GUIDANCE ON TREATMENT OF CARBAPENAMASE PRODUCING ENTEROBACTERIACEAE

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UKCPA Pharmacy Infection Network  
Carbapenamase producing Enterobacteriaceae (CPE) treatment guidance

Acknowledgements
This document has been developed on behalf of the UK Clinical Pharmacy Association by a Working Group comprising the following members:

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Other members of the Pharmacy Infection Network Committee provided feedback.

Definitions

**Enterobacteriaceae** are commensal bacteria of the gut of humans and animals. However, these organisms are some of the most common causes of opportunistic urinary tract infections, intra-abdominal and bloodstream infections. Enterobacteriaceae include species such as *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp.

**Carbapenems** are a structurally related and similar group (class) of antibiotics normally reserved for serious infections caused by drug-resistant Gram-negative bacteria (including Enterobacteriaceae). They include meropenem, ertapenem and imipenem. The carbapenem class of antibiotics are commonly regarded as “last line” treatment for the most serious of infections.

**Antimicrobial resistance** (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it. Several mechanisms exist by which bacteria can display resistance to carbapenem antibiotics. A full discussion on the mechanisms of resistance is beyond the scope of this guidance.

**Carbapenemases** are enzymes that destroy carbapenem antibiotics, conferring resistance. They are produced by a small but growing number of Enterobacteriaceae strains. The presence of a carbapenemase does not always result in high level resistance to carbapenems in vitro.

<table>
<thead>
<tr>
<th>Beta-lactamase class</th>
<th>Variant(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class A (Serine)</strong></td>
<td>KPC</td>
</tr>
<tr>
<td><strong>Class B (Zinc)</strong></td>
<td>NDM, VIM, IMP</td>
</tr>
<tr>
<td><strong>Metallo-beta-lactamases</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Class D (Serine)</strong></td>
<td>OXA</td>
</tr>
</tbody>
</table>

¹ Carbapenemases include enzymes from beta-lactamases classes A, C and D (Ambler classification). The main classes of acquired carbapenemases are listed above.
Scope

The aim of this guideline is to support the guidance outlined in the Public Health England Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae (CPE).

A key recommendation of this guidance was that “Treatment of the patient with an infection caused by CPE should be undertaken under the advice of the microbiologist”. It is hoped that this document will support Trust antimicrobial committees, microbiology and pharmacy teams in developing the most effective strategies to treat these highly resistant infections.

This guidance was developed following a review of the published literature to propose a series of treatment principles, review the place in therapy of antibiotic treatments that may be effective and provide information on dose optimisation to maximise response for treatment. Information is provided on unlicensed doses and methods of administration that have been used in the literature or theoretically have potential to maximise effect. It is the responsibility of Healthcare organisations to review the suitability of these options on an individual patient basis. Clinicians and patients must be made aware of the unlicensed status when using doses outside of the UK marketing authorisation. There are a number of drugs in development that may have activity against some CPE. These have not been included and are outside of the scope of this document.

This guideline refers principally to treatment of acquired carbapenemases in Enterobacteriaceae, specifically NDM, VIM, IMP, KPC, OXA-48 (as defined by UK Standards for Microbiology Investigations. Laboratory Detection and Reporting of Bacteria with Carbapenem-Hydrolysing β-lactamases (Carbapenemases). Public Health England May 2014).

Other bacteria such as multi-drug resistant Acinetobacter and Pseudomonas may host several mechanisms conferring resistance to carbapenems including carbapenemases (class D, class B), reduced porin channels and multi-drug efflux pumps. An attempt has been made to include information relating to these organisms where possible.

The recommendations assume treatment of infection rather than colonisation.

Data in children is extremely limited and information relating to drug dosing in children has not been included.
Treatment Principles and Recommendations

General principles

The statements below are based on best practice for management of infection and national guidance.

- Treatment of the patient with an infection caused by CPE should be undertaken under the advice of the microbiologist
- Start treatment promptly
- Treatment should be guided by susceptibility results. These may vary between strains, including samples obtained from a single patient during a single infection.
- Only treat if patient has symptoms of infection. Patients may be colonised with CPE. Usually identified by a rectal swab or stool sample but may also be colonised at other sites.
- Review treatment daily to confirm effectiveness and check for adverse effects.

