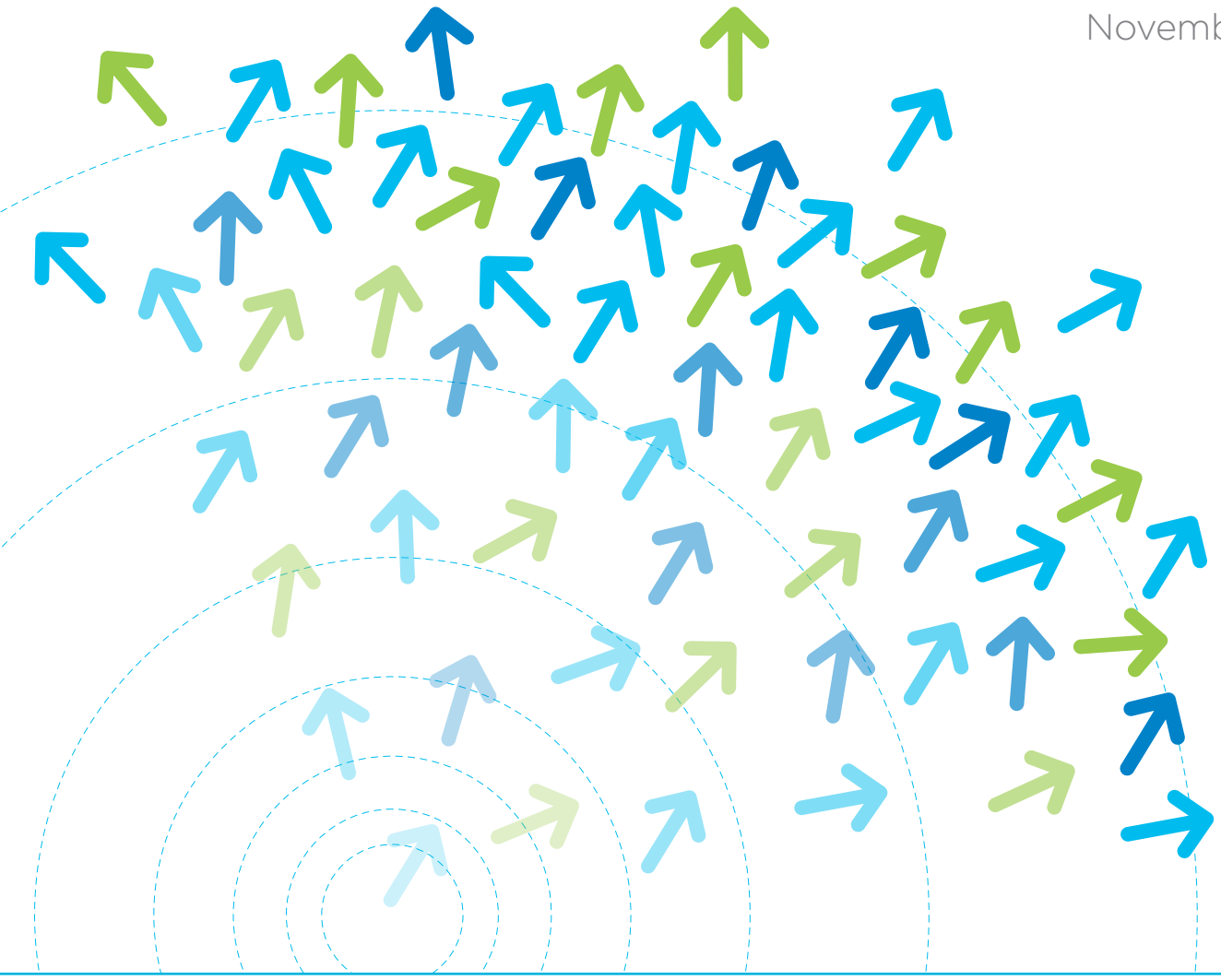
Recommendations for the control of Multi-drug resistant Gram-negatives: **carbapenem resistant Enterobacteriaceae**

November 2013



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This guidance has been developed through a consultative process to represent current opinion on appropriate and best practice to limit the impact of multi-drug resistant Gram-negative bacteria on Australian healthcare institutions, residential aged care facilities, patients and carers.

The key contributors to its development represent the following organisations:

AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

ACIPC
Australasian College for Infection Prevention and Control

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Conflicts of interest

No conflicts of interest were declared by contributors in relation to this document and the recommendations therein. The conflicts considered included those:

- at the time of authoring the document
- in relation to the scope of the work
- prior interests or benefits which subsequently related directly to the work.

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Contents

Executive summary and recommendations

The Commission, working together with clinical and laboratory experts, has developed this information as advice to health professionals and consumers. This guidance has a threefold purpose:

1. to alert healthcare professionals and the community to the emerging threat by CRE in Australia;
2. to provide recommendations in preventing, detecting and containing CRE; and
3. to provide informational resources for healthcare professionals and consumers.

Gram-negative bacteria have now emerged that are resistant to most types of antibiotics, including a key "last resort" class of antibiotic, the carbapenems. These organisms are referred to as carbapenem resistant Enterobacteriaceae (CRE). Multi-resistant Gram-Negative bacteria, such as CRE, place Australian patients at greater risk of potentially untreatable infection and increased mortality. CRE is of particular concern because Enterobacteriaceae cause infections at a high frequency and resistant infections are associated with high mortality.

Patients in residential aged care facilities are also potentially at increased risk. Multi-drug resistant Gram-negative organisms have been isolated more frequently in overseas long term care facilities than some other Gram-positive multi-resistant organisms.

Over the past 2 years there have been an increasing number of cases of CRE in Australian patients. Some patients contracted the infection overseas and unfortunately some within Australia. In November 2011, the National Healthcare Associated Infection Advisory Committee of the Australian Commission on Safety and Quality in Health Care discussed the potential implications of CRE in Australian hospitals. A taskforce was established in partnership with the Australasian Society Infectious Diseases, Australasian College of Infection Prevention and Control, Public Health Laboratory Network and Australasian Society of Antimicrobials to develop recommendations for the management and testing of patients with CRE.

This paper incorporates recommendations for patient management that are contained in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the National Safety and Quality Health Service Standards. These include the use of standard and transmission based precautions, especially for patient placement, patient movement, cleaning and disinfection and antimicrobial stewardship. There are also additional recommendations for laboratory screening methods.

The advice is divided into four sections:

Section 1: Reducing community and individual risk from CRE

- Standard precautions
- Antimicrobial stewardship
- Information resources

Section 2: Detection and surveillance for CRE

- Screening of patients for CRE colonisation or infection on admission to hospital

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- Facility/organisational governance and management
- Patient placement considerations
- Patient movement
- Cleaning and disinfection
- Non-inpatient settings and residential aged care facilities

Section 4: Laboratory screening methods

- Recommended screening for asymptomatic colonisation in at-risk patients
- Detection of CRE with 'routine' susceptibility testing of clinical isolates
- CRE confirmation
- Reporting and notification of suspected CRE

Companion resources include:

- Information for clinicians
- Information for consumers

Introduction

Gram-negative bacteria that have developed high levels of resistance to a wide range of available antibiotics are an emerging threat worldwide. Of particular concern is a group of organisms called 'carbapenem resistant Enterobacteriaceae' (CRE). These bacteria have had a significant impact on morbidity and mortality in a number of international settings.

Adapted from the Australian Guidelines for the Prevention and Control of Infection in Health Care, NHMRC 2010

Gram-negative bacteria are widespread in humans, animals and the environment. Because of their diverse mechanisms of antibiotic resistance, these organisms present a different kind of threat from Gram-positive organisms. Urgent and sustained efforts are required to contain resistance in Gram-negative bacteria, and to limit their impact on human health.

Gram-negative bacteria have now emerged overseas that are resistant to most, or even all types of antibiotics, including a key last-resort class of antibiotic, the carbapenems. The spread of these multi-drug resistant Gram-negative bacteria is occurring worldwide, promoted by indiscriminate antibiotic use, poor hygiene and sanitation and international travel.

Australia has not seen a significant number of CRE cases, partly because of its geographic isolation. This creates an opportunity for proactive measures to prevent, detect and contain CRE and thereby limit their impact on human health.

Multi-drug resistant Gram-negative bacteria, such as carbapenem-resistant Enterobacteriaceae (CRE), place Australian patients at increased risk of potentially untreatable infection following invasive procedures or other modern hospital care. Patients in residential aged care facilities are also potentially at risk.

The guidance focuses on CRE. This group of multi-drug resistant Gram-negative organisms is of particular concern because:

- Enterobacteriaceae cause infections at a high frequency and CRE infections are associated with a high mortality.[1]
- bacterial genes that code for this type of antibiotic resistance are easily transferred between bacteria, rapidly spreading the antibiotic resistance.[2]
- carbapenems have been valuable antimicrobial agents and, as the last class of β-lactam antibiotics retaining near-universal anti Gram-negative activity,[3] have been used as agents of last resort in treating life-threatening infections caused by drug-resistant Enterobacteriaceae.[4]
- in some recent studies in long-term care facilities overseas, multi-drug resistant Gram-negative organisms have been isolated more frequently than some other Gram-positive multi-resistant organisms.[5]

The objectives of this guidance are to:

- alert healthcare professionals and the community to the emerging threat posed by CRE in Australia.
- provide recommendations to assist healthcare professionals in preventing, detecting and containing CRE.
- provide resources and links to other sources of guidance for healthcare professionals and consumers.

Who should read this guidance?

Healthcare professionals who work in the following areas should consider this information and recommendations:

- hospitals and healthcare facilities.
- aged care and other long-term residential care environments.
- clinical microbiology laboratories.
- general and specialist practice and allied health professionals with responsibility for care of hospitalised patients and those in long-term care facilities.

It should be noted that, in other countries, CRE have been implicated in community-acquired infections.[6,7] Those caring for non-hospitalised patients should be alert to the possibility of CRE infection in patients presenting with infections involving multi-drug resistant bacteria.

Carbapenem-resistant Enterobacteriaceae

Carbapenem-resistant Enterobacteriaceae

The mechanism of resistance of Enterobacteriaceae to carbapenem antibiotics is most commonly through the production of an enzyme that breaks down the antibiotic before it can affect the bacterium. This enzyme, called a carbapenemase, first developed as a result of a mutation in *Klebsiella pneumoniae* that had been exposed to antibiotics. Carbapenemases have the ability to hydrolyse a range of antibiotics, including penicillins, cephalosporins, monobactams and carbapenems. The bacteria that can produce these enzymes become resistant to a broad range of antibiotics via a single mechanism.

