Treatment of Suspected or Confirmed Infection with Enterobacterales or Acinetobacter spp. Resistant to Carbapenems

Surgical Prophylaxis in the Context of Colonisation with such organisms.

APRIL 2019

Scope

This document is intended to support those who must manage or give advice on antimicrobial management of people with suspected or confirmed infection with carbapenem-resistant Enterobacterales and *Acinetobacter spp*. This document does not apply to *Pseudomonas spp*., *Burkholderia spp*. or *Stenotrophomonas spp*. It addresses both empiric therapy for suspected CPE infection and targeted therapy after a pathogen has been identified.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Antimicrobial therapy is only one element of the care of people with suspected or confirmed infection. Guidance on screening for sepsis and the management of sepsis and septic shock are available at https://www.hse.ie/eng/about/who/cspd/ncps/sepsis/

The guidance is based on best available evidence as of December 2018. Given the rapidity with which new evidence and therapies are emerging, the approach to treatment is likely to evolve over time. This document is therefore intended to guide Consultant Microbiologists and Infectious Disease Physicians who have the expertise to integrate emerging evidence into their decision making. The document will need to be reviewed regularly.

Those managing CPE infection are encouraged to retain a record of experience with the use of this guideline and where possible to share anonymised information with the Antimicrobial Resistance and Infection Control Division of HPSC etc to inform future revision of the guidance. Note the HPSC enhanced surveillance for CPE blood stream infection process and Appendix 1 of this document.

This document provides a framework to support a generally consistent approach to treatment. Given the complexity of clinical situations and antimicrobial susceptibility patterns, treatment must be tailored to individual patients. This document is not intended to restrict the appropriate application of clinical judgement.

Many infections in those colonised with carbapenem-resistant organisms/CPE will be considered unlikely to be CPE related on clinical grounds. Examples include many soft tissue infections. This guidance does not apply to those situations. Similarly many surgical procedures performed on patients with carbapenem-resistant organisms/CPE will be at sites where carbapenem resistant organisms/CPE is not likely to be associated with surgical site infection. This guidance does not apply to those situations.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

CPE infection may be suspected in a setting where a person has clinical features of infection and is known to be colonised with CPE. It may also be appropriate to suspect CPE infection in some cases where the person is not known to be colonised with CPE but is at high risk of CPE colonisation for example because they are a CPE Contact.

CPE infection may be considered confirmed when CPE is detected in a clinical sample of body fluid or tissue in the context of relevant clinical evidence of infection. Detection of CPE in a sample such as urine, sputum or wound swab does not of itself confirm infection.

All of the doses and treatment recommendations in the document are based on managing infections in adults: dosing and potential contraindications may be different in children.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Table of Contents

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Abbreviations and Glossary of Terms

AMRO = Antimicrobial-Resistant Organism

ED = Emergency Department

ESBL = Extended Spectrum Beta-lactamase

IPC = Infection Prevention and Control

Isolation = Isolation refers to accommodation of one person in a single room

Person/People = the terms person/people are generally used in this document and are in general interchangeable with the terms client, service user or patient.

CPE = Carbapenemase Producing Enterobacterales* The following in alphabetical order are some of the more common carbapenemase enzymes. There are a number of other carbapenemase enzymes.

IMP = Imipenemase

KPC = Klebsiella pneumoniae carbapenemase

NDM = New Delhi metallo-beta-lactamase

OXA = Oxacillinase-type carbapenemase (OXA-48 is the most common variant)

VIM = Verona Integron-encoded metallo-beta-lactamase

***Enterobacterales** is a new term encompassing all those genera of bacteria formerly encompassed by the term *Enterobacteriaceae*. The term *Enterobacteriaceae* now encompasses a more limited number of genera.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Background

Acquired carbapenem resistance poses a very significant challenge in the treatment of life threatening Gram-negative infection.

The pandemic spread of highly mobile genetic elements encoding for carbapenemase enzymes enables Enterobacterales to become Carbapenemase Producing Enterobacterales (CPE). The dissemination of CPE has been a key driver of emerging carbapenem-resistance globally and the control of CPE is a major public health challenge. Acquired resistance to carbapenems may also be related to mechanisms other than carbapenemase production, for example loss of porin channels, or increased efflux of the antibiotic. In relation to therapeutics for an individual patient it is the pattern of resistance rather than the mechanism that is most important therefore this advice relates to management of carbapenem resistant Enterobacterales regardless of the mechanism and may also be relevant to management of certain other taxa with acquired carbapenem resistance including *Acinetobacter spp*.

Note on the use of carbapenem for treatment of carbapenem-resistant Enterobacterales

Antimicrobial susceptibility test (AST) interpretation guidelines have historically advised discounting *in vitro* susceptibility test measurements in the presence of certain specific resistance mechanisms. For example, avoidance of cephalosporins and beta-lactam/beta-lactamase inhibitor combinations was often recommended in the treatment of ESBL producing Enterobacterales even when such isolates had minimum inhibitory concentrations within the susceptible range. In recent years, following downward revision of the interpretive breakpoints, AST guidelines have generally advised that if an isolate tests susceptible to an agent then the agent may be used regardless of detection of any gene or mechanism associated with resistance. This approach, however, should take note of a recent paper which suggested that a particular beta-lactam/beta-lactamse inhibitor combination (piperacillin/tazobactam) may be less effective than meropenem for the

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

treatment of patients with ceftriaxone-resistant *E. coli* or *Klebsiella pneumoniae* bloodstream infection [1].

By applying that AST interpretation principle to CPE, carbapenems are used to treat CPE isolates that test susceptible to a carbapenem by EUCAST criteria (for example meropenem MIC of less than or equal to 2 mg/L). For isolates that are non-susceptible but not resistant by EUCAST criteria (meropenem MIC of less than or equal to 8 mg/L), the addition of meropenem to a combination of other agents is an appropriate option.

Note on Combination Therapy

Combination therapy is widely recommended and widely used in the treatment of severe infection related to carbapenem-resistant organisms and CPE. Combination therapy is generally recommended in what follows in this document. However, in the INCREMENT study combination therapy was only associated with improved survival among patients with a high probability of death as measured by the INCREMENT-CPE mortality score. This scoring tool can be used to assist in selecting patients for whom monotherapy may be appropriate [2]. Also of note, a recent study of colistin compared with colistin plus meropenem failed to show added value from the combination [3, 4].

Recommendations in accordance with the Start Smart, then Focus Care Bundle

For additional information on Start Smart then Focus see https://www.rcpi.ie/news/publication/start-smart-then-focus-an-antibiotic-care-bundle-for-hospitals

Key principles of management

1. A Consultant Microbiologist or Infectious Disease Physician should be consulted early in relation to people with suspected or confirmed severe infection with carbapenem resistant Enterobacterales or *Acinetobacter spp*.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

2. Generally such patients should be managed in a hospital with an on-site Consultant Microbiologist or Infectious Disease Physician to manage or to consult on treatment and diagnostics. This may not be appropriate for all patients, in particular for those where the priority is comfort, rather than intervention and active management.
3. There should be input from an Antimicrobial Pharmacist in relation to antibiotic therapy, particularly given the role of pharmacokinetic (PK)/pharmacodynamic (PD) considerations in the likely success of therapy and the fact that these infections frequently occur in patients who are already receiving multiple other medications, who are usually critically ill, and who may have altered drug kinetics.
4. Every effort should be made to ensure early and effective source control is achieved, in the setting where the focus of infection is amenable to drainage, debridement, or removal.

