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Is it time to reconsider initial antibiotic treatment strategies for severe urinary tract infections in Europe?

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ABSTRACT

Until recently, most reported cases of bacteraemia caused by multidrug-resistant strains of Enterobacteriacae producing an extended-spectrum β-lactamase (ESBL) in Europe have been nosocomial in origin. However, increasing numbers of reports of community-acquired bacteraemia and urinary tract infection caused by ESBL-producing microorganisms suggest that the geographical origin of patients should be taken into account as a risk-factor for possible ESBL production. Early identification of patients at high-risk of infection with ESBL-producing microorganisms, based on their geographical origin and travel history, should help to optimise initial antibiotic treatment strategies for severe urinary tract infections in Europe.

Keywords Antibiotic therapy, bacteraemia, extended-spectrum β-lactamase, geographical origin, risk-factor, urinary tract infection

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Key features distinguishing the antibiotic resistance of Gram-negative bacteria from that of Gram-positive bacteria include the rapid spread of transmissible elements containing multiple antibiotic resistance genes, and the higher relative complexity of antibiotic resistance mechanisms. Extended-spectrum β-lactamases (ESBLs) are plasmid-encoded β-lactamases that confer significant resistance to all β-lactams except carbapenems on their Gram-negative hosts. A series of different enzymes with ESBL activity have been identified in the past decade [1,2]. Microorganisms producing ESBLs are multidrug-resistant and constitute a significant public health threat.

Until recently, ESBL-producing Enterobacteriaceae were considered to be exclusively nosocomial pathogens [3]. However, recent studies suggest that ESBLs are not restricted exclusively to nosocomial bacteria, but can also be found in strains causing urinary tract infection (UTI) and bacteraemia in individuals with no previous hospital contact [4]. Infection caused by ESBL-producing organisms may become an emerging problem in outpatient settings in various parts of the world. Indeed, during the past 3 years there have been reports from Spain, Israel, the UK, Canada and Tanzania of significant community-acquired UTI, bacteraemia or colonisation with ESBL-producing isolates of *Escherichia coli* [3]. Typically, patients initially develop UTI caused by CTX-M-producing strains of *E. coli*. In particular, *E. coli* strains belonging to groups B2 and D may exhibit a highly virulent phenotype, although some studies have associated antibiotic resistance with low-virulence phylogenetic groups because multidrug-resistant *E. coli* strains are commonly non-B2 group [6].

As an example of the difficulties that can be encountered, a female, aged 42 years, from an urban area in Lebanon was admitted to the Hôpital Necker-Enfant Malades (Paris, France) with acute fever. She had a recent medical history of abdominal pain, diarrhoea and fever, suggesting diverticulitis, and received an oral fluoroquinolone and metronidazole for 10 days. A computerised tomography scan of the abdomen revealed a heterogeneous hypodense lesion of the right kidney, consistent with an extensive

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pyelonephritis. Urine and blood were collected for microbiological cultures, and the patient received intravenous cefotaxime and gentamicin. Urine cultures yielded an *E. coli* isolate that was susceptible only to imipenem and amikacin. Tests with cefotaxime and clavulanate disks disclosed a double-synergy indicating the production of an ESBL. Therapy was switched to imipenem and amikacin for 2 weeks. The patient was discharged on day 21 and, 1 month later, was clinically and microbiologically cured.

A retrospective analysis of files to assess the impact of ESBLs at the same hospital revealed an ESBL prevalence among clinical isolates of 4.7% in 2004 and 5% in 2005, with *E. coli* representing 41% (2004) and 38% (2005) of these isolates. Moreover, the percentage of ESBL-producing microorganisms isolated within the first 48 h of hospitalisation, i.e., community-acquired, was 10% in 2004 and 6% in 2005, with *E. coli* representing 6% of these isolates. These findings highlight the spread of ESBL-producing Enterobacteriaceae in the community in France, and also the increased risk of inadequate antibiotic therapy when patients are referred from geographical areas with a high prevalence of ESBL-producing organisms.

There is considerable geographical heterogeneity in the occurrence of ESBLs throughout the world. The asynchrony in the emergence of these enzymes among different countries may be a consequence of differences in cephalosporin usage, different methods of detecting ESBL-producing bacteria, and disparities in terms of travel to and from regions with a high prevalence of ESBLs. As travel between Europe and neighbouring countries with high ESBL prevalence rates in Enterobacteriaceae is increasing, it can be anticipated that further spread of ESBLs may occur in the near future.

In support of this prediction, two recent reports from Lebanon [6,7] noted a clear decrease in the susceptibility of Enterobacteriaceae to all antibiotics in 1999–2001, and a continuous rising trend over a 5-year period (1997–2001) in the percentage of ESBL-producing isolates of *Klebsiella pneumoniae*. In the first study, ESBL-producing Enterobacteriaceae were isolated from patients, healthcare workers and healthy subjects, thereby indicating the extent of the spread of these microorganisms within the country. A study from Israel [8] reported that 13.7% of 80 isolates of Enterobacteriaceae from blood samples obtained at hospital admission produced an ESBL. A Spanish study observed a significant increase in the frequency of ESBL stool carriers (from 2.1% to 7.5%) between 2001 and 2002 [9]. A further study from Israel [11] of 311 non-hospitalised patients with community-acquired UTI, including 128 patients infected with EBSL-producing strains and 183 patients infected with non-EBSL producers, revealed that hospitalisation or antibiotic treatment in the preceding 3-month period, an age >60 years, diabetes, male gender (OR 2.47, 95% CI 1.22–5.01), infection with *Klebsiella pneumoniae*, and previous use of third-generation cephalosporins, second-generation cephalosporins, a fluoroquinolone or a penicillin, were all independent risk-factors for episodes of infection caused by ESBL-producing bacteria.

The findings described above, in addition to the reports in the literature, confirm that ESBL-producing Enterobacteriaceae are responsible for community-acquired infections in Europe. Early identification of high-risk patients, based on their geographical origin and travel history, should help to optimise initial antimicrobial therapy for severe UTIs in Europe. Production of ESBLs by *E. coli* in the community setting is an emerging problem that is still greatly underestimated. Considering the implications for public health that might result from the spread of organisms producing ESBLs in the community, enhanced surveillance efforts to monitor the spread of these pathogens are clearly required.

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