Specific principles

From a review of the available literature the working group recommend the following principles be used in managing infections caused by CPE. All recommendations relating to treatment assume that the organism is susceptible on testing (below MIC breakpoint) unless specified.

Combination verses monotherapy

Recommendations relating to combination therapy are based on clinical outcomes of published cases / retrospective reviews. There is currently no data to inform whether combination therapy prevents or promotes emergence of resistance in this setting. There are no studies that compare the efficacy of different combination of antibiotics against infections caused by CPE. The following combinations have been quoted in the literature as being successful in some cases. A review from 2012 describes mortality outcomes in relation to each antibiotic regime but numbers are too small to draw conclusions.

Recommendations and Supporting Evidence

- For bacteraemias and severe infection, including respiratory tract infections, use a minimum of 2 antibiotics to which the organism is susceptible. There is insufficient evidence to conclude which combinations are most effective.

In a review of 105 cases with a variety of KPC infections, significantly more treatment failures were seen with monotherapy (49% vs. 25% p= 0.01). Higher rates of treatment failure with monotherapy for respiratory tract infections were observed (67% vs. 29% p=0.03).

A systematic review of antibiotic treatment of infections caused by carbapenemase producing Enterbacteriaceae found that the majority of studies did not show statistically
significant differences in mortality or treatment failures between combination and monotherapy. However, 3 studies reviewed including a total of 194 patients with bacteraemia demonstrated a significantly lower mortality with combination therapy. colistin/polymyxin B or tigecycline combined with a carbapenem. The mortality in this group was 12.5% (1/8). Despite in vitro susceptibility, patients who received monotherapy with colistin/polymyxin B or tigecycline had a higher mortality of 66.7% (8/12) than those patients receiving combination therapy.\(^1\)

In another study of 35 patients with KPC blood stream infections, appropriate antibiotics (defined as in-vitro susceptibility) were administered for at least 48 hours. All 20 patients that received combination therapy had favourable infection outcome; in contrast, seven of 15 patients given appropriate monotherapy died (p = 0.001). The study found that appropriate antimicrobial therapy was the only modifiable predictor of infection outcome.\(^5\) The optimal number of agents has not been established; one study noted a survival benefit with the addition of a carbapenem to tigecycline and colistin therapy.\(^5\)

- **Carbapenems may be used in combination with other agents. Outcomes are likely to be improved if the organism appears susceptible on in vitro testing (meropenem and imipenem MIC < 1µg/mL, ertapenem < 0.5µg/mL) or is close to the breakpoint.** There is limited data to support the addition of meropenem to other agents if the MIC is ≤4µg/mL leading to improved outcomes.

Several studies\(^1,4,5\) demonstrate that combination therapy involving a carbapenem may be effective. In a review of 105 cases of KPC infection, treatment failure was higher with carbapenem monotherapy compared to carbapenem-based combination therapy (60% vs. 26%).\(^2\) In an Italian multicentre study of 125 patients with KPC producing *K. pneumoniae* bacteraemia combination therapy with tigecycline, colistin and meropenem (2g eight hourly infused over an extended period of 3 hours) was associated with lower mortality (OR 0.11, p=0.01).\(^4\) It is unknown whether this benefit translates to traditional meropenem dosing and administration. 36 patients were treated with this combination, in 17 patients the meropenem MIC was >16µg/L. Survival in this group was 64%. Survival was 100% for patients treated with the combination were meropenem MIC <2mg/L (n=5). Numbers are too small to draw any firm conclusions, but may be suggestive of a survival benefit. The authors concluded that addition of meropenem may be helpful if the MIC ≤4µg/mL.

