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# ESBL-producing Enterobacteriaceae, an Unnoticed Pandemic with Challenges in Clinical Practice, a mini-review

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## Abstract

Antimicrobial resistance in gram-negative bacilli is an ecological problem with a major impact on public health. Extended-spectrum β-lactamases (ESBLs) are enzymes that inactivate broad-spectrum antibiotics, penicillins, third and fourth generation cephalosporins. There are many factors associated with the global spread of ESBLs, such as the use of over-the-counter antibiotics, the food industry, travel abroad, and the lack of implementation of control strategies in hospitals and at the community level. Fecal carriers of ESBLs are increasingly commonly encountered in routine hospital settings as many hospitals have implemented rectal screening for ESBLs, however, the utility of this clinical practice and the routine isolation of patients carrying these bacteria has controversial benefits. There are challenges in selecting suitable patients for empirical therapy with carbapenems for the treatment of presumed severe ESBLs infections. Inappropriate empirical therapy is associated with high mortality in bloodstream infections. Carbapenems are the standard of care for severe invasive ESBL-E infections outside the urinary tract, however, overuse of carbapenems may lead to the emergence of carbapenem-resistant Enterobacterales. This mini review is intended to contribute to understanding about ESBLs as a global ecological problem, causing a considerable impact on health care services and posing enormous challenges in everyday antimicrobial therapy.

## Background

Beta-lactamases (BLs) enzymes are the main antimicrobial resistance mechanism of gram-negative bacilli[1]. Beta-lactam antibiotics are perhaps the most widely used antibiotics and therefore the most important in clinical practice[2]. Extended-spectrum β-lactamases (ESBLs) are enzymes that inactivate broad-spectrum antibiotics, penicillins, third and fourth generation cephalosporins (oxyimino-cephalosporins such as cefotaxime, ceftazidime, ceftriaxone, cefuroxime, cefepime), as well as monobactams. ESBLs do not degrade cefoxitin (cephamycins) or carbapenems (imipenem, meropenem, ertapenem, doripenem)[2].

ESBLs can be found in any gram-negative organism, but are most commonly found in *Escherichia coli* and *Klebsiella pneumoniae*. Most ESBLs are enzymes called SHV (sulfhydryl reagent variable), TEM (Temoniera) and CTX-M (cefotaxime-M)[3,4]. These are the most common ESBLs and belong to Ambler's structural class A[2]. Typically the ESBLs phenotype is defined by its characteristic inhibition by clavulanic acid[2,5].

## The Silent Pandemic, Global Spread Of Antimicrobial Resistance And Esbls

From a conceptual point of view, antimicrobial resistance (AMR) has been acknowledged as a pandemic(6-8), one that remains unnoticed, as many international efforts are required for its control. AMR is an ecological problem with a major impact on public health given the capacity of dissemination of resistance genes contained in plasmids, transposons, and integrons, which favors bacteria to acquire genes expressing ESBLs[9]. ESBL-E infections are a public health threat due to their ease of global dissemination, treatment costs and hospital screening costs, as well as the poor outcomes and mortality that bear severe infections[10, 11].

The first reports of ESBLs enzymes came from Europe, in Germany in 1985 when an SHV-type enzyme was described in Klebsiella ozaenae[12]. In South America, the first reports were back in 1989 in Argentina[13]. Initially, TEM- and SHV-type enzymes were the most prevalent. TEM and SHV ESBLs have been observed mainly in *Klebsiella* spp and *Enterobacter* spp and; they have spread mainly in hospitals settings[14]. On the other hand, CTX-M ESBLs observed mainly in *E. coli*, has spread both, in hospitals and at the community level[1, 15]. CTX-M enzyme, might be the dominant type of ESBL, has globalized and evolved towards a pandemic[16]. Particular attention has been drawn to the CTX-M-15-producing enzyme from ST131 *E. coli* clones, which also carries other resistance genes against other groups of antibiotics[17]. Nowadays, ESBL-E are found in both the hospital and community settings[18].

