Interim Guidance:

Non-prescribing control measures to prevent cross transmission of Carbapenemase-Producing Enterobacteriaceae in acute settings
### Consensus statement

<table>
<thead>
<tr>
<th>Purpose:</th>
<th>To present a review of the evidence to inform the content of interim guidance for non-prescribing control measures to prevent the cross transmission of Carbapenemase-Producing Enterobacteriaceae within acute settings (CPE).</th>
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<tr>
<td><strong>It is anticipated that this document will be used to inform local action plans and risk assessments as appropriate.</strong></td>
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<td>Target audience:</td>
<td>Infection Prevention and Control Teams in NHS boards and other settings advising frontline staff on the management of patients who are at risk of having CPE and patients from whom CPE has been isolated.</td>
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<tr>
<td>Description:</td>
<td>Key recommendations from a rapid targeted review of the scientific evidence and consensus of expert opinion.</td>
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<tr>
<td>Update/review schedule:</td>
<td>Every three years; and if significant new evidence or other implications for practice are published</td>
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<td>The Generic Control Measure Trigger Tool (CPE) <a href="http://www.hps.scot.nhs.uk/pubs/Publication_Detail.aspx">http://www.hps.scot.nhs.uk/pubs/Publication_Detail.aspx</a></td>
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1. Executive summary

The following recommendations are based on a synthesis of evidence and expert opinion used to generate consensus statements. This methodology was chosen as a pragmatic way to produce timely guidance to inform Infection Prevention and Control Teams (IPCTs) dealing with patients who are at risk of having CPE and patients from whom CPE has been isolated. This is interim guidance that will be superseded by either, a UK wide developed guidance, or by review of new evidence.

1.1. Organisational factors (See Section 4)

- Each NHS board should develop a CPE action plan to promote preparedness, clinical awareness, systems to rapidly identify high-risk patients i.e. admitted from abroad or previously colonised/infected with CPE and early instigation of effective control measures to minimise the risk of CPE cross-transmission and outbreaks.

- The development of the action plan should include representatives of all staff involved in the care of patients at high risk of having CPE as well as microbiology staff.

- The action plan should include the internal communications to be adopted to ensure the timely receipt of specimens and specimen results.

- Staff e.g. bed managers, who are involved with the transfer of patients from hospitals abroad should be alerted to the importance of isolation and screening of these patients.

- There should be engagement of the local microbiology laboratory to ensure that laboratory methods for CPE detection are in place and results communicated promptly.

- Ensure active surveillance of high risk patients takes place and isolation of these patients is implemented at admission until the results are known.

- The action plan should include the external communications (HPS, AMT Team) when there are any confirmed cases.

- The ICM/ICD should inform the senior hospital management and HPS depending on the HIATT status, of any confirmed case of CPE.
1.2. Clinical risk assessment (see Section 5)

All patients admitted to acute healthcare settings should be assessed for a variety of infection risks (as per Standard Infection Control Precautions (SICPs): http://www.hps.scot.nhs.uk/haiic/ic/nationalinfectionpreventionandcontrolmanual.aspx) including CPE. A clinical risk assessment for risk factors must be used as the approach to screening as set out below:

1.2.1. Who to screen

High risk patients:

1. All inter-hospital transfers from healthcare facilities abroad or patients with a history of admission to a hospital abroad in the last 12 months (including holiday dialysis patients)

2. Patients with a known history of infection or colonisation with CPE in the last 12 months

Patients falling into the categories above must be isolated in a single room, preferably with en-suite facilities, and screened on admission.

If positive, the patient(s) must be screened weekly thereafter until the ICD, in conjunction with clinical colleagues, is satisfied that there is no further risk of cross transmission.

Where CPE colonisation/infection IS identified

- In high risk clinical areas e.g. ICU, renal units, transplant units, haematology and oncology and infectious disease wards,
  - The identification of a new patient case with CPE will require weekly screening of all patients in the unit while any patient remains positive for CPE.
- In other clinical areas e.g. general medical/surgical wards
  - The identification of a new patient case with CPE will require all patient contacts to be screened for CPE e.g. those who have shared / sharing the same bay / room.
1.2.2. How to screen

- A rectal swab (or stool sample) is the sample of choice for screening. If present, further samples e.g. urinary catheter or wound should also be obtained.

