Extended-Spectrum Beta-Lactamases: The End of Cephalosporins?

Raul Colodner PhD[1] and Raul Raz MD[2,3]

[1]Clinical Microbiology Laboratory and [2]Infectious Diseases Unit, HaEmek Medical Center, Afula, Israel
[3]Affiliated to Technion Faculty of Medicine, Haifa, Israel

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In the last two decades, third-generation cephalosporins have become an important tool in the treatment of severe infections. Unfortunately, extended spectrum β-lactamases, a heterogeneous group of plasmid-encoded enzymes, are now responsible for the resistance against penicillins, all cephalosporins (except cephamycins) and other monobactams [1]. Since the above-mentioned drugs were often found to show *in vitro* susceptibility but were not effective *in vivo*, it is strongly recommended today that ESBL-producing organisms be reported as resistant to all ESBL substrates [2]. From the β-lactam antibiotics, only susceptibility to carbapenems is retained. This type of antimicrobial resistance is now recognized worldwide [3–5]. The number of identified ESBL is growing so rapidly that a Web site tracks the number and properties delineating these enzymes [6].

Being under-diagnosed by conventional laboratory methods, the prevalence of ESBL may be underestimated. Furthermore, and much more worrisome, the lack of detection of this resistance mechanism at the level of the individual patient often leads to inappropriate antibiotic treatment.

Mostly found in *Klebsiella pneumoniae* and *Escherichia coli*, ESBL were also detected recently in *Klebsiella oxytoca, Proteus mirabilis*, Enterobacter spp., non-typhoid Salmonella species, other members of the Enterobacteriaceae, *Pseudomonas aeruginosa* and Acinetobacter spp. [7,8].

The first ESBL described were point mutations derived from both "classical" β-lactamases TEM and SHV families. In the last few years, however, new families of ESBL enzymes were discovered. CTX-M type, a group of enzymes with an increased activity against cefotaxime, has been widespread in Europe and other continents in the last few years [9]. OXA-type enzymes were predominantly found in *Pseudomonas aeruginosa* isolates from Turkey and France, and PER-type enzymes were isolated mainly in Turkey. In addition, newer enzymes not related to any of the above-mentioned groups have been isolated. Recently, VEB, GES, and KPC series of enzymes were described in multiresistant organisms such *P. aeruginosa* and *A. baumanii*. Some of these enzymes may hydrolyze carbapanems very efficiently – a very important finding in terms of future therapeutic alternatives.

In general, there is a considerable geographic difference in the prevalence of ESBL in different countries. Different enzymes differ in their ability to hydrolyze different antibiotic substrates and present different behavior in terms of laboratory detection. Moreover, different antimicrobial susceptibility patterns could be expected within the same country, and this should be considered when analyzing the ESBL phenomenon in a particular environment.

In their article published in this issue of *IMAJ*, Bishara et al. [10] propose that their data could be useful to empirically treat ESBL-caused infections in Israel. Their findings are an important contribution for the design of the local formulary, and more studies like this are required. However, other Israeli centers should compare these data with their own. In other words, given the wide geographic variation of ESBL enzymes observed in other countries, local surveillance in every Israeli center is recommended.

As mentioned above, the prevalence of ESBL is probably underestimated. Estimates of ESBL-producing isolates among Enterobacteriaceae range from a national average of 3% in the United States [11] to much higher numbers in Europe. In Europe, the prevalence of ESBL varies greatly from less than 1% in the Netherlands [12] to as much as 11.4% of *K. pneumoniae* isolates and 47.7% of *Enterobacter aerogenes* in some centers in France [13]. An international surveillance program demonstrated a global prevalence of 25% [14].