Global dissemination of ESBLs have affected mostly the tropical and subtropical regions of the world which are now considered endemic for ESBLs[15, 19]. A rapid and progressive increase in ESBL-E has been identified in healthy adults[20]. The ease of dissemination of various ESBL-encoding genes explains the community-level dissemination, causing an increasing global prevalence of fecal carriers of ESBL-E[14]. The highest prevalence rates of ESBL-E fecal carriage are in the Western Pacific, Eastern Mediterranean, and Southeast Asia[16]. Intestinal colonization by ESBL-E has been increasing in the last decades; the worldwide prevalence of ESBLs producing *E. coli* shows a trend of increasing annually; data show that ESBL-producing *E. coli* carriage among healthy individuals had a prevalence approaching to 30% in 2020[21]. There are many factors that contribute to the spread and increased prevalence of ESBLs, in South America there is also a high burden of ESBL-E that has been attributed to several factors such as poverty, hospital overcrowding, high patient/nurse ratios, poor hand hygiene in hospital settings, and over-the-counter antibiotics[19]. The lowest prevalence of fecal carriage has been reported in Europe[21], consequently, traveling abroad to tropical/subtropical regions is a risk factor for ESBL-E acquisition. Nevertheless, most colonized patients remain asymptomatic and the risk of developing an infection appears to be low15.

The spread of ESBL throughout the world has been favored by various factors: I) colonization among travelers due to human-to-human transmission[21]; II) sources of bacterial resistance in wastewater, especially in hospital wastewater. It's important to acknowledge that hospitals and clinics act as sources of AMR that can spread to the community [22, 23]; III) nursing homes at the community level, which serve as reservoirs of ESBLs in *E. coli and K. pneumoniae*[24]; IV) the use of antibiotics in the food industry and in veterinary medicine [25-28], including the use of antimicrobial agents in aquaculture for seafood production[29, 30] and; V) poor implementation of Antimicrobial stewardship programs in hospitals, which has proven utility in reducing the incidence of ESBL *E. coli* and ESBL *Klebsiella*[31].

## Controversies And Clinical Importance Of Esbl-E Fecal Carriers

As the dissemination of ESBLs is a worldwide phenomenon, it is increasingly common to find hospitalized patients being fecal carriers of ESBL-E[32]. In order to achieve optimal infection control to reduce the transmission of ESBL-E in hospitals, strategies for screening for ESBL-E colonization have been implemented. Fecal carriage screening to detect ESBL-E colonized patients has been controversial. Some evidence has shown that identification of colonized patients, for subsequent isolation, may contribute to prevent nosocomial transmission[33], however, this strategy also has proved to be highly costly[33], which may limit its widespread implementation in hospitals and clinics in low-income countries.

Identifying fecal carriers may also help to correctly assign empirical treatment with carbapenems when these patients develop an infection, especially in intensive care units and for patients with hematologic malignancies, as they might have increased risk of bloodstream infection (BSI) caused by the same bacteria colonizing the intestinal mucosa[34]. Contrariwise, there are conflicting reports regarding the benefit of ESBL-E screening on hospital admission, and an adapted empirical antibiotic therapy based on rectal swab results exhibits ambiguous clinical outcomes[35-37]. Therefore, realizing which patients are fecal carriers of ESBL-E poses challenges in the selection of empirical antimicrobial therapy, i.e., the identification of a ESBL-E fecal carriage might prompts physicians to prescribe empirical antimicrobial therapy with carbapenems, especially in intensive care units and immunosuppressed hematological patients at risk of BSI; but, this may lead to overuse of carbapenems and subsequently to the emergence of carbapenem-resistant Enterobacterales (CRE)[37]. Some efforts have been made to create predictive tools for ESBL-E

causing BSI in specific populations (solid organ transplant recipients) for guiding empirical therapy[38]. Interest has also grown in finding effective decontamination strategies like selective digestive decontamination (SDD) and fecal microbiota transplantation (FMT)[39].

## Treatment Approaches For Presumed Esbl-E Infections

Guidelines recommend nitrofurantoin and TMP-SMX as therapeutic options for the treatment of ESBL-E infections causing uncomplicated cystitis; aminoglycoside and oral fosfomycin (only for ESBL *E. coli*) are therapeutic alternatives. For the treatment of pyelonephritis, TMP-SMX, ciprofloxacin, or levofloxacin, as well as carbapenems, may be used. For infections outside of the urinary tract, the use of carbapenems is preferred[40]. Although ESBLs are strongly inhibited by clavulanic acid and tazobactam, this does not imply that in clinical practice antibiotics such as piperacillin-tazobactam have therapeutic utility, as has been shown in the MERINO trial (*Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible Escherichia coli and Klebsiella spp*)[41]. However, there is still some controversy regarding the usefulness of piperacillin/tazobactam for ESBL-E infections because in the MERINO trial there were inaccuracies in piperacillin/tazobactam antimicrobial susceptibility testing and the antibiotic was not administered in extended infusion[42]. Recent research had showed that if piperacillin/tazobactam is started empirically for a urinary tract infection or pyelonephritis (which later turns out to be caused by an ESBL-E on urine culture), continuing this same antibiotic could be reasonable if clinical improvement has occurred[43], however, the use of piperacillin/tazobactam is not currently recommended in infections caused by ESBL-E outside the urinary tract, and not even in an empirical manner (when there is a high clinical suspicion of ESBL-E causing infection)[40].