The epidemiology of CRE varies because of diversity in the carbapenemase enzymes that these bacteria produce.[8] A range of enzymes with different structural characteristics have developed, seemingly independently, in different parts of the world. They have in common the ability to render Enterobacteriaceae highly resistant to a broad range of antibiotics, and the ability to spread rapidly once they emerge. Analysing and classifying the resistance genes from bacterial isolates provides greater insight into the epidemiology and spread of different CRE clones.

CRE infections are associated with high morbidity and mortality and are spreading rapidly worldwide.[9] They contribute to death in up to 40% of patients who become infected.[10]

Status of CRE in Australia

Australia has not seen a significant number of CRE cases, partly because of its geographic isolation. This creates an opportunity for proactive measures to prevent, detect and contain CRE and thereby limit their impact on human health.

The Australian Group on Antimicrobial Resistance (AGAR) reported in its 2011 national hospital-onset Gram-negative survey that resistance to carbapenems appears to be slowly rising, as a result of dissemination of a carbapenemase gene that has been reported in three Australian states.

Status of CRE internationally

In the United States, carbapenemase-producing *Klebsiella pneumoniae* were first reported in North Carolina in 1996,[11] and then spread across the country. They were subsequently reported in several European countries and then spread to many other parts of the world. The genes in these *Klebsiella* that code for carbapenemases are contained on plasmids – genetic structures that can replicate independently of chromosomes and can be highly mobile between bacteria, even moving between different species. The ability to produce the *Klebsiella pneumoniae* carbapenemase (KPC) has been transferred to other species of Enterobacteriaceae.

Another type of enzyme that produces multi-drug resistance is a metallo-β-lactamase. A significant example that emerged from the Indian subcontinent was first reported in 2009 in a Swedish patient who travelled to New Delhi and developed a highly resistant urinary tract infection. The *Klebsiella pneumoniae* that caused the infection was shown to have a new type of metallo-β-lactamase that was also found in *Escherichia coli* from the same patient's faeces, demonstrating that the genetic material can be transferred between different Enterobacteriaceae species. This new enzyme, called NDM-1, potentially presents a major global health problem. It has now been isolated in a number of cities in India, as well as in other countries, including Pakistan, the United Kingdom[13] and Canada.[14] Initially, this was usually from patients who had received medical care in India or Pakistan.

Key risk factors for CRE

Studies[15,16,17,18] have demonstrated that CRE are more likely to affect patients who have:

- a poor functional status
- a prolonged hospital stay
- a hospital stay within the previous 12 months
- multiple exposures to different antibiotic agents
- diabetes mellitus
- mechanical ventilation
- a higher severity of illness
- admission to the intensive care unit
- an indwelling medical device, such as a central venous catheter, urinary catheter, biliary catheter or wound drainage
- an organ or stem-cell transplant

People who come into contact with CRE organisms may spread or become infected with multi-drug resistant bacteria. The increased frequency of international travel for work, leisure and migration, potentially contributes to the spread of CRE from country to country.[19]

Introduction of CRE into healthcare settings has occurred in two sets of circumstances:

- when patients have been transferred directly between healthcare facilities, as inter-hospital transfers.
- when patients have received medical care abroad in areas with high rates of CRE, and have subsequently been admitted to facilities where CRE are absent or uncommon.

Even in the absence of direct inter-hospital transfers of patients, it is known that patients can remain colonised for several months with bacteria harbouring antibiotic-resistance genes following return to their home countries.

Key factors in the control of CRE

Internationally, organisations in areas where CRE have existed for some time recommend aggressive infection control strategies to limit the impact of the organisms.[20] Important objectives include preventing both transmission of, and infections with, CRE.[17]

A key lesson can be learned from an outbreak of CRE in Israel in 2006. Before this outbreak, CRE cases were extremely rare. The rapid spread of a clone of carbapenem-resistant *Klebsiella pneumoniae* that was not controlled by local measures resulted in more than 1200 patients being infected in 27 hospitals across the country. A centrally coordinated, nationwide intervention was launched to contain the outbreak and control further transmission. The measures that were imposed had a high impact on resources, clinical staff and patients and placed a significant financial burden on the healthcare system. The pathogen displayed an exceptional combination of multi-drug resistance, virulence and efficiency of spread and threatened the country's entire hospital system.[4]

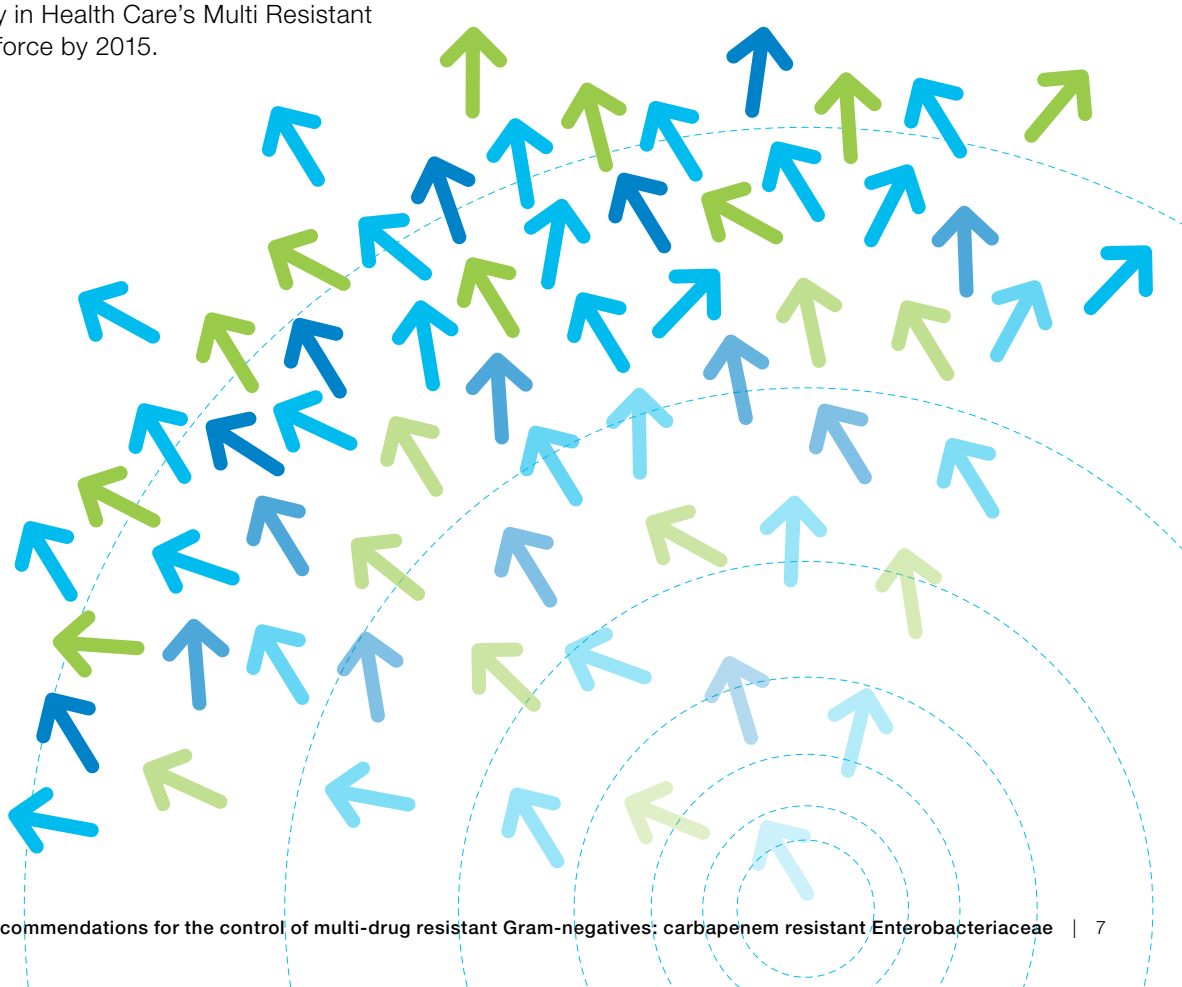
A number of classes of antibiotics have been associated with colonisation of, or infection by, CRE, including cephalosporins, fluoroquinolones and carbapenems. All control strategies should include antimicrobial stewardship measures that aim to minimise overall antimicrobial use and ensure that use of key Gram-negative antibiotics, such as cephalosporins, fluoroquinolones and carbapenems, is appropriate.[18]

The 'Key resources' section contains links to further sources of information for consumers and healthcare professionals.

Methodology

Information on the surveillance, identification and control of CRE was obtained from assessment of peer-reviewed literature (obtained via PubMed), local jurisdictional guidelines and factsheets and international guidelines and recommendations. For example, the Centers for Disease Control and Prevention Guidance for Control of Carbapenem Resistant Enterobacteriaceae and the Community and Hospital Infection Control Association – (Canadian Association for Professionals in Infection Control and Epidemiology) document on best practices for infection prevention and control related to multi-drug resistant Gram-negative bacteria. A collaborative process was utilised whereby infectious diseases physicians, clinical microbiologists and infection control professionals had regular teleconferences to generate recommendations based on the available evidence. This document has been developed in consultation with Australian jurisdictions, learned societies, healthcare institutions and individuals prior to publication. As higher levels of evidence are almost completely lacking in this area, grading of evidence for each of the recommendations is not provided.

The recommendations outlined in this document will be further reviewed by the Australian Commission on Safety and Quality in Health Care's Multi Resistant Gram-Negative Taskforce by 2015.



1 Reducing community and individual risk from CRE

1.1 Standard precautions

Statement of intent

The intent of Recommendation 1.1 is to prevent or reduce the transmission of infectious agents from one person to another through the use of existing infection control strategies by the health workforce.

The Recommendations within Section 1.1 are consistent with information on standard precautions outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

1.1.1 Staff within healthcare and residential aged care facilities should maintain high levels of hand hygiene **before** and **after** patient care in accordance with the 5 Moments of Hand Hygiene.

1.1.2 Patient and resident hand hygiene should be facilitated in healthcare and residential aged care facilities.

1.1.3 In healthcare and residential aged care facilities, clean general and frequently touched surfaces at least daily, and when visibly soiled and after every known contamination or spillage (refer to section B5.1 *Australian Guidelines for the Prevention and Control of Infection in Healthcare*).[21]

1.1.4 Clean all reusable patient equipment in accordance with the manufacturer's instructions **before** and **after** each patient use.

