clinical use of tigecycline for the treatment of infections caused by Enterobacteriaceae with clinically significant resistance patterns

<table>
<thead>
<tr>
<th>Author, publication year, type of study</th>
<th>Patient characteristics</th>
<th>Type of infection</th>
<th>Type of pathogens; resistance characteristics (tigecycline MIC)</th>
<th>Dose and duration of tigecycline</th>
<th>Concomitant antimicrobials</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infections</td>
<td></td>
<td></td>
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<tr>
<td>Anthony 2008 <em>(case series)</em></td>
<td>63-year-old female with history of cancer</td>
<td>tracheobronchitis</td>
<td>AmpC-producing <em>E. cloacae</em> with tigecycline MIC of 3 mg/L</td>
<td>standard dosing for 8 days</td>
<td>none</td>
<td>clinical response uncertain; death (unrelated to infection)</td>
</tr>
<tr>
<td></td>
<td>57-year-old male solid organ transplant recipient</td>
<td>ventilator-associated pneumonia with empyema</td>
<td>ESBL- and carbapenemase (KPC)-producing <em>K. pneumoniae</em> with tigecycline MIC of 1.00 mg/L</td>
<td>16 days</td>
<td>gentamicin</td>
<td>no clinical response; death</td>
</tr>
<tr>
<td></td>
<td>69-year-old female with diabetes</td>
<td>nosocomial pneumonia</td>
<td>MDR <em>K. pneumoniae</em> with tigecycline MIC of 0.75 mg/L</td>
<td>11 days</td>
<td>none</td>
<td>good clinical response</td>
</tr>
<tr>
<td></td>
<td>69-year-old male</td>
<td>aspiration pneumonia</td>
<td>ESBL-producing <em>K. pneumoniae</em> with tigecycline MIC of 0.75 mg/L</td>
<td>15 days</td>
<td>inhaled tobramycin</td>
<td>good clinical response</td>
</tr>
<tr>
<td>Daly 2007 <em>(case report)</em></td>
<td>49-year-old woman with history of multiple infections due to anastomotic leak after gastric bypass surgery</td>
<td>nosocomial pneumonia and empyema</td>
<td>carbapenemase (KPC)-producing <em>K. pneumoniae</em> with tigecycline MIC of 0.75 mg/L</td>
<td>standard dosing for 5 weeks</td>
<td>ciprofloxacin</td>
<td>resolution of infection; recurrence of empyema; resolution after re-treatment; death during hospitalization; increase in tigecycline MIC of 2 mg/L</td>
</tr>
<tr>
<td>Kneuppel 2007 <em>(case report)</em></td>
<td>46-year-old man who underwent CABG after myocardial infarction</td>
<td>pneumonia</td>
<td>carbapenem-resistant <em>K. pneumoniae</em></td>
<td>standard dosing for 29 days</td>
<td>polymyxin B</td>
<td>positive blood cultures for <em>K. pneumoniae</em> with same resistance profile after 2 weeks of therapy; resolution of infection</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Author, publication year, type of study</th>
<th>Patient characteristics</th>
<th>Type of infection</th>
<th>Type of pathogens; resistance characteristics (tigecycline MIC)</th>
<th>Dose and duration of tigecycline</th>
<th>Concomitant antimicrobials</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis/bacteraemia/endovascular infections</td>
<td></td>
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</tr>
<tr>
<td>Anthony 2008 (retrospective case series)</td>
<td>44-year-old male heart transplant recipient</td>
<td>endovascular infection with recurrent bacteraemia</td>
<td>ESBL-producing <em>K. pneumoniae</em> with tigecycline MIC of 1.50 mg/L</td>
<td>standard dosing for 23 days plus 18 days (recurrence)</td>
<td>meropenem, colistin (recurrence)</td>
<td>no clinical response; death</td>
</tr>
<tr>
<td>Souli 2008 (retrospective case series)</td>
<td>53-year-old male with diabetes, congestive heart failure under haemodialysis</td>
<td>bacteraemia (septic thrombophlebitis due to retained venous catheter)</td>
<td>standard dosing for 133 days</td>
<td>none</td>
<td>uncertain clinical response</td>
<td></td>
</tr>
<tr>
<td>Cobo 2008 (case report)</td>
<td>74-year-old male with diabetes, chronic renal failure and soft tissue infection receiving mechanical ventilation</td>
<td>breakthrough primary bacteraemia</td>
<td>MBL (VIM-1)-producing, colistin-resistant <em>K. pneumoniae</em> with tigecycline MIC of 0.75 mg/L</td>
<td>50 mg twice daily for 4 days</td>
<td>none</td>
<td>death</td>
</tr>
<tr>
<td>Knueppel 2007 (case report)</td>
<td>80-year-old man with diabetes mellitus and end-stage renal disease on haemodialysis</td>
<td>persistent bacteraemia for 7 days</td>
<td>MBL (VIM-1)-and ESBL (SHV-12)-producing <em>K. pneumoniae</em> with tigecycline MIC of 0.5 mg/L</td>
<td>standard dosing for 24 days</td>
<td>colistin initially followed by 9 days of tigecycline monotherapy</td>
<td>resolution of infection</td>
</tr>
<tr>
<td>Cunha 2007 (clinical trial)</td>
<td>3 patients</td>
<td>bacteraemia</td>
<td>MDR <em>K. pneumoniae</em> susceptible to tigecycline</td>
<td>standard dosing</td>
<td>NA</td>
<td>resolution of infection in 3/3 patients</td>
</tr>
<tr>
<td>Intra-abdominal infections</td>
<td></td>
<td></td>
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<tr>
<td>Anthony 2008 (retrospective case series)</td>
<td>49-year-old female solid organ transplant recipient</td>
<td>pelvic abscess</td>
<td>AmpC-producing <em>E. cloacae</em> with tigecycline MIC of 3 mg/L</td>
<td>standard dosing for 7 days</td>
<td>none</td>
<td>uncertain clinical response; death (unrelated to infection)</td>
</tr>
<tr>
<td>Oliva 2005 (Phase 3, double-blind RCT)</td>
<td>13 adults</td>
<td>complicated intra-abdominal infections</td>
<td>6 ESBL-producing <em>K. pneumoniae</em>; All susceptible to tigecycline, (MIC ≤ 1 mg/L)</td>
<td>standard dosing for ≥ 5 to ≤ 14 days</td>
<td>none</td>
<td>eradication or presumed eradication of infecting strains; 5/6 (83%) <em>E. coli</em>; 5/7 (71%) <em>K. pneumoniae</em></td>
</tr>
</tbody>
</table>
standard dosing for ≥5 to ≤14 days none

Eradication or clinical cure in 2/2 (100%)
for infections caused by these pathogens, particularly for bacteremia and complicated urinary tract infections, are required.

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Transparency declarations
None to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References
Systematic review


