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Extended-Spectrum Beta-Lactamase Producing *Escherichia coli*: Increasing Incidence of a Resistant Pathogen

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Definitions:

Beta-lactam antimicrobials are characterized by having a four-membered cyclic amide (beta-lactam ring) as part of their chemical structure (Figure 1) [1]. This broad group includes the penicillins, cephalosporins, carbapenems, and monobactams [1]. All beta-lactams have a similar mechanism of action; they inhibit bacterial cell wall synthesis [1]. Resistance to beta-lactam antimicrobials may be mediated by several mechanisms. Among clinically important gram-negative bacteria, antimicrobial resistance is commonly the result of beta-lactamase production [2]. Beta-lactamases are enzymes capable of hydrolyzing beta-lactam antimicrobials, thereby inactivating them [2]. There are hundreds of different beta-lactamase enzymes which differ in terms of the specific beta-lactam antimicrobials they are able to inactivate [2]. Extended-spectrum beta-lactamases (ESBLs) are beta-lactamase enzymes capable of hydrolyzing extended-spectrum/third generation cephalosporins (e.g., ceftriaxone and/or ceftazidime) [2,3]. They do not hydrolyze carbapenems and are susceptible, in turn, to inhibition by conventional beta-lactamase inhibitors (clavulanate) [2,4]. ESBL-producing *Escherichia coli* typically demonstrate resistance to penicillins, cephalosporins (first, second, and third generation), and monobactams [2,4,5]. They remain susceptible to carbapenems and may or may not be susceptible to beta-lactam/beta-lactamase inhibitor combinations [2,4,5]. However, it is important to note that there are many different types of ESBL enzymes and the susceptibility profile of a given clinical isolate will depend on the specific enzyme present.

Clinical Disease

ESBL-producing *E. coli* are responsible for a similar spectrum of infections as non-ESBL-producers. They are an important cause of urinary infections, intra-abdominal infections, bacteremia, hospital-acquired/ventilator associated pneumonia, and wound infections [6,7]. Of concern, infections caused by ESBL-producing bacteria have been associated with adverse patient outcomes [8,9]. In a meta-analysis by Schwaber et al., bacteremia with an ESBL-producing organism was associated with increased mortality relative to bacteremia with a non-ESBL-producer (RR 1.85, 95% CI 1.39 to 2.47) [8]. These investigators also found a significantly increased delay in effective therapy for patients with bacteremia due to ESBL-producers relative to non-ESBL-producers (RR 5.56, 95% CI 2.94 to 10.51) [8].

Epidemiology

Infections caused by ESBL-producing *E. coli* are becoming increasingly common in Canada. In a recent antimicrobial surveillance study of bacterial isolates recovered from patients at Canadian hospitals (CANWARD), the proportion of

E. coli that produced an ESBL enzyme was found to increase from 3.4% in 2007 to 7.1% in 2011 [6]. Similarly, when evaluating *E. coli* isolates recovered from the blood of patients in the Calgary Health Region, Peirano et al. found an increase in the percentage of ESBL-producers over an 11 year period, from 0.3% in 2000 to 14% in 2010 [10]. ESBL-producing *E. coli* are also being recovered with increased frequency from patients in Manitoba. In a retrospective review of *E. coli* bloodstream isolates recovered at the Health Sciences Centre, the percentage that produce an ESBL-enzyme was found to increase from 2.5% in 2008 to 15.2% in 2015 (Figure 2). Increased bloodstream infections due to ESBL-producing *E. coli* have similarly been seen at other hospitals in Winnipeg (Figure 3). The most common ESBL-enzymes among *E. coli* in Canada currently are CTX-M-15 and CTX-M-14 [6,10].

Community-onset and community-acquired infections caused by ESBL producing *E. coli* are also becoming increasingly common [10-12]. In reviewing 34 ESBL-positive *E. coli* bloodstream isolates recovered at the Health Sciences Centre in 2015, at least 76.5% had onset of infection in the community (blood culture collected at an outpatient clinic, emergency room, or nursing station).

Laboratory Detection

E. coli isolates that have reduced susceptibility to third generation cephalosporins undergo additional testing for ESBL production. Diagnostic Services Manitoba (DSM) microbiology laboratories currently use the ESBL confirmatory test recommended by the Clinical and Laboratory Standards Institute [13]. Briefly, susceptibility of the isolate in question to cefotaxime and ceftazidime is evaluated by disk diffusion with and without the addition of clavulanic acid. ESBL production is confirmed by an increase in zone diameter of the isolate around a third-generation cephalosporin disk with clavulanic acid relative to the corresponding disk without the inhibitor (Figure 4). Isolates that demonstrate a positive phenotypic test for ESBL production have a comment added to the report clearly identifying the organism as an ESBL-producer. Note that ESBL-producers may still test susceptible to certain third generation cephalosporins (e.g., ceftazidime) depending on the specific enzyme.