Rationale and commentary

- Standard precautions should be used at all times by staff working in healthcare settings. Standard precautions also specify other important elements of care. Refer to the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* for specific information regarding standard precautions.
- Pathogenic organisms can be frequently detected on hands of acute care patients.[22] Studies have not yet taken place to advise on the relationship between patient hand contamination and the acquisition of healthcare associated infection.
- As residential aged care facility residents interact with other residents, adherence to hand hygiene by residents is important.
- There is international evidence that infection control strategies can limit the impact of CRE by reducing transmission in healthcare settings. Standard precautions provide the basis for all infection control safe work practices. A high level of compliance with hand hygiene, environmental cleaning and control of potential fomites are essential generic measures to prevent spread of microorganisms via the contact route.
- The contact route (both direct and indirect) is the major mode of patient-to-patient transmission of multi-drug resistant Gram-negative bacteria such as CRE.
- Transmission based precautions are an additional range of measures that reduce the risk of spread via contact even further; these measures are indicated for management of individual cases of CRE and in outbreak situations (see Section 3.2).
- The use of standard precautions is outlined in B1 Standard Precautions; B2 Transmission based Precautions; and C6.2.2 Reducing infections spread through the physical environment in the Australian Guidelines for the Prevention and Control of Infection in Healthcare.

1.2 Antimicrobial stewardship

Statement of intent

The intent of Recommendation 1.2 is to ensure that appropriate prescribing of antimicrobials as part of a broader plan to reduce the development of resistant organisms is in place; and antimicrobial use and resistance within health service organisations is monitored.

The Recommendations within Section 1.2 are consistent with information on antimicrobial stewardship outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3; 3.14.*

Recommendations

1.2.1 Implement facility antimicrobial stewardship programs, in accordance with the National Safety and Quality Health Service Standards, element 3.14.

1.2.2 Implement effective antimicrobial stewardship programs in community general practice that include attention to residential aged care facilities.

1.2.3 To optimise the impact on antibiotic resistance in Gram-negative bacteria, antimicrobial stewardship programs should include:

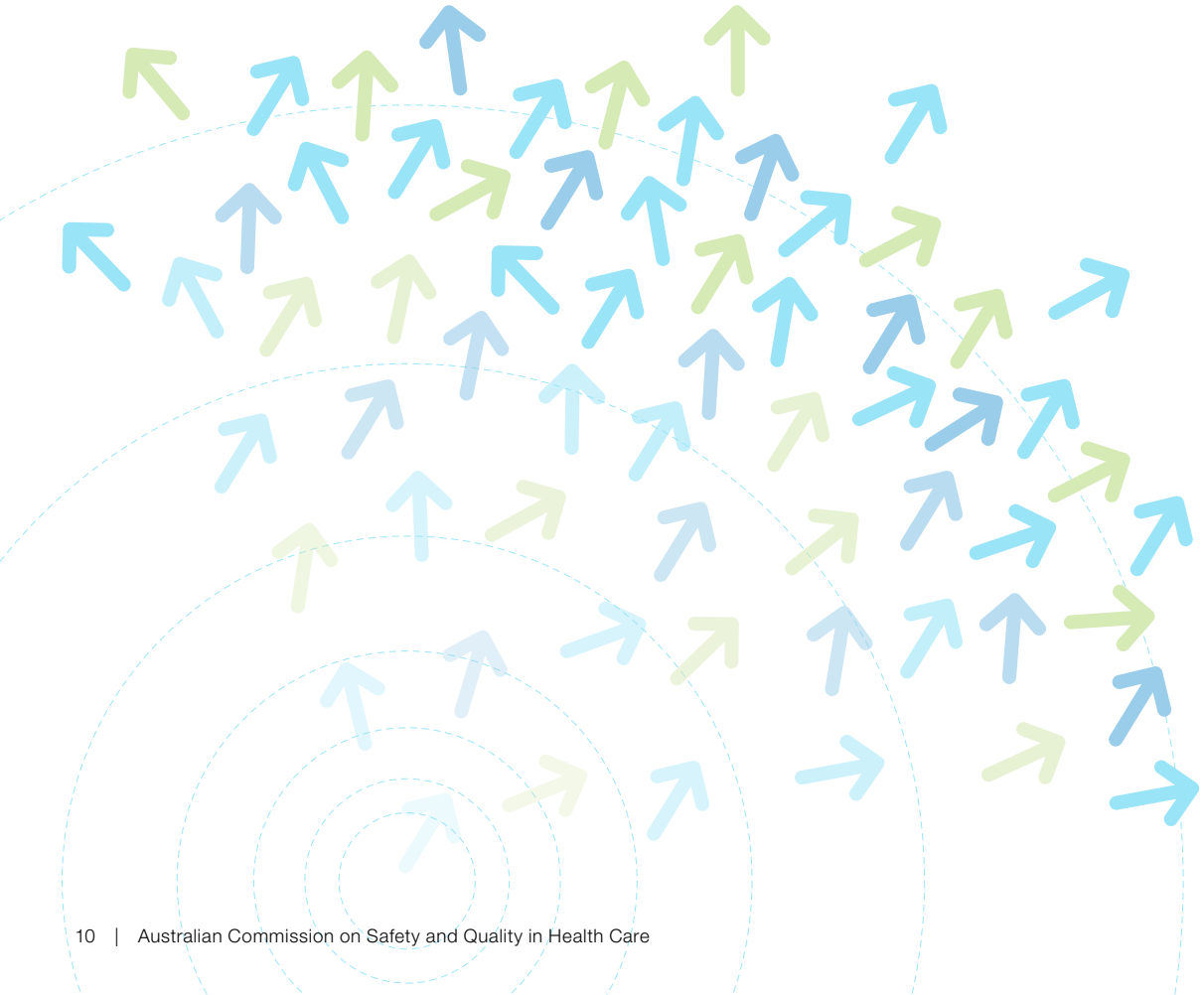
- systems of audit to identify and reduce inappropriate empirical, directed or prophylactic use of cephalosporins, fluoroquinolones, carbapenems, β-lactamase inhibitor combinations and aminoglycosides, referencing therapy requirements against *Therapeutic Guidelines: Antibiotic*.[23]
- Measurement of antimicrobial use for antibiotics commonly used to treat Gram-negative infections, including cephalosporins, fluoroquinolones, carbapenems, β-lactamase inhibitor combinations and aminoglycosides.
- Monitoring antimicrobial resistance at a facility level for key Gram-negative organisms commonly causing infection.

Rationale and commentary

- Many studies show that prior antimicrobial use is a significant risk factor for individual patients to acquire multi-drug resistant organisms, including CRE.
- On an ecological level, prescribing at a country, community, hospital or individual clinical unit level is associated closely with resistance patterns, as shown by time-series analysis[24] and collective usage and resistance data.[25]
- Some antimicrobial classes are more likely than others to drive emergence and spread of multi-drug resistant pathogens. In the case of multi-drug resistant Gram-negative bacteria such as CRE, reports strongly implicate fluoroquinolones, extended-spectrum cephalosporins and carbapenems.[26,27]
- Gram-negative resistance in the community is increasingly detected in Australia.[28] Extended-spectrum β-lactamase (ESBL) producing bacteria and CRE have been detected in travellers who have recently returned from Asia.[29] ESBL bacteria are becoming prevalent in residential aged care patients in Australia and overseas.[30]

1 Reducing community and individual risk from CRE

- Gram-negative resistance in food-borne zoonotic bacteria is a major worldwide problem, driven by use of the antibiotics in animal production. However, until recently, Gram-negative resistance has not been detected to a major degree. Restrictions on use of quinolones in agriculture have been associated with a low incidence of quinolone resistance in Australia, in contrast to the experience overseas.[31,32] It has been reported in recent data from Western Australia that the prevalence of quinolone-resistant *Escherichia coli* in retail poultry may be higher than previously recognised.[33]
- Overall, antibiotic use is relatively high, and poorly targeted, in Australia compared with international use rates.[34,35] A recent study of RACF in one area health service found that 40% of antibiotics prescribed were not in accordance with recognised guidelines.[36]
- Antimicrobial stewardship programs aim to reduce overall antibiotic exposure and target treatment more effectively, through a number of measures. Antimicrobial stewardship principles apply across all situations in human and animal health where antibiotics are required. Although antimicrobial resistance is a worldwide problem and antimicrobial stewardship is required worldwide to reduce resistance, stewardship programs that operate locally or at a national level can also have significant benefits. Reduction in antibiotic use during animal meat production is a particular priority.[37]
- Many studies show that reductions in hospital and/or community antimicrobial use may be followed by reductions in bacterial resistance rates, even where patients or communities have high levels of colonisation with multi-drug resistant organisms.[38] However, this does not always occur due to a number of possible factors.[39]



1.3 Information resources

Statement of intent

Engaging consumers to work with health service organisations may further enhance evaluation of patient information relating to infection prevention and control and existing resources to inform and educate patients and carers about safety and quality activities relating to infection prevention and control (*National Safety and Quality Health Service Standards*; 3.19).

The Recommendations within Section 1.3 are consistent with information on information resources outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

1.3.1 Distribute national CRE information resources to relevant stakeholders, including clinicians and community members.

Rationale and commentary

- Because CRE are a significant threat but are not yet highly prevalent in Australia, it is important that healthcare professionals are aware of the potential for this group of bacteria to emerge, and of relevant risks and mitigation measures.
- Consumer awareness is an important aspect of the healthcare system. Awareness of risks such as CRE can help consumers to avoid becoming infected and to know what to do if they suspect they have become infected with CRE.
- Much of the transmission of CRE from country to country has resulted from a person being colonised or infected with these bacteria in one country, and then carrying them to their home or another country.
- Patients, family and visitors may experience concern when not given sufficient information about infections. Clearly explaining the process and importance of infection control measures to patients, family and visitors may assist them in understanding CRE and the importance on compliance with infection control directives (adapted from *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (B3.2.2 p127) and *National Safety and Quality Health Service Standards*: Standard 3; 3.19).

  It is also important to provide education to key stakeholders and clinicians about CRE, the mode of transmission and the behaviour of CRE, refer to B3.2.2 *Australian Guidelines for the Prevention and Control of Infection in Healthcare*.

Refer to the 'Key resources' section for links to two fact sheets that are targeted at:

- clinicians
- consumers.

2 Detection and surveillance for CRE

2.1 Screening of patients for CRE colonisation or infection on admission to hospital

Statement of intent

The intent of Recommendation 2.1 is to minimise exposure of other patients and staff members to infectious agents (*National Safety and Quality Health Service Standards:* Standard 3, *Safety and Quality Improvement Guide* Standard 3; 3.12).