Initial evaluation and investigations

1. As with all patients with severe infection, diagnostic samples, including blood cultures, should be collected before initiation of antimicrobial therapy if at all possible. In addition to diagnostic samples rectal swabs for testing for CPE should also be submitted if they have not been submitted in the previous 7 days. This should be done even in patients with known CPE colonisation as the patient may have acquired additional CPE (for example acquisition of NDM in addition to pre-existing KPC) or the susceptibility of the CPE they carry may have changed in a way that may impact on treatment.
2. In patients with suspected infection with carbapenem resistant Enterobacterales, any Gram-negative bacilli cultured from blood, or other normally sterile body site, should be directly subjected to rapid testing for carbapenemase (gene) direct from blood cultures if possible. If this is not possible a test for carbapenemase should be performed as soon as colonies are available on solid media (enzyme or gene). Suitable rapid methods may include lateral flow or molecular methods.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

3. In patients with suspected infection with carbapenem-resistant Enterobacterales, direct provisional susceptibility testing should be performed on any Gram-negative bacilli cultured from blood.
4. All first isolates of CPE from bloodstream or other normally sterile body site should be submitted to the national reference laboratory. This should be done even if previous colonisation isolates were submitted. Testing for susceptibility to colistin and ceftazidime-avibactam should be requested (where relevant).

Empiric antimicrobial therapy

1. Treatment and treatment response should be discussed at least daily with a Consultant Microbiologist or Infectious Disease Physician until the patient's condition has stabilised.
2. Where the infecting organism is not identified and treatment is therefore empiric inclusion of a broad spectrum beta-lactam or carbapenem may be appropriate even when the suspected infecting organism is resistant to beta-lactams and carbapenems. This is because the infecting organism may, in fact, be a beta-lactam or carbapenem susceptible organism and in that case an appropriate beta-lactam may be the preferred approach to treatment.
3. Given the current evidence suspected or confirmed severe infection with carbapenem resistant Enterobacterales or *Acinetobacter* spp. should generally be treated in the first instance with a combination of at least two antimicrobial agents likely to be effective. The choice of antimicrobial agents should take account of the type of carbapenemase (if known) and the most recent susceptibility test result of the CPE isolate from that person (if known). In people in septic shock, the addition of a third antimicrobial is often appropriate.
4. Where no susceptibility testing/results are available to guide treatment, for initial empiric therapy of infection for a person known or suspected to be colonised with a KPC or OXA-like carbapenemase, a combination of ceftazidime-avibactam with tigecycline and colistin may be appropriate. If there is concern regarding co-infection

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

with resistant Gram-positive bacteria vancomycin or other suitable agent may also be required.

5. Where no susceptibility testing/results are available to guide treatment, for initial empiric therapy of infection for a person known or suspected to be colonised with an organism containing an NDM/VIM/IMP carbapenemase, a combination of colistin, tigecycline and fosfomycin may be appropriate. If there is concern regarding co-infection with resistant Gram-positive bacteria, vancomycin or other suitable agent may also be required.

Directed antimicrobial therapy (carbapenem resistance/CPE confirmed)

1. Where isolates have tested susceptible to one or more carbapenems by a validated and reliable method carbapenems may be included in treatment regimens, regardless of resistance genes /enzymes detected in the organism unless the patient is intolerant of carbapenems.
2. Where isolates have tested susceptible to an aminoglycoside and there is no specific contraindication to their use an aminoglycoside should generally be used for at least the first 48 hours in patients who are in septic shock due to infection with carbapenem resistant Enterobacterales or *Acinetobacter spp*.
3. De-escalation to monotherapy should be considered within 48 hours or if the patient is improving. Antimicrobial susceptibility test results should be used to guide de-escalation.
4. The requirement for continuation of antimicrobial agents or combinations of antimicrobial agents with significant nephrotoxic potential should be reviewed daily. Where relevant antimicrobial blood levels should be measured at appropriate intervals and considered in making decisions on treatment.
5. For treatment of carbapenem-resistant organisms with confirmed antimicrobial susceptibility the combination of agents chosen should generally favour agents with the greatest evidence /experience of efficacy for treatment of Gram-negative infection such as beta-lactams, carbapenems and aminoglycosides.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

6. In circumstances where CPE is repeatedly isolated from a patient during treatment for CPE infection, susceptibility testing of the new isolate should be performed if the interval between samples cultured positive for CPE is 5 days or more. In some cases testing at more frequent intervals may be required.

De-escalation of antimicrobial therapy (carbapenem resistance/CPE becomes unlikely)

When a specific pathogen that is not a carbapenem-resistant organism/CPE is identified from blood culture or another relevant site, the antimicrobial treatment should generally be modified to target the identified organism based on its susceptibility. The patient should generally not be continued on a regimen directed towards treatment of a carbapenem-resistant organism after this point, even if the patient is known to be colonised with CPE.

Examples of approaches to antimicrobial treatment

A priority in a person with septic shock is the rapid administration of an antimicrobial agent(s) likely to be effective. The following general questions should be considered in relation to choice of treatment but incomplete information should not unduly delay initiation of treatment. The potential scenarios outlined attempt to provide advice in a specific set of circumstances. However, all treatment decisions should take account of the individual person's circumstances and needs.

- Does the patient have a history of drug allergy (document allergy type: minor (rash only) or major (anaphylaxis, angioedema))?
- Does the patient have any contraindications to individual antimicrobials?
- Is the patient receiving concomitant medications likely to interact with individual antimicrobials?
- Does the patient have organ dysfunction (e.g. renal or hepatic impairment) requiring adjusting of dose/frequency of individual antimicrobials?

Health Protection Surveillance Centre Contact email: hpsc@hse.ie
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

- Are there other factors relating to PK/PD that need to be considered to maximise efficacy and minimise toxicity for individual antimicrobials?

No identified pathogen but suspect KPC or OXA carbapenemase based on known colonisation or exposure, susceptibility of isolate not accessible	
Patient with septic shock	Ceftazidime-avibactam plus tigecycline plus colistin
Patient with septic shock, with a clear history of anaphylaxis to penicillin /cephalosporin	Tigecycline plus colistin plus fosfomycin. [Addition of a carbapenem* may be appropriate, if benefit outweighs risk, and is directed towards the possibility of infection with a susceptible organism]
Patient with severe infection but not septic shock.	Ceftazidime-avibactam plus tigecycline
Patient with sepsis but not septic shock with a clear history of anaphylaxis to penicillin /cephalosporin	Tigecycline plus colistin
Identified pathogen as KPC or OXA carbapenemase, susceptibility of isolate available	
Patient with septic shock	Aminoglycoside (whichever agent is susceptible) plus one of: meropenem [if susceptible] or ceftazidime-avibactam
Patient with septic shock, with a clear history of anaphylaxis to penicillin /cephalosporin	Tigecycline plus aminoglycoside. [If tests susceptible, use of a carbapenem* may be appropriate instead of tigecycline if benefit outweighs risk]
Patient with severe infection but not septic shock.	Meropenem [if susceptible] or ceftazidime-avibactam. **Note caution with the use of ceftazidime-avibactam alone if the isolate is a KPC-3 producer.**
Patient with severe infection but not septic shock and with a clear history of anaphylaxis to penicillin /cephalosporin	Tigecycline plus colistin. [Use of a carbapenem* as a single agent may be appropriate if the isolated tests

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	susceptible and the benefit outweighs the risk]
No identified pathogen but suspect NDM/VIM/IMP carbapenemase based on known colonisation, susceptibility of isolate not accessible	
Patient with severe infection including those with septic shock. This example is equally applicable to patients with a clear history of anaphylaxis to penicillin /cephalosporin.	Tigecycline plus colistin plus fosfomycin. [Addition of a carbapenem* may be appropriately directed towards the possibility of infection with a susceptible organism]
Identified pathogen as NDM/VIM/IMP carbapenemase, susceptibility of isolate available	
Patient with severe infection including those with septic shock. This example is equally applicable to patients with a clear history of anaphylaxis to penicillin /cephalosporin.	Colistin plus tigecycline OR aminoglycoside plus tigecycline (choice of agent based on susceptibility test).