- **Colistin is not recommended as monotherapy for systemic infections**

In a review of 105 cases of KPC infection, polymyxin monotherapy was associated with higher rates of treatment failure compared to polymyxin based combination therapy (73% vs. 29%; 8/11 vs. 10/34; p=0.02).\(^2\) This review did not give details of the doses of polymyxin used. It has been hypothesised by Lee *et al.* that combination therapy may prevent the development of resistance to polymyxin B whilst on therapy.\(^6\)

- **Where tigecycline is used for treatment of respiratory tract infections it should be used in combination with a second agent.**

The Summary of Product Characteristics for Tigecycline (Tygacil) states it is only licensed for complicated skin and soft tissue infections, excluding diabetic foot infections, and complicated intra-abdominal infections and that “Tygacil should be used only in situations where other alternative antibiotics are not suitable.”
In clinical studies in complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), diabetic foot infections, nosocomial pneumonia and studies in resistant pathogens, a numerically higher mortality rate among tigecycline treated patients has been observed as compared to the comparator treatment. The causes of these findings remain unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.\textsuperscript{7}

The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) has recommended that tigecycline should only be used within its licensed indications as a pooled analysis of clinical studies showed an increased mortality associated with tigecycline versus comparator agents.\textsuperscript{8} A similar communication from the Food and Drug Administration noted that the greatest increase in risk of mortality in the tigecycline arm was seen in ventilator associated pneumonia (19.1\% vs. 12.3\%).\textsuperscript{9}

However in a single review of a small number of CPE cases there was no difference in failure rates between tigecycline monotherapy and combination therapy (29\% vs. 37\% \(p=0.4\)) (n=2/7 and 7/19 respectively).\textsuperscript{9} Treatment failures included patients treated for urosepsis and pneumonia with empyema.

- **Fosfomycin should be used in combination with other agents when used for systemic therapy, due to its vulnerability to acquired resistance.**

The Summary of Product Characteristics states that Fosfomycin should be used only when conventional therapy is considered inappropriate.

It has been demonstrated that resistance to intravenous fosfomycin can develop rapidly when it is used for monotherapy.\textsuperscript{10}

An in vitro study investigating the synergistic effect and impact on development of resistance of fosfomycin with colistin, meropenem or gentamicin found that all combinations showed improved bactericidal activity compared to fosfomycin alone and prevented the development of resistance in the majority of fosfomycin-susceptible isolates.\textsuperscript{11}

In a small case series of critical care patients with carbapenem resistant *Klebsiella pneumoniae* intravenous fosfomycin (4g every 6 hours adjusted for renal impairment) was administered as combination therapy with colistin (n=6), gentamicin (n=3) and piperacillin/tazobactam (n=1). All-cause mortality was 18.1\% but no patient developed a relapse of infection.\textsuperscript{12}

- **Temocillin and aztreonam may be used in combination with non-beta-lactams if organisms appear to be susceptible.**

These agents must not be used as monotherapy. Temocillin is not active against most CPE but remains effective against KPC-producing Enterobacteriaceae in in vitro studies.

**Urinary tract infections**

- **Urinary tract infections may be treated with a single agent that is known to concentrate in the urine and which the isolate is susceptible to.**

The review by Lee and Burgess found an 81\% success rate (9/11) in patients treated for urinary tract infections, with 8 of these cases treated with monotherapy.\textsuperscript{2}
- Aminoglycoside antibiotics should be considered for treatment of urinary tract infections where sensitivities allow

Aminoglycoside therapy resulted in a significantly higher rate of microbiologic clearance of carbapenem resistant *K. pneumoniae* in the urine compared to polymyxin B or tigecycline in one study.\(^\text{13}\)

There was no difference in failure rates between aminoglycoside monotherapy and combination therapy (0/6 and 4/24 respectively, \(p=0.6\)) in the study by Lee et al above.\(^2\)

Patients successfully treated with monotherapy included blood stream infections (\(n=3\)) and urinary tract infections (\(n=2\)).

- Tigecycline is not recommended for treatment of urinary tract infections

Low levels of tigecycline are excreted into the urine.

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**Limitations**

Due to the lack of randomised controlled trials the recommendations in this guide are based on limited or low quality evidence. However it is intended as a practical guide based on the best information available.

Meta-analyses show there is lack of consistency in outcome data.

Due to the heterogeneity and low patient numbers in the studies it is not possible to compare the outcomes of different combination therapies.

When well conducted meta-analyses / review papers collating data on outcomes from individual studies were available there were used in preference.

The majority of the studies report on KPC carbapenemase producing *Klebsiella pneumoniae* as the most common CPE mechanism.