Treatment Options

ESBL-producing *E. coli* are frequently resistant to antimicrobials from several different classes [5]. For serious infections caused by ESBL-producing *E. coli*, carbapenems (e.g., meropenem, ertapenem) are often regarded as the antimicrobials of choice [5]. Piperacillin-tazobactam may be an option if the isolate tests susceptible, particularly for less severely ill patients with a urinary focus of infection [14]. For the treatment of cystitis, many isolates remain susceptible to

nitrofurantoin and fosfomycin [15]. Trimethoprim-sulfamethoxazole and ciprofloxacin are also viable treatment options for the small subset of ESBL-producers that remain susceptible to these antimicrobials. The susceptibility profile of *E. coli* isolates (all isolates and the ceftriaxone-resistant subset) from patients at the Health Sciences Centre in 2015 is presented in Table 1 (N.B. many but not all of the ceftriaxone-resistant subset are ESBL-producers).

Key Points:

- Infections caused by ESBL-producing *E. coli* are becoming increasingly common.
- Treatment options for infections caused by ESBL-producing *E. coli* are limited. For serious infections, carbapenems are generally regarded as the antimicrobials of choice. For the treatment of cystitis, many isolates remain susceptible to nitrofurantoin and fosfomycin.

Figure 1. Chemical Structure of the Beta-Lactam Ring

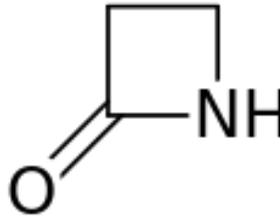


Figure 2. Percentage of *E. coli* Bloodstream Isolates that are ESBL-Producers (HSC Data)

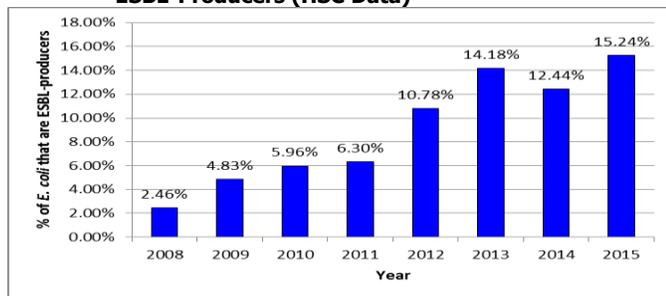


Figure 3. Percentage of *E. coli* Bloodstream Isolates that are ESBL-Producers (Data from all DSM Winnipeg Microbiology Laboratories)

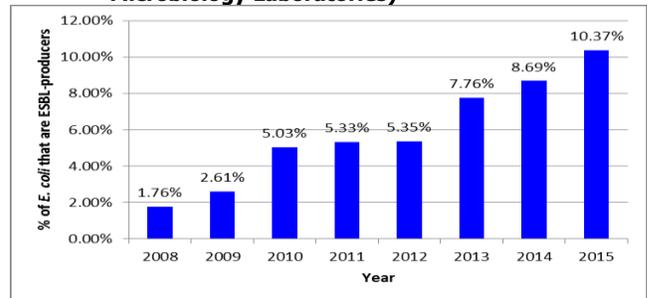


Figure 4. ESBL Confirmatory Test



An increase in zone diameter of more than 5 mm around a third-generation cephalosporin disk with clavulanic acid relative to the same disk without clavulanic acid confirms the presence of an ESBL enzyme. A positive test is shown here. *Image A:* ceftazidime disks with and without clavulanic acid. *Image B:* cefotaxime disks with and without clavulanic acid. The larger zone of inhibition for both disk pairs is seen around the disk that includes clavulanic acid.

Table 1. Susceptibility of *E. coli* isolates (all isolates and ceftriaxone-resistant subset) recovered from patients at the Health Sciences Centre in 2015

Organism (number tested): January through December 2015	Percent Susceptible												
	Ampicillin	Amoxicillin-Clavulanate	Piperacillin-Tazobactam	Cefazolin	Ceftriaxone	Ceftazidime	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim-Sulfamethoxazole	Nitrofurantoin
All <i>E. coli</i> isolates:													
<i>Escherichia coli</i> : all (2320)	44	76	97	58	89	95	100	100	90	87	76	65	96
<i>Escherichia coli</i> : bloodstream isolates (143)	31		94	43	78	94	100	99	87	75	61	49	
Ceftriaxone-Resistant <i>E. coli</i> isolates:													
<i>Escherichia coli</i> : ceftriaxone-resistant, all (280)	0	36	87	0	0	58	99	99	75	48	19	26	95
<i>Escherichia coli</i> : ceftriaxone-resistant, bloodstream isolates (32)	0		94	0	0	69	100	100	88	41	6	16	

 = Not tested, not routinely reported, or not recommended

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