

## Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

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### Use of carbapenems in children

#### Summary

Carbapenems are betalactams with the broadest antibacterial spectrum currently available. They are well tolerated and drug related adverse events are few. Members of this group have a definite role in empiric and definitive therapy of serious and multi drug resistant (MDR) bacterial infections, especially where MDR Gram negative bacilli (GNB) are involved and other drugs are ineffective or inappropriate. Currently, imipenem-cilastatin, meropenem and ertapenem are approved by the FDA for use in children, the latter two only for those above 3 months. BNF C 2006 states that imipenem-cilastatin is not licensed for use in children < 3 months. However, imipenem-cilastatin and meropenem dosages for neonates are provided. Doripenem is very recently approved for use in adults. There are some differences between carbapenems in the spectrum of activity, AMR rates, safety profiles, pharmacological properties, indications and dosages.

Carbapenems have a time dependant bactericidal activity and so the duration of optimal drug concentrations in plasma is important for efficacy. These are administered usually as IV infusions over 15-60 min depending on the drug and dose. Stability of the drug after reconstitution can vary depending on the drug and the medium used for reconstituting. Imipenem-cilastatin is administered every 6-8hrs and meropenem every 8 hrs. Ertapenem has a longer half life and so can be used every 12-24 hrs. These are mostly eliminated through the kidneys and so dosage has to be adjusted in those with renal impairment.

Carbapenems have comparatively low toxicity.

Imipenem-cilastatin and meropenem have better activity against *P aeruginosa* and *Acinetobacter* spp as compared to ertapenem and so are recommended for nosocomial infections. Ertapenem is recommended for severe community acquired infections.

Imipenem-cilastatin has the potential to induce seizures in those on treatment for CNS infections and is contra indicated in such infections. This effect is dose related and uncommon at lower doses used for treating other infections. Meropenem is the only

carbapenem approved for use in patients including children with meningitis. Studies comparing imipenem-cilastatin and meropenem for indications other than meningitis, found no significant differences in efficacy or safety between the two or other comparator drugs, either used alone or in combination. However, a recent meta analyses suggests that meropenem may be better than imipenem-cilastatin in efficacy and safety.

AMR is emerging among GNB especially *P aeruginosa*, but at a slower rate compared to most other beta lactams. AMR is currently lowest towards meropenem. Several lines of evidence show that resistance to carbapenems can be induced by treatment with carbapenems. Although there are some concerns that monotherapy facilitates emergence of resistance among *P aeruginosa*, there is no evidence to prove this. Carbapenem resistant GNB are usually resistant to most other clinically useful antibiotics. Hence, clinicians have to consciously restrict use of this group to very serious infections, where benefits clearly out weigh risk of inducing resistance. Meropenem is costlier than imipenem-cilastatin, but pharmacoeconomic modelling show use of meropenem to be cost effective.

FDA approved indications for Imipenem-cilastatin are lower respiratory infections, UTI, septicaemia, intra abdominal infections, bone and joint infections, skin and skin structure infections, endocarditis and polymicrobial infections. Those for meropenem are skin and skin structure infections, intra abdominal infections and meningitis and for ertapenem, skin and skin structure infections, UTI, community acquired pneumonia (CAP), intra abdominal infections, and prophylaxis for colorectal surgery in adults.

#### Recommendations

Consider including meropenem since it is the only carbapenem suitable for meningitis, systematic reviews and meta analyses show that this may be better in efficacy and safety than imipenem-cilastatin for other indications, potential to induce resistance is lower, BNF C gives dosages for neonates as well

Imipenem-cilastatin is the only carbapenem currently approved by FDA in all age groups.