The Recommendations within Section 2.1 are consistent with information on screening patients with multi-resistant organisms outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

2.1.1 All the following should be actively screened for CRE colonisation or infection:

- Patients directly transferred from any overseas hospital.
- Patients who have been admitted overnight to any overseas hospital or who have resided in an overseas residential aged care facility within the past 12 months.
- People who are identified as a CRE contact during their hospitalisation and have not been shown to have negative post-contact cultures.
- Patients with past demonstrated CRE colonisation or infection.

These risk factors should be specifically elicited in the clinical history. See Recommendation 4.1.1 for recommended screening specimens.

Rationale and commentary

- The transfer of patients infected or colonised with CRE across borders has been identified as a major risk factor for the introduction and spread of CRE into a healthcare facility.[40] This has been clearly documented at a global level: cross-border transfer of patients from countries with high rates of CRE has resulted in the introduction of CRE into countries that, until then, had detected few or no CRE isolates.[19] In countries with high rates, CRE exist not only within acute care facilities (hospitals) but also in residential aged care facilities.[40] It is likely that CRE are distributed widely across many countries, although it is not possible to obtain an accurate global epidemiological picture because of the lack of surveillance data in many regions.[19]
- The transfer of patients from a healthcare facility with endemic CRE to another healthcare facility in the same country has also been reported to result in the introduction of CRE into the receiving healthcare facility.[40,41,45] This has not been as widely documented in international transfer.
- Reports of transmission associated with cross-border transfer from hospitals in endemic countries to non-endemic countries consistently demonstrate the risk of secondary transmission within the receiving facility.[19] Although evidence is lacking, tracing of contacts using surveillance cultures for patients sharing the same environment may be effective in reducing secondary transmission of CRE.[41]
- For additional information refer to the *Australian Guidelines for the Prevention and Control of Infection in Healthcare:* B3.1.3 Organisms specific response.

Detection and surveillance for CRE 2

- A number of less well defined risk factors for infection or colonisation with CRE have been identified. These include: prior exposure to antimicrobial agents;[40, 43, 44, 45] recent transplantation (both solid-organ and stem-cell transplant);[19, 44] severity of illness; including admission to intensive care and mechanical ventilation;[40, 44] surgery; prior hospital stay (within the previous 12 months);[40, 44] and the presence of indwelling medical devices such as wound drainage or biliary catheters.[40]
- In healthcare services where CRE has been detected in patients outside the risk groups specified under recommendation 2.1, enhanced screening is recommended. Enhanced screening may target individuals with risk factors identified as significant by the health service; or may preferably involve broader systematic surveillance of specific populations or ward-locations on a regular basis.[45] Systematic surveillance will allow for a more rapid detection of any change in the prevalence of CRE within the health service.

Timing and frequency of screening

- The exact duration of CRE colonisation is uncertain. In a study of returned travellers, more than half of those carrying resistant *E.coli* post-travel had no detectable resistant strains two months after their return, but at least 18% remained colonised at six months.[46] Some organism clones appear better adapted to prolonged colonisation than others. Antimicrobial use has also been associated with prolonged duration of colonisation.
- False negative results from CRE screening tests may occur early after acquisition of the CRE, in the presence of certain antimicrobial agents and when the organism is present in low numbers.
- Multiple screens performed over a period of time are likely to improve screening sensitivity.[45] However, no consensus recommendations can be made about the optimal timing and frequency of screening, because of insufficient data.
- In the absence of high quality evidence to show that clearance of colonisation will occur, many recommend a cautious approach that requires contact precautions for all future inpatient care for patients with a history of CRE colonisation or infection.[40, 41, 45]
- Some health services may elect to assess and screen low-risk patients with previous CRE infection or colonisation upon readmission, with the aim of 'clearing' a patient of CRE colonisation. Any patient that is deemed 'cleared' should be monitored to identify any relapse in detectable CRE colonisation. Assessment of CRE 'clearance' should only be done in consultation the health system's infection prevention and control service and a clinical microbiologist or infectious disease physician.

3 Additional control measures to reduce cross-transmission

3.1 Facility/organisational governance and management

Statement of intent

The intent of the recommendation 3.1 is to ensure the presence of a governance framework that incorporates executive responsibility and commitment to a risk management approach in minimising infection risk to patients and the workforce (*National Safety and Quality Health Service Standards: Standard 3: Preventing and Controlling Healthcare Associated Infections; 3.1*).

The Recommendations within Section 3.1 are consistent with information on organisational governance outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

3.1.1 All facilities and organisations should establish systems to ensure implementation, monitoring and oversight of measures to establish and maintain CRE control.

3.1.2 Clinical laboratories should have an established protocol for notifying clinical and/or infection prevention and control personnel when CRE are identified from clinical or screening specimens.

3.1.3 Facilities and organisations should have in place systems to detect and manage clusters or outbreaks of CRE.

Rationale and commentary

- National Safety and Quality Health Service Standards 1 and 3 provide detailed advice on governance requirements and risk management for infection prevention and control. The 'Key resources' section in this document also provides further information to assist in developing strategies.
- Where infrastructure exists, 'micro-alerting' may facilitate these processes. Micro-alerting refers to application of a tag or flag to a patient's medical record (soft or hard copy) that alerts a facility of a patients status with regard to prior colonisation or infection with multi-drug resistant organisms, including CRE.
- All staff should receive education and training regarding CRE (see clinician information sheet), including the proper use of and rationale for, contact precautions.
- The *Australian Guidelines for the Prevention and Control of Infection in Healthcare* provide further information on contact precautions and approaches to outbreak management.
- Additional information on organisational governance is outlined in the Australian Guidelines for the Prevention and Control of Infection in Healthcare B1 Standard Precautions; B2 Transmission based precautions and B3 Management of multi-resistant organisms and outbreak situations; and the *National Safety and Quality Health Service Standards: Standard 3, Safety and Quality Improvement Guide: Standard 3; 3.1*.

Additional control measures to reduce cross-transmission

3

3.2 Transmission-based precautions, including patient placement considerations

Statement of intent

The intent of Recommendation 3.2 is to reduce the risk of transmission of CRE to patients using available resources, including single and cohort rooms, to protect other patients and the healthcare workforce from CRE transmission (adapted from the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* B3.1.2).

The Recommendations within Section 3.2 are consistent with information on transmission based precautions outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

3.2.1 Facilities should risk assess the need for pre-emptive isolation and contact precautions for patients being screened for CRE, until results of screening are negative.

3.2.2 All patients with CRE should be managed using contact precautions in a single room with their own toilet facilities. If a single room is not available:

- Prioritise single rooms for those at highest risk of secondary transmission, such as those who have diarrhoea or are incontinent (urine or faeces), those who have wounds with uncontrolled drainage and those with medical devices in situ.
- CRE positive patients should not be grouped together without prior approval by the infection prevention and control service.

3.2.3 Contact precautions should remain in place for the length of the patient stay (that is, the stay during which the CRE were isolated).

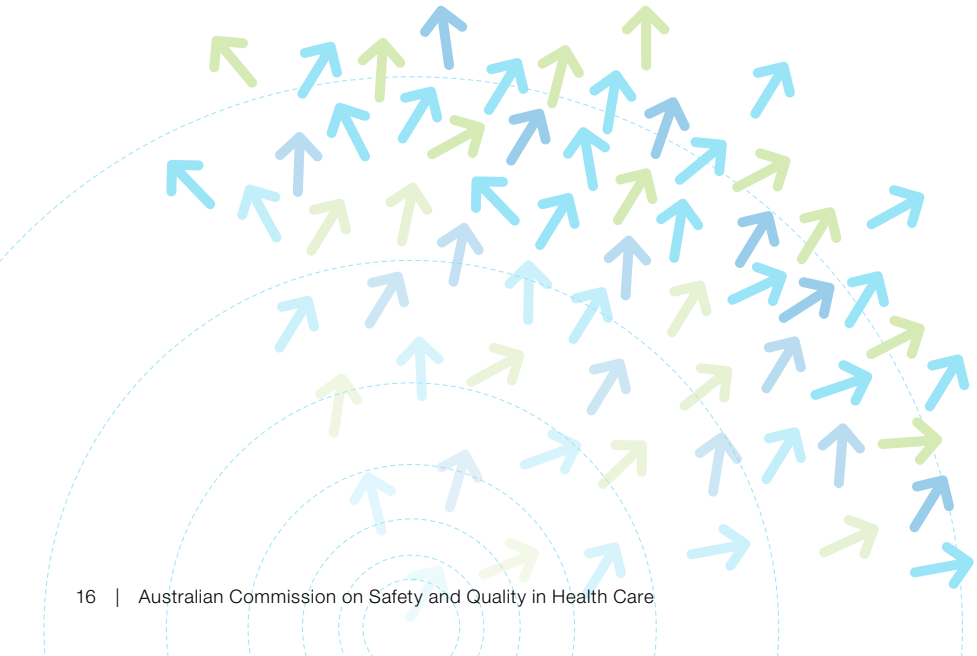
3.2.4 Ensure that there is a process to monitor and improve adherence with contact precautions. This might include conducting periodic surveillance of compliance and providing feedback of results to staff (*National Safety and Quality Health Service Standard 3*).

3 Additional control measures to reduce cross-transmission

Rationale and commentary

- Healthcare outbreaks of CRE are well described.[47,48,49] Since all outbreak responses have involved attention to multiple factors, it is not possible to define the most important elements for control. Usual elements include optimised use of standard precautions, enhanced patient screening, contact precautions including patient isolation and the use of personal protective equipment and enhanced environmental cleaning and disinfection. Studies that implemented isolated changes to antibiotic use have also been effective in reducing Gram-negative resistance within a clinical unit.[50]
- Currently, there is insufficient evidence to support attempts to decolonise CRE-positive patients and no recommendation can be made.
- Refer to the 'Key resources' section for information on standard precautions and contact precautions.
- When patients are placed in transmission based precautions due to infection or colonisation with a CRE, efforts should be made to ensure patients continue to receive appropriate medical care; and to counteract the potential psychological effects of isolation.

  Information on transmission based precautions and patient placement is outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* B2.2 Contact Precautions; B3.1.2 Core strategies for MRO prevention and control.



Additional control measures to reduce cross-transmission

3

3.3 Patient movement

Statement of intent

The intent of Recommendation 3.3 is for health services to develop or review processes to communicate a patient's infectious status whenever the responsibility for care is transferred between health service organisations, departments or facilities. (*National Safety and Quality Health Service Standards*: Standard 3, *Safety and Quality Improvement Guide*: Standard 3; 3.13.3)

The Recommendations within Section 3.3 are consistent with information on patient management outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

Transfers

3.3.1 The presence of CRE infection or colonisation should not preclude transfer of a patient from one facility to another.

3.3.2 The transferring facility should notify the receiving facility before transfer of a CRE-positive patient, to ensure that appropriate bed management occurs.

