Multi-resistant Gram negative Enterobacteriaceae 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

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 sub-continent, 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 bloodstream 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
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 cephemycins 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-beta-lactamases 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. Imipenem Metallo-beta-lactamase (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 hydrolyzing 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 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 CRE 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 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.
Treatment

There is no conclusively proven evidence-based strategy. Whilst randomized controlled trials are lacking in children and adults, current approaches rely upon an understanding of the mechanisms of resistance combined with a working knowledge of the mechanism of action of the various antibiotic groups. Observational studies suggest that combination therapy (usually a carbapenem with polymixin or Tigecycline) is more effective than monotherapy with considerable reduction in mortality. Benefits of combination therapy will include reduction of initial inappropriate antimicrobial therapy, potential synergistic effects, and suppression of emerging resistance. However, in the paediatric population use of combination therapy may become challenging because of limitations in antibiotic licensing in these age

![Figure 1: Illustration of resistance and prevalence of invasive K. Pneumonia infections in four European countries by the European Antimicrobial Resistance Surveillance Network. Originally produced by the European Centre for Disease Prevention and Control (ECDC).](image)

UK laboratory confirmed cases of carabapenemase producing *Enterobacteriaceae* (CPE) 2003–2015; Courtesy of Public Health England

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Table 1

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groups. Additionally, side effect profile of broad spectrum antibiotics and complications such as Clostridium difficile infection should be taken into account.

Carbapenems
Carbapenems are often used in treatments in paediatric populations based on the available literature and experience of usage. However with increasing prevalence of carbapenem-resistant Enterobacteriaceae these agents can be rendered ineffective.

Polymyxins
Polymyxins including Colistin (Polymixin E) and Polymixin B are increasingly utilised following emergence of CRE. Polymyxins are rapidly bactericidal and have good activity on biofilms. However their use is limited due to their potential nephrotoxicity. Additionally there are challenges with bioavailability in certain tissue compartments e.g. lung parenchyma, as well as intrinsic resistance in Proteus spp. and Serratia spp. Colistin is currently viewed as last line antibiotic for CRE infections and therefore the emergence of MCR1 (The Mobilised Colistin Resistance Gene) is concerning.

Fosfomycin
Fosfomycin is usually active against most CREs. Intravenous forms have been used in combination with another antibiotic (to avoid risk of resistance) in adults. It is also licensed for use in children as an intravenous formulation.

Tigecycline
Tigecycline is a bacteriostatic broad-spectrum antimicrobial and active against majority of Enterobacteriaceae. It has been used as monotherapy or in combination with another agent in adults. There is an association with enamel hypoplasia and tooth discoloration (as a tetracycline) as well as the potential to cause severe diarrhoea and/or abdominal pains. It is not licensed for use in children and usage is limited although it has an increasing role in treating resistant Pseudomonas infections in children with cystic fibrosis.

Ceftazidime/avibactam
This is a novel non-beta-lactam beta-lactamase inhibitor combination product. It is licensed to use in complicated intra-abdominal infections, complicated urinary tract infections, hospital acquired and ventilator-associated pneumonia. The avibactam component inhibits Ambler class A (i.e. KPC and CTXM), class C (i.e. AmpC beta-lactamases), and some class D enzymes (i.e. OXA 48). It does not inhibit class B enzymes (metallo-beta-lactamases). It has no activity against gram positive organisms and anaerobes. It is safe to use in children.

Ceftolozane/tazobactam
This is a novel cephalosporin combined with a beta-lactamase inhibitor. It is mainly used as an anti-pseudomonal agent and is licensed for use in complicated intra-abdominal infections and complicated urinary tract infections. The addition of tazobactam to ceftolozane improves the spectrum of activity against resistant strains, including some of the Ambler class A, ESBL-producing organisms (i.e. CTX-M in E. coli and Klebsiella, SHV- in Klebsiella and TEM- in E. coli). It has limited action against CRE enzymes (does not inhibit NDM, KPC and OXA-type carbapenemases) with limited Gram positive activity and no known anaerobic activity. Its safety to use in children has not been established.

Infection prevention and control
Guidelines have been published on preventing the spread of multi-resistant Gram-negative bacteria. Eradication of these organisms is difficult due to gastrointestinal carriage.

Screening for multi-resistant gram negative bacteria
Generally, active screening rather than passive surveillance is recommended, particularly for high-risk specialties such as intensive care units. Screening using rectal and wound swabs is usually undertaken for patients at risk. This would include patients transferred from, or with a history of admission to, healthcare facilities with known endemic CRE in the preceding year. Advice on screening is usually based on local policies and varies across organisations.

Prevention of transmission
Where possible, single-room isolation should be provided for patients with multi-resistant Gram-negative infection/colonisation. Strict standard infection control and contact precautions should be utilised. Healthcare workers should wear gloves and gowns or aprons while caring for these patients.

Cleaning and the environment
Environmental reservoirs can play a role in the transmission of these bacteria. Cleaning is an important aspect for reducing cross-transmission. In healthcare environments, additional terminal disinfection of vacated areas with hypochlorite and hydrogen peroxide can be considered, particularly during outbreaks. Environmental screening can be performed when there is unexplained transmission in healthcare facilities.

FURTHER READING


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**Practice points**

- Emergence of CRE has become a major infection prevention and control challenge.
- Five major carbapenemases are: KPC, OXA-48, NDM, IMP and VIM.
- Limited data are available on the management of CRE related infections in children.
- No CRE outbreaks have yet been reported in UK based paediatric wards or hospitals.
- There are limitations to antibiotic usage due to licensing in paediatric age groups.
- Horizontal gene transfer is the major contributing factor in cross-transmission of resistance.