***Caution: the use of carbapenems in penicillin / cephalosporin allergy is recommended in guidelines. Both prospective and retrospective studies have found low cross-reactivity rates between carbapenems and penicillins, with the likely risk as being less than 1%. [5]**

Reviews of the literature and microbiology data in Appendices 2, 3 & 4 have informed the choices detailed in the examples. A monograph for each of the individual antibiotics is included in Appendix 3 to assist in prescribing these agents. Appendix 3 also includes monographs for some of the newer antibiotics: meropenem-vaborbactam, plazomicin (licensed by US FDA but not commercially available until early 2019), eravacycline (licensed by US FDA but not commercially available until early 2019)

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

New agents in the pipeline

Other agents in the pipeline but not approved are: imipenem-relebactam, cefiderocol, aztreonam-avibactam, cefepime-zidebactam. Cefiderocol, a new siderophore cephalosporin, appears the most promising, with activity against KPC, NDM, VIM, IMP & OXA carbapenemase producers and carbapenem resistant *A. baumannii*.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Appendix 1

Table 1: Template to record experience of the treatment of an individual patient with a carbapenem resistant bloodstream infection – please submit this template to hcainational.lead@hse.ie.

Amended EARS-Net/Enhanced Bacteraemia Surveillance (Source HPSC website)			
			Circle items that apply
PART OF CORE DATA	Same as each EARSS-Net isolate	EARS-Net Laboratory Code	
		EARS-Net Hospital Code	
		Patient number	
		Specimen number	
		Specimen date (dd/mm/yyyy)	
		Organism & CPE type & AST results	
		Date of admission (dd/mm/yyyy)	
LEVEL 1		Probable contaminant	Y | N | *(do not complete the rest of form if 'Y')*
		Healthcare-association	This Hospital | Other Hospital | Long Stay Facility | Community | Unknown |
	Device	Device (catheter)-associated	Y | N |
		Type of device	PVC | CVC | CVC-PICC | Dialysis Catheter | Urinary Catheter | Other |
	Implant	Implant-associated	Y | N |
		Type of implant (free text)	
	Procedure	Procedure-associated	Y | N |
		Name of procedure (free text)	
		Any additional information (free text)	
LEVEL 2		Source organ site (one from list):	Respiratory | Gastroinstestinal | Hepatobilliary | Bone and joint | Head and neck | Central nervous system | Urinary tract | Genital tract | Skin/Soft tissue – surgical wound | Skin/Soft tissue–other | Cardiovascular | Other | Unknown |
		Further information on source	
		Neutropaenia	Y | N |
		Acquired in critical care	Y | N |
		Outcome	Discharged | Died | Still in Hospital | Unknown |
		Date of discharge or death (dd/mm/yyyy)	

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

		Antibiotic exposure including doses & durations (free text list)	
HSE-HPSC	EARS-Net Enhanced V5		April-19
	amendments to form		

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Appendix 2

Literature review of combination therapy versus monotherapy.

Until more robust evidence is available combination therapy is recommended as empiric therapy and monotherapy should only be considered when susceptibility results are available to support this approach and the patient is clinically stable.

- A meta-analysis of studies to the end of 2015 demonstrated that compared with carbapenem susceptible Enterobacterales, infection with carbapenem resistant Enterobacterales was associated with a significantly higher risk of overall mortality (OR, 3.39; 95% confidence interval [CI], 2.35-4.89. Monotherapy (vs. combination therapy) for carbapenem-resistant Enterobacterales infections was also associated with higher mortality (OR, 2.19; 95% CI, 1.00-4.80). The overall findings across the included studies indicate that the differences in mortality between people with infections due to carbapenem-resistant and carbapenem-susceptible Enterobacterales are possibly due to the treatment- or organism-related factors rather than differences in study population baseline characteristics. [6]
    - Seven studies included in the analysis compared monotherapy with combination therapy for carbapenem-resistant Enterobacterales; 5 were retrospective and 2 were case-control. Four of the studies included people with bloodstream infections, and 3 studies included people with a mix of infection types attributed to carbapenem resistant Enterobacterales.
    - Monotherapy in people with bloodstream infection led to a further increased mortality risk. Those treated with monotherapy were 3.8 times more likely to die compared with those people receiving combination therapy.
    - The treatment-related factors as a reason for increased mortality include: increased risk for delayed administration of an active antibiotic, optimal treatment remains undefined and often involves use of agents with a greater propensity for adverse effect, i.e. tigecycline, colistin, gentamicin and amikacin.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

  - This meta-analysis was conducted before the availability of ceftazidime-avibactam and meropenem-vaborbactam.
- In 2014 Falagas *et al*. [7] reported on 20 studies involving 692 people. Studies up to early 2013 were included.
  - Fifteen studies reported on CPE, five others were on carbapenem-resistant Enterobacterales.
  - In 8 out of 20 studies, the total or majority (>50% of the included infections) of the included infections were bloodstream infections. Pneumonia and urinary tract Infection were the most common infections among the remaining 12 studies.
  - Eight studies reported data on KPCs, five others on MBLs and OXA-producing *Klebsiella* spp.
  - Methodological issues with the studies precluded a meta-analysis
  - The following conclusions were made on the data:
    - Among critically ill people with bloodstream infection due to carbapenemase-producing *Klebsiella* spp., a combination antibiotic treatment may result in lower mortality than monotherapy
    - Tigecycline in combination with colistin, carbapenem in combination with colistin, and tigecycline in combination with gentamicin were the commonly administered antibiotic treatment regimens among the included studies and might result in lower mortality than other combinations of antibiotics. An effectiveness similar to that of the aforementioned combinations was observed among patients treated with monotherapy with colistin, tigecycline and carbapenems. However, the data were from studies often including fewer than 50 people.
    - There were few cases of successful treatment of bloodstream infection with gentamicin monotherapy
- In the INCREMENT study (2017) combination therapy was only associated with improved survival among people with a high probability of death as measured by the INCREMENT-CPE mortality score [2]

Health Protection Surveillance Centre Contact email: hpsc@hse.ie
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

  - The cohort was 480 people with blood stream infection due to CPE
    - Of 437 people, 69 had infection with OXA-48-, 329 with KPC- and 39 with MBL-producers
  - This study could not make estimations of efficacy of particular combinations [2]
  - Active antimicrobials should be administered as soon as possible. Consider relevant aspects of the HSE sepsis management Sepsis 6 bundle [8].
  - Although the ideal is administration of active antimicrobial agents as soon as possible there is evidence of benefit if active antimicrobial agents are given within 3-5 days of onset of infection [2]

- In most trials targeting CPE, combination therapies have included the use of (i) colistin and a carbapenem; (ii) colistin and tigecycline, or colistin and fosfomycin; or (iii) double carbapenem therapy. [9]
- Laboratory (*in vitro)* studies suggest that dual carbapenem combinations might work against carbapenemase-producing strains. Significant synergy was reported when using imipenem and another carbapenem [9]
- Ertapenem and doripenem together have been reported to have enhanced activity compared to either agent alone against KPC-producing *K. pneumoniae*.
- The phenomenon of increased activity in studies of two carbapenems may be because ertapenem is “trapped” by KPC more readily and acts as an “inhibitor” due its low turnover, which frees doripenem to act on penicillin binding proteins [10]
- An earlier systematic review highlighted that the lowest failure rate was observed in the group treated with a carbapenem-containing antimicrobial combination [10]
- Recommendations from professional groups and well-respected guidelines vary between monotherapy and combination therapy as shown in Table 1 below.
- Antibiotics with generally reliable activity against carbapenem-resistant organisms and CPE of all classes, typically include tigecycline, colistin and fosfomycin. There are, however, important concerns regarding the limited efficacy of these options because of their pharmacologic characteristics. There are also reports of increasing resistance, selection of resistance when used as monotherapy against carbapenem-resistant Enterobacterales and concerns regarding toxicity and adverse events. The

Health Protection Surveillance Centre Contact email: hpsc@hse.ie
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

risk of emergence of resistance is a further reason for the use of combination therapy when these agents are used. [10]

Table 1: Recommendations from professional groups and well-respected guidelines for the treatment of CPE.

