Outbreak Column 15: Carbapenemase-producing Enterobacteriaceae

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Outbreak Column 15 covers the often confusing 'carbapenemase producing Enterobacteriaceae' (CPE), the epidemic curve which has yet to reach base camp. Although there is no doubt that this family of organisms presents a formidable public health challenge, there is some debate about what needs to be done to prevent and control outbreaks. Although the challenge from CPE has only been recognised since the mid-1990s (Queenan and Bush, 2007), the task for the Outbreak Column appears equally as daunting as that presented by *Staphylococcus aureus* – which has been a nosocomial challenge for considerably longer (Curran, 2014a). The high-reliability characteristic 'deference to expertise' (Weick et al, 1999), is being demonstrated in this column in that it has been co-authored by Dr Jon Otter, whose personal expertise has enabled the topic to be tackled from a more learned perspective.

In this review, we provide:

- A synopsis of the CPE challenge
- An assessment of the strengths and weaknesses of the available guidance and toolkits
- Guidance on developing a strategy to prevent CPE outbreaks

To supplement this column an online appendix is available to the readers.

This is a narrative review that drew from the following three sources of information: The online appendix is available at <http://jip.sagepub.com/supplemental>.

- Reviews of CPE epidemiology
- National and international guidelines to control the organisms
- Outbreak reports

The challenge from antibiotic resistant Enterobacteriaceae

Gram-negative bacteria of the Enterobacteriaceae family, more commonly *Klebsiella pneumoniae* and *Escherichia coli*, were found to be the most frequent organisms detected in relation to healthcare associated infections in recent national prevalence surveys (Health Protection Agency, 2012; Health Protection Scotland, 2012; Zarb et al, 2012). The Enterobacteriaceae are also a substantial cause of infections in

community settings (Farrell et al, 2003). These organisms have become sequentially resistant to several classes of antibiotics: first beta-lactams, then extended spectrum beta-lactams (ESBLs) and most recently the carbapenems (Carmeli et al, 2010; Ho et al, 2010; Peleg and Hooper, 2010). Of note it was only resistance to the third generation carbapenems that posed a therapeutic challenge, as these antibiotics are first-line treatments. Although non-Enterobacteriaceae Gram-negative bacteria that are resistant to carbapenems, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, represent both a therapeutic challenge and an infection control problem at times, they are largely restricted to intensive care units and other high risk settings (Dijkshoorn et al, 2007; Loveday et al, 2014a; Paterson, 2006). CPE present the most serious threat to a broader group of patients, with the additional capacity for spread outside of hospitals. Effective therapy for CPE is more difficult and can be limited to older, less effective and less well-tolerated agents such as colistin (Carmeli et al, 2010).

Resistance mechanisms

Enterobacteriaceae may be resistant to carbapenems either through the production of an acquired carbapenemase, or the production of an extended-spectrum beta-lactamase (ESBL)/AmpC combined with porin loss (Nordmann and Poirel, 2013).

Key differentiation:

- Carbapenem-resistant Enterobacteriaceae (CRE) are resistant to carbapenems by any mechanism, including the production of an acquired carbapenemase, or the production of an ESBL/AmpC combined with porin loss
- Carbapenemase-producing Enterobacteriaceae (CPE) are resistant to carbapenems by means of an acquired carbapenemase.

The key issues with CPE arise because higher levels of resistance are produced by acquired carbapenemases (typically KPC, VIM, IMP, NDM and OXA-48 types); the organisms themselves are, like all Gram negatives, easily transmissible, plus they have the potential for horizontal gene transfer between related bacteria (Ho et al, 2010; Gupta et al, 2011; Canton et al, 2012; Nordmann and Poirel, 2013). Horizontal gene transfer between bacteria means cross-infection and

Table 1. Comparing the epidemiology of multidrug-resistant organisms and <i>Clostridium difficile</i>					
Pathogen	CPE	CPAB	MRSA	VRE	<i>C. difficile</i>
Resistance	+++	+++	++	+	+/-
Resistance genes	Multiple	Multiple	Single	Single	n/a
Species	Multiple	Single	Single	Single	Single
Healthcare associated (HA)vs community associated (CA)	HA & CA	HA (ICU)	HA	HA	HA
At-risk patients	All	ICU	Unwell	Unwell	Old
Virulence	+++	+/-	++	+/-	+
Environment	+/-	+++	+	++	+++

CPE=Carbapenemase-producing Enterobacteriaceae; CPAB=Carbapenemase-producing *Acinetobacter baumannii*; MRSA=Meticillin resistant *Staphylococcus aureus*; VRE=vancomycin resistant enterococci

outbreaks can arise that involve different organisms with the same resistance patterns. Carbapenemase genes can also be acquired by *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Hidron et al, 2008; Canton et al, 2012). Rapid clonal dissemination of CPE or the spread of carbapenemases within the clinical settings is a real concern. Therefore the detection and surveillance of CPE has become increasingly important for the rapid implementation of 'transmission-based' infection control measures and to maintain the available therapeutic options.