NB: Staff screening is not routinely recommended.

1.2.3. Additional risk factors for CPE colonisation

Other factors have been associated with CPE colonisation/infection including:

- Sharing a room with a colonised patient during this admission
- Previous admission to ICU
- Prior exposure or current use of antibiotics particularly fluoroquinolones, carbapenems, cephalosporins, and anti-pseudomonal penicillins
- History of admission/transfer from hospitals within parts of the UK

1.3. Patient decolonisation (see Section 6)

- Routine decolonisation regimens are not currently recommended.

1.4. Infection prevention and control (see Section 7)

- Any patient who has a risk factor identified on clinical risk assessment must be isolated immediately in a single room, preferably with en-suite facilities,

- Infection prevention and control precautions as per the National Infection Prevention and Control (NIP&C) Manual applied:
  - Chapter 1; Standard Infection Control Precautions
  - Chapter 2; Transmission Based Precautions

http://www.hps.scot.nhs.uk/haiic/ic/nationalinfectionpreventionandcontrolmanual.aspx

- If a patient screens positive for a CPE they must remain in isolation for the duration of their hospital stay or until the ICD, in conjunction with clinical colleagues, is satisfied that there is no further risk of cross transmission.

2. **Aim of the review**

To produce a set of recommendations based on scientific evidence (where available) and consensus of expert opinion to prevent cross transmission of carbapenemase producing Enterobacteriaceae (CPEs) within acute healthcare settings in NHSScotland.

2.1. **The problem**

CPEs have become a major public health issue and active surveillance is vital to identify an increase in clinical episodes. There is an urgent need for clear guidance for infection control and healthcare staff to enable recognition of high risk patients and healthcare settings and infection prevention and control measures to prevent cross transmission.

2.2. **Out of scope for this review**

Prescribing measures and evidence specific to other Multi Drug Resistant-Gram Negatives (MDR-GNs) have not been included within this review.

2.3. **Assumptions**

The Infection Prevention and Control measures referred to in this document are generic and therefore are likely to be suitable for other MDR-GNs.
3. Background

3.1. Microbiology

The emergence of multidrug resistant bacteria has been of increasing concern for a number of years and particularly since the identification of resistance to extended-spectrum β-lactams in Gram-negative bacteria.¹ CPEs were first identified in Europe in the 1990s and since then there has been a sustained increase.² Carbapenems are often viewed as the last therapeutic option to treat complex infections caused by multidrug resistant bacteria and this makes the increase of CPE a major public health concern.³

Although resistance to carbapenems can occur through a variety of different mechanisms, the main focus of concern is on Carbapenemase producing Enterobacteriaceae. Carbapenemases hydrolyse the majority of β-lactam antibiotics, including carbapenems, and tend to be plasmid mediated giving potential for spread between strains and species. They are increasingly found in Enterobacteriaceae (particularly Klebsiella pneumoniae and Escherichia coli), but are also seen in Pseudomonas aeruginosa and Acinetobacter baumannii.³ Carbapenemase producing Klebsiella pneumoniae is associated with increased morbidity and mortality.⁴ CPE strains frequently carry additional resistance determinants to other non-β-lactam antibiotics, making these organisms resistant to most antibiotics.¹⁵ Currently CPEs remain susceptible to only a few classes of antimicrobials, commonly colistin and tigecycline⁵, and pan-resistant strains have been described.⁶ Treatment of any infection caused by CPE should always be guided by an infection specialist.

CPEs have been identified throughout the world.¹ Though the exact prevalence of CPE in healthcare facilities and in the community in Europe is not known, there are indications that it is endemic in certain countries.³ Although existing surveillance systems are able to identify the presence of carbapenem resistant bacteria, molecular methods are required to identify whether bacteria carry the genes for carbapenemase hydrolysis.⁷ A recent ECDC risk assessment on the spread of CPE suggests that the elements necessary to curb the spread of CPE include active surveillance cultures, confirmation of carbapenemase enzymes and timely use of control measures.²

3.2. Epidemiology

The exact prevalence of CPEs within Europe is difficult to determine due to a lack of systematic surveillance systems. In Europe, antimicrobial susceptibility testing data and trends for K. pneumoniae resistant to carbapenem antimicrobials have been reported annually since 2005 through the European Antimicrobial Resistance Surveillance Network (available from
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Data from 2009 showed that, whereas in most countries in Europe the percentage of carbapenem-resistance in invasive *K. pneumoniae* isolates from blood and cerebrospinal fluid was below 1%, Greece, Cyprus and Italy reported resistance percentages of 43.5%, 17.0% and 1.3%, respectively. It should be noted that these figures will constantly change and lack of data from a country may reflect lack of reporting/detection rather than lack of a CPE problem.

Even though global data on this topic are not available, some insight into community and healthcare distribution of NDM (New Delhi Metallo-betalactamase)-producing Enterobacteriaceae is given by the results of a large study from the Indian subcontinent and the UK. These results show that most cases in India were community acquired, whereas those from the UK were travel-healthcare-associated, being acquired following hospital admissions in India, Pakistan and Bangladesh.

4. **Organisational factors**

There is an emerging theme that health boards take an aggressive approach to the detection of CPEs and to their control. This includes active surveillance of patients considered at risk and instigation of infection prevention and control precautions before microbiology results are confirmed. It is crucial therefore that organisational factors are in place to support this type of approach. Indeed the advice document which was issued by the HPA in 2011 emphasises the need to make minimising the risk of spread of CPEs a priority at Board and Executive level to ensure support for prevention and eradication programmes.

Within NHSScotland, the local microbiology laboratory must inform the Infection Prevention and Control Team (IPCT) of any patient(s) identified with a CPE. Ideally the IPCT should be alerted electronically in addition to verbal communication. If possible, the patient’s electronic notes, and/or the patient administration system need to be tagged electronically to alert healthcare workers to these patients as they move around the hospital system.

**Incident reporting**

The Infection Control Doctor (ICD) must inform the Senior Hospital management and HPS of any confirmed case of CPE. The standard tool for assessing the severity of an incident or outbreak and facilitating effective communication between NHS boards, HPS and the Scottish Government must be followed (Hospital Infection Investigation Advisory Tool or HIIAT). CNO (2010) 1.11

4.1. Recommendations

- Each NHS board should develop a CPE action plan to promote preparedness, clinical awareness, systems to rapidly identify high-risk patients i.e. admitted from abroad or previously colonised/infected with CPE and early instigation of effective control measures to minimise the risk of CPE cross-transmission and outbreaks.

- The development of the action plan should include representatives of all staff involved in the care of patients at high risk of having CPE as well as microbiology staff.

- The action plan should include the internal communications to be adopted to ensure the timely receipt of specimens and specimen results.

- Staff e.g. bed managers, who are involved with the transfer of patients from hospitals abroad should be alerted to the importance of isolation and screening of these patients.

- The action plan should include the external communications (HPS, AMT Team) when there are any cases.

- There should be engagement of the local microbiology laboratory to ensure that laboratory methods for CPE detection are in place and results communicated promptly.

- Ensure active surveillance of high risk patients takes place and isolation of these patients is implemented at admission until the results are known.

- The ICM/ICD should inform the senior hospital management and HPS depending on the HIATT status, of any confirmed case of CPE.

5. Clinical risk assessment

5.1. Screening

It is important for the organisational management and control of CPE that clinical and patient risk factors for colonisation and infection are identified to inform screening protocols and infection control measures. Detection of infected patients and carriers with carbapenemase producers is necessary for prevention of their spread.

The search of the literature revealed mainly observational studies of outbreaks in which screening has formed part of the multi-factorial interventions. However, there was substantial consensus of
evidence that a suite of measures which included screening formed part of successful outbreak control.\textsuperscript{2} Despite being relatively low quality, the volume of evidence demonstrates that active screening for CPE colonisation is effective when used to enable infection control precautions.\textsuperscript{4,12-22} In terms of the site sampled there is consensus that a rectal swab should be taken, although several studies have recommended perineal screening. It is important to note that the HPA point out that prolonged urine carriage has been noticed in some patients without faecal carriage.\textsuperscript{10} Therefore, there is clearly further research required with regards to which body site to sample, and also if this should be a combination of sites.

No conclusive evidence was found on when to screen. CDC have recommendations for responding to a single case of CPE by conducting a single round of active surveillance of patients with epidemiologic links to an index case.\textsuperscript{4} The HPA recommend that weekly and discharge screening of all patients in affected units/wards should be implemented until the organism is eliminated or the last patient is discharged.\textsuperscript{10} There is some evidence from studies describing outbreaks of CPE that screening of all admissions to high risk units helped control the outbreak.\textsuperscript{4,20,23,24} However, it has also been noted by some authors that admission screening alone may miss a significant proportion of CPE, as they are often acquired 48 hours after admission to a high-risk unit.\textsuperscript{20,23} The patients CPE status should be logged in their patient records. Admission, weekly and discharge screening of all patients in affected units/wards should be implemented until there is no further risk of cross transmission.\textsuperscript{25}

5.2. High risk patients

The ECDC risk assessment concludes that there is strong evidence that patients infected or colonised with CPE, who are transferred across borders, increases the risk of CPE being introduced and spread within the healthcare facilities of the recipient country.\textsuperscript{2} This includes situations when patients have transferred from or received medical care abroad in areas with high rates of CPE.

Geographical origin, and transfer from a long term care facility, has been associated with patient colonisation, and therefore it is recommended that these patient groups should be isolated while awaiting results as a proactive measure.\textsuperscript{26} Numerous risk factors have been described in the literature. These include co-morbidities, certain treatments, hospital specialties, and length of stay. Of these, cross border transfer (especially from countries with a known high prevalence) plus hospitalisation appears to be the risk factor most associated with acquisition and these are recommended by the European\textsuperscript{2} and CDC\textsuperscript{3} guidance as part of a risk assessment process.
Cross border transfer from other countries, particularly from areas with high rates of CPEs should be included in a clinical risk assessment. It may be pragmatic to consider a time limit of 12 months in a clinical risk assessment consistent with the approach of the HPA\textsuperscript{25} (interim guidance currently in draft). Holiday dialysis patients should also be screened on return from high risk countries. Certain regions of England have increased CPE prevalence and as such may need considered as high risk when it comes to screening patients.

A review of a number of epidemiological studies of CPE outbreaks also concluded that screening of patients with epidemiological links to an index case is recommended.\textsuperscript{20,23,24}

Therefore in conclusion high risk patients include:

- All inter-hospital transfers from abroad or patients with a history of admission abroad in the last 12 months (including holiday dialysis patients)
- Patients with known history of infection or colonisation with CPE in the last 12 months

### 5.3. Additional risk factors for CPE colonisation

A number of additional risk factors have been identified from the review of the literature and are detailed below

#### 5.3.1. Sharing a room with a patient colonised with CPE

Sharing a room with a patient colonised with a carbapenemase producing *K. pneumonia* was identified as an independent risk factor. However hospitalisation, in a ward with a policy of admission screening which guided patient placement has been shown to be an effective control measure.\textsuperscript{27}

#### 5.3.2. Previous admission to ICU

A review of the available evidence shows that admission to ICU is a risk factor for infection with CPEs.\textsuperscript{2,28-30} There is also a growing body of evidence that severity of disease and intensity of care required are also risk factors.\textsuperscript{17} A case review of 5 years data in a paediatric facility demonstrated that chronic medical conditions, frequent hospitalisations, a history of recurrent infections and immunosuppression were risk factors for acquisition.\textsuperscript{31} Previous admission to ICU should be included in a clinical risk assessment with consideration given to other patient factors such as severity of illness.
5.3.3. **Prior exposure or current use of antibiotics**

A systematic literature review by ECDC identified prior exposure to antibiotics as a common risk factor.\(^2\) These included: fluoroquinolones, carbapenems, cephalosporins, and anti-pseudomonal penicillins. A further targeted literature review also identified a number of studies with similar findings. Previous antibiotics, specifically carbapenem, were shown to be independent risk factors for infection with carbapenem resistant *K. pneumoniae* and strains of *Acinetobacter baumannii*.\(^{32,33}\) Furthermore, imipenem use was identified as being associated with gut carriage of imipenem resistant *Pseudomonas aeruginosa*.\(^{29,34-36}\) This has led to some authors concluding that antibiotic stewardship interventions should be tailored to specific settings based on local epidemiology.\(^{37}\) An ECDC report concludes that similar risk factors to those associated with other multidrug-resistant organisms (MDROs) have been identified for CPE: prior exposure or current use of antibiotics particularly fluoroquinolones, carbapenems, cephalosporins, and anti-pseudomonal penicillins should be included in a clinical risk assessment.\(^2\)

5.3.4. **History of admission/transfer from hospitals within parts of the UK**

Outbreaks and clusters of CPE have occurred in some parts of the UK and in some geographical ‘pockets’ CPE has become endemic.\(^{25}\)

5.4. **Staff screening**

There is currently insufficient evidence to support screening of staff as part of the infection prevention and control measures required. This is supported by the paucity of data implicating colonised healthcare workers in an outbreak.\(^{38}\) However several studies used staff screening to either control outbreaks of MDR-GNB\(^{20,23}\) or to assess the burden of colonisation in high-risk units.\(^{24,39-41}\) Staff screening may be considered following a local risk assessment by the Infection Prevention and Control Team in an outbreak situation, particularly if there is a suspected or known epidemiological link to specific staff members. If required, staff screening should be carried out as per the HDL: Healthcare associated infection (HAI): Human Resources policy for staff screening during incidents and outbreaks. This letter sets out the approach to be taken by NHS Boards and Special Health Boards in ensuring effective staff screening processes in the event of an incident or outbreak of infection, and the management of staff who test positive or where treatment fails. [http://www.sehd.scot.nhs.uk/mels/HDL2006_31.pdf](http://www.sehd.scot.nhs.uk/mels/HDL2006_31.pdf)
5.5. **Recommendations**

All patients admitted to clinical areas should be assessed for a variety of infection risks (as per SICPs) including for CPE. A clinical risk assessment for risk factors **must be** used as the approach to screening.

### Who to screen

**High risk patients:**

1. All inter-hospital transfers from healthcare facilities abroad or patients with a history of admission abroad in the last 12 months (including holiday dialysis patients)

2. Patients with known history of infection or colonisation with CPE in the last 12 months

Patients falling into the categories above **must be** isolated in a single room, preferably with en-suite facilities, and screened on admission.

**If positive, the patient(s) must be screened weekly** thereafter until the ICD, in conjunction with clinical colleagues, is satisfied that there is no further risk of cross transmission.

### Where CPE colonisation/ infection IS identified

- In high risk clinical areas e.g. ICU, renal units, transplant units, haematology and oncology and infectious disease wards,
  - The identification of a new patient case with CPE **will require weekly screening of all patients in the unit** while any patient remains positive for CPE.

- In other clinical areas e.g. general medical/surgical wards
  - The identification of a new patient case with CPE will require **all patient contacts to be screened for CPE** e.g. those who have shared / sharing the same bay/room.
How to screen

- A rectal swab (or stool sample) is the sample of choice for screening. If present, samples from other sites e.g. urinary catheter or wound should also be sent.

NB: Staff screening is not routinely recommended.