## Review

Among the many different structurally distinct beta-lactams, carbapenems are considered to be the most potent and have the widest spectrum of activity [1-3]. They are used for the treatment of suspected or proven multi drug resistant severe bacterial infections. Imipenem in combination with cilastatin (primaxin®), meropenem (Merrem®), ertapenem (Invanz®) and doripenem (Doribax®) are approved by FDA and all are for parenteral use. Of these, doripenem is the most recent carbapenem to be approved and is currently only for those above 18yrs of age. Meropenem and ertapenem are approved for use in adults and in children above three months of age. Imipenem-cilastatin, the first in the group, is approved for use in children including neonates. However, according to BNF C 2006, it is not licensed for use in those less than 3 months of age, but provides dosages for this and meropenem in neonates. Panipenem and biapenem are also available in some other countries[1]. Although they are mostly similar, individual members of the carbapenem group possess distinct pharmacological properties, spectra of activity and safety profiles [2].

### Spectrum of activity

Carbapenems bind to penicillin binding proteins (PBP) and disrupt cell wall synthesis [2, 4, 5]. They are rapidly bactericidal and demonstrate time dependant killing[2].

They have a broad spectrum of activity and include many Gram positive and negative, aerobic and anaerobic clinically important bacteria. Aerobic pathogens like enterobacteriaceae, streptococci (including penicillin-resistant *S. pneumoniae*), enterococci (excluding *E. faecium* and non-beta-lactamase-producing penicillin-resistant strains), methicillin susceptible staphylococci, *H influenzae*, *Listeria*, most strains of *Pseudomonas* and *Acinetobacter* are susceptible. Important aerobic pathogens known to be inherently resistant to imipenem-cilastatin are few and include *S maltophilia*, MRSA and *E faecium*. Most anaerobes are also susceptible [3-5].

Since carbapenems are not destroyed by most beta lactamases including extended spectrum beta- lactamases (ESBL) and Amp C chromosomal type, they are as a group, active against third generation cephalosporin resistant and several multi drug resistant Gram negative bacilli [1, 4, 5]. Carbapenems are the drugs of choice for treatment of infections due to ESBL producers[1]. Such bacteria are increasingly

being reported from all parts of the world as frequent causes of serious infections [6, 7]. National Nosocomial Infection Surveillance (USA) in 2004 reported 39.1% of *P aeruginosa* and 20.6% of *K pneumoniae* to be resistant to third generation cephalosporins [7].

Based on their affinity for various PBPs, there can be differences in the activity of individual carbapenems [7] and can be broadly grouped into three [1, 2]. There are subtle differences between drugs within a group also. Group 1 includes ertapenem which has lesser action on bacteria like *Pseudomonas* and *Acinetobacter* but suitable for community acquired infections caused by ESBL producing bacteria [2]. Ertapenem may also be less stable to some beta-lactamases compared to imipenem. Group 2, has imipenem, meropenem, biapenem and doripenem with better action on *Pseudomonas*, *Acinetobacter* and enterococci and hence better suited for nosocomial infections. Within the group, imipenem has better activity against Gram positive cocci while meropenem is better against GNB [2, 5]. In vitro, meropenem and doripenem are more potent than imipenem-cilastatin against enterobacteriaceae, *P aeruginosa* and *Acinetobacters* [8]. Group 3 has investigational carbapenems with activity on MRSA as well.

Increasing AMR to carbapenems is being reported. Acquired resistance can be due to a variety of mechanisms like enzymes that destroy the drug - carbapenemases or metallo betalactamases, loss of permeability or increased efflux, reduced binding to PBP and combinations of mechanisms [1, 2]. There was a 15% increase in imipenem resistance among *P aeruginosa* isolated between 1998-2002 and 2003. Overall, resistance to meropenem has remained lower than that of imipenem and the rate of increase in resistance is slow [3]. Meropenem yearly susceptibility test information collection (MYSTIC) data from paediatric ICU show that more than 90% isolates are susceptible to carbapenems, the rate of increase in AMR is slow and that a greater number of *P aeruginosa* are susceptible to meropenem as compared to imipenem-cilastatin [9]. Enterobacteriaceae can also have differential AMR to imipenem and meropenem. In one study 8% and 32% of *Klebsiella* and *Enterobacter* respectively were resistant to imipenem, while 26% each were resistant to meropenem [1].