3.3.3 Facilities and organisations should avoid the unnecessary transfer of CRE-positive patients within the facility.

Discharge

3.3.4 CRE-positive patients should be provided with the CRE information sheet and information on CRE colonisation or infection should be included in the discharge summary to the general practitioner.

Rationale and commentary

- Communication between facilities and practitioners may be assisted by use of an inter-facility or community transfer form, in addition to verbal communications. This should include information on whether the patient has been colonised and/or infected with CRE or other multi-drug resistant organisms, the dates and results of any relevant clinical and/or surveillance cultures and an assessment of the risk of secondary transmission (taking into account conditions such as diarrhoea or incontinence of urine or faeces, wounds with uncontrolled drainage or medical devices in situ).
- For additional information on the application of contact precautions when moving patients within or between facilities, refer to the *Australian Guidelines for the Prevention and Control of Infection in Healthcare*, B2.2.3 How should contact precautions be applied and the *National Safety and Quality Health Service Standards*: Standard 3, *Safety and Quality Improvement Guide*: Standard 3; 3.13.3

3 Additional control measures to reduce cross-transmission

3.4 Cleaning and disinfection

Statement of intent

The intent of Recommendation 3.4 is to provide a clean and hygienic environment for patients and the workforce to minimise infection risk to patients and the workforce. (*National Safety and Quality Health Service Standards*: Standard 3 and *Safety and Quality Improvement Guide*: Standard 3; 3.15.1).

The Recommendations within Section 3.4 are consistent with information on cleaning and disinfection outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

3.4.1 Rooms occupied by CRE-positive patients, including frequently touched items, should be cleaned and disinfected at least once per day.[21,41]

3.4.2 Following discharge or transfer of CRE-positive patients, a cleaning and disinfection process should be completed for the room, its contents and bathroom used by the patient.

3.4.3 Standard precautions apply for management of linen and waste from CRE-positive patients.

Rationale and commentary

- Environmental reservoirs for multi-drug resistant Gram-negative organisms are potentially an important factor in healthcare associated transmission. Patients colonised or infected with CRE widely contaminate their immediate patient environment.[51]
- The review by Otter[52] summarises the evidence on the relationship between the environment and transmission of multi-drug resistant Gram-negative bacteria. A prospective cohort study in intensive care patients showed that prior room occupancy by a patient colonised or infected with *Acinetobacter baumannii* or *Pseudomonas aeruginosa* was a significant risk factor for the acquisition of these pathogens (odds ratios of 4.2 and 2.3, respectively). Numerous outbreaks of *A. baumannii* have been associated with contaminated fomites and have resolved once the common source was identified and removed, replaced or adequately disinfected. Several outbreaks in which environmental surfaces were contaminated with a clinical strain(s) but a common source was not identified have also been described.[52]
- For additional information refer to the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* B1.4 Routine management of the physical environment; B2.2.3 How should contact precautions be applied; and B3.1.2 Core strategies for MRO prevention and control).

3.5 Non-inpatient settings and residential aged care facilities

Statement of intent

That patients with carbapenem resistant Enterobacteriaceae are identified and managed to reduce the risk of CRE transmission in non-inpatient and residential aged care facilities; and when care is transferred between health service organisations.

The Recommendations within Section 3.5 are consistent with information on the management of patients with multi-resistant organisms in non-inpatient settings outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* and the *National Safety and Quality Health Service Standards: Standard 3*.

Recommendations

Residential aged care facilities (RACFs)

3.5.1 Acute-care facilities should ensure that pre-transfer notification occurs to RACFs for patients known to be colonised or infected with CRE.

3.5.2 RACFs should establish systems for appropriate risk-based management of CRE-positive patients.

3.5.3 RACFs should have systems in place to notify acute-care facilities or other health service providers of CRE-positive patients before transfer.

Hospital non-inpatient settings[a]

3.5.4 Each location should establish systems for appropriate risk-based management of CRE-positive patients (see Section 3.2.2).

Rationale and commentary

- Studies have shown that residents in residential aged care facilities are a potential source of multi-drug resistant Gram-negative bacteria, including ESBL-producing organisms and CRE.[5,53]

The following measures might be considered:

- Discuss an infection control management plan with infection control staff at a referring facility before transfer of a CRE-positive resident.
- Manage a CRE-positive resident with no risk factors for transmission (see Section 3.2.2) using standard precautions.
- Reserve single rooms with ensuite facilities for CRE-positive residents with risk factors for transmission (see Section 3.2.2). Manage such patients using contact precautions.
- Perform cleaning and disinfection as outlined for CRE-positive hospital inpatients (see Section 3.4).
- Recommendation 3.5 is consistent with information documented in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* B2.1 Transmission based Precautions and B3.1 Management of multi-resistant organisms.

a These include departments where the patient is not admitted to the facility overnight and invasive services are provided e.g. Emergency, Day Surgery, Endoscopy, Haemodialysis, Outpatients clinics and Radiology.

4 Laboratory screening methods

This section addresses laboratory procedures for screening patient specimens or their cultures for Enterobacteriaceae harbouring transmissible carbapenemase genes. It provides advice and recommendations on the detection of CRE for all medical diagnostic microbiology laboratories in Australia.

As laboratory testing for CRE, and their genes, is a rapidly developing field, these recommendations should continue to be considered in the light of new evidence. The advice of the relevant organisations should be considered as implementation progresses, and additional evidence becomes available.

This document does not address how to conduct molecular confirmation on suspected CRE isolates. The use of molecular methods depends on the availability of resources and hardware, which can vary from site to site. As at June 2013, there is no Australian jurisdictional agreement on which laboratories are, or should be, resourced to undertake this molecular testing.

The document does not address the detection of transmissible carbapenemases in *Pseudomonas* or *Acinetobacter* species.

4.1 Recommended screening for asymptomatic carriage in at-risk patients

Statement of intent

The intent of Section 4 is to provide recommendations for laboratory procedures for screening patient specimens or cultures for Enterobacteriaceae harbouring transmissible carbapenemase genes; and on the detection of CRE for all medical diagnostic microbiology laboratories in Australia.

The Recommendations within Section 4 are consistent with current evidence on laboratory methods for screening, detection, confirmation and reporting and notification for carbapenemase resistant Enterobacteriaceae.

Recommendations

4.1.1 Recommended screening specimens include rectal or perianal swabs, or faeces. Also consider screening open wounds and/or urine.

4.1.2 No firm recommendation can currently be made for a carbapenem-specific primary screening medium for use under Australian conditions.

4.1.3 Laboratories may choose to evaluate one or all of the carbapenem-specific media specified, or simply choose to detect potential CRE using the 'routine' testing method described below (potentially delaying detection by a day or more).

4.1.4 Commercial ESBL screening media may be used as described, with the added advantage of ESBL detection. However, the lower specificity of these media for CRE detection will also lead to significant delay in obtaining a definitive result.

Laboratory screening methods

4

Rationale and commentary

- A majority of colonised people carry CRE in their faeces and sampling of rectal swab or faeces is the minimum standard. Perianal swabs may be inferior. Isolated urinary carriage of Enterobacteriaceae carrying CTX-M ESBL enzymes was documented by Widmer.[54] Thurlow demonstrated isolated urinary carriage of KPC strains in 24% of colonised patients.[55]
- There is currently no internationally accepted 'gold standard' laboratory screening method for carbapenemases in Enterobacteriaceae. Highly sensitive and specific molecular methods for detection of carbapenemase genes are well described but not yet widely in use for direct detection from patient specimens.[56]
- Commercial screening media[57] have been developed, but their suitability to Australian circumstances has not been fully evaluated. Their utility, including sensitivity and specificity, are strongly dependent on national, regional and local prevalence and no screening medium with adequate sensitivity and specificity for CRE has yet been developed. At the time of publication, there are three commercial media:
  - ChromID Carba (Biomérieux)
  - Brilliance CRE (Oxoid)[58]
  - CHROMagar KPC (Chromagar, Paris)[59]
- These media have undergone limited trialling in at least one site in Australia. A modified Supercarba (Trypticase soy instead of Drigalski medium) and Brilliance CRE performed better than the ChromID Carba in a setting where endemic IMP-4-positive strains were the only carbapenemases found. A recent study from the United Kingdom also showed poorer performance of Brilliance CRE than ChromID Carba, in a setting where NDM and KPC predominated.
- A more recent development had been so-called 'Supercarba'. This is Drigalski agar incorporating 0.25mg/L ertapenem, 70 mg/L ZnSO4 and 250 mg/L cloxacillin This medium is currently not available commercially.

4.2 Detection of CRE with 'routine' susceptibility testing of clinical isolates

Recommendations

4.2.1 As a minimum standard, laboratories should test meropenem susceptibility on all isolates of Enterobacteriaceae with the extended-spectrum beta-lactamase phenotype or that are non-susceptible to gentamicin.

4.2.2 CRE (as defined by the breakpoints documented for the susceptibility testing methods being used) should always undergo confirmatory testing.

4.2.3 Laboratories using semi-automated methods for susceptibility testing should also undertake or seek molecular confirmation of all Enterobacteriaceae with a meropenem minimum inhibitory concentration (MIC) of > 0.25 mg/L, especially from high-risk patients or units.

Rationale and commentary

- The aim of laboratory screening methods is to provide early detection of carbapenemase genes in Enterobacteriaceae and thereby prevent the dissemination and establishment of CRE, which is known to be a particular problem with organisms carrying the KPC and NDM carbapenemase classes, the great majority of which are resistant to multiple other drug classes.
- A range of suggestions have been made in recent years about screening methods, including:
  - use of specifically designed screening media[60] (see above)
  - using the susceptibility testing results on positive cultures.[61]
- Some carbapenemase-producing strains may test as susceptible to meropenem in routine testing and laboratories may choose to seek these carbapenemase producers. It is possible to detect these strains with the current Australian configurations of Vitek™ cards and the proposed Australian Phoenix™ Gram-negative panels.[b]
- Both CLSI and EUCAST now have lower clinical breakpoints for the carbapenems, but none were specifically set to ensure high sensitivity to the presence of carbapenemases. Current experience suggests that ertapenem has the highest sensitivity to the presence of carbapenemases, but specificity remains a major issue. Using the ertapenem susceptibility test result as first screen will result in a day's delay in detecting possible CRE carriers, and will probably result in a large amount of unnecessary additional laboratory confirmation work. Therefore, this approach is not recommended.
- AGAR and other data indicate that CRE are mostly likely to show a phenotype that includes gentamicin non-susceptibility or either ceftazidime or ceftriaxone non-susceptibility (ie. ESBL phenotype).[62]

b Experience gained through AGAR surveys, plus referral of isolates for confirmation, suggests that there is reasonable capture of Enterobacteriaceae that harbour carbapenemases using the meropenem 0.25 mg/L well in these panels. This concentration is the same as, or only slightly above, the wild-type cut-off values for the common Enterobacteriaceae. In contrast, nonsusceptibility to ertapenem is not sufficiently sensitive or specific for Enterobacteriaceae that harbour carbapenemases and is not recommended as a 'screening' agent in routine tests.