Carbapenemase type	KPC	Metallo-beta-lactamases (MBL) (NDM, VIM, IMP)	OXA-48
BSAC [11]	Colistin & meropenem (if unknown/S in past)	Fosfomycin & colistin	Aztreonam. *(note many such isolates are resistant to aztreonam by an independent mechanism).*
	Consider addition of tigecycline to above	Consider tigecycline	Ceftazidime *(note many such isolates are resistant to ceftazidime by an independent mechanism).*
	Ceftazidime-avibactam & meropenem		Ceftazidime-avibactam
Sanford Guide [12]	Ceftazidime-avibactam	Colistin	Colistin
	Meropenem-vaborbactam	Aminoglycoside if susceptible	
	Colistin		
John Hopkins [13]	Gentamicin	Aztreonam (for IMP & VIM)	No recommendation
	Tigecycline	Tigecycline	
	Colistin	Colistin	

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Appendix 3

Individual monographs for antimicrobial agents with activity against carbapenem resistant bacteria with a literature review of their place in therapy and recommendations on dosing

Optimising dosing strategies to give the highest drug exposure according to PK/PD parameters is recommended. The tables below provide information on how this can be achieved. Please note that some recommendations reflect dosing strategies not covered by the product license.

1. Aminoglycosides & plazomicin
2. Aztreonam
3. Carbapenems – ertapenem, meropenem, meropenem-vaborbactam
4. Ceftazidime
5. Ceftazidime-avibactam
6. Colisitin
7. Co-trimoxazole
8. Eravacycline
9. Fosfomycin
10. Tigecycline

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Aminoglycosides

Aminoglycosides	
Place in therapy	• Could use gentamicin in combinations for urinary, intra-abdominal and bloodstream infections due to gentamicin-susceptible CPE including KPC-producing *Klebsiella* spp [11]. • NDM-1 producing organisms frequently carry resistance to aminoglycosides [14]. • Case reports most frequently cite amikacin as a treatment option [14].
Optimal administration & dosing	• This guideline recommends standard optimal once daily regimens based on local guidelines for both gentamicin & amikacin. • Note: use dose determining weight in obesity [15].
PK/PD characteristics	• Concentration dependent killing [12] • Cmax : MIC ≥ 10 [16]

Practical issues	• Monitor for ototoxicity in any patients receiving aminoglycoside for more than 3 days [13].
	  ○ Vestibular toxicity monitoring: check baseline visual acuity using a Snellen pocket card. After 3 days of treatment have patient shake head (side to side) while reading a line, Early sign of ototoxicity if patient loses 2 lines of visual acuity. Check Romberg sign.
	  ○ Cochlear toxicity monitoring: audiology test.
	• Monitor for nephrotoxicity, reviewing other potential nephrotoxins on a daily basis.
	• Routine stock in most hospitals.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Plazomicin – a new aminoglycoside	
Place in therapy	• Plazomicin is a semi-synthetic aminoglycoside derived from sisomicin [12]. • Approved by US FDA June 2018 [3], supply not available in Ireland until early 2019. • Most aminoglycoside modifying enzymes (AMEs) do not affect plazomicin, as this drug is structurally modified to prevent inactivation by plasmid-borne AMEs [17]. • It has potent activity *in vitro* against MDR Enterobacterales, including against aminoglycoside-resistant carbapenem resistant Enterobacterales that encode AMEs [17]. • However**, plazomicin is not active against strains with 16S ribosomal RNA methyltransferases that confer pan-aminoglycoside resistance [17]. Significant numbers of NDMs seem to carry this resistance.** • Plazomicin has potent activity against MDR Enterobacterales with multiple AMEs in several species that renders these organisms non-susceptible to amikacin, tobramycin, and gentamicin [17]. In this same laboratory study, by both checkerboard and time-kill analyses, plazomicin clearly exhibits synergy when combined with piperacillin/tazobactam and ceftazidime against MDR Enterobacterales. Clear evidence of synergy was not exhibited for plazomicin in combination with other agents. Antagonism was not observed with any combination [17]. • It may be an option for NDM carbapenemase producers based on a Brazilian *in vitro* study of CPEs [18], however, other studies are disputing its activity against NDM carbapenemase producers. • In an *in vitro* study of *K. pneumoniae* carrying VIM-1 carbapenemase synergy was observed when plazomicin was combined with meropenem, colistin or fosfomycin against both isolates, whilst the combination with tigecycline resulted in indifference. Antagonism was not observed for any of the

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	combinations tested [19]. • Significantly improved activity was seen in OXA-producing *A. baumannii* isolates compared with other aminoglycosides [20].

Optimal administration & dosing	• Adult usual dose: 15 mg/kg IV every 24 hours [12].
	• Dose adjustment for renal impairment [12].
	  ○ Creatinine Clearance ≥30 to <60: 10 mg/kg IV every 24 hours.
	  ○ Creatinine Clearance ≥15 to <30: 10 mg/kg IV every 48 hours.
	  ○ Renal replacement therapies or Creatinine Clearance of less than 15: no information currently available.

PK/PD characteristics	• 24 hour AUC/MIC [12].
Practical issues	• Therapeutic drug monitoring required. • Although plazomicin may be associated with nephrotoxicity and neurologic side effects, based on available data, rates appear to be lower than for other aminoglycosides. • Currently not included in the list of assays available from the Antimicrobial Reference Laboratory North Bristol NHS Trust http://www.bcare.nbt.nhs.uk/services/clinical-antimicrobial-assays • Should be available to purchase in 2019.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Aztreonam	

Place in therapy	• Use aztreonam for MBL- or OXA-48 producing strains if they are not resistant to this agent by other mechanisms [11] Aztreonam is not hydrolysed by MBL alone. It is readily hydrolysed by a number of other beta-lactamases and carbapenemases [20].
	  ○ Data from the CPE national reference laboratory service for Ireland indicate 79% and 44% of MBL- or OXA-48 respectively co-produce ESBL and/orAmpC.
	• **No activity against KPC producing Enterobacterales [14].**
	• A new pipeline agent aztreonam-avibactam has shown superior *in vitro* activity compared with aztreonam against ESBL-, class C B-lactamase- MBL- and KPC carbapenemases-producing strains of Enterobacterales [20].
	  ○ Until this agent becomes available a number of clinical observations have now been published evaluating aztreonam combined with ceftazidime-avibactam. These have shown successful outcomes in a small numbers of patients with infections due to NDM-producing Enterobacterales. [20] .

