Multi-resistant Gram negative Enterobactericeae in paediatrics: an infection prevention and control challenge

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Abstract

Antibiotic resistance is not new. However, the microbiological landscape is changing for paediatricians. Increasingly resistant Gram-negative bacteria such as *Escherichia coli* and *Klebsiella* spp. Have, historically, resulted in infections in children. More recently, carbapenem resistant *Enterobacteriaceae* (CRE) have emerged and they have become one of the greatest challenges for clinicians and public health. Since their discovery, the number of cases of colonisation and infection in adults and children have increased worldwide. Overall, the number of reported cases remains lower in paediatric and neonatal populations compared to adults. KPC and OXA-48 carbapenemase producing *Enterobacteriaceae* are the most common phenotypes seen in the United Kingdom both in adults and children. These plasmid mediated transmissible resistance genes pose the highest risk due to the potential of horizontal gene transfer amongst different *Enterobacteriaceae*. Combination broad-spectrum antibiotic therapy has proven effective. Antibiotic stewardship and good infection control are necessary to tackle this rising challenge in healthcare; to reduce significant morbidity and mortality. This article discusses the current epidemiology and offers an overview of treatment options.

Keywords carbapenem resistance; carbapenemase; combination therapy; *E. coli*; *Enterobacteriaceae*; infection control; *Klebsiella*; paediatric infection

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Introduction

Emergence of carbapenem resistant *Enterobacteriaceae*

Enterobacteriaceae with extensive antimicrobial resistance have become a significant public health challenge in the recent years. They can lead to poorer clinical outcomes when treating serious infections in vulnerable patient groups such as neonates and children due to limited antibiotic options. In addition, these resistance genes are often found on plasmids which can be transferred between bacteria within an individual patient as well as cross-transmission between patients. In particular carbapenemase producing *Enterobacteriaceae* (CPE), are an emerging problem but the number of infections in the UK remain low. Increasing usage of broad spectrum antibiotics including carbapenems plays a significant role in the emergence of these resistant phenotypes.

Which children are at risk?

There are two main at risk groups. Children with immunosuppression for any cause e.g. post chemotherapy or on immunosuppressive treatment regimens and children with invasive medical devices e.g. catheters. Other at risk groups include children who have congenital gastrointestinal abnormalities that can reduce GI function such as necrotising enterocolitis or Hirschprung's disease and those receiving broad-spectrum antibiotics for other reasons e.g. children with CF. Travel from or recent hospitalisation in endemic regions such as Indian subcontinent, the Middle East or higher risk European countries will also add to the risk.

Colonisation or infection can also be acquired from the healthcare environment e.g. hospital wards, or from repeated surgical procedures; especially in those with premature birth and underdeveloped organs who require prolonged hospitalisation. Previous exposure to antibiotics, including beta-lactams such as third-generation cephalosporins and carbapenems or fluoroquinolones; and previous colonisation by a multidrug-resistant organism will also put patients in these age groups at a greater risk. Lastly contact with a known case of CRE infection or colonisation is an important risk factor.

Clinical syndromes

The most commonly encountered infections caused by CRE in any age group are hospital acquired infections such as blood stream infections, ventilated associated pneumonia, empyema, surgical wound and urinary tract infections. Carbapenem resistance accompanied by independent risk factors such as severity of infection i.e. septic shock, extremes of age (most of the data have been collected in adults) and other associated comorbidities (e.g. haemodialysis or cardiac disease) are directly proportional to higher mortality rates in CRE infections.

Resistance mechanisms in *Enterobacteriaceae*

Antimicrobial resistance in *Enterobacteriaceae* results from the expression of enzymatic (breakdown of antibiotic molecules) or non-enzymatic mechanisms. Non-enzymatic mechanisms involve induction of efflux pumps and down-regulation of outer membrane porins as a consequence of broad-spectrum antibiotic

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exposure. Resistance genes may be intrinsically expressed (chromosomal genes) or acquired. Chromosomally encoded genes such as *bla* in *Enterobacteriaceae* can be induced or fully derepressed through mutation leading to reduced susceptibility. Horizontal transfers of mobile genetic elements carrying resistance genes (beta-lactamases) mostly consist of plasmids. Since these plasmids generally carry multiple resistance determinants, a single plasmid conjugation may be sufficient to transfer resistance to multiple classes of antibiotics.

There are three main groups of beta-lactamases:

1) AmpC Type Beta-lactamases

AmpC beta-lactamases are chromosomally encoded in a number of clinically relevant *Enterobacteriaceae*, notably *Enterobacter* spp., *Citrobacter freundii* and *Serratia marcescens*. These enzymes are able to hydrolyse broad-spectrum cephalosporins and most penicillins. AmpC beta-lactamases can also weakly hydrolyse carbapenems and can appear like CPE usually in conjunction with down-regulated porins. Normally repressed, chromosomal AmpC enzymes can be induced through antibiotic exposure leading to ongoing expression of the enzyme. Some AmpC enzymes are located on transmissible plasmids and can appear in bacteria lacking a chromosomal AmpC gene such as *Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis*.