Disc testing

- Many laboratories perform direct disc susceptibility testing on urine specimens, without repeat testing if the results of direct testing are satisfactory. Few, if any, of these laboratories routinely include meropenem discs in the range of agents used for direct susceptibility testing. Many smaller laboratories, especially regional laboratories, also use disc susceptibility testing exclusively.
- Since the majority of CRE detected in AGAR surveillance studies during the past few years have come from urine specimens, there is the potential to fail to detect the bulk of CRE in Australia if some kind of CRE screening method is not included for disc susceptibility testing.
- If meropenem is routinely include in urine disc susceptibility, for either direct or standard testing, it should be noted that the published EUCAST and CLSI zone diameter breakpoints for meropenem are correlated to the clinical (pharmacodynamic) breakpoints, and not the lower 'screening' concentration of 0.25 mg/L. In view of this, a suggested option for disc testing in laboratories using Mueller-Hinton agar plates (EUCAST and CLSI methods) is to add meropenem to the routine disc testing range for both direct and standard testing – this will has the potential to capture emerging resistance because the wild-type zone diameter distributions of meropenem (using a 10µg disc) and the Enterobacteriaceae are known (http://mic.eucast.org/Eucast2/). Strains with a zone diameter of <23 mm on Mueller-Hinton agar should then undergo confirmation testing. Note that this method is meant to detect non-wild type isolates, and the recommended cutoff here does not correspond to published clinical breakpoints.
- Based on early experience, the CDS routine disc method appears to be able to detect a range of carbapenemases in Enterobacteriaceae.[63]

4.3 CRE confirmation

4.3.1 All suspected CRE isolates should be subjected to molecular screening for at least the known suite of carbapenemase gene families that have so far been seen in Enterobacteriaceae in Australia: IMP, VIM, OXA-48 and OXA-48-like, KPC and NDM.

4.3.2 The testing laboratory may choose to undertake preliminary 'phenotypic confirmation' on such isolates with the newly described Carba NP test[64] or the enhanced Carba NP test II[65] before referring the isolates for molecular testing.

4.3.3 The modified Hodge test, originally promoted as a 'phenotypic confirmation' test, has now been shown to be unreliable and is not recommended.[56]

Rationale and commentary

- Limited published evidence indicates that the Carba NP test is a reliable rapid phenotypic carbapenemase detection method.
- At the national level, the most commonly reported carbapenemase is IMP, which is mostly found to be IMP-4 on sequencing. However, all of the carbapenemase classes known to have spread internationally have been seen in Australia since 2009, including VIM, KPC, OXA-48 and 48-like, and NDM classes.

4.4 Reporting and notification of suspected CRE

Recommendations

4.4.1 For inpatients, infection prevention and control staff and treating clinicians should be notified of suspected or proven CRE, so that appropriate precautions and necessary alerts can be put in place, in line with recommendations in Sections 2 and 3.

4.4.2 In a situation analogous to that of ESBL detection, suspected or proven CRE should only be reported as resistant to meropenem if their MICs are greater than the clinical (pharmacodynamic) breakpoint of 1 mg/L (CLSI) or 2 mg/L (EUCAST). For isolates associated with disease and requiring treatment, this may require discussion with the treating clinician at the time to indicate the possibility of carbapenem treatment failure. Laboratories should add a comment to the report about the presence of a carbapenemase (e.g. 'This isolate harbours a suspected/proven transmissible carbapenemase with infection control implications. Infection prevention and control has been notified').

4.4.3 Strains of CRE that have been confirmed by molecular means to have carbapenemase gene(s) should be reported by the laboratory formally to health authorities in the state or territory if the jurisdiction requires such reporting, and also reported on the Australian Society for Antimicrobials ALERT website,[c] pending the development of a formal national notification system.

4.4.4 It is preferable that the notification be done by the laboratory that originally detected the CRE, rather than by the laboratory undertaking the molecular confirmation.

4.4.5 Carbapenem-resistant isolates that do not have carbapenemase genes demonstrated by molecular means should not be notified.

Rationale and commentary

- Prompt notification provides important information for the clinician and may alter the required patient treatment. Infection control requires prompt notice to ensure that patient isolation and other precautions can be put in place as soon as possible. This also enables surveillance for local clusters or outbreaks.
- National notification provides critical information for public health purposes and informs policy development at government levels.
- There are a large number of individual case reports, and a small number of clonal outbreaks of carbapenem resistant isolates mediated by non 'carbapenemase' – mediated mechanisms of resistance.[66] On review these reports appear to be confined to individuals and locations with very high levels of antimicrobial selection pressure i.e. heavy use of carbapenem antimicrobials in the infected individual or health service.[67] On current evidence, patients carrying such isolates represent a lower infection control risk and do not warrant attention unless cross transmission is demonstrated.

c ASA ALERT! Critical Resistance Reporting (http://www.asainc.net.au/alert)

Key resources

The following resources provide additional information and guidance for healthcare professionals and for patients and international travellers who may be exposed to CRE.

Standard precautions and contact precautions

Document:	***Australian Guidelines for the Prevention and Control of Infection in Healthcare* (NHMRC 2010)**	
Sections:	B1	Standard precautions
	B 2.2	Contact precautions
Obtain from:	http://www.nhmrc.gov.au/node/30290	
Intended for:	Healthcare professionals	

Document:	**National Safety and Quality Health Service Standards 2012**	
Sections:	Standard 3	Preventing and controlling healthcare-associated infections
	3.11	Criterion: managing patients with infections or colonisations
	3.12	Assessing the need for patient placement based on the risk of infection transmission
	3.13	Developing and implementing protocols relating to admission, receipt and transfer of patients with an infection
Obtain from:	http://www.safetyandquality.gov.au/wp-content/uploads/2012/10/Standard3_Oct_2012_WEB.pdf	
Intended for:	Healthcare professionals	

Multi-drug resistant organisms

Document:	***Australian Guidelines for the Prevention and Control of Infection in Healthcare* (NHMRC 2010)**	
Sections:	B3.1	Multi-drug resistant organisms
Obtain from:	http://www.nhmrc.gov.au/book/australian-guidelines-prevention-and-control-infection-healthcare-2010/b3-1-management-multi-re	
Intended for:	Healthcare professionals	

Key resources

Document:	Centres for Disease Control Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE) 2012 CRE Toolkit
Obtain from:	http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf
Intended for:	Healthcare professionals

Document:	Infection Prevention and Control of Carbapenem-resistant Enterobacteriaceae (CRE) in Western Australian Healthcare Facilities
Obtain from:	http://www.health.wa.gov.au/CircularsNew/attachments/712.pdf
Intended for:	Healthcare professionals

Antimicrobial stewardship programs

From 2013, all Australian hospitals are required to have in place antimicrobial stewardship programs that optimise use of antimicrobials in patients. National antimicrobial therapy guidelines or state/territory-based therapeutic guidelines consistent with *Therapeutic Guidelines: Antibiotic*[25] should be used.

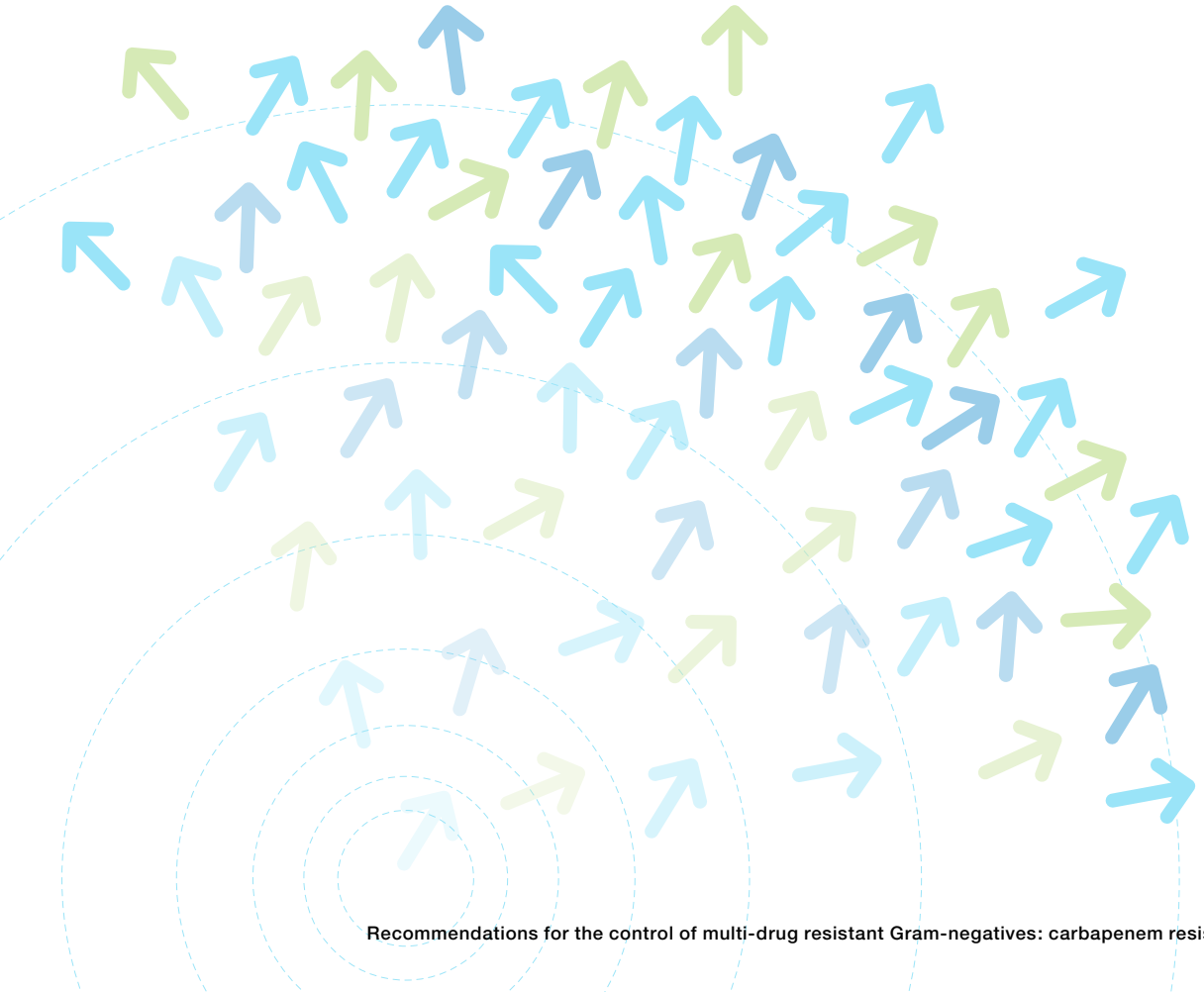
Document:	National Safety and Quality Health Service Standards 2012	
Sections:	Standard 3	Preventing and controlling healthcare-associated infections
	3.14	Criterion: antimicrobial stewardship
Obtain from:	http://www.safetyandquality.gov.au/publications/rtf-safety-and-quality-improvement-guide-standard-3-preventing-and-controlling-healthcare-associated-infections/	
Intended for:	Healthcare professionals	

