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POSITION STATEMENT: APPROPRIATE USE OF THE CARBAPENEMS

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Website: www.samedical.org

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POSITION STATEMENT

Appropriate Use of the Carbapenems

A J Brink, C Feldman, D C Grolman, D Muckart, J Pretorius, G A Richards, M Senekal, W Sieling

The carbapenems are a group of broad-spectrum beta-lactam antibiotic agents of which there are three parenteral preparations currently available in South Africa, namely imimpenem/cilastatin, meropenem and ertapenem. Owing to the fact that imipenem/cilastatin and meropenem have a broad spectrum of activity that includes *Pseudomonas* and *Acinetobacter* species, they are ideal antibiotics for treatment of severe nosocomial infections. In contrast, ertapenem has limited *in vitro* activity against the latter non-fermentative Gram-negative bacteria and is therefore more suitable for the treatment of certain severe community-acquired infections. This statement arises out of concerns about the general abuse of antibiotics such as the carbapenems, with the primary intention of highlighting the appropriate use of these agents.

1. Introduction

The statement is an update of the original document first published in the *Southern African Journal of Critical Care* in 2001,[1] which was necessitated by the recent licensing of the newest member of this class of antibiotics, ertapenem.

Ertapenem is the first of a new group of carbapenems, which differ significantly from the earlier agents.[2,3] The activity of ertapenem, similar to that of the earlier agents, includes amp-C beta-lactamase, extended spectrum beta-lactamase (ESBL)-producing pathogens and anaerobes. However, it has only marginal activity against non-fermentative Gram-negative bacilli. This spectrum is more suitable for the treatment of severe infections acquired outside the hospital and certain hospital-acquired infections, where *Pseudomonas* spp. and/or *Acinetobacter* spp. are not suspected. Furthermore, the appropriate use of this agent in these settings may help to reduce selective pressure for resistance development in the latter pathogens. An additional differentiating characteristic of ertapenem is its once-daily intravenous or intramuscular dosing, compared with the multiple dosing required for the earlier agents.

Imipenem/cilastatin and meropenem have a broad spectrum of activity against a number of bacterial species, including non-fermentative Gram-negative bacteria such as *Pseudomonas* and *Acinetobacter* spp. This makes them ideal for the treatment of severe nosocomial infections.

Based on these differences Shah and Isaacs[3] have proposed the following carbapenem classification scheme.

- **Group 1** includes broad-spectrum carbapenems, with limited activity against non-fermentative Gram-negative bacilli, that are particularly suitable for community-acquired infections (e.g. ertapenem).
- **Group 2** includes broad-spectrum carbapenems, with activity against non-fermentative Gram-negative bacilli, that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem).
- **Group 3** includes carbapenems with clinical activity methicillin-resistant *Staphylococcus aureus* (none currently licensed).

2. Ertapenem (group 1)

2.1 Appropriate use

- This agent is most appropriately used for the treatment of **severe community-acquired infections**. However, the agent should not be used as first-line empirical therapy, except in certain specific circumstances.
- This agent may be also be used in a few specific instances for nosocomial infections where *Pseudomonas* spp. are not deemed important pathogens, such as early nosocomial pneumonia acquired out of the intensive care unit (ICU).
- This agent is ideal for directed therapy based on the results of microbiological testing, and especially for the treatment of infections with isolates demonstrating ESBLs.
- This agent is well suited for the treatment of chronic and recurrent or persistent infections in cases in which cultures are most likely to demonstrate resistant Enterobacteriaceae or that are polymicrobial in nature; however, it is not effective against *Pseudomonas* and *Acinetobacter* spp.
- It is indicated for the treatment of the following infections, with specific indications:
  - Pneumonia
  - Surgical infections including intra-abdominal, skin and soft-tissue and gynaecological infections
  - Urinary tract infections.

Please forward all comments to: **Dr A J Brink, PO Box 1873, Houghton, 2041, tel. (011) 726-6260, e-mail brinka@ampath.co.za**

Table I. Ertapenem (group 1) — pneumonia

Appropriate use	Inappropriate use
• The elderly, especially high-risk cases with underlying co-morbid illness and patients living in long-term care facilities where no risk factors for pseudomonal infections are present* • Alcoholics • Hospital-acquired pneumonia where no risk factors for pseudomonal infections are present* • Nosocomial aspiration pneumonia/suspected anaerobic infection/lung abscess • Cases known to be, or suspected of being, infected with pathogens resistant to standard antimicrobial agents, particularly extended-spectrum β-lactamase-producing GNB • Patients who have failed standard first-line antibiotic treatment for CAP (particularly as part of directed antibiotic therapy based on the results of microbiological testing)	• Empirical treatment of nosocomial pneumonia in the ICU • First-line, empirical treatment of CAP • Presence of risk factors for pseudomonal infections*

*Risk factors for pseudomonal infections may include:
Infections acquired in the ICU
Patients with structural lung disease
Patients who have received broad-spectrum antibiotic Rx for > 7 days in the previous month
Patients who have recently been hospitalised (because of nosocomial colonisation)

GNB = Gram-negative bacilli; CAP = community-acquired pneumonia.

