**Introduction**

Imipenem is a carbapenem and member of the beta-lactam class of antimicrobials. It has a very broad spectrum of antimicrobial activity. Because it is inactivated by a renal dipeptidase, imipenem is formulated in combination with a dipeptidase inhibitor – cilastatin.\(^1\,^2\)

The 2004 WHO Model Formulary specifies the following uses: severe aerobic and anaerobic Gram-positive and Gram-negative infections in hospital (not indicated for central nervous system infections), including infections caused by resistant *Pseudomonas* and *Acinetobacter* spp.\(^3\)

Other drugs currently listed in the formulary with related but not identical uses include gentamicin, ceftriaxone (complementary list) and ceftazidime (complementary list). Meropenem, (another carbapenem), which has similar antimicrobial activity to imipenem, but attains better levels in the cerebrospinal fluid and has a lower incidence of seizures, is not listed.

**Product and Dosage**

Imipenem is available for either intramuscular injection or intravenous infusion. The powder for solution for intramuscular injection is available as imipenem monohydrate 500 mg with cilastatin sodium 500 mg. The powder for solution for intravenous solution is available as imipenem monohydrate 250 mg or 500 mg with cilastatin sodium 250 mg or 500 mg respectively.

Adult dosage (expressed in terms of imipenem) is 500 mg to 1000 mg every 6 to 8 hours. The maximum dosage is 4 g/day. Doses should be reduced in renal impairment.\(^1\,^2\)

**Evidence of value**

Imipenem has wide activity against enteric Gram-negative rods and *Pseudomonas aeruginosa* (comparable to that of aminoglycosides) and excellent activity against anaerobes (including *Bacteroides fragilis*) and many Gram-positive organisms. Imipenem is inactive against *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Mycoplasma*, *Chlamydia*, *Stenotrophomonas* and some *Pseudomonas* species.\(^1\,^2\)

The main indications (as a subset of the listed uses in the WHO Model Formulary) for which there is evidence and support for its use include:

- melioidosis – used often in combination with sulfamethoxazole/trimethoprim. The main alternatives are ceftazidime (complementary list) and meropenem (not listed). (Note: Melioidosis is caused by *Burkholderia pseudomallei* which is an important cause of community-acquired sepsis in South-East Asia, and a less important but an increasingly frequent cause of sepsis in parts of India and China.)\(^1\,^4\,^7\)

- pneumonia
  - caused by *Burkholderia pseudomallei* (see note in melioidosis, above)
    – used often in combination with sulfamethoxazole/trimethoprim. Alternatives include ceftazidime (complementary list) and meropenem (not listed).\(^1\,^5\,^6\)
  - caused by *Acinetobacter baumannii* – a less frequent cause of pneumonia of some significance in South-East Asia, but of much less importance in other regions. Community-acquired *A. baumannii* is
generally sensitive to gentamicin or sulfamethoxazole/trimethoprim. For hospital-acquired \textit{A. baumannii}, resistance is an increasing problem in South-East Asia, including to carbapenems. Widespread use of carbapenems may contribute to this problem.\textsuperscript{1,5,8}

- in regions where \textit{Burkholderia pseudomallei} or \textit{Acinetobacter baumannii} are prevalent – used with gentamicin as empirical treatment for severe community-acquired pneumonia. Alternatives include ceftazidime (complementary list) and meropenem (not listed).\textsuperscript{1}
- severe hospital-acquired pneumonia – directed therapy \textsuperscript{1,5}
- severe necrotising pancreatitis – alternatives include metronidazole plus ceftazidime (complementary list) and ceftazidime (complementary list) \textsuperscript{1,5,9-11}
- severe sepsis, neutropenic patients, with no obvious source of infection – one of many alternatives including gentamicin plus ceftazidime (complementary list) \textsuperscript{1,5,12,13}
- life-threatening foot infections in patients with diabetes and complicated cellulitis – one of many alternatives \textsuperscript{5,14,15}
- urinary tract infections in hospitalised patients – one of many alternatives including ceftriaxone (complementary list) and ceftazidime (complementary list). \textsuperscript{5,15}

Other uses include the treatment of intravascular catheter-related infections \textsuperscript{16}, anthrax \textsuperscript{17} and glanders.\textsuperscript{1} Imipenem is not recommended for use for surgical antibiotic prophylaxis because narrower spectrum antimicrobial drugs are available that are equally effective and less expensive.\textsuperscript{2}

The most frequent adverse effects of imipenem/cilastatin are injection site reactions, nausea and vomiting, diarrhoea, rash, fever, and seizures. Seizures are more likely to occur in patients with lesions of the central nervous system, a history of seizure activity, and when dosage is not adjusted appropriately in patients with renal impairment. Immune cross-reactivity with the penicillins occurs at a rate similar to the cephalosporins.\textsuperscript{2}

**Recommendation**

While imipenem/cilastatin is effective and acceptably safe for the treatment of a range of severe aerobic and anaerobic Gram-positive and Gram-negative infections, in most instances, products already available on the WHO Model List of Essential Medicines (ie ceftazidime, gentamicin, ceftriaxone) offer reasonable and cheaper alternatives. Imipenem/cilastatin should be deleted from the Model List. The need for a carbapenem (eg for resistant \textit{Acinetobacter baumannii} infections) should be addressed at a local level.