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**UK Guidance and supporting references**


## APPENDIX

### Drug dosing information

Optimising dosing strategies to give the highest drug exposure according to pharmacokinetic and pharmacodynamic parameters is recommended. The tables below provide information on how this can be achieved. Please note that some recommendations reflect dosing strategies not covered by the product license. For details of side effects and interactions please refer to Summary of Product characteristics [http://www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/) and the current British National Formulary [https://www.evidence.nhs.uk/](https://www.evidence.nhs.uk/).

#### Aminoglycosides

<table>
<thead>
<tr>
<th>Place in therapy</th>
<th>Resistance to aminoglycosides is variable between strains. NDM-1 producing organisms frequently carry resistance to aminoglycosides. Case reports most frequently cite amikacin as a treatment option.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal administration and dosing</td>
<td>The working group recommends standard optimal once daily regimens based on optimal pharmacokinetic parameters: Gentamicin 5-7mg/kg daily Amikacin 15mg/kg daily</td>
</tr>
<tr>
<td>Cautions associated with high dose regimens</td>
<td>Caution should be applied to patients with pre-existing renal insufficiency, or pre-existing hearing or vestibular damage. Amikacin must not be used in patients with Myasthenia Gravis. Aminoglycosides should be used with caution in patients with muscular disorders such as parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.</td>
</tr>
<tr>
<td>Local experience / practical issues</td>
<td>Otoxicity is more common with amikacin, baseline audiology recommended if course is likely to be prolonged (&gt; 2 weeks).</td>
</tr>
</tbody>
</table>

#### Aztreonam

<table>
<thead>
<tr>
<th>Place in therapy</th>
<th>May be a treatment option for metallo-beta-lactamases. Not active against KPC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal administration and dosing</td>
<td>There is a paucity of evidence regarding use of aztreonam in CPE therefore dosing information has been extrapolated from information on carbapenem-resistant pseudomonas where 2g IV every 8 hours is advised. The dosing interval can be reduced to 6 hours for severe systemic or life-threatening infections.</td>
</tr>
</tbody>
</table>
Extended infusions of beta-lactams are advocated in difficult to treat infections because their activity is time-dependent and a positive correlation exists between their efficacy and the amount of time the drug concentration exceeds the MIC value during the dosing interval. There is one published case report of successful treatment of an MDR *P. aeruginosa* infection in an immunocompromised patient with a continuous of infusion of aztreonam (8.4g/day) in combination with tobramycin, ciprofloxacin, vancomycin, polymixin B, azithromycin and nebulized colistin.

| Cautions associated with high dose regimens | Neurotoxicity is one of the most serious potential side effects of beta-lactam antibiotics and may include confusion, disorientation, somnolence, twitching, myoclonus, and seizures. Risk factors for neurotoxicity include high dosages, history of seizures, other CNS disorders, renal failure, and concomitant drugs that lower the seizure threshold. If aminoglycosides are used concurrently with aztreonam, particularly in high doses or prolonged duration there is potential for nephrotoxicity and ototoxicity. |
| Clinical pharmacokinetics | **Absorption:** negligible oral bioavailability (<1%), completely absorbed after intramuscular injection

**Distribution:**
Vdss after intravenous or intramuscular injection is approx 0.16 L/kg (0.42 L/kg for the free drug).
Dose – concentration relationship: Over a large dosage range plasma concentrations increase linearly with dose. No accumulation occurs after multiple dosing.
Plasma binding: 56% in healthy subjects, not concentration dependent.
Diffusion into tissues is generally slow, and dependent upon tissue type. In inflamed meninges, penetration of aztreonam into CSF is more rapid than with uninflamed meninges. Diffusion through the placenta is poor, as is diffusion into breast milk.

**Metabolism** occurs to a very limited extent.

**Elimination:** primarily renal by active tubular excretion. Extra-renal clearance is probably due to excretion by the liver.
Total plasma clearance in healthy adults is about 140 ml/min (8.4 L/h) or 2 ml/min/kg (0.12 L/h/kg), and terminal half-life is 1.7 hours.

