Multiresistant E.coli septicaemia: a review

Multiresistant E.coli infections are an important cause of gram negative septicaemia, especially in the elderly. These infections have steadily increased in the UK since 2003, both in hospital and in the community. They are resistant to many commonly used antibiotics and currently carbapenems are the only agents with reliable activity. **Drs Sharada Gudur, Nawaraj Subedi, Ray George** and **John Chessbrough** highlight the problem and discuss the management options.

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E.coli is a frequent bacterial pathogen causing urinary tract infections (UTIs), and is the second most common agent to cause bacteraemia[1]. Since 2003, there has been an increasingly rapid rise in E. coli infections with multiresistant strains in the UK in both hospitals and the community. This resistance to all the antibiotics commonly used in patients with UTIs and/or sepsis (fluroquinolones, trimethoprim, cephalosporins and co-amoxiclav) makes their treatment more difficult. This is due to the acquisition of multiple genes conferring resistance to antibiotics on mobile elements of DNA, which can be exchanged between bacteria. Genes coding for extended spectrum beta-lactamase enzymes are a found in multiresistant E. coli (MREC).

Beta lactamases are enzymes that open the beta lactam ring and inactivate the antibiotic[2]. Mutations may enlarge the active sites of these enzymes, allowing attack on third generation cephalosporins; hence, the term 'extended spectrum beta lactamases' (ESBL)[2]. Types of beta-lactamases[3] are:

> TEM/SHV – classical plasmid mediated enzymes with a narrow spectrum of activity, long known sources of resistance to ampicillin;
> ESBL – these are variants with successive mutations of the TEM and SHV enzymes, which confer an ability to attack a wider range of beta-lactams. Recently, the CTX-M series (so named as they preferentially hydrolyse and confer resistance to cefotaxime[4]) has rapidly grown in importance internationally. It is thought to have originated as a chromosomal beta-lactamase gene in a commensal group of enterobacteriaceae called kluyvera[5, 6]. E.coli expressing CTX-M15 is an outbreak clone, which is now widespread in the UK. It was initially described in Shrewsbury, Southampton and Ulster[7];
> Amp-C – classically found in Enterobacter and Citrobacter sp as an inducible gene located within the chromosome. This may also escape and transfer to E.coli;
> others – include BES/SFO TLA, OXA Beta lactamases

Earlier ESBLs were largely identified in Klebsiella species and were exclusively associated with hospitalised patients. But, ESBL-producing E.coli have been found in both community and hospital patients[4]. CTX-M ESBLs have supplanted TEM and SHV types as the predominant ESBLs in the UK. CTX-M15 enzyme is the most common among the isolates referred to antibiotic resistance monitoring and research laboratory[3].

Sensitivities to antibiotics

Most of the CTX-M producing E.coli were

multiresistant to fluoroquinolones, trimethoprim and to all beta lactams except carbapenems (imipenem, meropenem and ertapenem) and temocillin[3]. Most of them are susceptible to nitrofurantoin, which is only suitable for use in lower UTIs; and fosfomycin, which cannot be readily sourced in UK[7]. Aminoglycoside sensitivity is variable, but in our area (Preston/Chorley) most isolates are sensitive. This essentially means quinolones and third generation cephalosporins are no longer a reliable choice for gram negative sepsis for at-risk patients. Using gentamicin in such circumstances would not be unreasonable. A single dose of gentamicin, pending results, would provide 24 hours of adequate cover while avoiding excess toxicity, especially likely in elderly and frail patients who are most often already on multiple drugs for other co-morbidities. Prolonged (10–14 day) courses of gentamicin, however, are likely to be associated significant oto and renal toxicity.

In a surveillance report from the Health Protection Agency, screening of diarrhoea samples showed faecal carriage of ESBL-positive E.coli, both in hospital and the community. This builds up a reservoir of organisms that may cause UTIs in future[1]. Of the patients we see in our trust, those most often affected are over 60 (median age of patients in Lancashire teaching hospitals so far is 79 years) and women. Most had UTIs, but a significant minority had bacteraemia, often with UTI as the underlying focus.