Optimal administration & dosing	• Life-threatening or other severe infections give 2g every 6 – 8 hours [14]. • Dose adjustment for renal impairment: consult usual references.
PK/PD characteristics	• Time above MIC.
Practical issues	• Routine stock in most hospitals.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Carbapenems

- Applying the AST interpretation principle to carbapenem-resistant isolates that test susceptible to a carbapenem by EUCAST criteria (meropenem MIC of less than or equal to 2 mg/L, ertapenem MIC of less than or equal to 0.5mg/L), they can be treated with meropenem / ertapenem respectively. For isolates that are non-susceptible but non-resistant by EUCAST criteria (meropenem MIC of less than or equal to 8 mg/L, ertapenem MIC of less than or equal to 1 mg/L) the addition of meropenem / ertapenem respectively to a combination of other agents is an appropriate option.
- Based on a meta-analysis it appears that extended or continuous infusion of carbapenems is at least as successful as intermittent dosing. It has been reported that there is reduced mortality among patients treated with extended or continuous infusion of carbapenems or piperacillin-tazobactam (pooled data) as compared to standard intermittent therapy regimens. The results were similar for extended and continuous regimens when considered separately. There was a mortality benefit with piperacillin-tazobactam but not with carbapenems [21]. Prescribers may choose to use an extended or continuous infusion to optimise the time above MIC for isolates with raised MICs that are not in the resistant range.
- Imipenem/cilastatin is not licensed in Ireland. It is not detailed as there is unlikely to be a reason to use over meropenem.
- Doripenem is not detailed as supply cannot be sourced, it has been withdrawn in many countries.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Ertapenem	
Place in therapy	• Of the licensed carbapenems, ertapenem is the most susceptible to carbapenemases produced by *Klebsiella* spp. and other aerobic Gram-negative bacilli [12]. • See General Carbapenems comments above .
Optimal administration & dosing	• 1g every 24 hours. • A study demonstrated the same serum-free concentrations with both intermittent infusion (at 1h, 12h & 24h) as continuous infusion with a 1g dose in 24 hours [22]. • If BMI is greater than 40 consider alternative agents as adequate levels may not be achieved [12]. • Dose adjustment for renal impairment: consult usual references.
PK/PD characteristics	• Time dependent killing [12]. • 40%-50% time above the MIC, higher time above MIC targets (at least 75% time above the MIC) may be more appropriate in patients who are critically ill or who are immunocompromised to increase the chance of clinical response [16].
Practical issues	• Seizures have infrequently been reported during treatment with carbapenems. Caution should be exercised with higher doses or if part of double carbapenem cover [16]. • Carbapenems dramatically reduce valproate concentrations and seizures have been reported. Avoid concurrent use. • Routine stock in most hospitals.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

<table>
<tr><th colspan="2">Meropenem</th></tr>
<tr><td>Place in therapy</td><td>

- See General Carbapenems comments above.

</td></tr>
<tr><td>Optimal administration & dosing</td><td>

- Intermittent infusion: 1-2g every 8 hours [14].
- Extended infusion: 2g every 8 hours administered as extended infusion over 3 hours [12], 4 hours [16] or 8 hours [14].
- Dose adjustment for renal impairment: consult usual references
- Extended Infusion [12].
  - Stability data for 4 hours at temp of 25°C.
  - Initial 1g loading dose then:
  - Creatinine clearance more than 50 mL/min: 2g (over 3 hours) every 8 hours.
  - Creatinine clearance 30-49 mL/min: 1g (over 3 hours) every 8 hours.
  - Creatinine clearance 10-29 mL/min: 1g (over 3 hours) every 12 hours.
- Continuous Infusion [23,24] – standard dose and higher dose.

<table>
<tr><td colspan="3">Standard dose</td></tr>
<tr><td>Loading dose irrespective of creatinine clearance</td><td>1g over 30 minutes</td><td>Dilute 1g vial with 20ml Water For Infusion & infuse directly</td></tr>
<tr><td>1st 48 hours irrespective of creatinine clearance</td><td>1g over 8 hours 3 times in 24h</td><td rowspan="3">Dilute 1g vial with 10ml Normal Saline & infuse in total of 50ml Normal saline (concentration = 20mg/ml)</td></tr>
<tr><td>After the first 48 hours creatinine clearance more than 20ml/min or Continuous Renal Replacement Therapy</td><td>1g over 8 hours 3 times in 24h</td></tr>
<tr><td>After the first 48 hours creatinine clearance less than or equal to 20ml/min</td><td>1g over 8 hours 2 times in 24h</td></tr>
</table>

<table>
<tr><td colspan="3">Higher dose for Central Nervous System or severe soft tissue infections</td></tr>
<tr><td>Loading dose irrespective of creatinine</td><td>2g over 30</td><td>Dilute 2g vial</td></tr>
</table>

</td></tr>
</table>

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

<table>
<tr><td></td><td>
<table>
<tr><td>clearance</td><td>minutes</td><td>with 20ml water for injection & infuse directly</td></tr>
<tr><td>1st 48 hours irrespective of creatinine clearance</td><td>2g over 8 hours 3 times in 24h</td><td rowspan="4">Dilute 2g vial with 20ml water for injection & infuse in total of 100ml normal saline (concentration = 20mg/ml)</td></tr>
<tr><td>After the first 48 hours creatinine clearance more than 20ml/min or CRRT</td><td>2g over 8 hours 3 times in 24h</td></tr>
<tr><td>After the first 48 hours creatinine clearance less than or equal to 20ml/min</td><td>2g over 8 hours 2 times in 24h</td></tr>
</table>
WFI = water for injection; NS = sodium chloride 0.9%
</td></tr>
<tr><td>PK/PD characteristics</td><td>

Time dependent killing [12].
40%-50% time above MIC, higher time above MIC targets (at least 75% time above MIC) may be more appropriate in patients who are critically ill or who are immunocompromised to increase the chance of clinical response [16].
Recent PK studies in critically ill patients suggest that plasma concentrations above the MIC are more likely to be achieved when meropenem is administered via extended or continuous infusion when compared to intermittent infusion [13].

</td></tr>
<tr><td>Practical issues</td><td>

Seizures have infrequently been reported during treatment with carbapenems; caution should be exercised with higher doses or if part of double carbapenem cover [16].
Carbapenems dramatically reduce valproate concentrations and seizures have been reported. Avoid concurrent use.
Routine stock in most hospitals.

</td></tr>
</table>

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Meropenem-vaborbactam	
Place in therapy	• Vaborbactam is a first-in-class, boronic acid pharmacophore, serine beta-lactamase inhibitor. • Approved in August 2017 by US FDA. • Has activity *in vitro* against KPC producing CPE [25]. • Meropenem-vaborbactam was very active against KPC-producers, and 99.5% of these isolates were inhibited by less than or equal to 4/8 mg/L. The single resistant isolate was shown to harbour an outer membrane porin alteration. • Meropenem-vaborbactam was active against contemporary carbapenem resistant Enterobacterales and wild-type Enterobacterales collected worldwide and this combination demonstrated enhanced activity compared with meropenem and most comparator agents against carbapenem resistant Enterobacterales and KPC-producers [26]. • Meropenem-vaborbactam has limited activity against MBL-producing isolates (including 49 NDM-, 1 IMP-64- and 2 VIM-producers) and/or oxacillinases (47 OXA-48/-232) that were detected mainly in European countries. • *In vitro* it is more active against KPCs than ceftazidime-avibactam [13]. • It has reduced activity against KPC-producing *K. pneumoniae* isolates with diminished expression of the porin genes *ompK35* and *ompK36.* • Little effect on *A. baumannii* containing OXA-type carbapenemases was observed [20]. • Meropenem-vaborbactam was evaluated for the treatment of carbapenem resistant Enterobacterales infections (Tango II study) in adult patients and resulted in higher cure rates at both the end of treatment and through a test of cure compared to best available therapy (64% vs. 33%, p=0.04 and 16% vs.4%, p=0.04). • Best available therapy included: carbapenem, aminoglycoside,

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	polymyxin B, colistin, tigecycline, or ceftazidime-avibactam (monotherapy only). Study was stopped early due to superiority of meropenem-vaborbactam [13].

Optimal administration & dosing [12,13]	• Meropenem-vaborbactam 4g (meropenem 2g + vaborbactam 2g) IV every 8 hours.
	• Each dose infused over 3 hours.
	• Dose adjustment for renal impairment.
	  ○ eGFR 30-49: Meropenem 1g + vaborbactam 1g IV every 8 hours.
	  ○ eGFR 15-29: Meropenem 1g + vaborbactam 1g IV every 12 hours.
	  ○ eGFR less than 15: Meropenem 0.5g + vaborbactam 0.5g IV every 12 hours.
	  ○ Haemodialysis: As for eGFR less than 15 (administer doses after dialysis).
	  ○ Continuous renal replacement therapy: no information currently available.