The unique challenges from CPE

CPE presents unique challenges to infection prevention and control teams (IPCTs) (Table 1). First, it is possible to have outbreaks with different species of Enterobacteriaceae but with the same mobile genetic resistant elements (Vlek et al, 2013). Second, CPE inhabits the gastrointestinal tract and decolonisation therapy merely suppresses the amount of CPE; elimination of the carrier state, which has been a central component of prevention and control interventions for meti-cillin resistant *Staphylococcus aureus* (MRSA), seems unlikely to be successful (Carmeli et al, 2010; Khan et al, 2012). Indeed, data suggest that gut colonisation with CPE and other resistant Enterobacteriaceae extends for many months and can recur after apparently resolving, which argues for a 'once positive, always positive' stance (Haverkate et al, 2014; Lubbert et al, 2014). Third, pan-drug resistant CPE, i.e. organisms resistant to all antibiotic treatment options, has already been reported and the pipeline for new agents is virtually empty, meaning that effective therapeutic options will be increasingly limited (Carmeli et al, 2010).

Many people are colonised without being infected. However, colonisation can precede endogenous infection and/or be a source for cross-transmission. For patients with invasive CPE infections the implications are significant (Patel et al, 2008; Daikos et al, 2009; Gupta et al, 2011; Snitkin et al, 2012). A recent meta-analysis found that the rate for CRE-attributable deaths ranged from 26%–44% in seven studies (and was –3% and –4% in two studies); CRE infected patients had a two-fold higher unadjusted number of deaths than for patients infected with Carbapenemase sensitive Enterobacteriaceae (Falagas et al, 2014).

CPE outbreaks, the majority of which involve *Klebsiella pneumo-niae*, have been reported in most parts of the world, and CPE appear to be endemic in a small number of countries, including, Greece, parts of Asia (particularly the Indian subcontinent) and some Central and South American countries (Nordmann et al, 2011; Canton et al, 2012). Most indications of prevalence come from outbreak reports and surveys of invasive isolates, therefore accurate prevalence and hence risk factors have been difficult to identify. However, travel to the Indian subcontinent, exposure to healthcare therein and antibiotics

seem to be important risk factors (Gupta et al, 2011; Bhargava et al, 2014).

Sizing the CPE problem in the UK and Europe

Data from EARS-Net suggest that the prevalence of CPE among bloodstream infections is low in most parts of Europe, but there have been dramatic recent increases in some countries (ECDC, 2013). In Greece, rates are exceptionally high, with the proportion of invasive carbapenem-resistant *K. pneumoniae* isolates increasing from 27.8% in 2005 to 68.2% in 2011 (Figure 1) (ECDC, 2013). Disturbingly, there has also been a dramatic increase in the prevalence of carbapenem-resistant *K. pneumoniae* in the last few years in Italy, from 1% in 2009 to 15% in 2010 to 27% in 2011 (Figure 1).

In the UK, data from Public Health England's AMRHAI Reference Unit indicate that the number of confirmed CPE cases referred from UK laboratories has increased from fewer than five per year in 2003–07 to almost 1,000 in 2013 (Personal communication, Professor Neil Woodford). Of note, Health Protection Agency data is based on iso-lates received and may not reflect overall prevalence. A small number of studies from other countries show that carriage rates of CPE vary considerably from 1% to almost 20% in Pakistan (Calfee and Jenkins, 2008; Wiener-Well et al, 2010; Day et al, 2013). Given the lack of UK studies on gastrointestinal prevalence of CPE, estimating carriage rates and advocating effective control measures is extremely difficult. Data from Ireland (intensive care units) and emerging data from the UK suggest a low carriage rate of <1% in the general healthcare popula-tion (Burns et al, 2013). However, this may be considerably higher in certain high-risk groups and in regions where outbreaks are occurring. The extremely rapid national increase in asymptotic carriage and infec-tions that arose in Israel is a salutary lesson (Schwaber et al, 2011; Schwaber and Carmeli, 2014). This means that the situation in the UK must be taken extremely seriously.