ESBL prevalence seems to be very high in other Mediterranean countries including Israel. In a Tel Aviv hospital, 42.5% of all cefuroxime-resistant Enterobacteriaceae were ESBL-producers [15]. Data gathered from all major hospitals in the country (Raul, Colodner, unpublished data) show an incidence of 10–40% among those *E. coli* and Klebsiella spp. causing hospital-acquired infections. Not limited to the hospital setting, ESBL-producing Enterobacteriaceae caused 5% of all community-acquired bacteremia in an 8 month period in the Negev region, as reported by Borer et al. [16]. In northern Israel, 1.25% of all gram-negative organisms causing community-acquired urinary tract infections during 1999 were reported to be ESBL producers [17], and these

ESBL = extended spectrum β-lactamases

figures are continuously growing. In an Israeli long-term care facility the overall prevalence of ESBL among *E. coli* and *K. pneumoniae* from urine was 25.6% [18]. In their present article, Bishara and colleagues report a prevalence of 32% and 10% for *K. pneumoniae* and *E. coli* respectively. These are very alarming figures, given the still predominant role of cephalosporins in the empiric treatment of gram-negative rod-caused infections. Moreover, it is possible that these numbers could be even higher, taking into consideration that Bishara and team used only one substrate (ceftazidime) for the ESBL detection – a method with reduced sensitivity leading to the possible missing of up to 29% of the present ESBL. The use of an additional substrate like cefotaxime raises the sensitivity of the method to 98% [19].

Several case-control studies have evaluated the risk factors for colonization or infection with ESBL-producing organisms in the hospitalized patient. Reported risk factors include the presence of intravascular catheters, emergency intra-abdominal surgery, gastrostomy or jejunostomy tube, gastrointestinal colonization, length of hospital or intensive care unit stay, prior antibiotics (including third-generation cephalosporins), prior nursing home stay, severity of illness, presence of a urinary catheter, and ventilatory assistance [20]. In general, it is well accepted that some third-generation cephalosporins are strong inducers for the appearance of ESBL outbreaks in hospitals and long-care facilities. Among them, ceftazidime has been reported to be the strongest inducer and its use should therefore be restricted to limit the possibility of development of ESBL-producing nosocomial strains. The risk factors for the acquirement of an infection due to ESBL-producing organisms in non-hospitalized patients include diabetes mellitus, previous hospital admission, previous use of cephalosporins, penicillins or fluoroquinolones, recurrent urinary tract infection, age over 60, and male gender [21].

The clinical significance of ESBL remains unclear. However, increased mortality was reported when patients infected with apparent susceptible ESBL-producing organisms were treated with cephalosporins [22]. ESBL-producing bacteria often show cross-resistance with other groups of antibiotics, like fluoroquinolones. The close relationship between ESBL production and quinolone resistance is particularly worrisome because the first reported instance of plasmid-mediated ciprofloxacin resistance was in an isolate of *K. pneumoniae* also possessing an ESBL. However, this phenomenon is still very rare [23].

Most ESBL are inhibited by clavulanic acid and tazobactam and, as already mentioned, this fact is used as a detection tool in the search for those enzymes in clinical specimens. However, the usefulness of compounds combining these inhibitory drugs with penicillins (like amoxicillin-clavulanate or piperacillin-tazobactam) in the treatment of infections due to ESBL-producing organisms remains unclear since failures have been reported [24].

Several studies have suggested that carbapenems are the best alternative for therapy of serious infections due to ESBL-producing Enterobacteriaceae. These compounds are highly stable to β-lactamase hydrolysis but are also very costly. In addition, plasmid-mediated carbapenemases have been reported from Japan [25]. Although extremely rare, this is a very scary finding: the possibility of a gram-negative bacterium hosting numerous plasmid-mediated resistance mechanisms like ESBL, AmpC and carbapenemases is no longer a fiction.

Bacterial resistance to antimicrobial treatment is emerging as one of the major public health threats of this century. The widespread use, and in some cases misuse, of antimicrobials in all healthcare settings over the past several decades has been cited as a contributing factor in the development of drug resistance in virtually all bacterial species. The widespread prevalence of ESBL and the increasing number of new enzymes could eventually spell the end of the cephalosporin era, leaving us with a very narrow formulary for severe infections.

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Correspondence: Dr. R. Colodner, Clinical Microbiology Laboratory, HaEmek Medical Center, Afula 18101, Israel.
Phone: (972-4) 649-4480
Fax: (972-4) 649-5428
email: colodner_ra@clalit.org.il