There is general agreement that carbapenems (meropenem, imipenem, ertapenem) are the standard of care for severe invasive ESBL-E infections outside the urinary tract[40,42]. In critically ill patients or those with hypoalbuminemia, meropenem or imipenem should be preferred. Ertapenem has high protein binding, so it should not be used in patients with serum albumin <2.5 g/dL[44]. Other carbapenem-sparing antimicrobial regimens such as Ceftazidime/avibactam, ceftolozane/tazobactam are more expensive [45] and are not available in all hospitals or clinics. Ceftolozane/tazobactam has good activity against ESBL-E infections[46]. Some experts suggest reserving the use of ceftolozane/tazobactam only for complicated urinary tract infection or sepsis due to *P. aeruginosa* and ESBL-E in geographical areas with high incidence of infections due to CRE[47]. Despite their utility in invasive ESBL infections and a possible role in sparing carbapenem exposure, recent guidelines advise against the use of the newer Beta-Lactam/Beta-Lactamase Inhibitors (ceftazidime-avibactam, ceftolozane-tazobactam) in ESBL-E infections, as these should be reserved for patients with CRE infections[40].

In everyday clinical practice, it is common to have a conundrum of when to start empirical treatment with carbapenems or when to start treatment with non-carbapenem antibiotics. Excessive use of carbapenems may pressure the appearance of CRE[37]. On the other hand, it has been reported that empirical treatment for ESBL-E causing BSI is only appropriate in 42%, also that 52% of deaths from ESBL-E causing BSI occur within the first 3 days from recognition of sepsis[48]; this is the same amount of time that usually takes to a conventional microbiology laboratory to identify the bacteria growing in blood cultures, meaning that accurate empirical treatment is crucial. The use of molecular diagnostic tests in positive blood cultures may facilitate a more timely and accurate prescription of antibiotics in BSI[49], but these tests are expensive and not widely available. Several studies have been carried out trying to create clinical prediction tools for ESBL-E infections by analyzing independent clinical risk factors of ESBL-E[50,51], among them, the one developed by Tumbarello et al[52]. Prediction scores are promising for clinical medical practice; however, these models cannot be generalized to all clinical settings. Therefore, validation of the prediction scores is required for each different local setting where they are intended to be applied[53].

## Conclusions

The characteristics of 21st century human society, with globalization, international commercial travel, the food industry, and many other social conditions specific to each region of the world, have favored the worldwide phenomenon of AMR. ESBLs are very problematic BLs. Better regulatory controls of the food industry, hospital and community antimicrobial stewardships implementation and policies to control self-prescription and over-the-counter antibiotics, are needed in all regions of the world in an effort to contain the increasing prevalence of ESBL-E. From a more pessimistic perspective, this is a neglected pandemic that is out of control and, it will continue to progress silently.

In the daily clinical practice in hospitals, we must advance, among other things, in: I) developing ESBL-E infection prediction scores adjusted to each local setting to correctly select patients with a higher clinical probability of ESBL-E infection to receive appropriate empirical antibiotic treatment; II) expand the use of molecular tests for rapid diagnosis, as these can improve the allocation of empirical treatment more quickly in BSI and; III) while colonization screening strategies are useful in isolating patients and controlling dissemination in the hospital

setting, further research is still required regarding strategies for decolonizing the intestinal mucosa and, in developing prediction scales for sepsis/BSI caused by the same colonizing bacteria in the intestinal mucosa, to adequately select empirical antibiotics in hospitalized fecal carriers, to prevent the overuse of carbapenems.

## Abbreviations

Beta-lactamases (BLs)

Extended-spectrum β-lactamases (ESBLs)

Sulfhydryl reagent variable (SHV)

Temoniera (TEM)

Cefotaxime-M (CTX-M)

Antimicrobial resistance (AMR)

ESBL-producing Enterobacterales (ESBL-E)

Bloodstream infection (BSI)

Carbapenem-resistant enterobacterales (CRE)

Selective digestive decontamination (SDD)

Fecal microbiota transplantation (FMT)

Bloodstream infection (BSI)

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