Imipenem resistance can emerge following treatment with imipenem [1, 2] and was identified as a significant independent risk factor in *P aeruginosa*. Such isolates are

usually resistant to other antipseudomonal drugs as well [2]. Although it remains unclear whether addition of other antipseudomonal drugs like aminoglycosides reduces the risk of resistance developing in *P. aeruginosa*[7], it is common practice to do so. Potential to induce resistance is lower with meropenem. Resistance emerges more easily with ertapenem use compared to others[2]. Ability of doripenem to induce resistance is lower than that of meropenem[3].

On comparing pharmacodynamic potencies by Monte-Carlo simulation using ESBL producers, ertapenem was found to be less effective than imipenem and meropenem[1]. Imipenem was the most active carbapenem against ESBL producers in another such study.

### Pharmacokinetics

Oral bioavailability is poor and so carbapenems are administered parenterally. Imipenem [4] and panipenem are destroyed by dehydropeptidase 1, a renal tubular enzyme and so are co-administered with an inhibitor of this enzyme – cilastatin or betamipron[1]. Features of carbapenems when used in adults are compared in table 1. Ertapenem has the longest half life and allows once daily dosing (Australian Medicines Handbook (AMH), 2006). In those aged 3m- 12 yrs, ertapenem half life is 2.5 hrs (INVANZ label, Merck and Co, 2008)

Table 1 Features of carbapenems

	Imipenem	Meropenem	Ertapenem	Doripenem
FDA approval	1985	1996	2001	2007
Dose (mg)	250-1000	500-2000	1000	
Administration	IV	IV	IV	IV
Duration of infusion	20-60 min	15-30 min	30 min	
Frequency	6-8 hrs	8hrs	24hrs	
IM	yes	no	yes	no
Half life	~ 1h	~1h	~4h	~1h
Protein binding	13-20%	2-10%	85-95%	9%
Renal excretion	70%	70%	80%	60-75% 38% unchanged

C max (mg/L)	12-20	23	155	
Stability	~4h	~6h	~6h	~12h
Spectrum	Better action on Gram pos cocci compared to meropenem	Better action on GNB compared to imipenem	Less action on <i>P aeruginosa</i> , Acinetobacter	Similar to imipenem and meropenem
AMR potential	high	low	high	low

Imipenem and meropenem have similar pharmacokinetic profile in children and show age associated changes[5]. Elimination half life is longest in preterm babies and decrease with increasing age. Mean half life of meropenem is 1.7hrs in infants 2-5 months of age [5] and is about 1.5hrs up to 2yrs[3]. Volume of distribution is also greater in infants. Area under the curve and  $C_{max}$  show almost linear increase with increasing doses of imipenem and meropenem in preterm and full term neonates and children as in adults [5]. Pharmacokinetics in children over 2 yrs are consistent with those in adults[3]. Carbapenems are widely distributed in the body and penetrate well into tissues and fluids. In children aged 1-48 months of age and receiving meropenem in doses 20 mg/kg or 40mg/kg, CSF concentrations varied from 0.1 to 2.8 mg/L and from 0.3 to 6.5mg/ respectively. The large individual variations were probably related to the degree of meningeal inflammation. At a dose of 40mg/kg the CSF concentrations were in excess of the reported  $MIC_{90}$  for most bacterial pathogens causing meningitis [5].

Major route of elimination is renal and dosage needs to be modified in renal insufficiency. However, there is very little information on this issue from children. BNFC 2006 states that imipenem-cilastatin is not licensed in children with renal impairment, but then recommends dose reductions in renal impairment. Cilastatin may accumulate more than imipenem in renal insufficiency [5].