## Carbapenems

**Place in therapy**
Carbapenems may be used in combination with other agents. In practice meropenem is the most commonly used carbapenem in the UK. Outcomes are likely to be improved if the organism appears susceptible on in vitro testing (meropenem, imipenem MIC ≤ 1μg/mL, ertapenem ≤ 0.5μg/mL) or close to the breakpoint. There is limited data to support the addition of meropenem to other agents if the MIC is ≤ 4μg/mL leading to improved outcomes.

**Optimal administration and dosing**
Because the killing activity of beta-lactams is time-dependent, a positive correlation exists between their efficacy and the amount of time the drug concentration exceeds the MIC value during the dosing interval. To optimize dosing strategies to achieve better bacterial killing, studies have evaluated the role of administering beta-lactams in extended infusions with encouraging results. Evidence suggests that using a high dose extended infusion has a lower mortality rate compared to short-term infusions. However, the data are based on case reports with small numbers and heterogeneity, and well-designed RCT are warranted to confirm these findings.

- Meropenem 1 – 2g tds
- Imipenem 500mg qds or 1g tds
- Ertapenem 1g od

It is important to note that, before adopting high-dose and extended-infusion regimens, consideration should be given to the safety and stability of the compounds used. For example, imipenem is not likely to be considered for this therapeutic strategy, in view of its lower stability at elevated room temperatures and its lower tolerability when administered in higher dosages.

Case reports suggest the following infusion regimen:
- Meropenem 3 hour infusion or 8 hour infusion.

**Cautions associated with high dose regimens**
Care with high dose imipenem – increased risk of neurotoxicity

**Clinical pharmacokinetics**
- Monte Carlo simulation models of different dosing regimens of carbapenems indicate that prolonging the infusion time from 30 min to 3 h increases the probability of bactericidal target attainment at each MIC value. The probabilities of attaining $T > MIC$ targets for at least 50% of the dosing intervals for an MIC of 4 mg/L were 69%, 93% and 100% for the 1 g prolonged infusion (PI) every 8 h, 1 g PI every 8 h and 2 g PI every 8 h dosing regimens, respectively.
- For an MIC of 8 mg/L, only the high-dose/prolonged-infusion regimen displayed a relatively high probability (85%) of bactericidal target attainment.
- Considering these observations in combination with the MIC distributions of CPKP isolates, the high-dose/prolonged-infusion regimen of meropenem achieves the bactericidal PK/PD targets with a high degree of certainty for CPE with MICs of ≤ 4 mg/L.
References


Daikos GL and Markogiannakis A. Carbapenemase-producing Klebsiella pneumoniae: (when) might we still consider treating with carbapenems? Clin Microbiol Infect 2011; 17: 1135–1141

Pankey GA, Ashcraft DS. Detection of synergy using the combination of polymyxin B with either meropenem or rifampin against carbapenemase-producing Klebsiella pneumoniae Diagnostic Microbiology and Infectious Disease 70 (2011) 561–564.


<table>
<thead>
<tr>
<th><strong>Colistin</strong></th>
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<tbody>
<tr>
<td><strong>Place in therapy</strong></td>
</tr>
<tr>
<td><strong>Optimal administration and dosing</strong></td>
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<tr>
<td><strong>Cautions associated with high dose regimens</strong></td>
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<tr>
<td><strong>Clinical pharmacokinetics</strong></td>
</tr>
<tr>
<td><strong>Local experience / practical issues</strong></td>
</tr>
</tbody>
</table>
References


Guideline for Intravenous Colistimethate Sodium Dosing and Monitoring in Critically Ill Patients at Tallaght Hospital, September 2012.

Critical Care Guideline for intravenous colistimethate sodium (Colistin). Guy’s and St Thomas’ NHS Foundation Trust, June 2014.


Visser Kift E, Maartens G, Bamford C. Systematic review of the evidence for rational dosing of colistin. SAMJ; 2014; 104 (3); 183-186


Alfahad W, Omrani AS. Update on colistin in clinical practice. Saudi Med J 2014; 35 (1); 9-19
**Fosfomycin**

| Place in therapy | Drug distribution, data from clinical studies and licensed indications in Germany support use **in combination** with other therapy in the following infections:  
- Generalised sepsis  
- Respiratory tract infections including pulmonary abscesses  
- Skin and soft tissue infections  
- Biliary tract infections  
- Central nervous system (CNS) infection  
- Osteomyelitis  
- Ophthalmic infections  

For treatment of urinary tract infections fosfomycin is routinely given as monotherapy.