Document:	National Prescribing Service initiatives
Sections:	All
Obtain from:	http://www.nps.org.au
Intended for:	General practitioners (GPs), GP registrars, GP-VMOs who provide care in hospitals

Document:	Therapeutic Guidelines : Antibiotic, Current edition
Sections:	All
Obtain from:	http://www.tg.com.au
Intended for:	General practitioners, hospital clinicians

Acronyms and abbreviations

AGAR	Australian Group on Antimicrobial Resistance
CLSI	Clinical and Laboratory Standards Institute
CRE	carbapenem-resistant Enterobacteriaceae
ESBL	extended-spectrum β-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
MRSA	methicillin-resistant *Staphylococcus aureus*
RACF	residential aged care facility
VRE	vancomycin-resistant enterococci



Definitions

β-lactam antibiotics	Antibiotics that have a four-carbon 'β-lactam' ring as part of their active structure; includes penicillins and their derivatives, cephalosporins, monobactams and carbapenems.
β-lactamase	An enzyme that can cleave β-lactam ring structures in certain antibiotics; produced by bacteria that carry the necessary genetic code.
Carbapenem	A class of broad-spectrum antibiotics that possess a β-lactam ring, with a structure that renders them highly resistant to most β-lactamase enzymes; includes imipenem, meropenem, ertapenem, doripenem.
Carbapenemase	An enzyme that can hydrolyse carbapenem antibiotics; produced by bacteria that carry a certain genetic code.
Clone	A population of genetically identical bacteria, in many cases that will contain a plasmid that introduces separate genetic material
Contact precautions	A set of practices that are used in addition to standard precautions to prevent transmission of infectious agents that are spread by direct or indirect contact with the patient or the patients environment. For example, isolation of a patient in a single room and the use of personal protective equipment.
CRE contact	A patient who has shared the same bed area and toilet facilities with a CRE colonised or infected patient where contact precautions were not in place.
Directed antibiotic use	Situations in which therapy is targeted against a bacterial pathogen that has been cultured and characterised by the microbiology service from a tested patient sample(s). Directed agents are usually narrower spectrum, and this may reduce the selection pressure for development of antimicrobial resistance.
Empirical antibiotic use	Use of an antimicrobial in a situation in which infection is possible but not proven. Often, a broad-spectrum agent is required to cover a range of possible pathogens.
Enterobacteriaceae	A family of Gram-negative bacteria that includes commensal and pathogenic enteric microorganisms found in humans, animals and the environment; includes Escherichia, Enterobacter, Klebsiella, Proteus, Salmonella, Serratia, Shigella species.
ESBL	Extended-spectrum β-lactamase enzyme, usually produced by an enteric Gram negative bacillus. The term is also used as a descriptor in a clinical setting to refer to an Enterobacteriaceae that is resistant to third-generation cephalosporins.
Fomite	An inanimate object or substance such as clothing, furniture, or soap, that is capable of transmitting infectious organisms from one individual to another
Metallo-β-lactamase	A carbapenemase that uses zinc in the hydrolysis of a broad range of β-lactam antibiotics.
Prophylactic antibiotic use	Application of antibiotics in the absence of symptoms or proven infection, in patients who are at high risk of succumbing to infection – for example, in association with surgery or in people who are immunosuppressed.
Standard precautions	Work practices that constitute the first-line approach to infection prevention and control in the healthcare environment. Examples of these work practices include hand hygiene, cleaning of equipment after patient use, environmental cleaning and appropriate use of personal protective equipment. Standard precautions are applied to everyone, regardless of their perceived or confirmed infectious status.

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Information for patients and their visitors

Carbapenem Resistant Enterobacteriaceae (CRE)

What is CRE?

Enterobacteriaceae is the name given to a family of bacteria that normally lives in our bowel. A well-known Enterobacteriaceae you may have heard of is *Escherichia coli* or *E. coli*.

Carbapenems are a group of antibiotics that usually work against these bacteria. But, some bacteria have become hard to treat because these antibiotics no longer work – the bacteria have become resistant to the antibiotics. These bacteria are called **Carbapenem Resistant Enterobacteriaceae** (CRE).

How do you get CRE?

In Australia, CRE infections are rare. When people do get a CRE infection, it often has been picked up when the person has had medical care overseas. CRE is found in patients in hospitals and clinics around the world, but particularly in Greece, India and South-East Asia.

Healthy people do not usually get CRE infections. However, it is important to know that people may carry CRE in their bowel or in a wound, without symptoms.

People who carry CRE are at risk of getting a CRE infection if they have an operation (especially on the prostate) or need treatment involving ventilators, catheters, or intravenous drips.

People who have taken some antibiotics for long periods of time are also at risk of developing CRE infections.

Treatment against CRE

There are not many options for treating CRE infections as the bacteria are usually resistant to most antibiotics. It is very important that people try to prevent the infection in the first place.

What does it mean to have CRE?

People may not know that they are carrying CRE and may never develop serious infection. However, in some people, CRE can become a serious problem and may cause pneumonia, abscesses, bloodstream infection, or many other types of infections and can sometimes result in death.

What happens if you have CRE?

If your doctor considers that you may carry or be infected with CRE, they will do some simple tests. This might involve taking a swab, blood or urine sample. The results of these tests will help your doctor work out the best form of treatment for you.

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To prevent the spread of CRE to other people when you are at home, it's important that you follow these precautions:

- Wash your hands with soap and water and dry them thoroughly. For example, after going to the toilet, before preparing and eating food and after touching animals.
- Use your own towels and face cloths. Do not share these items with other people.
- Avoid sharing grooming items such as nail scissors, tweezers, razors and toothbrushes.
- Cover any skin wounds whenever possible.
- Make sure you follow instructions and advice provided by your doctor or healthcare provider on how to care for wounds, or manage medical devices.

However:

- All your clothing and towels can be washed the way you normally do.
- All eating utensils and dishes can be washed the way you normally do.

If you are in a hospital, in addition to usual practice, such as staff regularly washing their hands or using alcohol based hand rub, the staff will use special practices to reduce the risk of spreading CRE to other patients. These may include:

- Caring for you in a single room.
- Wearing a gown and gloves while they are caring for you.

You can help prevent spreading CRE to other patients by:

- Regularly washing your hands with soap and water or using an alcohol based hand rub.
- Staying in your room, unless you need to be transferred for special tests or treatment.

If you have CRE, can you have visitors?

If you have CRE, you can have visitors, but it is important to know that CRE can affect people who have some long-term health problems. Talk with your doctor or nurse if someone is visiting you and has a long-term health problem.

It is important that your visitors wash their hands or use an alcohol based hand rub before and after visiting you. Visitors may also be asked to wear gloves or gowns.

Where can I get more information?

If you have any questions, the hospital's infection control professional or the doctor or nurse looking after you or your family can help.

More information on CRE is available from

The Australian Commission on Safety and Quality in Health Care *Recommendations for the control of Multi-drug resistant Gram-negatives: carbapenem resistant Enterobacteriaceae* (2013) www.safetyandquality.gov.au

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Information for clinicians

Carbapenem Resistant Enterobacteriaceae (CRE)

Carbapenems are a group of penicillin-related (broad spectrum beta-lactam) antibiotics that are effective against most Gram negative infections.[a] They are the last line of treatment for serious infections caused by multi-resistant *E. coli*, *Klebsiella* species and other Enterobacteriaceae.

Gram-negative bacteria that are resistant to most types of antibiotics, including carbapenems, are now emerging. This group of bacteria are known as Carbapenem Resistant Enterobacteriaceae (CRE).

CRE are resistant to all beta-lactam antibiotics, including penicillins, cephalosporins and carbapenems. They are usually also resistant to most aminoglycosides and fluoroquinolones.

CRE increase the risk of potentially untreatable infections in patients following invasive procedures or other hospital care. CRE infections are associated with a much higher mortality than infections with otherwise similar non-CRE bacteria.[1]

The duration of CRE carriage is variable and may be prolonged past 6 months in around 20% of people.

CRE in Australia: Who is at risk ?

Australia has not seen a significant number of CRE cases to date, due in part to our geographic isolation. However, the risk of CRE spreading to Australia is significant enough that it is recognised as an emerging public health issue.

International travel to affected areas (such as Greece, India and South-East Asia) creates an increased risk of spread of CRE to Australia. Exposure to healthcare services or residential care in these areas is a particularly significant risk factor for CRE colonisation.

Carbapenem antibiotics include: Meropenem, Imipenem, Ertapenem

Travellers to CRE endemic regions may acquire CRE or other resistant bacteria from food, water or environmental sources and, as a result, extra care should be taken by travellers.

CRE are more likely to affect patients who have:

- poor functional status
- prolonged hospital stay
- had a hospital stay within the previous 12 months
- had multiple exposures to different antibiotic agents
- diabetes mellitus
- had mechanical ventilation
- been admitted to an intensive care unit
- indwelling medical devices, such as a central venous catheter, urinary catheter, biliary catheter or wound drainage
- had an organ or stem-cell transplant
- been a resident in an aged care facility
- travelled to areas where CRE is endemic

Controlling CRE in healthcare

Early detection of CRE through targeted patient screening is essential to enable containment.

Infection control and antimicrobial stewardship measures are of proven value for limiting the spread and impact of CRE in healthcare settings.

The use of standard and contact precautions reduces the risk of transmission between patients.[2]

> “Multiple screens performed over a period of time are likely to improve screening sensitivity.[3]”

a The most common and important gram negative pathogens are the enterobacteriaceae, represented particularly by *Escherichia coli* and *Klebsiella/Enterobacter* spp.

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How should CRE patients be managed?