In summary, CPE presents a real and present danger within the UK because of their ability to spread and the extremely limited therapeutic options for people infected with CPE. Therefore IPCTs must be pre-pared to contain outbreaks while still enabling their health services to continue if it is safe to do so. The successive UK *Staphylococcus aureus* guidelines, with acknowledged hindsight bias, were recently scrutinised for weaknesses (Curran, 2014b). A similar scrutiny exer-cise was applied to the CPE guidance for this column. Let us be clear, this situation has been described as 'one of the most serious emerging infectious disease threats' (Catchpole, 2014); therefore the guidance merits such close scrutiny.

CPE guidelines and toolkits

There are a variety of CPE guidelines and toolkits written to guide CPE prevention and control that were reviewed for this column (Centers

Figure 1. Carbapenem-resistance in invasive *Klebsiella pneumoniae* isolates in Greece, Italy and in the UK. Data from EARS-Net

for Disease Control, 2012; ECDC Working Group, 2013; HPS Interim Working Group, 2013; Levy et al, 2013; Public Health England Working Group, 2013; Anon, 2014a; Tacconelli et al, 2014).

Infection control guideline challenges

Infection control guidance is often written by experts in infection control for frontline workers to follow – this can present challenges with implementation. The early description of infection control precautions being ‘exasperating impediments to medical and surgical work’ is unfortunately still considered apt by some clinical colleagues (Bagshawe et al, 1978). Therefore guideline writers must ensure that what is advocated is evidence based and meets a frontline-reality-check of being ‘doable’. Guideline writers should therefore include experts who understand the problem and who can devise effective solutions (microbiology, infection control specialists, frontline clinical staff and people with human factors expertise). The main CPE guidance issues identified relate to: a lack of clarity in general, a lack of outbreak epidemiology intelligence and a lack of uniformity in the use of Standard Precautions terminology – which is where the review will start.

What do we mean by Standard Precautions?

Despite what is suggested by the name, ‘Standard Precautions’ (SP) are by no means standard. There appears no doubt that SP include: hand hygiene, use of personal protective equipment, clean care equipment and safe environments (Garner, 1996; World Health Organization, 2007; Health Protection Scotland, 2014; Loveday et al, 2014b). However, some versions of SP include one or more of the following: risk assessment to identify high-risk patients requiring special management, patient placement, aseptic technique, management of blood and body fluid spillages and safe injection practices. A Venn diagram illustrating the inclusions and exclusions for SP or a variation in the name thereof is available in the online appendix.

Perhaps not surprisingly therefore several of the published CPE guidelines lack clarity in their use of the term ‘Standard Precautions’. For example, the ECDC Working Group (2013) advocates SP no less than seven times without ever specifying what is meant by the term. The use of the term ‘Strict Standard Precautions’ (Strict SP) by Public Health England (2013) is also generating uncertainty. It is difficult for the reader to be sure whether Strict SP are SP that should be *strictly* applied, or whether Strict SP include more actions than SP alone. Public Health England’s (2013) Toolkit contains examples that suggest both. Although listed as part of the routine admission procedure, what is not specified as being an SP action, or Strict SP action is the need to assess the infection risks from all patients on admission – which should lead to a *go/no go* for additional transmission-based precautions. The Toolkit (2013) contains no recommendation to adhere to SP when there are no cases. This is an omission.

Adherence to SP is for every patient, every HCW and every health-care environment – every time.

Advocated actions to prevent and control CPE are: the prompt recognition and screening of all persons at risk of being colonised with CPE using accurate diagnostic methods; isolation of patients with CPE for as long as is required; and screening of case contacts (ECDC Working Group, 2013; HPS Interim Working Group, 2013). The application of SP, including an assessment of patient risk factors, should result in patients at risk of carrying CPE being recognised. The remaining measures, including screening and isolation, are transmission-based precautions and used in addition to SP. It is imperative that SP are regarded as our first and best defence against CPE outbreaks in UK. If there remains confusion as to what is and what is not included in SP then the chances of full SP implementation are extremely limited.

