Part 1   Summary of Recommendations

Two cefalosporins are included in the 2004 WHO Model List of Essential Medicines (as complementary drugs): **ceftazidime** and **ceftriaxone**. These are both broad-spectrum ‘third-generation’ cefalosporins. They have a broad range of important uses for which there is strong evidence supporting their effectiveness. It is recommended that they be retained in the List. However, if cephazolin is added to the List (as recommended by this review), it is recommended that surgical prophylaxis be deleted from the indications for ceftriaxone. Also, it is not clear why the List includes only 250 mg vials of ceftazidime and ceftriaxone when the usual adult dose is 1 g and so it is recommended that 1 g vials be added to the List for both ceftazidime and ceftriaxone.

This review also recommends the addition of two moderate-spectrum ‘first-generation’ cefalosporins to the List: one for injectable use and one for oral use. Moderate-spectrum cefalosporins are particularly useful (when other agents on the List are inappropriate) as an alternative to cloxacillin or amoxicillin/ampicillin, for the treatment of conditions in patients who have suspected non-immediate penicillin hypersensitivity. If moderate-spectrum cefalosporins are not available, prescribers may resort to broad-spectrum cefalosporins, which have greater financial costs and exert greater impact on the development of resistant microorganisms.

Of the many cefalosporins available, **cefalexin** (oral use) and **cefazolin** (injectable use) are recommended for addition. They have been chosen based on the level of evidence for their use, and their utility, dosing convenience, available formulations, general availability and cost. However, if the relative importance of these factors is shifted, other cefalosporins may be preferred. For example, if cost were of less importance, moderate-spectrum cefalosporins with anti-*Haemophilus* activity may be preferred (eg cefuroxime). There may also be advantages (eg for simplicity) to including the same cefalosporin for both oral and injectable use (eg cefradine).

Moderate-spectrum ‘second-generation’ cefalosporins with anti-anaerobic activity (cefotetan and cefoxitin) have not been recommended for inclusion because of their relatively high cost and the fact that metronidazole, which *is* included in the List, can be included in regimens when anti-anaerobic activity is required.

**Imipenem with cilastatin** (see single drug review) is, at present, included in this section of the WHO Model List of Essential Medicines. Although 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, and it is recommended that imipenem/cilastatin should be deleted from the List.
### Recommendations for WHO Model List of Essential Medicines

<table>
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<th>Medication</th>
<th>STATUS:</th>
<th>PRODUCT:</th>
<th>INDICATIONS:</th>
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<tr>
<td>Ceftazidime</td>
<td>retain 250 mg formulation, and add 1g vial</td>
<td>powder for injection, 250 mg and 1 g (as pentahydrate) in vial</td>
<td>infections due to sensitive bacteria, especially those due to <em>Pseudomonas</em> spp. and including those resistant to aminoglycosides</td>
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<tr>
<td>Ceftriaxone</td>
<td>retain 250 mg formulation, and add 1g vial</td>
<td>powder for injection, 250 mg and 1 g (as sodium salt) in vial</td>
<td>serious infections due to sensitive bacteria, including septicaemia, pneumonia, and meningitis; prophylaxis of meningococcal meningitis; gonorrhoea. delete surgical prophylaxis</td>
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<tr>
<td>Imipenem/cilastatin</td>
<td>delete</td>
<td></td>
<td>(see single drug review)</td>
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<tr>
<td>Cefalexin</td>
<td>include</td>
<td>capsule or tablet, 250 mg and 500 mg, suspension 25 and 50 mg/mL</td>
<td>an alternative to cloxacillin or amoxicillin/ampicillin, especially in patients who have suspected non-immediate penicillin hypersensitivity when doxycycline, erythromycin and chloramphenicol are inappropriate</td>
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<tr>
<td>Cefazolin</td>
<td>include</td>
<td>powder for injection, 500 mg and 1 g (as sodium salt) in vial</td>
<td>surgical prophylaxis; as an alternative to cloxacillin or amoxicillin/ampicillin, especially in patients who have suspected non-immediate penicillin hypersensitivity</td>
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Part 2  Individual product reviews

2.1 Cefalexin

Introduction

Cefalexin is an oral ‘first-generation’ cefalosporin. It has a moderate spectrum of antimicrobial, broad utility and is relatively cheap and widely available.

