A Change in the Epidemiology of Infections Due to Extended-Spectrum $\beta$-Lactamase–Producing Organisms

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(See the article by Ben-Ami et al. on pages 925–34)

Extended-spectrum $\beta$-lactamases (ESBLs) form a heterogeneous group that share the property of hydrolytic activity against the oxyimino-$\beta$-lactams while remaining susceptible to inhibition by $\beta$-lactamase inhibitors, such as clavulanic acid. From a clinical point of view, they are important because they confer resistance to penicillins, aztreonam, and cephalosporins, and ESBL-producing organisms are typically also resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and quinolones [1].

Until recently, the main problem posed by ESBLs was related to nosocomial outbreaks caused by ESBL-producing Klebsiella species. These outbreaks are usually clonal, the strains are mainly spread through cross-transmission, and the risk factors are similar to those found for other multidrug-resistant nosocomial pathogens [2]. In Europe and the United States, most ESBL-producing Klebsiella isolates harbored enzymes belonging to the TEM and SHV families [3]. Detection of colonized patients by performing surveillance cultures within affected units, isolation precautions for colonized patients, and restriction of oxyimino-$\beta$-lactam use are frequently useful for the control of these outbreaks [1].

There is no evidence that hospital-acquired ESBL-producing klebsiellae are decreasing in importance—in fact, data from the Centers for Disease Control and Prevention show that 20.6% of Klebsiella pneumoniae isolates from United States intensive care units in 2003 were probable producers of ESBL [4]. This represented a 47% increase, compared with the preceding 5 years.

However, during the last few years, an impressive increase in the number of ESBL-producing Escherichia coli (and, less frequently, other Enterobacteriaceae) is being described in several parts of the world [5–8]. This emergent phenomenon shows some differences from the problem posed by Klebsiella species; many of these ESBL-producing E. coli are isolated from nonhospitalized patients [5–8], they may be less frequently clonally related (although some clonality has been found in the United Kingdom [7] and Canada [6]), and they most frequently produce CTX-M enzymes [5–8], a different family of ESBLs. (The CTX-M enzymes may also be found in Klebsiella and other species [3, 9]). Whether this emergent phenomenon originated within hospitals and is being transferred to the community or originated in the community and is being imported to hospitals is not clear; the increasingly blurred limits between hospitals and the community add a significant difficulty in assessing the origin of these organisms. Evidence that the problem originated in the community includes that the CTX-M enzymes derive from the chromosomally encoded enzymes found in some environmental bacteria, such as Kluyvera species [9], that colonization with isolates producing these enzymes has been found in farm animals [10, 11], and that some studies have found a significant proportion of colonized people in the community [12, 13]. Finally, Ben-Ami et al. [14], in this issue of Clinical Infectious Diseases, show that some patients with infections caused by ESBL-producing Enterobacteriaceae did not have any previous significant health care contact. Health care contact may indeed serve as a selecting mechanism for these isolates and for patients at greatest risk of infection.

In those areas where ESBL-producing Enterobacteriaceae are being isolated from nonhospitalized patients, the empirical treatment of serious community-acquired infections in which Enterobacteriaceae are potentially involved (mainly sepsis originating in the urinary tract, in intra-abdominal infections, or in polymicrobial...
soft-tissue infections) may need to be reconsidered. As Ben-Ami et al. [14] showed, 14% of non-nosocomial bloodstream infections due to Enterobacteriaceae in their hospital were caused by ESBL-producing organisms. Similar figures were recently found in Spain [15]. Thus, the identification of variables that could help to predict which patients are at higher risk of harboring one of these isolates is urgently needed. The study by Ben-Ami et al. [14] addressed this issue and found that nursing home residency and male sex were independent risk factors, but the model was only moderately predictive. Certainly, nursing home residency as a risk factor for colonization with ESBL-producing organisms has been well described in the past [16]. As Ben-Ami et al. [14] note, the situation is certainly complex, because the group of patients coming into the hospital who are at risk of carrying ESBL-producing organisms is heterogeneous, with their risk depending, not only on their previous exposures to health care facilities, but probably also on less well-described risk factors, especially for acquisition of the CTX-M type ESBLs. Further investigation of this, with larger numbers of patients with different epidemiological exposures and types of enzymes, is awaited.

Regarding empirical antimicrobial treatment for high-risk patients with serious infections, therapy with a carbapenem is recommended, because this class of drugs has been consistently found to be associated with better outcomes, compared with other agents [1, 17]. Another potential option for empirical treatment of presumed urinary sepsis is the use of an aminoglycoside (probably amikacin, because it is usually the aminoglycoside most active against ESBL-producing organisms), although this recommendation is dependent on local susceptibility patterns of ESBL-producing organisms. Clearly, prolonged aminoglycoside therapy is not recommended for elderly patients.

Another challenge for hospitals is the infection-control measures that should be implemented for patients harboring ESBL-producing isolates at admission to the hospital. In the study by Ben-Ami et al. [14], 11% of patients admitted to a medical ward had fecal carriage of ESBL-producing organisms. A relevant conclusion of that study is that patients with fecal carriage of an ESBL-producing organism of the Enterobacteriaceae family at admission are at increased risk of subsequent bacteremia due to a ceftazidime-resistant isolate of the same species [14]. Because no molecular analysis was performed, we do not know from this study whether the strain causing the bloodstream infection was the same that was previously colonizing the patient. Another problem is that fecal carriage was studied using plates supplemented with ceftriaxone (which would mainly detect CTX-M–producing isolates) and that subsequent bacteremic episodes were sought among ceftazidime-resistant isolates, which probably selected episodes caused by TEM- and SHV-producing isolates.

It seems impractical to implement routine surveillance of patients who are newly admitted to the hospital for fecal carriage of ESBL-producing organisms, but this may be open to debate. In a recent study of ESBL-producing *E. coli* isolated from hospitalized patients in Spain, CTX-M–producing isolates were clonally unrelated, with data suggesting that they might have been acquired before admission to the hospital [15]. In contrast, isolates producing TEM and SHV enzymes typically had an epidemic behavior [15]. However, some health care–related outbreaks caused by CTX-M–producing isolates have been reported [1]. Also, the dissemination of the genetic elements harboring these enzymes is potentially worrisome. For the moment, the use of standard hygiene precautions (particularly hand hygiene) and the controlled use of antimicrobials that might select for these organisms (mainly cephalosporins and fluoroquinolones) are the only measures that can be recommended for patients admitted to the hospital with a high risk of carriage of ESBL-producing organisms. On the other hand, contact isolation precautions should be implemented for patients colonized with ESBL-producing Enterobacteriaceae in the context of health care–related outbreaks of infection.

In conclusion, the present situation of ESBL-producing organisms is epidemiologically complex. Several species of the Enterobacteriaceae family, harboring different types of enzymes, are causing infections in patients in the hospital and outside of the hospital. Within this complexity, it seems that the emergence of Enterobacteriaceae (particularly *E. coli*) that produce CTX-M enzymes is a new and distinct phenomenon. Therefore, assumptions based on our previous knowledge of the behavior of ESBL-producing organisms might not be reliable. We need more data about the precise relationship between all of those variables that contribute to infection with ESBL-producing organisms, particularly in nonhospitalized patients, to better identify high-risk patients and avoid inappropriate or inadequate empirical antibiotic therapy. Finally, there is a clear need to investigate the epidemiological consequences of the influx of ESBL-producing organisms into the hospital in order to design adequate infection control measures. The study by Ben-Ami et al. [14] is another helpful step in this direction.

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**References**