Jonathan Dartnell, Jillian K Pope, and Jason Wasiak, Therapeutic Guidelines, Australia (with acknowledgements to Professor Bart J Currie, Royal Darwin Hospital, Northern Territory, Australia) (October 2004)

**References**


**Search Strategy**

The medical literature was searched to identify guidelines, systematic reviews or meta-analyses related to imipenem/cilastatin use for severe aerobic and anaerobic Gram-positive and Gram-negative infections. Table 1 lists the electronic databases, websites and journals searched.

**Table 1. Electronic databases, websites and journals searched**
<table>
<thead>
<tr>
<th>Database</th>
<th>Period Covered/Date Accessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline (OVID)</td>
<td>1996 to 4/52004</td>
</tr>
<tr>
<td>The Cochrane Library</td>
<td>Issue 2/2004</td>
</tr>
<tr>
<td>eTG complete (Therapeutic Guidelines)</td>
<td>April 2004</td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>Volume 10, 2004</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>National Guideline Clearinghouse</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>National Institute of Clinical Excellence</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>Guidelines International Network</td>
<td>31/5/2004</td>
</tr>
<tr>
<td>Management Sciences for Health</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>Prescrire</td>
<td>1994 to April 2004</td>
</tr>
<tr>
<td>The Medical Letter</td>
<td>25/5/2004</td>
</tr>
<tr>
<td>Therapeutics Initiative</td>
<td>25/5/2004</td>
</tr>
</tbody>
</table>

Except for Medline (see below), databases were searched using the search term 'imipenem'.

**Medline search strategy**

To identify relevant systematic reviews and meta-analyses, the search strategy included both Medical Subject Heading (MeSH) terms and text words found in the title, abstract, MeSH headings and subheadings. In addition, the search was limited to English language–only articles and those published in:
- New England Journal of Medicine
- The Lancet
- British Medical Journal
- Antimicrobial Agents and Chemotherapy
- Clinical Infectious Disease
- European Journal of Clinical Microbiology and Infectious Diseases
- Journal of Infectious Diseases
- Journal of Antimicrobial Chemotherapy
Table 2 indicates the final search strategy used for Medline (OVID)

### Table 2. The final search strategy for Medline (OVID)

| 1. meta.ab. | 17. articles.ab. |
| 2. synthesis.ab. | 18. reviewed.ab. |
| 3. literature.ab. | 19. english.ab. |
| 4. randomized.hw. | 20. language.ab. |
| 5. published.ab. | 21. comment.pt. |
| 7. extraction.ab. | 23. editorial.pt. |
| 9. controlled.hw. | 25. Human/ |
| 10. search.ab. | 26. 24 not (24 and 25) |
| 11. medline.ab. | 27. exp IMIPENEM/ |
| 12. selection.ab. | 28. imipenem.tw. |
| 13. sources.ab. | 29. or/27-28 |
| 14. trials.ab. | 30. 29 not (21 or 22 or 23 or 26) |
| 15. review.ab. | 31. or/1-20 |
| 16. review.pt. | 32. 30 and 31 |

#### LEGEND

/ = Medical Subject Heading (MeSH) as set out by Ovid  

tw = looks for the term/s in the abstract, title, MeSH headings and subheadings  

ab= looks for the term in the abstract only  

pt = describes the type of material the article represents  

$ = looks for variations in spelling (eg pre-operative, preoperative, pre operative)  

or = retrieves documents that contain at least one of the specified search terms  

and = retrieves a set in which each citation contains all the search terms.

### Results

A total of 263 articles/resources were identified. When English language–only and journal search filters were applied to the search, independent scrutiny of the titles and abstracts by two reviewers identified 179 potentially relevant articles. Of the 179 articles assessed, 154 were excluded for the following reasons:  

- wrong intervention (n= 52)  
- wrong patient group (n=24)  
- wrong study design (eg in vitro studies, narrative reviews) (n=86)
The remaining 25 articles/resources were considered to be relevant. Resources and articles used included: