



An overview of carbapenemase producing enterobacteriaceae (CPE) in trauma and orthopaedics

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ABSTRACT

Carbapenemase resistant enterobacteria (CPE) may be found in asymptomatic carriers. Its incidence is increasing worldwide. Surgical patients are at increased risk of immunocompromise and of carriage progressing to active infection. Active infection with CPE carries a high mortality rate, with the bacteria being resistant to many antibiotics. This article provides details on the epidemiology, screening and management of the orthopaedic patient with CPE. The guidelines advise orthopaedic staff on ways to avoid the spread of CPE amongst inpatients.

1. Introduction

Enterobacteriaceae comprise a large family of gram-negative bacteria that commonly colonise humans and sometimes cause disease. They are facultative anaerobes, frequently residing in the intestinal tract, as part of the normal gut microbiota. The common disease causing enterobacteriaceae include: *Escherichia coli*, *Klebsiella*, *Salmonella*, *Proteus*, *Yersinia Pestis*, *Shigella*, *Enterobacter*, *Serratia* and *Citrobacter*; with *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* accounting for 80–95% of all isolates identified¹

The beta-lactam family are the most widely used antibiotics. There are four groups: penicillins, cephalosporins, monobactam and carbapenems.² These antibiotics share a common molecular structure and mechanism of action, acting to inhibit transpeptidases, which catalyse peptide cross-linking during the final stages of cell wall biosynthesis. As a result bacterial cell walls are weakened and burst under osmotic pressure. Carbapenems, a subclass beta-lactam, are highly-effective antibiotic agents, especially against gram-positive and gram-negative bacteria and they are frequently reserved for multidrug resistant infections. They possess a unique variation on the core molecular structure. In addition to the beta-lactam ring they have a carbapenem conferring exceptional stability against most beta-lactamase enzymes that can inactivate beta-lactams³

Carbapenemase-producing Enterobacteriaceae (CPE) are described as 'superbugs', as they demonstrate resistance to the carbapenem class of antibiotics, considered the drugs of last resort for such infections, together with other beta-lactam antibiotics. Their resistance is conferred by the production of the carbapenemase enzyme which acts to

hydrolyze and disable the drug molecule.⁴ Examples of CPE include *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter aerogenes* and *Enterobacter cloacae* complex. Many of the genes coding for carbapenemase are located in plasmids which can be transferred between bacteria and hence this type of resistance is more likely to spread.⁵

Rates of CPE infection are endemic in parts of the UK. One study found a UK prevalence of 0.2%, with an incidence of 0.007 per 1000 patient-days. The same study identified the North-West England to be the most affected region at 0.033 per 1000 patient-days.⁶ The last decade has seen a marked increase in the prevalence of CPE, which is becoming more wide spread.^{7,8} When colonisation evolves to infection, the mortality rate for CPE bacteraemia can be as high as 57%.⁹ By comparison, in the past decade mandatory monitoring of MRSA has demonstrated a significant reduction in its incidence. The rate of all MRSA cases per 100,000 population per year fell from 8.6 in 2007/08 to 1.5 in 2017/18, whilst the rate of MRSA bacteraemia fell from 0.8 cases per 100,000 population in 2013/14 to 0.4 cases per 100,000 population in 2017/18.¹⁰ The mortality rate for MRSA bacteraemia had been documented at 27%.¹¹ CPE has not received the same awareness as MRSA and there are no set guidelines for Orthopaedic patients requiring surgery. This report aims to inform the Orthopaedic surgeon on screening and management of CPE.

2. Epidemiology

The increase in CPE is a serious problem worldwide. In Europe the highest rates of CPE are found in Mediterranean countries, especially

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Italy, Greece and Malta; wherein rates of CPE infection have been described as epidemic, with most hospitals in these countries repeatedly seeing cases admitted. Ireland, Hungary and Israel are at a stage of inter-regional spread, with multiple epidemiological related outbreaks occurring in different health districts. The UK, Spain, France, Belgium, Germany, Poland and Croatia are all at a stage of regional spread wherein there has been more than one epidemiological related outbreak confined to hospitals that are part of a regional referral network.¹² In the UK the incidence of CPE is highest in Manchester and London.¹³

Many countries in Europe have addressed the spread of CPE by creating guidelines or recruiting national task forces. Indeed in the UK, guidelines for the detection and management of CPE have been described.¹⁴ However, even with this guidance available awareness of CPE in the UK remains poor and there remains a lack of guidance on the approach to the surgical patient with CPE.

The highest rates of CPE are in those over 75 years of age¹³ and up to 75% of hospital admissions attributed to CPE are from long-term care facilities or transferred from another hospital.¹⁵ This is because patients resident in such centres are more likely to be exposed to and colonized by these bacteria.¹⁶ Suboptimal cleaning and disinfection is the leading cause for disease transmission.¹⁷ Treatment with long-term beta-lactam antibiotics, fluoroquinolones, mechanical ventilation, parenteral nutrition, permanent urinary catheters, organ transplantation and ICU admission pose independent risk factors.^{17–21} The risk is also increased in those patients with diabetes and immunocompromised.^{17,18} Carriers are often asymptomatic and yet mortality rates for active CPE infections are quoted as being as high as 57%.⁹ CPE infection has also been linked to an increased length of stay and decreased functional status on discharge²¹ posing an increased economic and social burden.

3. Screening

With the epidemiology of CPE, its risk factors and outcomes described it is clear that something must be done in attempt to limit its spread and reduce the associated mortality rate here in the UK and worldwide. Adopting an approach of targeted screening of high-risk admissions has proved effective at reducing MRSA bacteraemia.²² This approach has proven more cost-effective than screening of all admissions, irrespective of perceived risk.²³ Thus supporting an argument for a more selective screening protocol.

Currently Public Health England¹⁴ advises assessing all acute admissions for risk of CPE colonisation. If a patient has no known risk factors then screening for CPE is not required. If the patient is at risk of colonisation screening is necessary to determine the CPE status and direct further management. It is important that the screening test offered is acceptable to patients accurate, cheap and easy to perform, with the resources readily available at all hospitals and trusts.

Obtaining and testing a stool sample is the gold standard for suspected cases of infection or colonisation and yet is not feasible for a routine screening programme. Obtaining swabs is quick and easy. Rectal swabs have the highest overall sensitivity. However, different species yield differently at different anatomical sites. The addition of groin swabbing and urine sampling has been proven to increase rates detection²⁴ and hence there is an argument for multi-site swabbing. Subsequent testing involves either detection of specific DNA sequences or carbapenemase activity.

Carbapenemase genes can be detected using a polymerase chain reaction (PCR).²⁵ During the PCR process a specific target gene is identified using primers (DNA sequences that are complementary to the sequences on the gene to be copied). Subsequently, thermal culture cycles amplify the production of a target DNA strand. As the primers must be specific to the DNA sequence to be amplified some prior knowledge of the DNA sequence is necessary. Hence, this approach only permits the detection of known genotypes.²⁶ In contrast, phenotypic detection can detect carbapenemase activity irrespective of the gene coding sequence. With this in mind the current detection methods for

CPE currently in use include the carbapenem inactivation method (CIM), the Carba NP test and the Cica-beta test. These tests rely on culture using selective media. The CIM is based on the disk diffusion method and was developed to detect carbapenemase activity in gram-negative rods within 8 h. It involves the incubation of a potential carbapenemase producer with meropenem discs and use of the resulting supernatant to challenge a susceptible indicator strain. Growth of the indicator strain indicates that the meropenam has been inactivated. Studies have shown this method to be highly sensitive and specific for CPE.²⁷ The Carba NP test allows for rapid (< 2hrs) detection of carbapenemase activity through the hydrolysis of imipenem by a bacterial lysate and its resultant changes in pH using the indicator phenol red (from red to yellow-orange).²⁸ Similarly the Cica-beta test uses a filter paper test strip containing a chromogenic cephalosporin. If a culture of CPE is added to the filter paper, hydrolysis of the cephalosporin induces a colour change.²⁹

With an understanding of the epidemiology and screening tests for CPE, sensible recommendations would include multi-site swabbing (including rectal) be completed on:

- all patients over 75 years of age,
- all patients admitted from long-term care facilities or other hospitals,
- all those with a recent history of travel to destinations with high CPE prevalence.

If an inpatient has a positive result for CPE then there should be routine screening of all patients with whom there has been contact. Currently there is no evidence to support the routine screening of medical staff and yet strict infection prevention precautions need to be adopted, especially hand hygiene.

Patient and public education is essential to improve compliance to the proposed screening scheme, especially as multisite swabbing, and rectal swabbing in particular, may be perceived invasive by many patients. Hospitals have a duty to facilitate this through local advertisement of the problem. Further, the UK's media should be recruited to help. MRSA has received much media attention in the last decade, which has helped raise awareness, encourage patient compliance with screening and improve public adherence to in hospital infection control measures. CPE has yet to receive the same media attention and hence knowledge and understanding of its implications remains lacking.

Audit is an important tool to monitor adherence to guidelines. Regular audit is advised to assess CPE screening practises and should form part of the mandatory practise for local infection control teams. There should be regular publication of the results of such audits followed by education as necessary.

4. Management

Current guidance for the management of colonisation includes isolation, barrier nursing, good hand hygiene and monitoring of bowel habits.¹⁴ Furthermore, studies have demonstrated prolonged survival of bacterial on stainless steel surfaces at room temperature. This prolonged survival had been linked with gene transfer and can contribute to antibiotic resistance.³⁰ Rapid and regular decontamination is advised to limit the spread of CPE and the transmission of antibiotic resistance genes. When selective screening is used in combination with these simple infection control measures a massive decrease in the incidence of resistant strains can be achieved. One study at the Kaplan Medical Centre in Israel demonstrated a 16-fold decrease in the incidence of resistant *K. Pneumoniae*, which was sustained for 30 months.³¹

Colonisation alone is asymptomatic and does not necessitate antimicrobial treatment. Unlike methicillin resistant staphylococcus aureus (MRSA) skin decolonisation is not recommended, as CPE generally colonises the gut. Gut decolonisation with antibiotics is also not recommended, as there is concern that this would contribute to the

development of further resistant strains.¹⁴

Colonisation can progress to infection if CPE gains access to sterile body sites, e.g. lungs, urinary tract or bloodstream. Typically presentation is with non-specific signs of infection – high fever, sweating, rigors, tachypnoea, tachycardia and hypotension. Patients may progress to a state of septic shock or severe respiratory compromise with cyanosis. When there is active infection treatment must be started promptly after discussing with a microbiologist. This is typically with monotherapy for the stable patient using either polymyxins, tigecycline, fosfomycin (oral, for lower UTIs only) or aminoglycosides.¹⁴ Combination therapy is necessary to reduce mortality in systemic infections (including bacteraemia and respiratory tract infections), even when there is in vitro susceptibility to polymyxins or tigecycline.^{32–34} Recommended combination therapies include polymyxin and carbapenham; polymyxin and tigecycline; or polymyxin and aminoglycosides.¹⁴ Working closely with the microbiologists/infections diseases will help determine local antibiotic resistance patterns such to dictate the standardised antibiotic combinations.³⁵ However, there should always be comparison to results of susceptibility testing, with adjustment to the antibiotic regime as necessary.

5. CPE in orthopaedics

In 2014 the NHS Network published guidance on the early detection and management of CPE was published.¹⁴ This guidance advises on the management of patients on the ward and upon discharge from hospital, however, there remains no standardisation of practise in the theatre setting.

With routine screening of all at risk patients upon admission to hospital, the CPE status can be determined quickly. Hence it is reasonable that the CPE status be determined pre-operatively for both elective and trauma admissions.

Recommendation for ward care of CPE positive patients involves isolation and strict infection prevention protocols. It stands to reason that the same principles be adopted when the patient attend theatres. As such our guidance for CPE positive patients attending theatre involves:

- Routine multi-site swabs (including rectal) to be obtained at pre-assessment for all high-risk elective cases.
- Routine multi-site swabs (including rectal) to be obtained for all at risk patients upon admission. This includes
 - all those over 75,
 - all those to be admitted from long term care institutions or transferred from another hospital,
 - all those with a history of recent travel to high risk destinations.
- Every effort should be made to determine the CPE status before the patient is taken to theatre.
- If an inpatient is found to be colonised with CPE they must be isolated.
- There must be screening, by way of multi-site swabs, for all patient contacts.
- Clear identification of positive CPE status by way of brightly a coloured wrist-band, clear documentation on the theatre checklist and at the front of the patient notes.
- Review and documentation of the CPE status for each patient during the morning and afternoon theatre team brief.
- Delay operating on CPE positive patients until the end of the theatre list. If it is not suitable to delay surgery until the end of the list then there will need to be a deep clean of the theatre before the next case can proceed.
- Minimise time in transit to the operating theatre, such to minimise contact with other patients and staff and avoid any wait in theatre reception. This mandates good communication between theatre and ward staff such to ensure that the operating theatre and anaesthetic room are clear before the patient is transferred.

- Where there is an unplanned delay upon arriving at theatres attempts should be made to isolate the patient. This must be followed by a deep clean of the waiting area. Reporting of delays in theatre should be used to facilitate root cause analysis and streamline the system of patient transfer.
- Following surgery CPE patients should be taken to a separate recovery suit. This will require a deep clean after each patient. It is important that there is robust communication between staff to ensure that there is space to recover the patient. If the designated recovery suit is already in use the patient should not leave the theatre until this is available.
- Regular mandatory audit to assess adherence to guidelines. This should be the responsibility of theatre management with quarterly departmental presentation of results and spot checks by infection control teams.

Further advice involves raising awareness amongst medical staff and public. Each hospital should establish mandatory training on CPE. CPE specific infection control announcements should be made on a regular basis with clear advertisement within hospitals. Local and national media should be approached to help raise public awareness of CPE and encourage engagement in the strategies proposed. Further research will be required to evaluate the clinical and cost effectiveness of the proposed guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jor.2019.06.026>.

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Conflicts of interest

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