PK/PD characteristics	• Time dependent killing [12]. • As for meropenem. ○ 40%-50% time above MIC, higher time above MIC targets (at least 75% time above MIC) may be more appropriate in patients who are critically ill or who are immunocompromised to increase the chance of clinical response [16].
Practical issues	• Meropenem-vaborbactam is generally well tolerated, with a tolerability profile generally similar to that of piperacillin/tazobactam. • Seizures have infrequently been reported during treatment with carbapenems, caution should be exercised with higher doses or if part of double carbapenem cover [16]. • Carbapenems dramatically reduce valproate concentrations and seizures have been reported. Avoid concurrent use. • Unlicensed in Ireland, not stocked by any wholesaler in Ireland. Available from the US with a lead time of at least one week.

Health Protection Surveillance Centre Contact email: hpsc@hse.ie
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

Ceftazidime	
Place in therapy	• Effective against some OXA-48 carbapenemase producers, principally those that do not co-produce ESBLs or AmpC enzymes [11].

Optimal administration & dosing	• Severe infections or meningitis: 2g every 8 hours (max 8g/day)
	• Dose adjustment for renal impairment: consult usual references
	• Continuous Infusion Dose [12].
	  ○ Initial dose of 15 mg/kg IV infused over 30 min, then immediately start continuous infusion:
	  ○ Creatinine clearance greater than 60 mL/min use 6g IV over 24 hours.
	  ○ Creatinine clearance 31-50 mL/min use 4g IV over 24 hours.
	  ○ Creatinine clearance 11-29 mL/min use 2g IV over 24 hours.
	  ○ Creatinine clearance less than 11 & Continuous renal replacement therapy: no information currently available for continuous infusion.
	  ○ Formulation: 3g in 250ml sodium chloride 0.9% given over 12 hours [27].

PK/PD characteristics	• Time dependent killing [12].
Practical issues	• Routine stock in most hospitals.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Ceftazidime-avibactam	
Place in therapy	• Has no inhibitory activity against the MBLs [11]. • Has activity against KPC-2 producing isolates, MICs are higher for KPC-3 producing isolates. • KPC-3 producing *Klebsiella* spp. are vulnerable to mutations in the bla_{KPC-3} gene causing resistance [11]. • Has activity against most OXA-48 producers [11]. • Consider whether ceftazidime-avibactam should be used with a carbapenem or colistin to treat infections with KPC-3 producers [11]. • Less active against *Acinetobacter* spp [20]. • In a study of treatment of CPE bloodstream infection in haematology patients combination treatments with ceftazidime-avibactam included: an aminoglycoside (87.5%), carbapenems (37.5%), fosfomycin (25%), tigecycline (25%) or colistin (25%) [28].

Optimal administration & dosing	• 2.5g (ceftazidime 2g + avibactam 0.5g) every 8 hours [12, 28].
	• Infuse all IV doses over 2 hours [12].
	• Dose adjustment for renal impairment [12, 13].
	  ○ Creatinine clearance 31-50: 1.25g every 8 hours.
	  ○ Creatinine clearance 10-30: 0.94g every 12 hours.
	  ○ Creatinine clearance <10: 0.94g every 48 hours.
	  ○ Haemodialysis: 0.94g every 48 hours (give dialysis day dose after dialysis).
	  ○ Continuous veno-venous haemodialysis : 1.25g every 8 hours.
	  ○ The dose recommended above is low in comparison to the dose recommended in the Renal Drug database for ceftazidime alone.
	  ○ Consider referring to this reference for the ceftazidime component of ceftazidime-avibactam if the patient is on Continuous Renal Replacement Therapy (CRRT). CRRT has been identified as an independent predictor of the

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	development of resistance with ceftazidime-avibactam [29, 30].
PK/PD characteristics	• Time dependent killing [12].
Practical issues	• Due to the emergence of ceftazidime-avibactam resistance susceptibility testing should always be performed when ceftazidime-avibactam is used [31]. • May be stock in some hospitals. Stocked by one wholesaler in Ireland.

Colistin	
Place in therapy	• Generally used in combination with other agents [11]. • Consider colistin with aminoglycosides or tigecycline in infections with CPE strains that are susceptible to these agents but resistant to meropenem [11]. • Give careful consideration to the use of higher dosage regimens in critically ill patients [11]. • No difference between monotherapy or combination colistin in meta-analysis but most were *Acinetobacter* spp., no difference in dose – high or low or loading dose or not [32]. • Monotherapy vs. combination meta-analysis – poor quality data so difficult to make assumptions [33]. • Combination therapy with rifampicin did not improve clinical response or 30-day mortality in patients with *Acinetobacter* spp. infections [12]. • *In vitro* and *in vivo* exposure to polymyxins results in rapid selection of resistant sub-populations. *In vitro*, minocycline prevented emergence of resistance and augmented colistin activity but no clinical trial data. Tigecycline may function similarly, but no data. [12].
Optimal	• Adult loading dose.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

administration & dosing [9]

Body weight	Loading Dose	Notes
Over 50kg	9 million units (MU)	▲In obese patients (BMI>30) dosing should be based on Ideal Body Weight. Use of actual body weight in these patients is associated with increased incidence of nephrotoxicity. ▲In critically ill patients, irrespective of body weight, a dose of 9MU should be used. The loading dose is unaffected by renal impairment.
50kg or under	6 million units (MU)	

- Adult Maintenance Dose – increasing maintenance dose from 4.5 MU 12 hourly to 6 MU 12 hourly may be considered in critically ill depending on patient response and MIC – discuss with an Infection Specialist and review daily

Creatinine Clearance (mL/min)	Dose and Frequency (based on SPC)	Starting time after loading dose
Greater than 50	4.5 MU 12 hourly	12 hours
30-50	3 MU 12 hourly	24 hours
10-30	2.5 MU 12 hourly	24 hours
Less than 10	1.75 MU 12 hourly	24 hours
Haemodialysis	Non-HD days: 1.12 MU 12 hourly HD days: 1.5 MU 12 hourly after dialysis	No information currently available, suggest 24 hours
Continuous veno-venous haemodialysis diafiltration	3 MU 8 hourly	8 hours