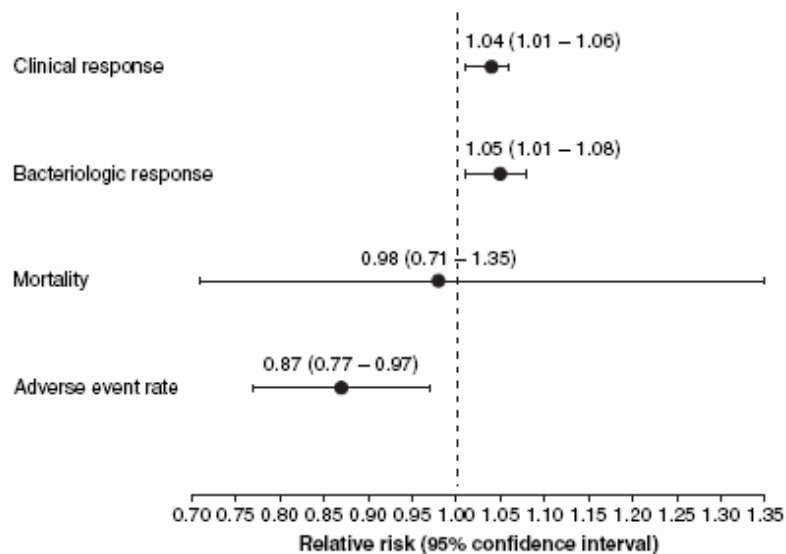
### Clinical efficacy

Clinical efficacy of carbapenems has been proved in numerous clinical trials. While most studies involve adults, there are a few studies in children also. Most trials have shown non inferiority of carbapenems as compared to other classes of antibiotics or combinations of antibiotics recommended for similar indications. Comparisons

between carbapenems especially between imipenem and meropenem also show that efficacy and safety are mostly similar for indications other than meningitis. However, meropenem appears to be better in some respects. Only meropenem is recommended for meningitis. There are several recent reviews on clinical efficacy and safety of carbapenems[1-3, 5-7, 10]. All agree on efficacy and safety. Comparative information on ertapenem is limited.

In a meta analyses of clinical trials evaluating imipenem and meropenem (figure 1), meropenem had significantly better clinical and bacteriological cure rates as compared to imipenem, but there were no significant differences in mortality rates [2, 11]

Figure 1 Meta analyses comparing meropenem to imipenem



A review published in 1999, on clinical trials in children, showed that meropenem is effective for several infections in children [6]. The comparators were cephalosporin based regimens.

Efficacy data from paediatric clinical trials of meropenem versus comparator<sup>a</sup>

Indication	Satisfactory response/number evaluable (%)	
	Meropenem	Comparator
Meningitis	165/184 (90%)	162/176 (92%)
Lower respiratory tract	142/144 (99%)	118/123 (96%)
Urinary tract	85/86 (99%)	43/44 (98%)
Septicaemia	39/39 (100%)	26/27 (96%)
Skin/skin structure	47/48 (98%)	38/41 (93%)
Intra-abdominal	20/22 (91%)	12/13 (92%)

### Use in children

Imipenem (Primaxin label, Merck and Co, Inc 2006) is approved for use in children including neonates. Meropenem and ertapenem are approved for children above 3 months. However, BNF C has imipenem and meropenem dosages for neonates.

Carbapenems are reserved for use in serious and life threatening infections suspected or proven to be caused by bacteria resistant to other commonly used antimicrobials but susceptible to carbapenems [2, 5]. They are mostly used in the ICUs for initial empiric therapy or as definitive therapy after susceptibility testing, for a variety of serious infections especially hospital acquired infections and in situations where other regimens are considered ineffective or inappropriate (e.g. combinations containing aminoglycosides contraindicated). Infections for which carbapenems may be useful include VAP, severe sepsis, intra abdominal and other infections which may be polymicrobial, including mixed aerobic and anaerobic aetiology[6]. Potent and early anti GNB cover can be life saving in most of these infections and imipenem-cilastatin and meropenem are excellent options. BNF C recommends imipenem-cilastatin and meropenem for serious infections unresponsive to standard therapy.

Duration of treatment will vary, but has to be kept to the minimum necessary[7].

Carbapenems are used mostly as monotherapy. Carbapenems have to be used judiciously to prevent emergence of resistance. Out breaks due to imipenem resistant bacteria related to increased use of carbapenems have been reported [2, 5]. A systematic review did not find any additional advantage in adding aminoglycosides to beta lactams, but the risk of adverse events increased [12]. There was no difference in the rate of development of resistance with combination as compared to monotherapy.