Standard precautions include hand hygiene, use of personal protective equipment, effective cleaning of all equipment and the healthcare environment.[2]

Contact precautions include; isolation in a single room, use of personal protective equipment (gloves and gowns), dedicating equipment to patients where possible and enhanced cleaning and disinfection in selected instances.[2]

Contact precautions should be used in the following circumstances:[3]

- when patients are identified as being at high risk of colonisation with CRE
- whilst waiting for the results of screening swabs
- when patients are known to be colonised with CRE.

If there are insufficient single rooms available, patient placement should be discussed with the Infection Control Service.

Antimicrobial stewardship

Antimicrobial stewardship measures aim to minimise overall antimicrobial use and optimise use of key Gram-negative antibiotics. These measures are critically important to reduce the emergence and spread of antibiotic resistant pathogens like CRE.

Clinicians should follow best practice prescribing principles for antibiotic prescription – **MINDME**[4]

M icrobiology guides therapy wherever possible

I ndications should be evidence based

N arrowest spectrum required

D osage appropriate to the site and type of infection

M inimise duration of therapy

E nsure monotherapy in most cases

It is essential that clinical practice ensures that use of antibiotics is consistent with *Therapeutic Guidelines: Antibiotic*,[5] taking into consideration local susceptibility information.

Health care organisations should monitor the use of antibiotics and aim to reduce overall use of cephalosporins, carbapenems and quinolone classes in ICU and non-ICU settings.

Antibiotic prescribers should also:

- Avoid the empirical use of broad spectrum beta-lactam antibiotics including third and fourth generation cephalosporins and carbapenems in respiratory tract infection, surgical prophylaxis and urinary tract infection.
- Avoid the empirical use of quinolone antibiotics in community-acquired pneumonia, skin/soft tissue infection, surgical prophylaxis and urinary tract infection.

Screening for CRE

Recommended screening specimens include rectal or perianal swabs, or faeces. Screening open wounds, or urine from indwelling urinary catheters should also considered for CRE screening.

False negative results from CRE screening tests may occur early after acquisition of the CRE, in the presence of certain antimicrobial agents and when the organism is present in low numbers.

Multiple screens performed over a period of time are likely to improve screening sensitivity. No consensus recommendation can be made about the optimal timing and frequency of screening.[3]

Contact precautions should be used for patients with a history of CRE colonisation or infection at least for the duration of the initial episode of inpatient care.[3]

Re-assessment of CRE carriage upon re-admission may be feasible. Any patient assessed and 'cleared' of CRE carriage must be followed up by the health service to detect possible relapse.[3]

Laboratory testing for CRE

Laboratory screening methods provide early detection of carbapenemase genes in Enterobacteriaceae and thereby prevent the dissemination and establishment of CRE.[3]

There is currently no internationally accepted 'gold standard' laboratory screening method for carbapenemases in Enterobacteriaceae.[3]

Additional information on laboratory testing for CRE is outlined in *Recommendations for the control of Multi-drug resistant Gram-negatives: carbapenem resistant Enterobacteriaceae*, www.safetyandquality.gov.au

Acknowledgement

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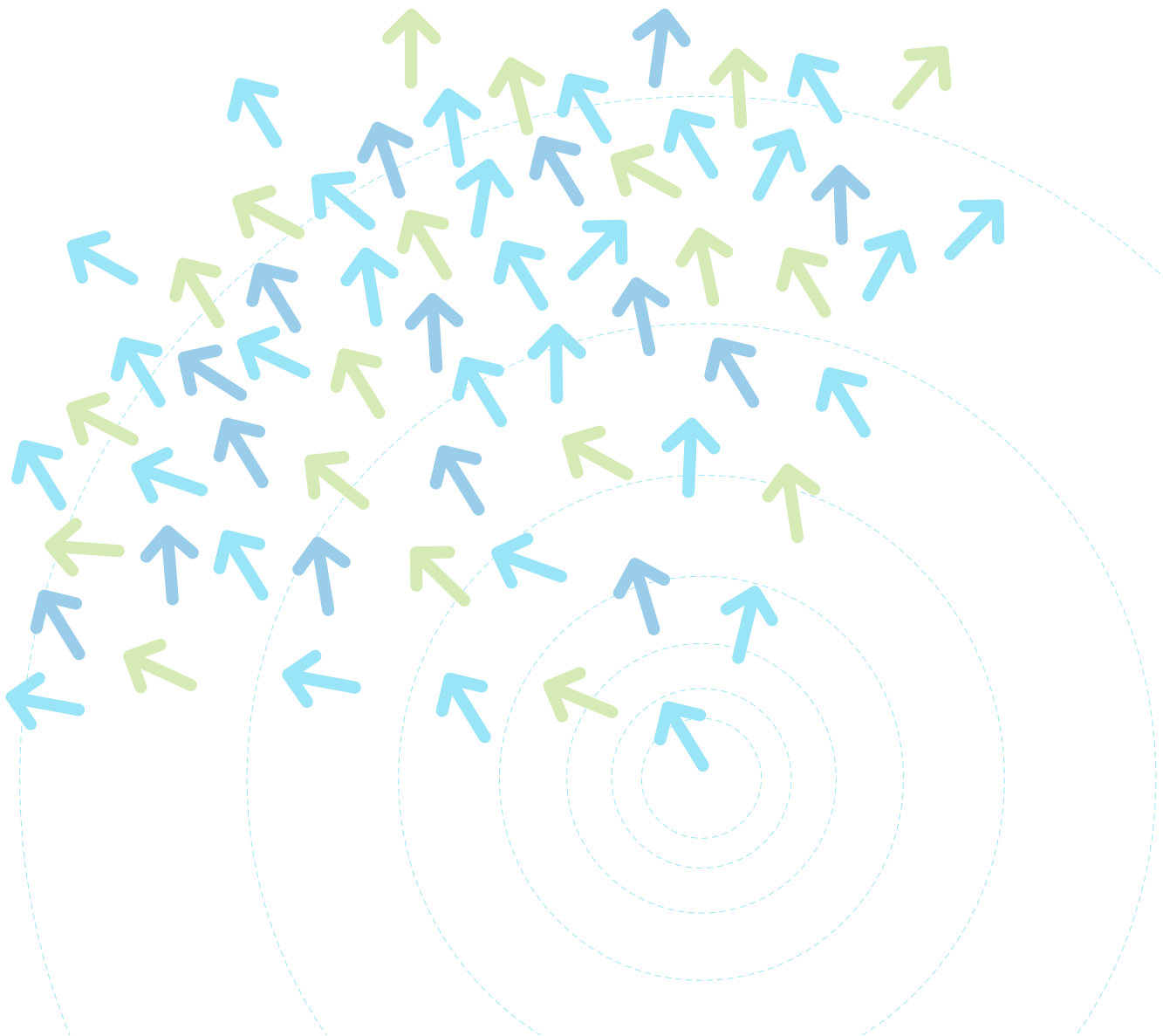

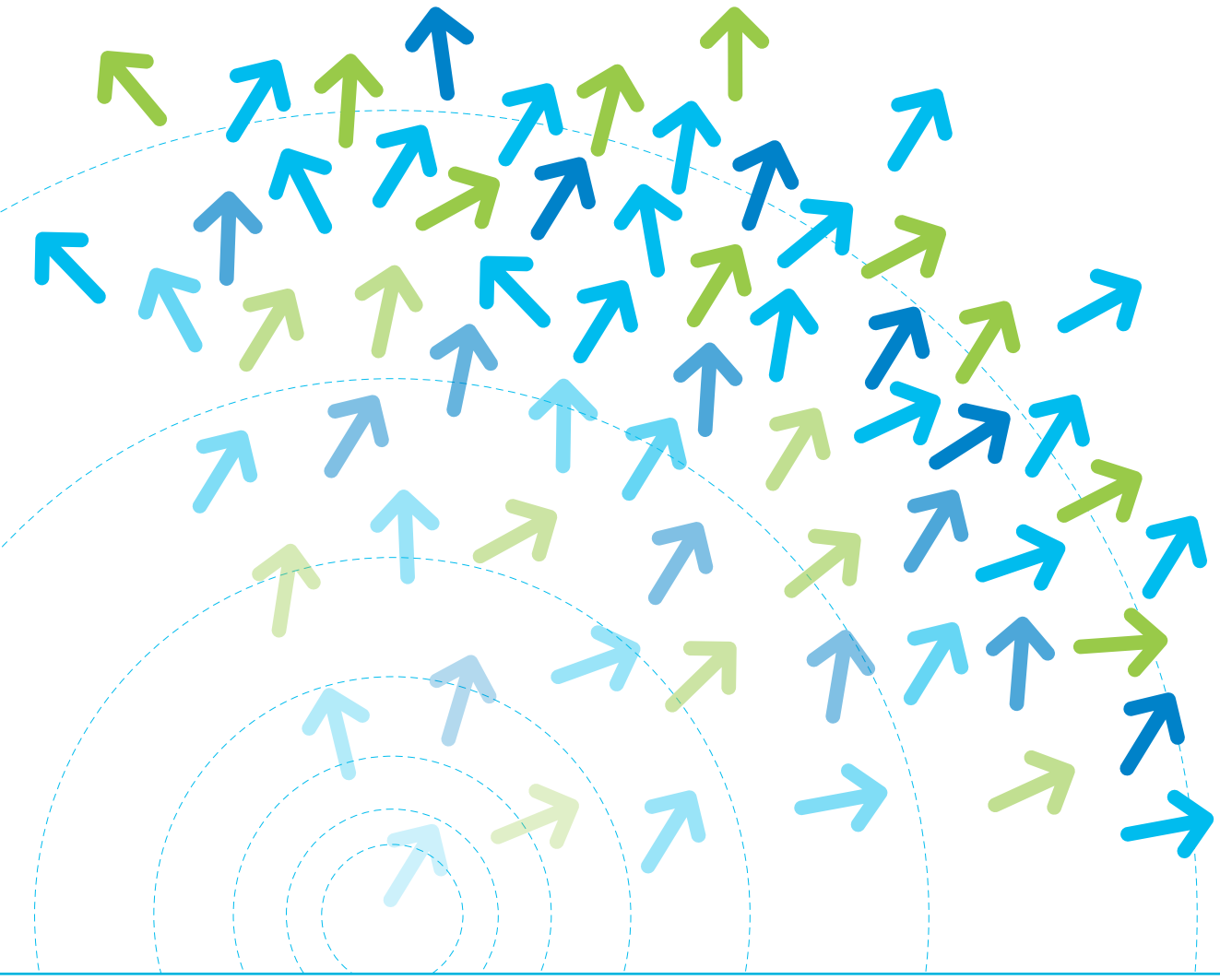

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