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	• The distribution of colistin to the pleural cavity, lung parenchyma, bones, and cerebrospinal fluid (CSF) is relatively poor [14]. • Dose and administration instructions for nebulised or intrathecal colistin are available in the SmPC available at www.hpra.ie
PK/PD characteristics	• Area Under the Curve /MIC [16], i.e. concentration-dependent bactericidal activity [34]. • This suggests that if levels come back low then the total daily dose should be increased and the dosage interval reduced e.g. if 6 MU 12 hourly is not achieving adequate levels consider increasing to 4.5 MU or 6 MU 8 hourly.
Practical issues	• Plasma levels are required and are measured at Antimicrobial Reference Laboratory North Bristol NHS Trust . Guidance on up-to-date target trough levels is available on the Antibiotic Assay Guideline Ranges document at: http://www.bcare.nbt.nhs.uk/services/clinical-antimicrobial-assays . Other antibiotics can interfere with the assay therefore the laboratory will require these details. • Monitor for signs of neurotoxicity, more common with high doses e.g. apnoea, peri-oral and peripheral paraesthesia, vertigo, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances. Some may not be apparent if the patient is ventilated in the ICU. • Closely monitor renal function, especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents e.g. aminoglycosides [11]. • As per SmPC, use with caution in hepatic impairment. • No dose adjustment for hepatic impairment suggested [12]. • May be stock in some hospitals. Available as routine stock in wholesalers in Ireland.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Co-trimoxazole	
Place in therapy	• An agent with an option of the oral route for carbapenem-resistant organisms depending on susceptibility results. • May be a last-line agent in management of MDR *Acinetobacter baumannii* infections [13], use can be guided by *in vitro* testing [11].
Optimal administration & dosing	• Directed treatment of Gram negative infection where organism and susceptibilities known: 960mg every 12 hours [35]. As per the BNF dose can be increased to 1.44g every 12 hours in severe infections. • Dose adjustment for renal impairment: consult usual references • For critically ill patients the findings from a paper analysing PK/PD and MICs to inform dose regimens for co-trimoxazole may be of use [36].
Practical issues	• Risk of hyperkalemia in patients with renal insufficiency, angiotensin-converting enzyme inhibitors or blockers (ACEI, ARB) or on other potassium-sparing drugs. Due to trimethoprim component, functioning like amiloride in the distal renal tubule. [13]. • Several cases of severe bone marrow depression (several fatal) have resulted from the concurrent use of low-dose methotrexate and co-trimoxazole. • Can cause myelosuppression, monitor full blood count. • Routine stock in most hospitals.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Eravacycline	
Place in therapy	• Approved by US FDA August 2018 for the therapy of complicated intra-abdominal infections. Supply not available in Ireland until early 2019. • Eravacycline is a synthetic fluocycline tetracycline antibiotic [12]. • Eravacycline was the most potent antibiotic of those tested against *A. baumannii*, including isolates that were resistant to sulbactam, imipenem/meropenem, levofloxacin and amikacin/tobramycin [37]. • Eravacycline and comparators were tested against carbapenem- and tigecycline-resistant Enterobacterales and *Acinetobacter* spp. isolates received at the United Kingdom's national reference laboratory. Eravacycline MICs correlated closely with those of tigecycline but mostly were around 2-fold lower [38]. • Has activity against Enterobacterales including strains that exhibited carbapenem resistance associated with KPC, OXA and NDM production [20].
Optimal administration & dosing	• 1 mg/kg IV infused over 60 min every 12 hours (increased to 1.5 mg/kg if co-administered with a strong CYP3A4 inducer) [12]. • Dose reduction required in severe hepatic impairment [12]. • Can be dosed orally and parenterally with oral bioavailability estimated at 28% in phase I studies [20].
Practical issues	• The most common side effects with eravacycline therapy were nausea (8%) and vomiting (4%). • Should be available to purchase in early 2019.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

<table>
<tr><th colspan="2">Fosfomycin</th></tr>
<tr><td>Place in therapy</td><td>• As a result of its mechanism of action (inhibition of the first stage of peptidoglycan synthesis) and safety profile, fosfomycin may be expected to show synergistic combination therapy, including in regimens containing beta-lactams and aminoglycosides [10].</td></tr>
<tr><td>Optimal administration & dosing</td><td>• Total daily doses of 12-24 grams/day IV used in 2-3 divided doses depending on the indication, with doses on the higher end of the dose range in critically ill patients for first 24-48h before de-escalating dose [13, 29]. Maximum single dose is 8g.
• Dose adjustment for renal impairment [12, 29].
<table>
<tr><th>Creatinine clearance (mL/min)</th><th>Recommended dosage</th></tr>
<tr><td>Greater than 40</td><td>No dose adjustment</td></tr>
<tr><td>31–40</td><td>Normal loading dose for 1st dose. 70% of dose in 2–3 divided doses</td></tr>
<tr><td>21–30</td><td>Normal loading dose for 1st dose. 60% of dose in 2–3 divided doses</td></tr>
<tr><td>11–20</td><td>Normal loading dose for 1st dose. 40% of dose in 2–3 divided doses</td></tr>
<tr><td>Less than 10</td><td>Normal loading dose for 1st dose. 20% of dose in 1-2 divided doses</td></tr>
<tr><td>Haemodialysi</td><td>2-4g post dialysis [29]</td></tr>
<tr><td>Continuous veno-venous haemodialysis diafiltration</td><td>No dose adjustment</td></tr>
</table></td></tr>
<tr><td>PK/PD characteristics</td><td>• Unclear if time dependent or concentration dependent killing [16].
• 60%-70% time above the MIC.</td></tr>
<tr><td>Practical issues</td><td>• Generally well tolerated with minimal toxicity [39].
• Licensed in Ireland. May be stocked in some hospitals. Available as stock in wholesaler in Ireland.</td></tr>
</table>

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Tigecycline	
Place in therapy	• The role of tigecycline remains uncertain in the treatment of infections due to MDR GNB [11]. • Majority of evidence is for use is in combination with other agents [14]. • A low achievable serum concentration makes treatment of bloodstream infection problematic [13]. However, due to limited options for carbapenem-resistant organisms, it is used in this context in combinations with other agents. • There are published reports of a higher risk of death among patients receiving tigecycline compared to other antibacterial drugs, the greatest increase in mortality was observed in patients with ventilator-associated pneumonia, a review by the FDA suggested the increased mortality was associated with progression of disease, its bacteriostatic nature and suboptimal dosing [10]. • Should not be used for urinary tract infections due to poor urine drug concentrations [16]. • For therapy of CPE infections, tigecycline combination therapy and high-dose regimens may be more effective than monotherapy and standard-dose regimens, respectively [40]. ○ 21 studies included in this meta-analysis. ○ 15 studies related to CPE, *Klebsiella* spp. being the main pathogen and bloodstream infection the most common manifestation. ○ 30-day mortality was significantly lower in the combination group than the monotherapy. Moreover, the 30-day mortality in the triple tigecycline-containing combinations group was significantly lower than that in the dual combinations group. ○ Tigecycline combined with colistin, carbapenems or aminoglycosides were the most common combinations regimens used. However the study could not assess

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

	which combination might be the best choice. ○ The meta-analysis showed that with pooled data from 2 studies, the ICU mortality was significantly lower in high-dose groups than in standard-dose groups. Conversely, pooled analysis from 2 further studies showed no difference between the 2 groups in terms of 30-day mortality. High –dose = 200mg stat then 100mg every 12 hours, standard dose = 100mg stat then 50mg every 12 hours.
Optimal administration & dosing	• Use higher than licensed dosing, such as 100mg twice daily, for infections due to MDR GNB in critical care [11]. • Tigecycline regimens: 150 mg load and then 75 mg every 12 hours vs. 200 mg load and then 100 mg every 12 hours. Higher dose achieved best serum levels and superior in efficacy to lower tigecycline dose but also had the highest frequency of GI side effects [12].
PK/PD characteristics	• Time dependent killing [12]. • Area under the curve : MIC 1 [16].
Practical issues	• Owing to the increased adverse effects associated with unlicensed high doses the following advice is recommended: [14]. ○ Prescription of anti-emetic medication. ○ Weekly monitoring of liver function tests. ○ Weekly monitoring of platelet counts. • May be stock in some hospitals. Available as routine stock in wholesalers in Ireland.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

Tables 2 & 3: Antibiogram of CPE isolates from National CPE Reference Laboratory Service (January to September 2018 data).