## 1. Meningitis

Only meropenem is FDA approved for this indication in children above 3 months[3]. Clinical and bacteriological cure rate was 97% and comparable to that of cefotaxime in clinical trials involving more than 200 children[3, 5, 13, 14]. Seizures and other neurological abnormality rates were also similar. Higher doses 40 mg/kg/dose, every 8 hrs are required. Imipenem-cilastatin is also effective, but is associated with higher incidence of seizures [15] and hence not approved for this indication. Monotherapy with meropenem is an alternative for initial treatment of meningitis in children where cefotaxime resistance in *S pneumoniae* is high. Clinical trials have shown meropenem to be effective in treating meningitis caused by highly penicillin and cephalosporin resistant *S pneumoniae* [15]. A more recent study however, showed that 17 out of 20 cefotaxime non susceptible *S pneumoniae* isolates were resistant to meropenem also[15]. Meropenem is recommended as one of the alternate therapies for *S pneumoniae* meningitis, for meningitis following trauma or neurosurgery and for GNB meningitis based on susceptibility testing, in IDSA guidelines [15].BNF C lists meningitis as one of the indications.

## 2. Febrile neutropenia.

Broad spectrum cover including a potent anti GNB cover is essential in the initial empirical regimen and a combination of betalactam and aminoglycoside/glycopeptide is usually the choice. RCTs in children show that monotherapy with imipenem-cilastatin or meropenem is at least as effective and safe as ceftazidime alone or in combination for empirical therapy of febrile neutropenia [3, 16-18]. In one trial, meropenem was superior to ceftazidime monotherapy with respect to success rates, duration of treatment, resolution of culture negative febrile episodes and comparable results were obtained in documented infections[5, 18]. A meta analyses concluded that imipenem-cilastatin, meropenem, ceftazidime and piperacillin-tazobactam are suitable agents for monotherapy for febrile neutropenia [19]. Carbapenems were associated with fewer treatment modifications, including addition of glycopeptides, than ceftazidime or other comparators. However, adverse events were significantly more frequent with carbapenems, specifically pseudomembranous colitis (RR 1.94, 95% CI 1.24-3.04, 2025 participants). All-cause mortality was unaltered. This is not an FDA approved indication, but listed in BNF C as an indication for meropenem use and in AMH for both imipenem-cilastatin and meropenem use.

### 3. Lower respiratory infections

Carbapenems can be used for the treatment of multi drug resistant lower respiratory infections like nosocomial pneumonia (NP), pseudomonas infections in cystic fibrosis and severe CAP. Intra pulmonary penetration is good.

**NP** are most often caused by GNB like Enterobacteriaceae (e.g. *E coli*, *Klebsiella*), *P aeruginosa* and Acinetobacter spp. *S aureus* and *S pneumoniae* are the Gram positive cocci most often associated with such infections. Polymicrobial aetiology is also possible [7]. Incidence of MDR bacteria causing NP is increasing rapidly. Broad spectrum antibiotics which cover these bacteria are used for empirical therapy. Imipenem and meropenem are recommended as options by IDSA and ATS [7]. Carbapenems have been evaluated for NP in several RCTs and found at least equal to comparators in bringing about clinical and bacteriological cure [7]. The comparators included cefepime, ceftazidime, piperacillin/tazobactam and fluoroquinolones either as monotherapy or combination therapy. Meropenem and imipenem were also found to be similar in efficacy and safety [7]. In those with NP clinical response rate was 75-91% with the former and 75% with the latter. Bacteriological cure rate varied from 50-76% for both. Meropenem is not FDA approved for this indication. BNF C and AMH recommend imipenem-cilastatin and meropenem for nosocomial infections. Ertapenem is not recommended for empirical therapy of late onset NP[2]. It has however been found useful for treating early onset nosocomial infections and severe CAP. Doripenem appear to be useful.