Unclear adjectives (hand hygiene)

In attempting to promote the importance of hand hygiene, guideline writers have forsaken clarity by the use of adjectives. Adjectives are used throughout the CPE guidelines presumably with the aim of stressing the importance in undertaking the required actions. For example, Levy et al (2013) advocate an ‘aggressive infection control strategy’ for CPE control. The measures listed are similar to those in other guidelines so it is presumably in its implementation that the IPCT should be aggressive. For example, with regard to hand hygiene, Levy et al (2013) state that: *hand hygiene is a core measure ..., a corner stone ..., hand hygiene should always be reinforced*. The Public Health England (2013) Toolkit also promotes hand hygiene with adjectives or adverbs, e.g. ‘... *good hand hygiene*..., ... *especially hand hygiene* ..., ... *strict hand hygiene* ..., ... *effective hand hygiene* ...’, before a specific instruction of ‘Reinforce and optimise hand hygiene with soap and water or, *on visibly clean hands only*, an alcohol hand rub as an alternative’. The point is this: the guidance fails to explore or specify whether hand hygiene as it is currently recommended by the World Health Organization (WHO) (WHO, 2009a,b), in terms of *how*, *when* and *with what*, changes because of CPE. Section 7 of the WHO guidance (WHO, 2009b) cites studies which show:

- Some colonised people have been found to have up to 10^6 *K. pneumoniae* on their skin
- *K. pneumoniae* transfers easily during ‘clean procedures’ to health-care workers’ skin.
- [Without hand hygiene] hands remain contaminated with the risk of transmitting organisms.
- Some studies showed that hand washing with plain soap failed to remove Gram-negative bacilli from healthcare workers’ hands (WHO, 2009b) [Sections 8.1; 11.2].

It is unclear whether this cross-transmission opportunity arises from a *failure of the process* (e.g. soap and water being insufficient to remove pathogens) or a *failure to follow process* (HCWs not applying the soap and water, manoeuvring hands, rinsing and drying etc., in the approved way). The WHO advocates hand hygiene with alcohol-based hand rubs first (WHO, 2009a); soap (plain or antimicrobial) and water is recommended when hands are visibly dirty or soiled, or after using the toilet. For the above reasons it could be argued that hand hygiene with alcohol-based hand rub should have been recommended first in the Public Health England (2013) Toolkit.

The IPC community needs assurance that hand hygiene with plain soap and water is sufficient and consequently safe following contact with a patient, a patient’s environment or following removal of personal protective equipment, after which hands may become heavily contaminated with CPE. To ensure healthcare workers have clear guidance, SP must include the WHO hand hygiene recommendations. Any new guidelines for the control of emerging pathogens must

evaluate the evidence to determine whether there is any need to change the SP hand hygiene recommendations as currently advocated. By emphasising that it is performed 'effectively' or 'strictly' there is a risk of implying that it is acceptable not to do so on other occasions.

Infection prevention and control interventions

The CPE literature on transmission is at present limited since CPE outbreaks are relatively new. However there is a much larger body of information available from outbreaks of non-CPE. Although transfer of carbapenemases is novel, there is no suggestion that CPE outbreaks will have novel transmission pathways because of their resistance.

The ESCMID Guidelines (Tacconelli et al, 2014) are the result of a systematic review of published studies on infection prevention and control interventions aimed at reducing the transmission of multidrug-resistant Gram-negative bacteria. The interventions evaluated are hand hygiene, active screening cultures, alert flagging/code (note-marking), contact precautions, isolating patients, cohorting patients, cohorting staff, environmental cleaning, environmental screening, antimicrobial stewardship, healthcare worker screening, education and IPCT infrastructure. However, by focusing on whether specific measures are effective, the guideline writers have missed the opportunity to evaluate the IPCT investigations that identify transmission pathways and 'procedures of interest', i.e. Time, Place and Person epidemiology. Intelligence derived from such data is used to direct IPCT actions. Some of the IPCT recommended actions based on epidemiology findings may not reach a GRADE recommendation but they will pass the parachute test (i.e., there are no randomised controlled trials providing evidence of the effectiveness of using parachutes when jumping out of planes, but no one would advocate not using them) (Smith and Pell, 2003). Although outbreak epidemiology has limitations, including a lack of scientific controls, and suffers the potential for regression to the mean, collective evaluation of multiple reports can provide useful data on what works. Such outbreak epidemiology can indicate:

- Which clinical units, patients and procedures are most likely to be involved in CPE outbreaks?
- What factors contributed to these outbreaks to better understand what is likely to be outbreak-provoking conditions?