2.2 **Pneumonia** (Table I)

2.2.1 Appropriate use in pneumonia

In the case of pneumonia, this agent may be indicated in the following circumstances:

- The elderly, especially high risk-cases with underlying co-morbid illness and/or those living in long-term care facilities (LTCF) or in alcoholics where no risk factors for pseudomonal infections are present.*
- Hospital-acquired pneumonia where no risk factors for pseudomonal infections are present.*
- Nosocomial aspiration pneumonia/suspected anaerobic infection/lung abscess such as may occur in patients with neurological disorders or swallowing dysfunction.
- Cases known to be, or suspected of being, infected with pathogens resistant to standard antimicrobial agents but retaining susceptibility to ertapenem, especially in cases where Gram-negative pathogens are involved.
- Patients who have failed standard first-line antibiotic therapy for community-acquired pneumonia particularly as part of directed antibiotic therapy based on the results of microbiological testing.

1.2.2 Inappropriate use in pneumonia

- This agent should not be used for empirical therapy of nosocomial pneumonia in the ICU.
- This agent should not be used for first-line, empirical therapy of community-acquired pneumonia.
- This agent should not be used for the empirical treatment of pneumonia in patients at risk of pseudomonal infections.*

2.3 **Surgical infections** (Table II)

2.3.1 Appropriate use in intra-abdominal infections

In the case of community-acquired intra-abdominal surgical infections, this agent could be used for treatment of patients in the following settings:

- Severe sepsis, e.g. patients with organ dysfunction, requiring inotropes, with an Acute Physiology and Chronic Health Evaluation (APACHE II) score > 20 or requiring ICU admission for conditions such as:
  - Acute appendicitis, ruptured or perforated appendix and peri-appendiceal abscess
  - Acute diverticulitis with perforation and/or abscess
  - Acute cholecystitis (including gangrenous) with either rupture or perforation
  - Acute gastric and duodenal perforation
  - Traumatic perforation of the intestine
  - Intra-abdominal abscess including liver and spleen.
- Cases at risk of having ESBL-producing and/or fluoroquinolone-resistant micro-organisms, e.g. LTCF residents; this should be culture driven as these patients are also at risk of *Pseudomonas* and *Acinetobacter* spp. infections.
- As part of directed therapy in cases with isolates

*Risk factors for pseudomonal infections may include:[4-7]

- Infections acquired in the ICU
- Patients with structural lung disease, in particular patients with cystic fibrosis and/or bronchiectasis
- Patients who have received broad-spectrum antibiotic therapy for more than 7 days in the previous month
- Patients who have recently been hospitalised (because of nosocomial colonisation).

Table II. Ertapenem (group 1) — surgical infections

Appropriate use	Inappropriate use
Intra-abdominal infections (IAIs)	
• Severe community-acquired IAI in patients with organ dysfunction, requiring inotropes, with an APACHE II score > 20 or requiring ICU admission • Cases at risk of having ESBL-producing and/or fluoroquinolone-resistant micro-organisms, e.g. LTCF residents (this should be culture-driven as these patients are also at risk of *Pseudomonas* and *Acinetobacter* spp. infections) • Directed treatment in cases with isolates demonstrating the presence of ESBL and/or based on the results of other microbiological testing, including evidence of polymicrobial infections	• Empiric treatment of nosocomial IAI • Community-acquired IAI at risk of infection with *Pseudomonas spp:* • Prior hospitalisation (as late-onset sequelae of nosocomial colonisation) • Immunosupression resulting from prior therapy for transplantation, cancer or inflammatory diseases
Skin and soft-tissue infections	
• Severe cases of community-acquired necrotising fasciitis or Fournier's gangrene requiring ICU admission • Severe cases at risk of having ESBL-producing and/or fluoroquinolone-resistant micro-organisms e.g. LTCF residents • As part of directed treatment in cases with isolates demonstrating the presence of ESBLs and/or based on the results of microbiological testing including evidence of polymicrobial infections • As directed outpatient monotherapy in cases with confirmed polymicrobial and/or resistant infections, e.g. LTCF residents	• Mild skin and soft-tissue infections • Directed treatment for infections caused by *Staphyloccus aureus*, whether due to methicillin-sensitive or resistant isolates

ESBL = extended spectrum beta-lactamase; LTCF = long-term care facility.

demonstrating the presence of ESBLs and/or based on the results of other microbiological testing, including evidence of polymicrobial infections.