2) Extended Spectrum Beta-Lactamases (ESBLs)

ESBLs can confer bacterial resistance to beta-lactams including aztreonam, and most cephalosporins, but not to cephamycins or carbapenems. The most common ESBL genes can be found in the plasmids within *E. coli* and *Klebsiella*. They include SHV- (usually found in chromosome of *Klebsiella*), TEM- (usually found in *E. coli*) and CTX-M (found in both *Klebsiella* and *E. coli*) genes. SHVs are more common in Europe; TEMs are dominantly present in the USA while the CTX-Ms are being increasingly detected worldwide.

3) Carbapenemases

Carbapenemases are beta-lactamase enzymes with wide hydrolytic spectrum of activity against most beta-lactams including penicillins, cephalosporins and carbapenems. Some metallo-betalactamases have little activity on monobactams. The most commonly distributed carbapenemases include the following:

i. *K. pneumoniae* Carbapenemase (KPC):

This is a plasmid-encoded beta-lactamase originally described in *K. pneumoniae* in North America but now found worldwide in other *Enterobacteriaceae* such as *E. coli, Enterobacter cloacae* and *S. marcescens*. KPC enzymes have hydrolytic activity against extended spectrum cephalosporins, aztreonam and carbapenems.

ii. Imipenemase Metallo-betalactamase (IMP)

IMP gene was first found in *Pseudomonas aeruginosa and Acinetobacter baumanii.* It was later found in transferrable plasmids in *Enterobacteriaceae*. It is capable of hydrolysing all beta-lactams and carbapenems.

iii. Verona Integron-encoded Metallo-beta-lactamase (VIM).

It was first detected in *P. aeruginosa*, although also found widely disseminated in plasmid of *Klebsiella* spp., and *E. coli*. Its mechanism of action is similar to KPC.

iv. New Delhi Metallo-beta-lactamase (NDM).

A recently emerging carbapenemase detected in the chromosome of *A. baumanii*, but later found in plasmids within *Enterobacteriaceae*. Its mechanism of action is similar to IMP and VIM metallo-beta-lactamases.

v. Oxacillinase Type Carbapenemases (OXA-)

There are a number of OXA- enzymes and they possess a broad hydrolysing spectrum of activity against penicillin and carbapenems but excluding extended-spectrum cephalosporins and aztreonam. OXA-type beta-lactamases are common in *Acinetobacter* species, although OXA-48 has now been found in *Enterobacteriaceae*, mainly *K. pneumoniae* and *E. coli*.

Epidemiology of carbapenem resistant *Enterobacteriaceae*

Although epidemiological studies in children concerning CRE infections or colonisations are limited, there has been a noted rise globally. A five year look back study from 2007 to 2011 in a neonatal intensive care unit in Kolkata India revealed 14% of neonatal gram negative septicaemias were secondary to NDM-1 type *Enterobacteriaceae* (six cases of *E. coli*, six cases of *Klebsiella pneumonia* and two cases of other *Enterobacter* spp.).

The SMART (Study of Monitoring Antimicrobial Resistance Trend) surveillance programme collected data in children with CRE infections from 2002 to 2010 with five countries included from four continents: India, Israel, Spain, USA and Greece. India had the highest number of cases 39%, followed by Israel 29%, Spain 19%, USA 11% and Greece 3% respectively. Three major isolates found were *Enterobacter* spp. (highest number of cases), *K. pneumoniae* and *E. coli*. NDM, KPC and VIM were the most common phenotypes and more than half of the cases were isolated from neonatal or paediatric ITU. All NDM cases were from India, KPC cases were from the United States or Israel, and all VIM cases were from Europe.

According to WHO's global report on anti-microbial resistance, areas with the highest CRE prevalence are the Indian subcontinent (NDM); USA, Greece and Italy (KPC); Turkey and North Africa (OXA 48).

There has been a steady rise over the years in multi-drug resistant *K. pneumoniae* (resistant to third-generation cephalosporins, fluoroquinolones and aminoglycosides) in some European countries (Figure 1) with the potential for further spread of these organisms through-out Europe.

Limited published data on CRE are available in the UK. Data published by Public Health England on laboratory confirmed cases of CPE has revealed an epidemic rise in the numbers of KPC, OXA 48, NDM and VIM in the UK from 2003 to 2015 (Table 1). A European Survey of CPE (EuSCAPE) was carried out from November 2013 to April 2014 from 21 Sentinel UK laboratories. This showed that of 102 submitted carbapenem resistant *K. pneumoniae* and *E. coli* isolates, 32% were confirmed carbapenemase enzyme carriers. Of these, 94% were susceptible to colistin, 63% to gentamicin, 56% to tigecycline and 53% to amikacin; but resistant to all other antibiotics.

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