The SPC clearly states fosfomycin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of the infections listed above, or when these alternatives antibacterial agents have failed to demonstrate efficacy.

| Optimal administration and dosing | Doses in the literature recommend 8 to 16g daily depending on the site and severity of infection. The working group recommend IV fosfomycin for treatment of severe infections with multi-resistant organisms at a dose of 16g daily (divided doses 4g four times daily).  
  
  Oral therapy for UTI  
  Complex UTI or other indication: 3g PO every 48 hours for up to 2 weeks. Usual duration = 3 doses

| Dosing in renal impairment | IV preparation: Reduce dose in renal impairment  
  GFR 20-50ml/min: 4g every 8 hr  
  GFR 10-20ml/min : 4g every 12-hr  
  GFR <10ml/min: 4g every 24 hr  
  HD/HDF: 4g every 12 hr , CVVH: Dose as normal kidney function  
  Oral preparation GFR <50ml/min:  
  Complex UTI or other indication: 3g every 72 hr for up to 14 days  
  HD: 3g at the end of the haemodialysis.

| Clinical pharmacokinetics | The concentrations in serum are higher when oral doses are administered before food intake. Pharmacokinetic parameters indicate oral absorption is significantly reduced after food intake. Fifty-eight per cent of the administered dose is found in the urine within 24 hours. Urinary concentrations are high and may exceed 2000 mg/L after administration of a single dose. Urinary levels remain high for a prolonged period (over 24 hours).  

| Local experience / practical issues | Experience from Manchester suggests that resistance may rapidly develop in patients treated for urinary tract infection and hence they recommend a prolonged course of oral therapy.

**Place in therapy**

The review was unable to locate any clinical outcome data relating to treatment of CPE infections with fluoroquinolone agents. CPE isolates may be sensitive in vitro. Where isolates demonstrate in vitro sensitivity the working group recommends that fluoroquinolones may be included within therapy regimes as they have been proven to be effective treatments in numerous clinical settings where carbapenemase producing enzymes are not present.

**Optimal administration and dosing**

**Ciprofloxacin**

Standard doses for ciprofloxacin:
- Oral 500mg every 12 hours
- Intravenous infusion 400mg every 12 hours

Maximal licensed and recommended doses of ciprofloxacin in adults are 750mg every 12 hours orally and 400mg every 8 hours via the intravenous route. For severe and deep seated infections maximal licensed doses should be used.

**Clinical pharmacokinetics**

**Ciprofloxacin**

For optimal efficacy the AUC:MIC ratio of unbound drug should be greater than 125 for fluoroquinolones. BSAC breakpoint MIC Enterbacteriaceae: $\leq 0.5$mg/L

Based on the published pharmacokinetic data values close to the optimal AUC:MIC ratios are only likely to be achieved for organisms with an MIC of less than 0.25mg/L. However this does not take into account the degree of distribution into tissues

**Pharmacokinetic data**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Regime</th>
<th>Fraction unbound</th>
<th>Mean AUC mg/h/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>IV</td>
<td>400mg 12h</td>
<td>70%</td>
<td>22.8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Po</td>
<td>750mg 12h</td>
<td>70%</td>
<td>40</td>
</tr>
</tbody>
</table>

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

**Local experience / practical issues**

Experience from Manchester suggests that ciprofloxacin used at standard doses can achieve clinical cure where the MIC $< 0.5$mg/L. Local experience includes treatment of urinary tract infections. For other infections use combination therapy where possible.
**References**


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### Rifampicin

**Place in therapy**

Rifampicin has been shown to have synergistic activity with meropenem and colistin, and may be considered for combination therapy.

**Optimal administration and dosing**

Very little data in literature of doses used.

One case report where rifampicin used in combination with colistin.

Rifampicin 300mg bd.

**References**

- Pankey GA, Ashcraft DS. Detection of synergy using the combination of polymyxin B with either meropenem or rifampin against carbapenemase-producing *Klebsiella pneumoniae* Diagnostic Microbiology and Infectious Disease 70 (2011) 561–564.