2.3.2 Appropriate use in skin and soft-tissue infections

In the case of community-acquired skin and soft-tissue surgical infections, this agent should be reserved for treatment of patients in the following settings:

- Severe cases of established necrotising fasciitis or Fournier's gangrene requiring ICU admission.
- Cases at risk of having ESBL-producing and/or fluoroquinolone-resistant micro-organisms, e.g. LTCF residents.
- As part of directed therapy in cases with isolates demonstrating the presence of ESBLs and/or based on the results of microbiological testing including evidence of polymicrobial infections.
- As *directed* out-patient monotherapy in cases with confirmed polymicrobial and/or resistant infections, e.g. LTCF residents.

2.3.3 Inappropriate use in surgical infections

- This agent should not be used for the empirical treatment of *nosocomial* intra-abdominal infections, particularly not in cases with prolonged pre-operative length of hospital stay and prolonged pre-operative antimicrobial therapy (more than 2 days); these factors are significant predictors of antibiotic failure resulting in recurrent infection.[8]
- This agent should not be used in community-acquired intra-abdominal infections in patients at high risk of post-operative mortality, where the presence of infection with multiresistant bacteria including *Pseudomonas* spp. might be common. In these high-risk patients, use of broader-spectrum, antipseudomonal antibiotics may be warranted:[9,10]
  - Immunosupression resulting from prior therapy for transplantation, cancer or inflammatory diseases
  - Prior hospitalisation (as late-onset sequelae of nosocomial colonisation).
- This agent should not be used for mild skin and soft-tissue infections.
- This agent should not be used as directed therapy for infections caused by *S. aureus*, whether due to methicillin-sensitive or resistant isolates.

2.4 Urinary tract infections (Table III)

2.4.1 Appropriate use in urinary tract infections

- This agent is indicated for the treatment of severe, complicated urinary tract infections particularly in cases at risk of having resistant Gram-negative pathogens.
- As part of directed therapy in cases with isolates demonstrating the presence of ESBLs and/or based on the results of microbiological testing.

Table III. Ertapenem (group 1) — urinary tract infections (UTIs)

Appropriate use	Inappropriate use
• Severe, complicated UTI particularly in cases at risk of having resistant pathogens including ESBL- producing GNB, e.g. LTCF residents	• First-line empirical treatment of community-acquired UTI

ESBL = extended spectrum beta-lactamase; GNB = Gram negative bacilli; LTCF = long-term care facility.

2.4.2 Inappropriate use in urinary tract infections

- This agent should not be used for first-line, empirical therapy of community-acquired urinary tract infections.

2.5 Other considerations for ertapenem therapy

- This agent may be used as therapy for infections acquired in the ICU, but only as part of directed therapy based on results of microbiological testing, and especially for the treatment of infections with isolates demonstrating ESBLs.
- There is emerging evidence that shorter duration of therapy is as effective as longer therapy and has the potential benefit of less impact on resistance development.
- If indicated for cases of severe community-acquired pneumonia, empirical treatment with this agent should be combined with a macrolide or fluoroquinolone until culture results become available.

3. Imipenem/cilastatin and meropenem (group 2) (Table IV)

Table IV. Imipenem/cilastatin and meropenem (group 2)

Appropriate use	Inappropriate use
• Empiric treament of severe nosocomial infections in critically ill patients or in ICU • Failure of first-line antibiotics for Gram-negative bacterial (GNB) infections • Directed treatment according to results of culture and susceptibility testing • Chronic multiresistant pseudomonal infections • In certain settings of neutropenic sepsis, severe nosocomial intra-abdominal sepsis and meningitis	• Routine treatment of otitis media • Routine treatment of acute exacerbations of chronic bronchitis • Surgical prophylaxis • Routine treatment of community-acquired pneumonia (CAP) • Routine treatment of community-acquired gynaecological infections • Routine treatment of community-acquired urological infections • Nosocomial or community-acquired Gram-positive sepsis