**CAP:** Carbapenems have been evaluated for the treatment of severe CAP requiring IV antibiotic therapy. In adults, meropenem and imipenem-cilastatin were found to be equally effective in bringing about bacteriological and clinical cure and were safe. The results were comparable to that obtained with ceftazidime and combinations of clarithromycin and amikacin or ceftriaxone [3]. In children near 100% cure rates were observed with meropenem as compared to 93-96% in the comparator arms [5, 20, 21]. Ertapenem is comparable in clinical efficacy, bacteriological cure and tolerance to ceftriaxone and cefepime. It is an option for out patient parenteral therapy (AMH) of CAP since once a day dosing is possible.

**Cystic fibrosis:** Meropenem + tobramycin was compared with ceftazidime + tobramycin for acute exacerbations or for chronic infections in cystic fibrosis in two

randomised clinical trials where children also were included [3, 22, 23]. Meropenem significantly improved pulmonary function in both acute and chronic infections and brought about bacteriological cure. Efficacy and safety were comparable in both groups. Cure rates of 98% and 90% respectively were observed with meropenem monotherapy (60 episodes) and ceftazidime monotherapy (21 episodes) in children and young adults with cystic fibrosis and pseudomonas chest infections [24]. Emergence of resistance was low in all three trials even though several children received repeated courses. BNF C recommends imipenem-cilastatin and meropenem for this indication.

#### 4. Intra-abdominal infections

These are polymicrobial infections caused by bacteria, including MDR bacteria, mostly susceptible to carbapenem. Here again, potent early anti GNB cover is required. Clinical cure rates of 91% with meropenem as compared to 92% in the comparator arm is reported in children [6]. Clinical trials also show that both imipenem and meropenem are equally effective [5, 6]. This indication is FDA approved. This is listed as one of the indications for carbapenems in AMH. BNF C recommends imipenem-cilastatin and meropenem for mixed infections in general.

#### 5. Skin and soft tissue infections

Clinical trials show imipenem and meropenem to be effective in treating complicated skin and soft tissue infections[3, 5]. These infections and bone and joint infections were included in clinical trials in children and showed similar results[5]. This is an FDA approved indication.

#### 6. Septicaemia

Meropenem and imipenem have been proven to be effective in treating septicaemias in adults and children [3, 6] and comparable to cephalosporin based regimens. BNF C recommends imipenem-cilastatin and meropenem for hospital acquired septicaemia

#### 7. UTI

For complicated UTI requiring inpatient IV therapy, imipenem-cilastatin and meropenem were found to be useful alternatives [3, 6]. Although most data is from adults, children with UTI were included in paediatric trials evaluating carbapenems. AMH lists this as an indication.

Imipenem-cilastatin and meropenem may be used in melioidosis along with other agents (AMH)

### Adverse events

Adverse events are comparatively rare with carbapenems and are mostly minor. In an analyses of 6154 hospitalised patients including over 1000 children treated with meropenem, 16% developed drug related adverse events compared to 11% in the cephalosporin group[3]. Similar figures were obtained for adverse events in children analysed separately [25]. With imipenem-cilastatin also incidence of adverse events is low when used for non CNS indications [25]. However, a recent meta analyses showed that these events were significantly lower with meropenem as compared to imipenem (RR 0.87; 95% CI: 0.77-0.97) [11]. The common adverse events recorded in a review of about 5000 patients, are listed in table 2. Labels of all carbapenems record low rates of adverse events.

Most trials record nausea and vomiting are the most common adverse reactions (1% to 20%). GI symptoms are dose dependant for imipenem, but not for meropenem[2]. Therefore higher meropenem doses and can be administered as bolus doses[3, 6] and at faster rates without inducing nausea [2]. *Clostridium difficile* associated pseudomembranous colitis can occur, but is rare.