Temocillin

Place in therapy
In vitro data shows that KPC-producing Enterobacteriaceae are often susceptible to temocillin. The most recent and largest dataset is from the ARHAI Reference Unit, Public Health England where susceptibility rates of 51% and of 94% were observed using, the systemic (8 mg/L) and the urinary (16 mg/L) breakpoints, respectively. Temocillin is not a treatment option for organisms producing other carbapenemases (e.g. VIM, OXA). The review was unable to locate any clinical outcome data relating to treatment of CPE infections with temocillin.

Optimal administration and dosing
Maximal licensed and recommended dose in adults is 2g every 12 via the intravenous route. Higher doses of temocillin (2g IV TDS) may be recommended in severely septic patients hospitalised in intensive care, although this regimen is not licensed. Although not licensed, temocillin (4g/day or 6g/day) is suitable for continuous infusion which allows reaching better PK/PD target. In this case, a loading dose of 2g is required.

Cautions associated with high dose regimens
No specific side effects have been reported with both the maximal recommended dose (2g BD) and the high dose (6g/day) in critically ill patients but as with most beta-lactams, caution is required in regards to a potential neurotoxicity.

Clinical pharmacokinetics
There are no EUCAST or CLSI breakpoints for temocillin. Breakpoints following the BSAC method for Enterobacteriaceae are as follows:
- Susceptible organisms: MIC ≤ 8 mg/L
- Resistant organisms: MIC > 8 mg/L
- Uncomplicated urinary tract infections:
  - Susceptible organisms: MIC ≤ 32 mg/L
  - Resistant organisms: MIC > 32 mg/L

PK/PD of IV temocillin using Monte Carlo simulation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Mean ft&gt;MIC in % of free temocillin</th>
<th>MIC of 8 mg/L</th>
<th>MIC of 32 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g 24h</td>
<td>37%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>2g 12h</td>
<td>80%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>2g 8h</td>
<td>100%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

ft>MIC = Proportion of time that free temocillin above MIC
Studies indicate 24h continuous infusion provides longer ft>MIC.

The protein serum binding rate is 85% in healthy volunteers and temocillin is excreted unchanged mainly in the kidney (up to 80% of the dose is found in the urine after 24 hours). In patients with renal impairment, the dose must be adapted.

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Regimen</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 60</td>
<td>2g BD</td>
<td>6g</td>
</tr>
<tr>
<td>60 to 30</td>
<td>1g BD</td>
<td>2g TDS</td>
</tr>
<tr>
<td>10 to 30</td>
<td>1g OD</td>
<td>1g TDS</td>
</tr>
<tr>
<td>Less than 10</td>
<td>1g OD</td>
<td>1.5g OD</td>
</tr>
<tr>
<td></td>
<td>1g/48h or 500mg OD</td>
<td>750 mg OD</td>
</tr>
<tr>
<td>Local experience / practical issues</td>
<td>Some local treatment experience in Manchester for treating KPC-producing Enterobacteriaceae, most frequently for urinary tract infections. Minimum dose 2g BD. Monitor for development of resistance whilst on therapy or in recurrent infections.</td>
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### Tigecycline

<table>
<thead>
<tr>
<th>Place in therapy</th>
<th>Evidence for use particularly in combination with other agents.</th>
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| Optimal administration and dosing | Standard dosing (100mg loading dose followed by 50mg BD) and high dose regimen of 100mg BD have been used for treatment of CPE infections with success in critical care. Evidence evaluating outcomes comparing these regimens is scarce. These patient groups may benefit from high dose regimen:  
- Cultures with intermediate sensitivity to tigecycline  
- Patients with ventilator associated pneumonia |
| Cautions associated with high dose regimens | Increased incidence of side-effects  
- Nausea, vomiting and diarrhoea  
- Increased transaminases  
- Thrombocytopenia |
| Local experience / practical issues | Owing to the increased adverse effects associated with unlicensed high doses the following are recommended:  
- Prescription of anti-emetic medication  
- Weekly monitoring of LFTs  
- Weekly monitoring of platelets |