CPE isolates tested by Microbroth Dilution by the National CPE Reference Laboratory Service											
Class:		Ceftaz-avibactam number susceptible	% Suscept.	Colistin number susceptible	% Suscept.	Ceftol-Tazo number susceptible	% Suscept.	Meropenem number susceptible	% Suscept.	Pip-tazo number susceptible	% Suscept.
A	**KPC (n=44)**	44	100%	44	100%	3	7%	9 (n=20)	45%	1	2%
B	**VIM (n=13)**	0	0%	13	100%	0	0%	4 (n=5)	75%	0	0%
	NDM (n=19)	1	5%	18	95%	0	0%	3 (n=14)	21%	0	0%
	IMP (n=10)	0	0%	10	100%	0	0%	8 (n=10)	80%	6	60%
D	**OXA-48 (n=198)**	198	100%	196	99%	103	52%	159 (n=164)	96%	0	0%

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

CPE isolates tested by Minimum Inhibitory Concentration by the National CPE Reference Laboratory Service													
Class:		**Fosfomycin number susceptible**	**% Suscept.**	**Tigicycline number susceptible**	**% Suscept.**	**Amikacin number susceptible**	**% Suscept.**	**Gentamicin number susceptible**	**% Suscept.**	**Co-trim number susceptible**	**% Suscept.**	**Aztreonam number susceptible**	**% Suscept.**
B	**VIM**	9 (n=9)	100%	6 (n=9)	67%	9 (n=9)	100%	2 (n=9)	22%	3 (n=9)	33%	2 (n=9)	22%
D	**OXA -48**	35 (n=36)	97%	30 (n=36)	83%	35 (n=35)	100%	25(n=34)	74%	23(n=36)	64%	21 (n=36)	58%

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

Contact email: hpsc@hse.ie

References

1. Harris PNA et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance. A Randomized Clinical Trial. JAMA. 2018;320(10):984-994.
2. Gutierrez-Gutierrez B et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017; 17; 726-34.
3. Paul M et al. Colistin alone versus colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative resistant bacteria: an open-label randomised controlled trial. Lancet Infect Dis 2018;18:391-400.
4. Paul M et al. Colistin alone versus colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative resistant bacteria: an open-label randomised controlled trial. Author's reply. Lancet Infect Dis 2018;18: 495-6.
5. Pongdee T. Evaluation and Management of Penicillin Allergy. Mayo Clinic Proceedings. 2018; 93: 101-107.
6. Martin A et al. Association Between Carbapenem Resistance and Mortality Among Adult, Hospitalized Patients With Serious Infections Due to Enterobacteriaceae: Results of a Systematic Literature Review and Meta-analysis. Open Forum Infectious Diseases 2018; 5(7); 1-9.
7. Falagas ME et al. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. Antimicrob Agents Chemother 2014; 58:654–63.
8. HSE Sepsis Management. Accessed at: https://www.hse.ie/eng/about/who/cspd/ncps/sepsis/resources/ on 02/10/2018.
9. Bonomo RA et al. Carbapenemase-producing organisms: a global scourge. Clinical Infectious Diseases 2018; 66(8):1290-1297.
10. Perez F et al. Treatment Options for Infections Caused by Carbapenem-resistant Enterobacteriaceae: Can We Apply "Precision Medicine" to Antimicrobial Chemotherapy? Expert Opin Pharmacother. 2016 April ; 17(6): 761–781.
11. Hawkey P M et al. Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association joint working party. J Antimicrobial Chemother 2018; 73 Suppl 3:iii2-iii78.
12. Sanford Guide. Accessed online http://webedition.sanfordguide.com [login required] 28/08/18.
13. John Hopkins ABX Guide. Accessed via app [login required] 28/08/18.
14. UKCPA. Guidance on treatment of carbapenemase producing Enterobacteriaceae. June 2016.
15. RCPI. Gentamicin: Guidelines For Once Daily Usage In Adult And Paediatric Settings. Accessed at: https://rcpi-live-cdn.s3.amazonaws.com/wp-content/uploads/2016/12/111208_A4_GentamicinUsageGuide_V12_a-1.pdf.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie

16. Morrill HJ et al. Treatment options for carbapenem resistant Enterobacteriaceae infections. Open Forum Infectious Diseases. 2015 Apr; 2(2).
17. Thwaites M et al. Activity of plazomicin in combination with other antibiotics against multidrug-resistant Enterobacteriaceae. Diagn Microbiol Infect Dis (2018) https://doi.org/10.1016/j.diagmicrobio.2018.07.006.
18. Martins AF et al. Antimicrobial activity of plazomicin against Enterobacteriaceae-producing carbapenemases from 50 Brazilian medical centers. Diagnostic Microbiology and Infectious Disease 90 (2018) 228 – 232.
19. Rodriguez-Avial I et al. *In vitro* activity of the next-generation aminoglycoside plazomicin alone and in combination with colistin, meropenem, fosfomycin or tigecycline against carbapenemase-producing Enterobacteriaceae strains. Int J Antimicrob Agents. 2015 Dec;46(6):616-21.
20. Wright H et al. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? Clin Microbiol Infect. 2017 Oct;23(10):704-712.
21. Falagas ME et al. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clinical Infectious Diseases 2013: 56 272-282.
22. Breilh D et al. Pharmacokinetics of free ertapenem in critically ill septic patients: intermittent versus continuous infusion. Minerva Anestesiol. 2011 Nov;77(11):1058-62.
23. St George's University Hospitals NHS. Protocol for continuous tazocin and meropenem infusions in adult critical care areas. February 2018.
24. Minichmayr MK et al. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. Journal of Antimicrobial Chemotherapy, Volume 73, Issue 5, 1 May 2018, Pages 1330–1339. and use of supplementary data.
25. Zhou M et al. *In vitro* activity of meropenem combined with vaborbactam against KPC-producing Enterobacteriaceae in China. J Antimicrob Chemother. 2018 Jul 5 [epub ahead of print].
26. Pfaller MA et al. *In vitro* activity of meropenem-vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem-vaborbactam surveillance programme. Int J Antimicrob Agents. 2018 Aug;52(2):144-150.
27. Pea F et al. Ceftazidime in Acute Myeloid Leukemia Patients with Febrile Neutropenia: Helpfulness of Continuous Intravenous Infusion in Maximizing Pharmacodynamic Exposure. Antimicrobial Agents And Chemotherapy, 2005, 49, No. 8 p. 3550–3553.
28. Caston JJ et al. Clinical efficacy of ceftazidime-avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients. Int J Inf Dis 2017; 59; 118-23.
29. Renal Drug Database. Accessed at www.renaldrugdatabase.com [login required] on 29/08/2018.

Health Protection Surveillance Centre Contact email: hpsc@hse.ie
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie

30. Ryan K et al. Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother. 2018 May; 62(5): e02497-17.
31. ECDC. Rapid Risk Assessment: emergence of resistance to ceftazidime-avibactam in carbapenem-resistant Enterobacteriaceae. 12 June 2018.
32. Cheng IL et al. Intravenous Colistin Monotherapy versus Combination Therapy against Carbapenem-Resistant Gram-Negative Bacteria Infections: Meta-Analysis of Randomized Controlled Trials. J. Clin. Med. 2018, 7, 208.
33. Zusman O et al. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017; 72: 29–39.
34. Scottish Antimicrobial Prescribing Group. Consensus guidance on high dose colistimethate sodium (colistin) in management of carbapenemase producing Enterobacteriaceae (CPE) in adults. April 2016.
35. Scottish Antimicrobial Prescribing Group. Position Paper On Optimising Antimicrobial Prescribing In Possible Or Suspected Infections DueTo Multi-Drug Resistant Gram Negative Bacteria. April 2016.
36. Brown GR. Cotrimoxazole - optimal dosing in the critically ill. Ann Intensive Care. 2014; 4: 13.
37. Seifert H et al. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*. Int J Antimicrob Agents. 2018 Jan;51(1):62-64.
38. Livermore DM et al. *In Vitro* Activity of Eravacycline against Carbapenem-Resistant Enterobacteriaceae and *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2016 May 23;60(6):3840-4.
39. Reffert JL & Smith WJ. Fosfomycin for the Treatment of Resistant Gram-Negative Bacterial Infections Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2014;34(8):845–857.
40. Ni W et al. Tigecycline Treatment for Carbapenem-Resistant Enterobacteriaceae Infections A Systematic Review and Meta-Analysis. Medicine (Baltimore) 2016; 95 (11) 1-10.

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin, Ireland
D01 A4A3
www.hpsc.ie
Contact email: hpsc@hse.ie