Table 2 Percentage of patients (adults and children) developing adverse events with imipenem and meropenem [25]

	Meropenem (n= 5026)	Imipenem+ Cilastatin (n=1802)	Cephalosporin based (n=2423)	Clindamycin +Aminoglyc (n= 527)
Diarrhoea	2.3	1.4	2.3	3.8
Rash	1.4	1.3	1.8	1.0
Nausea/vomiting	1.4	3.2	0.4	1.7
Head ache	0.4	0.6	0.1	0.0
Injection site	1.1	1.3	0.7	0.2
Sepsis	0.1	0.2	0.0	0.2
Seizures	(n=4748)	(n=1802)	(n=2158)	(n=527)

	Meropenem (n= 5026)	Imipenem+ Cilastatin (n=1802)	Cephalosporin based (n=2423)	Clindamycin +Aminoglyc (n= 527)
Total	0.46	0.55	0.28	0.38
Drug related	0.08	0.28	0.05	0.00

Adverse events are low with ertapenem and doripenem also [2]. Those reported in children with ertapenem (INVANZ label, Merck and Co, 2008) are similar to those observed with other carbapenems and include diarrhoea 12%, abdominal pain 4.7%, vomiting 10%, fever 4.9%, rash 2.9%, diaper dermatitis 2.9%, URI 2.3%, head ache and cough 4.4%.

Of serious concern is the ability of carbapenems to induce seizures. Seizures develop if overdosed, in relation to body weight or renal function. Risk is highest with imipenem-cilastatin where the therapeutic margin is narrow [10]. The dose of imipenem required for treating meningitis is higher than what is safe and a study was terminated when 33% of children on imipenem for the treatment for meningitis developed seizures[5, 7]. Imipenem is therefore contra indicated in CNS infections. For all imipenem administrations seizure incidence in children is 2% and 3.6 % in cancer patients. With adult doses of 2gm/day, incidence of seizures is similar to that seen with meropenem [2]. However, it has to be used with caution where higher doses are required and in those with renal impairment since the drug can accumulate. BNF C and AMH advice caution while using in those with history of seizures.

Risk of seizures is low (0.07%) with meropenem even with high doses and is permitted for use in CNS infections [3]. Randomised trials in adults and children using doses of 40 mg/kg have shown seizure rates similar to comparator drugs as shown in table 3. The neurotoxicity recorded was mostly related to hearing. Dizziness, confusion, tremor etc are also reported especially with imipenem-cilastatin

Risk of seizures with ertapenem is also low and was 0.2 - 0.5% in phase 3 trials [7]. Evidence so far suggest that doripenem probably has little or no convulsive activity [7].

Table 3 CNS related toxicity with meropenem

Treatment	Clinical cure in evaluable patients no. (%)	Neurological sequelae in evaluable patients no. (%)	Seizures on treatment (all patients treated) no. (%)
Meropenem	23/23 (100)	16/28 (57)	0/28 (0)
Cefalosporin (cefotaxime or ceftriaxone)	17/22 (77)	11/28 (40)	0/28 (0)
Meropenem	75/75 (100)	21/98 (21)	5/98 (5)
Cefalosporin (cefotaxime or ceftriaxone)	62/64 (97)	10/98 (10)	3/98 (3)
Meropenem	75/78 (96)	34/78 (43)	15/129 (12)
Cefalosporin (cefotaxime)	71/75 (95)	29/75 (39)	22/129 (17)

Hypersensitivity and anaphylaxis are reported with carbapenem use in those allergic to penicillin and the labels, BNF C and AMH warn against this possibility. However, there is inadequate information on the frequency of this complication. Approximately 11% of individuals with proven hypersensitivity to penicillin can be allergic to carbapenem[3]. There is no difference between imipenem and meropenem in this respect [3]. True incidence of hypersensitivity with carbapenem is <3%[7]. Majority of these individuals have skin manifestations. Anaphylaxis occurs in 0.01% (AMH). Therefore, expert opinion is that in serious infections where there is no other alternative, carbapenem can be used even in those with penicillin allergy, especially in ICU settings where there is facility to manage anaphylaxis, if it occurs[2]

IV site irritation can occur in less than 5%.

Transient laboratory abnormalities like raised AST, ALT, reduced neutrophil counts, thrombocytosis etc can occur and reported in all labels.

