The Continuing Plague of Extended-spectrum β-lactamase–producing Enterobacteriaceae Infections

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KEYWORDS

• Gram-negative • MDROs • *Escherichia coli* • *Klebsiella pneumoniae* • *Proteus mirabilis*

KEY POINTS

- The continued spread of extended-spectrum β-lactamase (ESBL) infections is correlated with shifts in medical care.
- The overuse and misuse of prolonged 'prophylactic' courses of antimicrobials is a modifiable independent predictor for ESBL acquisition.
- Agriculture and food products might have an additional role in dissemination of ESBL-producing organisms in community settings.
- Emergence of a new class of ESBL enzymes, the CTX-Ms, might have resulted the epidemiologic evolution of human ESBL infections in community settings.
- Appropriate antimicrobial therapy is frequently delayed in patients with ESBL infections; rapid diagnostics and reliable clinical predicting tools could aid in reducing delays and might improve patient outcomes.

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INTRODUCTION

The incidence of infections caused by multidrug-resistant (MDR) Gram-negative bacilli pathogens, affecting humans in hospitals, outpatient health care facilities, and community settings, is continually growing worldwide.[1–3] The Infectious Diseases Society of America defined the "ESKAPE" pathogens as the pathogens that currently cause the majority of hospital infections and can effectively "escape" the effects of available therapeutics.[1] Among the ESKAPE pathogens are common Enterobacteriaceae (eg, *Klebsiella pneumoniae*, *Enterobacter* species, *and Escherichia coli*).[1] *Proteus mirabilis* is another enteric pathogen in which the rate of resistance to multiple antimicrobials is rising, more commonly outside of the United States.[4,5] Emergence of resistance to a wide range of antibiotics among the most common human pathogens,[6] namely, the Enterobacteriaceae, is hazardous, and it poses a huge burden on individual patients and the general public.[1,7,8]

THE EMERGENCE OF EXTENDED-SPECTRUM β-LACTAMASES

The incremental growth in resistance to β-lactam agents (eg, penicillins and cephalosporins) among Enterobacteriaceae is a worrisome trend. β-Lactams are among the oldest and safest therapeutics.[9,10] Given susceptible isolates, they are potent bacteriocidic agents.[11] In addition, well-controlled data on their clinical efficacy against Enterobacteriaceae are readily available because of their extended years of usage.[1,12] Owing to their safety, tolerability, potency, and (usually) low price, β-lactams are the most commonly prescribed drugs worldwide.[13] β-Lactams are used universally as first-line agents for many infectious clinical syndromes resulting from Enterobacteriaceae infections.[14,15]

The first report of a naturally occurring β-lactam hydrolyzing enzyme in *Escherichia coli* was published even before penicillin was marketed for use.[16] In 1960, the plasmid-mediated β-lactamase TEM was first reported from Greece.[17] Later, additional transmissible types of β-lactamases were identified, for example, SHV-1.[12] These β-lactamases confer resistance to penicillins and narrow-spectrum cephalosporins, but not to extended-spectrum penicillins or cephalosporins of advanced generations.[12] Soon thereafter, new broader spectrum β-lactam agents became widely used (eg, cephalosporins with oxymino side chain, cephamycins, carbapenems, and monobactam). Subsequently, new families of β-lactamases soon started to emerge.[18,19] One of the most epidemiologically 'successful' groups of such enzymes are the extended-spectrum β-lactamases (ESBLs).

The ESBLs are serine β-lactamases, characterized according to their biochemically functional Ambler classification as class A, and are therefore hydrolyzed by β-lactamase inhibitors such as clavulanate or tazobactam.[10] This feature constitutes the basis for the phenotypic diagnosis of ESBL-producing bacteria in many laboratories; measuring the zone of inhibition of the isolates in the presence and absence of a β-lactamase inhibitor (ie, the "ESBL test").[10] According to the functional Bush–Jacoby–Medeiros classification, ESBLs are classified under group 2be.[20,21]

ESBLs confer resistance to most β-lactam antibiotics, including third- and fourth-generation cephalosporins and monobactams, but not to carbapenems and cephamycins.[15,17,22] Although ESBL-producing Enterobacteriaceae hydrolyze penicillins, cephalosporins (excluding cephamycins) and monobactam, their degree of hydrolytic activity can vary greatly. This results in both diagnostic challenges and controversies pertaining to treatment efficacy of agents for which isolates are supposedly "susceptible."[23] It took several years before clinicians realized that treatment with β-lactams for an ESBL-producing strain, even when the strain is supposedly 'susceptible' (per