Additional risk factors for CPE colonisation

Other factors have been associated with CPE colonisation/infection and advice should be sought from the IPCT regarding clinical risk and requirement for IPCT precautions

- Sharing a room with a colonised patient during this admission
- Previous admission to ICU
- Prior exposure or current use of antibiotics particularly fluoroquinolones, carbapenems, cephalosporins, and anti-pseudomonal penicillins
- History of admission transfer from hospitals within the UK

6. Patient decolonisation

Decolonisation of patients with CPEs involves the use of methods of eradicating carriage in the gastrointestinal tract. Selective digestive decontamination (SDD), or variants thereof, aim to maintain normal anaerobic bacteria while eliminating aerobic coliform bacteria. There are relatively few published studies which describe SDD. One recent small placebo controlled study looking at carbapenemase resistant K pneumoniae found that SDD with oral gentamicin and polymyxin, for a period of 7 days, significantly reduced rectal colonisation. This study concluded that this may be suitable for certain vulnerable patient groups e.g. immunocompromised patients or for use in outbreak situations when there is difficulty establishing control. In addition, a non randomised study over an 8 year period using a revised SDD regimen plus antimicrobial treatment of the infecting ESBL resulted in elimination in >50% of cases. A non controlled observational study published in 2005 showed a decrease in acquisition rates from 5.5 to 1.9 / 1,000 patient days, although the actual SDD regime used was poorly defined.

The use of bathing with chlorhexidine containing products has been used to decrease the bioburden of other multidrug resistant organisms. This is currently recommended by the CDC as a supplementary precaution when there is ongoing transmission and particularly when there is difficulty achieving control.

Recommendation: Routine decolonisation regimens are not currently recommended
7. Infection Prevention and Control

There is a consensus within the available scientific literature that any patient who meets the ‘high risk’ criteria on clinical risk assessment must be isolated immediately and contact precautions should be implemented in addition to Standard Infection Control Precautions (SICPs). Contact precautions are used to prevent and control infections spread via direct contact with the patient’s skin/mucous membranes or indirectly from the immediate care environment (including care equipment). Available evidence, despite being of relatively low quality, consistently points to SICPs with special attention paid to hand hygiene and the cohorting of staff caring for affected patients. These prevention and control measures should be applied as part of a bundle approach with other precautions such as active surveillance, invasive device care and use of antimicrobial agents.

7.1. Recommendations:

- Any patient who has a risk factor identified on clinical risk assessment must be isolated immediately in a single room, preferably with en-suite facilities,

- Infection prevention and control precautions as per the National Infection Prevention and Control (NIP&C) Manual applied:
  - Chapter 1; Standard Infection Control Precautions
  - Chapter 2; Transmission Based Precautions
  http://www.hps.scot.nhs.uk/haiic/ic/nationalinfectionpreventionandcontrolmanual.aspx

- If a patient screens positive for a CPE they must remain in isolation for the duration of their hospital stay or until the ICD, in conjunction with clinical colleagues, is satisfied that there is no further risk of cross transmission.


8. Additional resources

8.1. Flow diagram (Appendix 1)

8.2. Example toolkit

8.3. Guideline development methodology

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References


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In addition the input of the following colleagues is acknowledged particularly for the content of the Toolkit, which may be used as a supporting document.

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Appendix 1 - CPE flow diagram clinical risk assessment/infection control precautions and screening

1. Other known risk factors:
   a) Known to have shared a room with a colonised patient during this admission
   b) Previous admission to ICU
   c) Prior exposure or current use of antibiotics particularly:
      - Ceftazidime
      - Cephalosporins
      - Anti-pseudomonal penicillins
      - Carbapenems
   d) Previous admission / transfer from hospitals within parts of the UK

2. In addition to Standard Infection Control Precautions (SICPs)
3. Patients in high-risk areas e.g. ICU, renal units, transplant units, haematology & oncology and HD wards: Weekly screening of all patients on the unit while any patient positive for CPE remains on the unit until the ICD in conjunction with clinical colleagues is satisfied that there is no further risk of cross transmission.
   Patients in other areas e.g. general medical/surgical wards: Screen all patient contacts (e.g. those who have shared / are sharing the same bay/ward until the ICD in conjunction with clinical colleagues is satisfied that there is no further risk of cross transmission.

4. The standard tool for assessing the severity of an incident or outbreak and communication must be followed (Hospital Infection Investigation Advisory Tool or HIAT CN1 (2011).