Meropenem had to be withdrawn in 2.7% of individuals due to adverse events as compared to 3.8% on imipenem-cilastatin and 1.1 to 2.8% on comparators[25].

Drug interactions are low. Concomitant probenecid use increases meropenem plasma half life. Meropenem and probably all carbapenems reduce serum valproic acid levels[3]

Incidence of adverse events in 135 children (new born to 3 months of age) receiving imipenem-cilastatin were as follows- 3% diarrhoea, 1.5% oral candidiasis, 1.5% rash, 2.2% oliguria, 1.5% tachycardia and 5.9% convulsions (Primaxin label)

### Dosage and Stability

Carbapenems have time dependent rather than concentration dependent bactericidal activity. Hence the dosing should be to optimise the duration of unbound drug concentration at or above MIC [7].

For meropenem, adult dose is recommended for children weighing over 50 kg and is 500mg to 1gm IV Q8h (BNF C). A dose of 2gm Q8h is recommended for meningitis and cystic fibrosis. For children above 3 months and weighing less than 50 kg, the dose is 10-40mg/kg IV Q8h. For febrile neutropenia and intra abdominal infections 20mg/kg and for meningitis and respiratory infection in cystic fibrosis 40mg/kg is recommended [3]. Dose for an individual can depend on type and severity of infection, pathogen involved and patient condition. The dose can be administered as bolus or as 15-30 min infusion. For neonates under 7 days, 20mg/kg every 12 hrs is used (BNF C).

Dose (Primaxin label) of imipenem for children is 15- 25mg/kg/dose administered every 12 hrs in those <1 wk of age, every 8hrs in those 1-4 wks of age, and every 6 hrs after 4wks of age. Premature infants can be given 20mg/kg Q12h. Doses less than 500 mg per dose are given as IV infusion over 15-30 min and those more than 500 mg over 40-60 min. Recommended adult dose is 2-4gm/day[2]. With 2gm/day, relapses and super infections were more common with imipenem than with ceftazidime [2]. Cure rate in intra abdominal infections were low when 2gm/day was used [26]. These results suggest that the doses which are safe may not be adequate for at least some infections. There are no double blind clinical trials comparing doses.

Ertapenem dosage for those aged 3m- 12 yrs is 15 mg/kg twice daily as infusion over 30 min. For those older 1gm per day is used (BNF C).

Dose of carbapenems has to be adjusted in renal impairment but there is paucity of data. BNF C has guidelines for meropenem use. These are to be used with caution in hepatic impairment.

Recent studies have evaluated continuous infusions and intermittent extended infusions over 3-4 hrs for imipenem and meropenem. Simulations show these to be better than the traditional 30-60 min infusions because of the time dependant bactericidal activity of carbapenems [7]. However stability of solutions at room temperature is a problem. A 10% degradation occurs at 25<sup>0</sup> C after 3 and 5 hrs respectively for meropenem and imipenem[7]. Following reconstitution meropenem is stable at RT (15-25<sup>0</sup> C) for 1-4 hrs (Merrim label). Meropenem also needs dedicated line for infusion[3]. Imipenem is stable for 4hrs at room temperature after reconstitution (Primaxin label). Doripenem is stable at RT for 8-12 hrs and is administered as 1 hr infusion. It is compatible with a wide range of IV medications [2]. Ertapenem stability after reconstitution is 6hrs. It also cannot be mixed with other medications.

There are restrictions on reconstitution fluids to be used for carbapenems.

### Cost

From International Drug Price Indicator Guide

Imipenem buyer price – 9.84/1gm (500 mg+500mg) vial

Meropenem buyer price - 25.3456/1 gm

Although cost of meropenem is higher than that of comparators, studies done in UK, US and Russia show that the overall cost of therapy for patients with severe infection in the ICUs is lower with meropenem as compared to imipenem-cilastatin and conventional combination antibacterial therapy [3]. Pharmacoeconomic models have several limitations and results may not be applicable to other areas.

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