3.1 Appropriate use

- These agents are most appropriately used for the early, timeous treatment of **severe nosocomial infections** in the critically ill patient or in the critical care setting, particularly when no other antibiotic appears to be suitable, or is available. In this setting these agents may be used as *empirical* therapy for severe nosocomial infections, based on knowledge of local surveillance data from a particular unit. They may also be suitable for use where first-line empirical therapy against Gram-negative organisms has failed.
- They should ideally be used as specific antibiotic therapy directed against significant isolates cultured from appropriate specimens, and should be prescribed according to the results of antibiotic susceptibility testing. This is where close interaction with the clinical microbiologist and the microbiology laboratory will be of major assistance.
- These agents may be necessary for antibiotic therapy of certain conditions in which there is chronic pseudomonal infection, such as bronchiectasis, cystic fibrosis, and immune deficiency disorders. Where these agents are used for the therapy of patients with pseudomonal infection in frail care settings, this should be done with consideration of the results of culture and sensitivity testing and they should not be considered as first-line therapy.
- Although not considered as primary therapy in most cases, these agents may be considered for use in neutropenic sepsis, severe abdominal sepsis in certain specific settings, and meningitis. The carbapenem recommended for the treatment of meningitis is meropenem.

3.2 Inappropriate use

- Neither of these agents is indicated for the routine treatment of otitis media, acute exacerbations of chronic bronchitis, surgical prophylaxis or first-line treatment of community-acquired infections, such as pneumonia or gynaecological or urological infections.
- Although these two agents provide Gram-positive cover, they are not indicated for the treatment of nosocomial or community-associated Gram-positive sepsis.
- Unnecessary use of these carbapenems, particularly in the ICU setting, may select for multiresistant and difficult-to-treat infections, such as *Stenotrophomonas maltophilia, Burkholderia* spp., etc.

3.3 Other considerations

- Monotherapy with these carbapenems is suitable in most circumstances, but where infections with *Pseudomonas* spp. are suspected or proven, particularly bacteraemic infections, combination therapy together with an aminoglycoside or an appropriate fluoroquinolone (e.g. ciprofloxacin) may be considered.

- The use of metronidazole or other anti-anaerobic agents together with these carbapenems is not necessary except in the case of infections with *Clostridium difficile*.
- Appropriate therapeutic dosing is essential since underdosing in the face of high minimum inhibitory concentrations (MICs) may be associated with decreased efficacy and increased resistance. Monitoring of the MIC is useful in that it may indicate future antibiotic susceptibility trends and may influence dosing. This is an area in which the advice of the clinical microbiologist is particularly helpful.
- There is emerging evidence that shorter duration of therapy for certain nosocomial infections such as ventilator-associated pneumonia is as effective as longer therapy and has the potential benefit of reducing the incidence of hospital-acquired superinfection or reinfection with multiresistant bacteria or *Candida* spp., while simultaneously reducing antibiotic pressures.
- Because of the risk of selecting for resistance, initial empirical broad-spectrum treatment with imipenem or meropenem should be 'de-escalated' or 'tailored' to a narrow-spectrum agent, once the identity and susceptibility profiles of the infecting pathogens are known. If a less resistant pathogen is identified, it should be mandatory to de-escalate antibiotic therapy with these carbapenems to an agent with a narrower spectrum of activity.

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6. Endorsement

Endorsed by the Critical Care Society of Southern Africa, the South African Thoracic Society, and the Federation of Infectious Diseases Society of Southern Africa.

7. Disclaimer

This statement is published for educational purposes only. The recommendations are based on currently available scientific evidence together with the consensus opinion of the authors.

7. Working group

A J Brink (Drs Du Buisson, Bruinette and partners, Ampath, Johannesburg), C Feldman (Division of Pulmonology, Department of Medicine, Johannesburg Hospital and University of the Witwatersrand, Johannesburg), D C Grolman (General Surgeon and Intensivist, Sandton Mediclinic, Johannesburg), D Muckart (Associate Professor of Surgery, Director of Surgical Intensive Care, Department of Surgery, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban), J Pretorius (Surgical Intensive Care Unit, Department of Surgery, Pretoria Academic Hospital and University of Pretoria, Pretoria), G A Richards (Director Critical Care, Johannesburg Hospital and Principal Physician, Division of Pulmonology, University of the Witwatersrand, Johannesburg), M Senekal (Drs Dietrich, Street, Senekal and partners, Pathcare, Cape Town), W Sieling (Infectious Diseases Specialist and General Physician, Pretoria East Hospital, Pretoria).

Notes