Cefalexin is active against streptococci and staphylococci, including beta-lactamase-producing staphylococci, but inactive against enterococci or Listeria monocytogenes. Its Gram-negative spectrum includes most Escherichia coli and Klebsiella species, but it is inactive against many Gram-negative aerobes, including Serratia, Enterobacter and Pseudomonas species. It does not have useful activity against the Gram-negative anaerobe Bacteroides fragilis and related species.

There are no oral cefalosporins included in the 2004 WHO Model List of Essential Medicines at present. Other drugs currently listed with related but not identical uses to cephalexin include amoxicillin, amoxicillin with clavulanic acid, cloxacillin, chloramphenicol, clindamycin, doxycycline, erythromycin and trimethoprim.

Cefradine, cefadroxil and ceftirizine are similar to cefalexin in terms of antimicrobial activity, uses, adverse effects, dosing convenience and cost. However, globally, cefalexin may be more widely available and used than the other drugs. Cefuroxime, cefaclor and cefamandole are similar moderate-spectrum cephalosporins to cefalexin, and they are more stable to some Gram-negative beta-lactamases and more active against Haemophilus influenzae; however, the oral forms of these drugs are generally more expensive than cefalexin. Cefaclor can cause serum sickness-like syndrome, unlike the first-generation cefalosporins.

Up to 10% of penicillin courses result in manifestations interpreted as due to hypersensitivity. Most of these reactions occur late and are a relative contraindication to further penicillin use. Between 3% to 6% of patients hypersensitive to penicillin exhibit cross-reactivity with cephalosporins; however this does not preclude the use of cefalosporins.

The product

Cefalexin is available as 250 mg and 500 mg tablets or capsules, and as 25 mg/mL and 50 mg/mL oral suspensions.

The usual adult cefalexin dosage is 250 to 500 mg orally 6- to 12-hourly. For children the usual dosage is 12.5 to 25 mg/kg up to 500 mg orally 6- to 12-hourly. Dosages should be reduced in renal impairment.

Evidence of value

The main indications for which there is evidence and support for the use of cefalexin (sometimes in combination with metronidazole) as an alternative to a penicillin such as amoxicillin/ampicillin or cloxacillin and, therefore, as the drug of first-choice in patients with suspected non-immediate penicillin hypersensitivity (but not in patients who have a history of immediate hypersensitivity) are:

- skin and soft tissue infections, including cellulitis and erysipelas, atopic dermatitis if secondary bacterial infection is present or suspected, infected perianal dermatitis, nappy rash with bacterial infection, boils and carbuncles, severe impetigo if...
*Staphylococcus aureus* is suspected or confirmed, acute paronychia and severely infected ingrowing toenails, diabetic foot infections (mild to moderate infection with no evidence of osteomyelitis), mastitis, and postoperative wound infections (if mild or moderate)

- vulvovaginitis and balanitis in children
- dacryocystitis, meibomianitis and periorbital cellulitis
- diverticulitis
- endocarditis prophylaxis for dental and upper respiratory tract procedures
- urinary tract infections including acute cystitis and acute pyelonephritis (if mild to moderate).

Cefalexin may be the drug of choice depending on the patient group (e.g., children, pregnant women, history of penicillin hypersensitivity) and local microbiological sensitivity data.

The most common adverse effects of cefalexin are diarrhoea, nausea, rash, and electrolyte disturbances. Less frequent reactions include vomiting, headache, dizziness, oral and vaginal candidiasis, eosinophilia, drug fever, and pseudomembranous colitis.

**Recommendation**

Cefalexin is a cheap and readily available moderate-spectrum oral cephalosporin. It is particularly useful as an alternative to cloxacillin or amoxicillin/ampicillin, for the treatment of conditions in patients who have suspected non-immediate penicillin hypersensitivity when doxycycline, erythromycin or chloramphenicol are inappropriate.

We recommend that the Expert Committee requests that an application for the inclusion of cefalexin be prepared for consideration at the next Expert Committee Meeting in 2007.

**References**

2.2 Cefazolin

Introduction

**Cefazolin** is an injectable ‘first-generation’ cefalosporin. It has a moderate spectrum of antimicrobial activity, broad utility, and is relatively cheap and widely available.

Cefazolin is active against streptococci and staphylococci, including beta-lactamase-producing staphylococci, but inactive against enterococci or *Listeria monocytogenes*. Its Gram-negative spectrum includes most *Escherichia coli* and *Klebsiella* species, but it is inactive against many Gram-negative aerobes, including *Serratia*, *Enterobacter* and *Pseudomonas* species. It does not have useful activity against the Gram-negative anaerobe *Bacteroides fragilis* and related species.¹

Two injectable cefalosporins are already included in the 2004 WHO Model List of Essential Medicines (as complementary drugs): ceftazidime and ceftriaxone. They are both ‘third-generation’ cefalosporins, and are more expensive and have a broader spectrum than first-generation cefalosporins. As they are the only cefalosporins in the List, they are probably overused, causing greater expenditure and exerting greater impact on the development of resistant microorganisms than would occur if narrower spectrum cefalosporins were used.²

Clindamycin, cloxacillin, gentamicin and vancomycin are drugs currently in the List with related but not identical uses³:

- **Gentamicin** is used for Gram-negative bacterial infections but should be avoided in patients with significant renal impairment, when cefazolin can be a useful alternative. Also, gentamicin is nephrotoxic and ototoxic, and routine blood level monitoring is recommended to facilitate correct and adequate dosing; however, monitoring is complex and may be difficult in many settings.

- **Clindamycin** is used for Gram-positive and anaerobic infections. However, its use is limited because of adverse effects.³ It is often recommended as an alternative to a penicillin for conditions in patients who have a history of immediate hypersensitivity reaction to a penicillin.

- **Vancomycin** is a complementary antibacterial that should be reserved for methicillin-resistant *Staphylococcus aureus* infections.³

- **Cloxacillin** is a drug used mainly for staphylococcal infection, but should not be used in patients with penicillin hypersensitivity, when cefazolin is a useful alternative.

Up to 10% of penicillin courses result in manifestations interpreted as due to hypersensitivity. Most of these reactions occur late and are a relative contraindication to further penicillin use. Between 3% to 6% of patients hypersensitive to penicillin exhibit cross-reactivity with cephalosporins; however this does not preclude the use of cefalosporins.¹⁴
Approximately 1 in 10,000 penicillin courses results in an immediate hypersensitivity reaction (urticaria, angioedema, bronchospasm, or anaphylaxis within 1 hour of drug administration). A history of an immediate hypersensitivity reaction to penicillin contraindicates exposure to cefalosporins.

**Cefalotin** is similar to cefazolin, but cefazolin may be preferred as it is less painful when given by intramuscular injection, has a longer half-life (with consequent longer dosing interval) and is generally cheaper.1

**Cefuroxime** and **cefamandole** are moderate-spectrum cephalosporins that are more stable to some Gram-negative beta-lactamases and more active against *Haemophilus influenzae*. However, the injectable forms of these drugs are generally more expensive than cefazolin.

**The product**

Cefazolin is available for either intramuscular or intravenous injection as 500 mg and 1 g vials.

Recommended cefazolin dosages (which should be reduced in renal impairment) are:

- 1 g intravenously 8-hourly (children: 25 mg/kg up to 1 g intravenously 8-hourly) for the treatment of infections caused by Gram-positive pathogens, and
- 2 g intravenously 8-hourly (children: 50 mg/kg up to 2 g intravenously 8-hourly) for the treatment of infections caused by Gram-negative pathogens.1

**Evidence of value**

There are some conditions where cefazolin is recommended in preference to other antibiotics. For many conditions, cefazolin is recommended as an alternative to a penicillin such as amoxicillin/ampicillin or cloxacillin.

The main indications for which there is evidence and support for the use of cefazolin as the antibiotic of first choice are:

- peritonitis complicating continuous ambulatory peritoneal dialysis (if Gram-positive pathogens are identified)1
- surgical prophylaxis—(sometimes in combination with metronidazole, sometimes as an alternative to gentamicin or cloxacillin) for abdominal, cardiac, vascular, orthopaedic, obstetric, gynaecological, and head, neck and thoracic surgery, and for neurosurgery1,5–8.

The main indications for which there is evidence and support for the use of cefazolin (sometimes in combination with metronidazole and/or gentamicin) as an alternative to a penicillin such as amoxicillin/ampicillin or cloxacillin and, therefore, as the drug of first-choice in patients with suspected non-immediate penicillin hypersensitivity (but not in patients who have a history of immediate hypersensitivity) are:

- skin and soft tissue infections1, 9–11, including cellulitis and erysipelas12, necrotising fasciitis and synergistic gangrene15, compound fractures16, mastitis17 and wound infections (both severe postoperative, and contaminated post-traumatic)
- septic arthritis and, in some circumstances, osteomyelitis1, 18–21
- staphylococcal pneumonia1
- severe sepsis—if the source is from the female genital tract, or the skin; if there is no obvious source; and for staphylococcal sepsis, staphylococcal toxic shock syndrome, and streptococcal sepsis including streptococcal toxic shock syndrome1, 22–24
- moderate to severe acute pyelonephritis requiring intravenous antimicrobial therapy. Cefazolin may be the drug of choice depending on the patient group (eg children,
pregnant women, history of penicillin hypersensitivity) and local microbiological sensitivity data.\textsuperscript{25, 26} The most common adverse effects of cefazolin are diarrhoea, nausea, rash, and electrolyte disturbances. Less frequent reactions include vomiting, headache, dizziness, oral and vaginal candidiasis, eosinophilia, drug fever, and pseudomembranous colitis.\textsuperscript{27}

**Recommendation**

Cefazolin is a cheap and readily available moderate-spectrum injectable cephalosporin. It is particularly useful for surgical antibiotic prophylaxis and as an alternative to cloxacillin or amoxicillin/ampicillin, for the treatment of conditions in patients who have suspected non-immediate penicillin hypersensitivity.

We recommend that the Expert Committee requests that an application for the inclusion of cefazolin be prepared for consideration at the next Expert Committee Meeting in 2007.

**References**

2.3 Ceftriaxone

Introduction

Ceftriaxone is an injectable ‘third-generation’ cephalosporin included in the 2004 WHO Model List of Essential Medicines (as a complementary drug).\(^1\)

Ceftriaxone has a wide spectrum of activity covering the majority of community-acquired enteric Gram-negative rods. It is less active against staphylococci than earlier cephalosporins and does not have clinically useful activity against enterococci or methicillin-resistant *Staphylococcus aureus*. Ceftriaxone enters the cerebrospinal fluid in therapeutically useful concentrations and is effective in meningitis. Some organisms, eg *Serratia, Citrobacter* and *Enterobacter* species, have chromosomal cephalosporinases and resistance may develop during treatment. Plasmid-mediated extended-spectrum beta-lactamases (ESBLs) inactivate ceftriaxone (eg in *Escherichia coli, Klebsiella pneumoniae*). It has a long half-life and can be administered once daily.\(^2\)

Cefotaxime is an alternative third-generation cephalosporin with very similar antimicrobial activity. However, it has a shorter half-life and requires more frequent administration than ceftriaxone (ie 8- or 12-hourly versus once daily).\(^2\)
The product

Ceftriaxone is available as 250 mg, 500 mg and 1 g vials for injection. Currently only the 250 mg vial (as the sodium salt) is on the WHO Model List of Essential Medicines.\(^1\)

Ceftriaxone can be administered by deep intramuscular injection, by intravenous injection (over at least 2 to 4 minutes) or by intravenous infusion.

The usual adult dosage is 1 g once daily.\(^1\)\(^-\)\(^4\) For severe infections the dosage may be increased to 2 to 4 g per day. For example, for typhoid and paratyphoid fevers, the dosage is 3 g intravenously daily, and for meningitis the dosage is 4 g intravenously daily.\(^2\) For uncomplicated gonorrhoea, 125 to 250 mg as a single intramuscular dose has been used.\(^2\)

In infants and children, the usual dosage is 25 to 50 mg/kg (up to 1 g) daily.\(^1\)\(^-\)\(^4\) For severe infections the dosage may be increased to 100 mg/kg daily. For example, for typhoid and paratyphoid fevers, the dosage is 75 mg/kg up to 3 g intravenously daily, and for meningitis the dosage is 100 mg/kg intravenously up to 4 g daily.\(^2\)

In neonates, the usual dosage is 20 to 50 mg/kg daily.\(^1\)

Evidence of value

The main indications for which there is evidence and support for the use of ceftriaxone include\(^1\)\(^-\)\(^9\):

- bone and joint infections – osteomyelitis and septic arthritis, if Gram-negative infection is suspected\(^2\)\(^,\)\(^5\)\(^,\)\(^10\)\(^,\)\(^11\)
- cardiovascular system infections – endocarditis, if Gram-negative infection is suspected\(^2\)\(^,\)\(^13\)
- central nervous system infections – empirical therapy for meningitis, if hospital-acquired, if caused by Gram-negative bacilli, in some other instances if the patient has non-immediate hypersensitivity to penicillin; prophylaxis for meningococcal meningitis; brain abscess or subdural empyema\(^1\)\(^,\)\(^2\)\(^,\)\(^5\)\(^,\)\(^14\)\(^,\)\(^15\)
- eye infections – gonococcal conjunctivitis (non-immediate hypersensitivity to penicillin); gonococcal ophthalmia in neonates; endophthalmitis (with gentamicin)\(^2\)
- gastrointestinal tract infections – severe diverticulitis (particularly if the patient has non-immediate hypersensitivity to penicillin or gentamicin is contraindicated)\(^2\)
- genital tract infections – gonococcal cervicitis and urethritis; chancroid; sexually acquired epididymo-orchitis; pelvic inflammatory disease\(^1\)\(^,\)\(^2\)\(^,\)\(^16\)
- intra-abdominal infections – empirical therapy particularly when the patient has non-immediate hypersensitivity to penicillin or gentamicin is contraindicated; ascending cholangitis; cholecystitis; peritonitis\(^2\)\(^,\)\(^5\)
- respiratory tract infections – acute epiglottitis; severe pneumonia (particularly if the patient has non-immediate hypersensitivity to penicillin)\(^1\)\(^,\)\(^2\)\(^,\)\(^5\)\(^,\)\(^17\)\(^-\)\(^19\)
- systemic infections – severe sepsis when Gram-negative infection is suspected, particularly if the patient has non-immediate hypersensitivity to penicillin or gentamicin is contraindicated; typhoid fever\(^1\)\(^,\)\(^2\)\(^,\)\(^8\)\(^,\)\(^20\)
- skin and soft tissue infections – infections from human and animal bites, and clenched fist injuries; orbital cellulitis; severe periorbital cellulitis\(^2\)\(^,\)\(^5\)
- urinary tract infections – severe pyelonephritis if gentamicin is contraindicated.\(^2\)\(^,\)\(^5\)\(^,\)\(^8\)\(^,\)\(^9\)
Ceftriaxone can be used for surgical prophylaxis; however, because broad-spectrum cefalosporins have a greater impact on the development of resistant microorganisms than narrower spectrum cefalosporins do, narrower spectrum cefalosporins are preferred. As cephalzin (a moderate-spectrum cephalosporin) is recommended for addition to the List, surgical prophylaxis should be removed as an indication for ceftriaxone.

The WHO Model Formulary notes the following adverse effects for ceftriaxone: diarrhea, nausea and vomiting, abdominal discomfort, headache; antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis and cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, confusion, hypertonia and dizziness; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated, or those who are immobilized) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis.

**Recommendation**

Ceftriaxone is a broad-spectrum ‘third-generation’ cefalosporin with a broad range of important uses for which there is strong evidence supporting its effectiveness.

It is recommended that ceftriaxone be retained in the WHO Model List of Essential Medicines. It is also recommended that the Committee asks for the 1 g vial to be added to the List. If cephalzin (a moderate-spectrum cephalosporin) is added to the List (as is recommended), it is recommended that the Committee remove surgical prophylaxis as an indication for ceftriaxone.

**References**

2.4 Ceftazidime

Introduction

**Ceftazidime** is an injectable ‘third-generation’ cefalosporin included in the 2004 WHO Model List of Essential Medicines (as a complementary drug).  

Ceftazidime is a broad-spectrum cefalosporin with an extended spectrum of activity covering the majority of the enteric Gram-negative rods, including *Pseudomonas aeruginosa*. It also is active against *Burkholderia pseudomallei* (which causes melioidosis).

Ceftazidime is susceptible to plasmid-mediated extended-spectrum beta-lactamases (ESBLs). Some organisms, eg *Serratia*, *Citrobacter* and *Enterobacter* species, have chromosomal cephalosporinases and resistance may develop during treatment.

The activity and use of ceftazidime is similar to cefepime and cefpirome.
The product

Ceftazidime is available as 250 mg, 1 g and 2 g vials for injection. Currently only the 250 mg vial (as the sodium salt) is on the WHO Model List of Essential Medicines.\(^1\)

Ceftazidime can be administered by deep intramuscular injection, by intravenous injection or by intravenous infusion.

The usual adult dosage is 1 g 8-hourly or 2 g 12-hourly.\(^1\)\(^-\)\(^4\) For severe infections, the dosage may be increased to to 8 g per day. For example for pseudomonal or neutropenic sepsis the dosage is 2 g intravenously 8-hourly, and for melioidosis the dosage is 2 g intravenously 6-hourly.\(^2\)

In infants and children, the usual dosage is 25 to 50 mg/kg 6- to 12-hourly (up to 3 to 4 g daily).\(^1\)\(^-\)\(^4\) For pseudomonal or neutropenic sepsis the dosage is 50 mg/kg up to 2 g intravenously 8-hourly, and for melioidosis the dosage is 50 mg/kg up to 2 g intravenously 6-hourly.\(^2\)

For neonates and infants less than 2 months old, the usual dosage is 12.5 to 30 mg/kg 12-hourly.\(^1\)

Dosages should be reduced in renal impairment.\(^2\)

Evidence of value

Ceftazidime is usually reserved for use for infections due to to *Pseudomonas* spp. including those resistant to aminoglycosides.\(^1\)

The main indications for which there is evidence and support for the use of ceftazidime include:

- melioidosis\(^2\)\(^,\)\(^5\)\(^,\)\(^6\)
- pneumonia (if caused by *Burkholderia pseudomallei* or *Pseudomonas aeruginosa*)\(^2\)\(^,\)\(^7\)\(^,\)\(^8\)
- severe sepsis (in patients with neutropenia)\(^2\)\(^,\)\(^8\)\(^,\)\(^9\)
- glanders\(^2\)

The WHO Model Formulary notes the following adverse effects for ceftazidime: diarrhoea, nausea, vomiting, abdominal discomfort, headache; rarely, antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reaction, fever and arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible interstitial nephritis; nervousness, sleep disturbances, confusion, hypertonia, and dizziness.\(^1\)

Recommendation

**Ceftazidime** is a broad-spectrum ‘third-generation’ cefalosporin with a broad range of important uses for which there is strong evidence supporting its effectiveness.

It is recommended that ceftazidime be retained in the WHO Model List of Essential Medicines. It is also recommended that the Committee asks for the 1 g vial to be added to the List.

References

2.4 Imipenem with cilastatin

See single drug review.

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 (i.e., ceftazidime, gentamicin, ceftriaxone) offer reasonable and cheaper alternatives. It is recommended that the Committee asks for imipenem/cilastatin to be deleted from the WHO Model List of Essential Medicines. The need for a carbapenem (e.g., for resistant Acinetobacter baumannii infections) should be addressed at a local level.

Part 3. Search Strategy

(for the strategy as it relates to imipenem with cilastatin see single drug review)

Identification of cefalosporins of interest


Two comprehensive treatment guidelines were reviewed to determine the indications for which cefalosporins are recommended, and which of the cefalosporins are recommended for each indication (eTG complete. July 2004. Melbourne: Therapeutic Guidelines Limited; 2004; Choice of antibacterial drugs. Treatment guidelines from the Medical Letter 2004;2(March (Issue 19)):13-26). A table was developed showing indications for cefalosporins versus choice of cefalosporin. From this table, the most frequently recommended cefalosporins were identified. These included:

- an oral moderate-spectrum first-generation cefalosporin: cefalexin
- an injectable moderate-spectrum first-generation cefalosporin: cefazolin or cefalotin
• an injectable broad-spectrum third-generation cefalosporin: **ceftriaxone** or **cefotaxime**
• an injectable broad-spectrum third-generation cefalosporin with antipseudomonal activity: **ceftazidime**.

Some less frequently recommended cefalosporins included:
• moderate-spectrum second-generation cephalosporins with anti-*Haemophilus* activity: **cefaclor, cefuroxime, cefamandole**
• moderate-spectrum second-generation cephalosporins with antianaerobic activity: **ceftetan, cefoxitin**
• other injectable broad-spectrum cefalosporins with antipseudomonal activity: **cefepime, cefpirome**.

Cefalexin is widely utilised, in particular as an alternative to cloxacillin or amoxicillin/ampicillin, for the treatment of conditions in patients who have suspected non-immediate penicillin hypersensitivity. Other oral first-generation cefalosporins could be used in this role. However, the Martindale drug reference and the International Drug Price Indicator Guide did not show that other first-generation cefalosporins are more widely available (Sweetman SC, editor. Martindale. The complete drug reference. 33 ed. London: Pharmaceutical Press; 2002; McFadyen JE, editor. International drug price indicator guide. Boston: Management Sciences for Health; 2003).

Cefazolin and cefalotin are widely utilised, also in particular as an alternative to cloxacillin or amoxicillin/ampicillin, for the treatment of conditions in patients who have suspected non-immediate penicillin hypersensitivity. Other first-generation cefalosporins could be used in this role. However, the Martindale drug reference and the International Drug Price Indicator Guide did not show that other first-generation cefalosporins are more widely available (Sweetman SC, editor. Martindale. The complete drug reference. 33 ed. London: Pharmaceutical Press; 2002; McFadyen JE, editor. International drug price indicator guide. Boston: Management Sciences for Health; 2003).

It was noted that ceftriaxone and ceftazidime were already listed as complimentary drugs on the WHO Model List of Essential Medicines. There is substantial evidence and support for their use in a range of indications in numerous guidelines; the primary literature was not reviewed to validate their position in the List. The literature was reviewed, however, to determine the place of ceftriaxone for surgical prophylaxis in view of the possible addition of a narrower spectrum cefalosporin to the List.

Cefotaxime’s role in a formulary would be virtually identical to ceftriaxone. Ceftriaxone has the advantage of once-daily dosing (versus 8-hourly or 12-hourly dosing for cefotaxime). The literature was not reviewed to challenge the position of ceftriaxone with cefotaxime in the List.

**Literature search**

The medical literature was searched to identify guidelines, systematic reviews and meta-analyses related to cefalosporins (as a group and as individual drugs) for the period between 1994 and 2004. Table 1 lists the electronic databases, websites and journals used in the search.
Table 1. Electronic databases (including edition), websites and journals searched

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<td>Guidelines International Network <a href="http://www.g-i-n.net">http://www.g-i-n.net</a></td>
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<td>Management Sciences for Health <a href="http://www.msh.org">www.msh.org</a></td>
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<td>Prescrire</td>
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<td>The Medical Letter <a href="http://www.medletter.com/">http://www.medletter.com/</a></td>
<td>26 July 2004</td>
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<tr>
<td>Therapeutics Initiative <a href="http://www.ti.ubc.ca/">http://www.ti.ubc.ca/</a></td>
<td>26 July 2004</td>
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</table>

In MEDLINE, the search strategy included both Medical Subject Heading (MeSH) terms and text words found in the title or abstract (see Table 2 for search terms used). 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. Search terms used to identify citations for the literature retrieval

<table>
<thead>
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<tr>
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<td>9.</td>
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<td>Human/</td>
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<tr>
<td>26.</td>
<td>24 not (24 and 25)</td>
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<td>27.</td>
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<td>38.</td>
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<td>39.</td>
<td>or/27-38</td>
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<td>40.</td>
<td>39 not (21 or 22 or 23 or 26)</td>
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<td>41.</td>
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<td>40 and 41</td>
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<td>39.</td>
<td>Limit 42 to English</td>
</tr>
</tbody>
</table>

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

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
The literature search identified guidelines, systematic reviews and meta-analyses related to cephalosporins (as a group and as individual drugs). The resources and articles used to inform our decisions included:


17 December 2004