Extent of the problem

Nationally there has been a year-on-year increase in numbers and rates of E.coli bacteraemia[1]. Since 2003 MREC has emerged as a common problem in our trust and now accounts for about three per cent of all urinary coliforms, but a much higher percentage when coliforms from elderly patients alone are analysed. This also accounted for 25 per cent of all E.coli bacteraemic episodes over last 12 months in our trust and is continuing to rise.

Problems in identification arise as ESBLs are heterogeneous. Clinical laboratories vary in their success in identifying ESBLs[1]. While determining exactly which ESBL is present in a particular strain is a job for a research laboratory, adopting simple screening tests is within the capacity of any clinical microbiology laboratory[8]. A survey of England laboratories has found that the ability to detect, report and investigate ESBL-producing E.coli was very patchy and not many centres had appropriate methods in place[1].

Risk factors

It is worth considering MREC in patients over the age of 60 with risk factors like recent hospital acquired infection with antibiotic exposure or history of other healthcare facility exposure, genitourinary pathology, accompanying co-morbidity (eg, cerebro-vascular accident, congestive cardia failure, renal failure, urinary catheter in-situ[9]).

Further research is needed to more fully define the risk factors for infection with ESBL producers and the extent of community acquired infection[1]. The extent of gut carriage of ESBL producers is

Case scenario

An elderly male patient presented to hospital complaining of visual hallucinations, confusion and tremors in both hands over the past few weeks. He had a background history of Parkinson's disease (PD), ischemic heart disease and osteoarthritis. He lived alone, was fully mobile and independent prior to admission.

On examination he was confused and agitated with resting tremors. He was haemodynamically stable. The systemic examination was normal apart from cogwheel rigidity from his PD. The patient was admitted into a rehabilitation unit with the diagnosis of worsening PD. On Day 21 of admission he deteriorated. He was pyrexial (temperature 39.4˚C) with rigors and drowsiness. General physical and systemic examination revealed no clear focus of sepsis. Investigations showed neutrophilic leucocytosis with raised inflammatory markers. His biochemical profile was normal as was his chest X-ray. Urine dipstick was positive for blood, leucocytes and nitrites. He was started on levofloxacin. Subsequently blood cultures grew E.coli resistant to levofloxacin, trimethoprim, cephalosporins and co-amoxiclav. He received a 10-day course of IV Ertapenem for this MREC infection. On day 52 of admission, patient became febrile again with no localising sign and MREC was isolated from urine culture. He was then discharged from hospital to enter a nursing home due to increasing problems with mobility.

Key points

- E.coli is an important cause of septicaemia in the elderly.
- The incidence has been on the rise since 2003.
- Resistant to commonly used antibiotics.
- Carbapenems are the only reliably effective antibiotics.

important, as it is recognised that prolonged carriage may occur following acquisition. Patients known to have had MREC infection on previous admissions should be considered likely to be at risk if readmitted.

Treatment

There are no randomised controlled trials of therapy for ESBL-producing E.coli infection. A poorer outcome is observed in serious infection when the initial choice of antibiotic has no activity against the infecting microbe[10]. To avoid this, an antibiotic with reliable activity should be selected when risk factors for MREC are present. In practice this means that for the patient with serious sepsis, the choice is between a carbapenem or possibly an aminoglycoside if local sensitivity data shows minimal resistance[11]. For less serious infection, such as UTI, nitrofurantoin may be adequate.

Prevention

Preventing spread is as important as treating for infections. It includes simple measures like barrier protection and hand decontamination before and after every patient contact[12,13]. The other important measure to control outbreak with these organisms is with cautious use of antibiotics in suspected UTIs in elderly patients as bacteriuria is common[14]. Antibiotics such as fluroquinolones, cephalosporins and Co-amoxyclav may promote gastrointestinal tract carriage and cause diarrhoea. In hospitals and nursing homes, isolation of colonised patients with diarrhoea should be considered.

Multidrugresistant E coli is isolated from an increasing number of cases, elderly patients in particular, making it an important cause of gram-negative septicaemia. The infection can be hospital or community acquired. The diagnosis is important as these organisms are resistant to several of the routinely used antibiotics. At present, carbapenems are the only antibacterial agents that are effective against the organisms.

Conflict of interest: none declared.

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