The Distribution of ESBL-Producing Enterobacteriaceae: Leicestershire UK Compared to Worldwide

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Introduction

Beta-lactam antibiotics are the most frequently used antibiotic worldwide, therefore, bacterial resistance has continued to rise since their introduction due to a permanent selective force for resistance mechanisms [1,2]. Extended-spectrum β-lactamases (ESBLs) are mainly plasmid-encoded enzymes that are able to inactivate a variety of β-lactam antibiotics, including penicillins, 2nd-, 3rd- and 4th-generation cephalosporins and monobactams (e.g. aztreonam) [3]. However, ESBLs are generally susceptible to clavulanic acid (a β-lactamase inhibitor), sulbactam and tazobactam [4]. There are two distinct classification systems for beta-lactamas: the Amerl molecular classification and the Bush–Jacoby–Medeiros functional classification. The protein homology of the beta-lactamas is used to determine the Amerl scheme of four classes [4]. The four classes can then be differentiated further; classes A, C and D are serine beta-lactamas and class B are metallo-beta-lactamas. In contrast, the Bush–Jacoby–Medeiros functional scheme takes advantage of the functional properties of the beta-lactamase enzymes to classify them, for example, their substrate and inhibitor profiles [4]. The Amerl Scheme shall be used from here onwards.

Clinically, the most important class A ESBLs include: TEM, SHV and CTX-M [5]. The highest diversification and quickest evolution is within the CTX-M family of class A. The most important class D beta-lactamase is the OXA-type. The TEM, SHV and OXA type ESBL enzymes originate from point mutations within the plasmid-mediated TEM-1, TEM-2, SHV-1 and OXA-10 enzymes. When first discovered in 1965, the TEM beta-lactamas substrate and inhibition profiles were comparable to SHV-1, for example, TEM-1 is only capable of hydrolyzing penicillins and first generation cephalosporins. Since 1965, the TEM beta-lactamas have evolved and diverged, variants now have increased activity against extended spectrum cephalosporins, for example TEM-3 [4]. The SHV beta-lactamas have been suggested to have originated from Klebsiella spp. Like the TEM beta lactamas, the SHV family has evolved from resistance to broad-spectrum penicillins such as ampicillin, tigecycline and piperacillin but not to the oxyimino substituted cephalosporins to conferring an extended spectrum resistance today [4]. ESBLs of the TEM and SHV-type were most frequently found in the 80’s and 90’s and are mainly associated with hospital outbreaks of Klebsiella pneumoniae [6].

To this date, there have been over 172 different CXT-M enzymes discovered, classified into five groups: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25, based on their amino acid composition [5]. Being part of the class A ESBLs, it would be assumed that CTX-M producing enzymes would be related to TEM and SHV groups. However, this is not the case. Each of the CTX-M groups presents a 94% amino acid homology within the group itself and 90% homology between the other CTX-M groups. The CTX-M family is unlike other ESBLs in that it includes a complex and non-homologous group of enzymes. It has been suggested by phylogenetic analysis that the CTX-M enzymes did not originate by mutations from plasmid mediated enzymes but through chromosomal mobilization of bla genes from the Klyuvera species through mobile genetic elements. Like the other ESBLs, after these genes had been incorporated, the CTX-M enzymes evolved through punctual mutations due to antibiotic selective pressure. This brought about the variants of CTX-Ms that can be seen today [5]. The OXA-type are ESBLs and are so named because of their oxacillin-hydrolyzing abilities [4].

OXAes are beta-lactamas that facilitate resistance to ampicillin, cephalothin, oxacillin and clavulacillin, however are resistant to the beta-lactamase inhibitor clavulanic acid and are generally encoded by plasmids. The first OXA ESBL is believed to have been discovered in Turkey, from P. aeruginosa isolates in a single hospital [4]. Here we will give a brief overview of the prevalence of ESBL-producing bacteria in the Leicestershire area of the UK and how the prevalence varies worldwide.

a) Epidemiology

b) Europe
Combined, these reports may indicate that the prevalence in Africa isolates from a urinary source varied from 1.5% to 22.8% [17]. In a recent study in Lebanon, it was found that 71.6% of ESBL-producing urinary tract infection isolates were of the CTX-M type, with TEM, SHV and OXA detected in ≤16% of isolates. Multiple ESBLs were also found in a number of isolates. Looking in to the CTX-M group further, we found that CTX-M-1 was present in 84.1% of isolates. We also found that CTX-M-producing isolates had a significant correlation with the plasmids IncI1/M, IncFII, IncFIA, IncN. Again multiple plasmids were common [8-14]. This is in correlation with what is found in the rest of the UK. Concerning the rest of Europe, different CTX-M subtypes are common in different countries. CTX-M-9 is common in Spain, whilst CTX-M-3 is common in Eastern Europe. Overall in Europe, the CTX-M-1 group (including CTX-M-15) is the most widespread and has been associated with isolates found in the community [4].

**United States of America**

It was estimated in 2001 that 5.3% of E.coli in America was ESBL-producing. A more recent study in 2009 in a cancer center revealed 9% of E.coli isolates were ESBL-producers.

**Asia and the Indian Subcontinent**

It has only been recently that we have begun to understand the degree to which ESBL-producing Enterobacteriaceae is effecting parts of Asia and the Indian subcontinent, and the incidence of ESBLs is continuing to rise [4]. In India specifically, three medical centers reported that 66% of third generation cephalosporin resistant Enterobacteriaceae harbored CTX-M-15. Ten other centers in India reported ESBL rates of 70% within Enterobacteriaceae [4].

**The Middle Eastern Countries**

Incidences of 26% for ESBL-producing Klebsiella pneumoniae isolates have been seen in Saudi Arabia, whereas a prevalence of 26.5% for E. coli and 43% for Klebsiella has been reported in Iran [15]. A different study in Iran reported that 42.1% of the E. coli isolates derived from patients with clinical symptoms of urinary tract infections were ESBL-producing [16].

**Africa**

In Tanzania, hospitals have described rates of ESBL-producing isolates in Klebsiella pneumoniae as high as 64%. An orphanage in Mali reported that 100% of the children carried ESBL-producing Enterobacteriaceae [4]. Likewise, in Madagascar, it was observed that 10% of non-hospitalised patients carried ESBLs. It has been suggested that poverty is an important risk factor for carriage of ESBLs [4]. A systematic search review that used Twenty-six studies (409215 isolates) from 13 African countries ESBL-producing isolates from a urinary source varied from 1.5% to 22.8% [17]. Combined, these reports may indicate that the prevalence in Africa may be increasing.

**Conclusion**

As can be seen here, there is substantial global variation in the incidence of antibiotic resistance. This variation has been linked to the usage of antibiotics. Some countries have been working hard to reduce their antibiotic consumption, whereas others have seen a rapid rise in usage. Despite the variation in antibiotic consumption and resistance rates, it is clear that antibiotic resistance is a concern worldwide.

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**References**