A strategy to prevent CPE becoming endemic in the UK

Outbreaks of Gram-negative bacteria were much more common in the days before single-use equipment and before the deployment of IPCTs in every hospital. CPE outbreaks will arise if the conditions that provoked such outbreaks are present or re-introduced. However, although the rarity of outbreaks of Enterobacteriaceae in our institutions should give us some confidence in our ability to control CPE, it must not result in complacency. It may well be that outbreaks with sensitive organisms were merely not being recognised (Vlek et al, 2013). Ergo, to address the CPE situation, IPCTs should adhere to all five high-reliability characteristics (Weick et al, 1999):

- Deference to expertise – ensuring that the topic matter experts and their know-how are sought and heeded
- Sensitivity to operations – being mindful in your policies and procedures that your patients and your care settings will always be vulnerable to CPE outbreaks
- Pre-occupation to failure – identifying where outbreaks are most likely to arise in your care settings and taking local actions to improve preparedness
- Reluctance to simplify – investigating thoroughly any alert signals in your data

- Commitment to resilience – considering, good as you are, how your IPCT can improve

From all the guidelines, tools, and CPE outbreak reports it can be concluded that the IPC strategy for this challenge needs actions on several fronts. These are summarised below.

Implementation of precautions to minimise CPE cross-transmission and outbreaks

CPE may arrive in our care settings on patients who will not look infected or infectious. Questions to the patient may or may not identify whether they are at high risk for carrying CPE. Microbiological screening may or may not identify colonised patients as being CPE positive. There may or may not be isolation or cohort facilities available to separate them from non-colonised persons. As a consequence the key infection prevention and control actions are to:

- Assess everyone on admission for infection risks, and apply additional transmission-based precautions (including isolation and screening) for persons who present an infection risk
- Apply and maintain Standard Precautions in all care settings for all people. (This includes hand hygiene as per the WHO 5 moments using alcohol-based hand rubs if hands are visibly clean.)
- Minimise invasive device* use and optimise invasive device care when they cannot be avoided.
- Implement transmission-based precautions to prevent cross-transmission when CPE cases are confirmed (including: contact tracing, contact precautions, placing colonised and infected patients in single rooms where possible, staff cohorting and environmental decontamination – including the consideration of enhanced terminal disinfection at the time of patient discharge (Tacconelli et al, 2014).

(*Invasive devices enable organisms to gain direct access to what should be sterile body areas; the device lumens and surfaces enable bacteria to develop biofilms causing infection at a later date. Whenever they are used they present a serious ongoing infection risk).

Keeping wash-hand basins free of CPE

Wash-hand basins have already been implicated in outbreaks of both non-CPE and CPE (Lowe et al, 2012). Therefore **do not** discard body fluids, bed-bath water, secretions or exudates into wash-hand basins (Lowe et al, 2012).

Providing safe injection and safe endoscopy practices

Bloodstream infections of both non-CPE and CPE have arisen from contamination of multi-dose vials and diluents (Curran, 2011; Gray et al, 2012) and inadequately decontaminated endoscopy equipment (Anon, 2014b). Prevention of infusate-related CPE outbreaks could be avoided by replacing multi-dose with single-dose vials; and making sure healthcare workers can adhere to safe injection practices. Endoscopy-related outbreaks may be more difficult to prevent as at least one report identified no failures to follow the decontamination process (Anon, 2014b).

Outbreak preparedness for specialist units

Although outbreaks of CPE can be hospital-wide, they seem to be reported as causing most harm when arising in specialist units (intensive care units, neonatal intensive care units, transplant units) (Leung et al, 2012; Tacconelli et al, 2014). Alongside alert organism surveillance, proactively assessing the SP practices in high-risk units and looking for other outbreak-provoking conditions in advance of any cases should minimise the vulnerability of these units to CPE outbreaks.

Antibiotic stewardship

Antibiotic stewardship is critical to reducing the selection pressure that promotes CPE and other antibiotic-resistant organisms in the care environment.

A driver diagram illustrating the above is included in the online appendix.

Summary

The evidence base for effective interventions to prevent and control CPE outbreaks is limited, and therefore a pragmatic approach is required. This column identifies four key findings:

- Although all guidance advocates SP, there is confusion over what is meant by the term; urgent harmonisation is needed
- New guideline writers must determine whether SP require alteration to control the organisms
- Guideline writing groups should include frontline workers, and test guidelines in practice pre-publication

- A strategy of actions on the following five fronts are required to prevent CPE outbreaks: apply SP for all and additional transmission-based precautions for those at risk of CPE, keep hand washing basins CPE free, provide safe injection and endoscopy practices, prepare for outbreaks on high-risk units, and perform antimicrobial stewardship.

In this column, we set out to make CPEs less confusing, identify the strengths and weakness in the CPE guidance and determine what else is needed. It appears that the most important task going forward is the standardisation and implementation of Standard Precautions.

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