The Utility of Admission Screening for the Prevention of Nosocomial Transmission of Extended-Spectrum β-Lactamase Producing *Enterobacteriaceae*

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science
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Abstract

**Background:** The efficacy of interventions to prevent in-hospital transmission of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) is poorly defined, particularly for admission screening.

**Methods:** Variability in ESBL-E infection control practices was evaluated with a survey of 15 hospitals. All ESBL-E positive clinical and screening specimens at 12 hospitals (6 screening and 6 non-screening) from 2005-2009 were included and defined as hospital-onset or community-onset using standard definitions. ESBL-E incidence and susceptibility were studied. Screening efficacy was evaluated with a negative binomial model, adjusting for study year and incidence of community-onset cases.

**Results:** Diverse practices in infection control for ESBL-E were found with 53.3% of hospitals utilizing admission screening. Overall incidence and hospital-onset cases increased 4-fold and 2-fold, respectively. Fluoroquinolone susceptibility for *E. coli* (12.8%) and *K. pneumoniae* (9.0%) was low. Hospital-onset cases were 49.1% lower in screening compared to non-screening hospitals (p<0.001).
Conclusion: Admission screening can reduce the incidence of hospital-onset ESBL-E cases.
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Chapter 1
The emergence of extended-spectrum β-lactamases

1 The challenge of treating infectious diseases in the modern era

1.1 The impact of antimicrobial agents in the 20th century.
At the beginning of the 20th century, before the discovery and clinical use of antimicrobials, the mortality rate attributable to infectious diseases was 797 deaths per 100,000 persons. Pneumonia, tuberculosis and diarrhea/enteritis were the most common causes of death in 1900 (14). Between 1900 and 1937, mortality rates decreased by 2.8% per year, corresponding to improvements in standards of living and medical care (2). The first antibiotics introduced for clinical use were sulfonamides in 1936, followed shortly thereafter by penicillin and streptomycin in the 1940’s (16). In the 15 years following the introduction of antibiotics (1937 – 1952), the mortality rate decreased from 283 deaths per 100,000 persons to 75 deaths per 100,000, with an average reduction of mortality of 8.2% per annum (2). Severe bacterial infections such as nosocomial pneumonia, bacterial endocarditis and bacterial meningitis had dramatic decreases in mortality rates: 30%, 75% and 60%, respectively (46).

By the end of the 20th century, the mortality rate associated with infectious diseases was 59 deaths per 100,000: a further decline of approximately 21% over the second half of the century (2). Unlike the beginning of the 20th century, none of the three most common causes of death (heart disease, cancer and stroke) in the beginning of the 21st century are due to infectious agents (14).

1.2 Emerging resistance in Enterobacteriaceae
Detection of antimicrobial resistance in Escherichia coli was reported even prior to the clinical introduction of penicillin (1). In this study, E. coli were found to possess enzymes (penicillinases) which were capable of inactivating penicillin. These enzymes were chromosomally expressed and thought to be present due to the selective pressure of soil organisms producing β-lactams in the environment (9). In 1965, a novel plasmid-mediated β-
lactamase was identified from a blood culture isolate in Greece. The enzyme was named TEM-1, after the patient (Temoneira) (23). Plasmid-mediated β-lactamases represented a significant shift enabling the spread of TEM-1 to other Enterobacteriaceae as well as other families (9).

Newer β-lactam antimicrobials developed, such as the 3rd generation cephalosporins in the 1980’s, were active despite the presence of narrow-spectrum β-lactamases. Corresponding to the introduction of newer agents was the discovery of further resistance. SHV-2 (sulphydryl variable) was the first enzyme exhibiting ‘extended-spectrum’ resistance, with only a 1 nucleotide mutation from the original narrow-spectrum SHV-1 β-lactamase (49, 83). In the past 3 decades, there has been a substantial proliferation of β-lactamases with over 1,000 different enzymes reported (10). β-lactamases are currently classified based on functional similarities of the enzyme (Bush-Jacoby classification scheme) or protein homology (Ambler classification system). For the purposes of this discussion, extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) will refer to Bush-Jacoby Class 2be or Ambler Class A (serine β-lactamases). These are plasmid-mediated enzymes capable of hydrolyzing penicillins, cephalosporins (1st, 2nd and 3rd generation) and aztreonam, but are inhibited by clavulanic acid. This group includes variants of TEM and SHV, as well as CTX-M (ceftaximase, isolated in Munich) (89). CTX-M β-lactamases are predominantly associated with community onset infections (99, 107), while TEM and SHV have traditionally been associated with hospital onset infections (83). In contrast, AmpC β-lactamases are categorized in the Ambler Class C group (Bush-Jacoby Class 1). They are primarily chromosomally mediated and identified in organisms such as Enterobacter spp., Citrobacter spp. and Serratia marcescens. Unlike the Ambler Class A ESBL’s, Ambler Class C enzymes are resistant to clavulanic acid and cefoxitin (47).

The prevalence of ESBL-E has increased worldwide (38, 41, 44). In highly endemic regions, such as India, 61.2% of E. coli and 46.8% of K. pneumoniae are ESBL-producers (44). Rates of ESBL-E in Canada are significantly lower, estimated at 4.1% of E. coli in a recent nationwide surveillance study. Ontario had one of the highest rates of ESBL-producing E. coli in Canada (6.3%) (113). Although currently low, surveillance from the past decade in the Calgary Health Region has identified a dramatic increase in ESBL-producing E. coli (0.1% to 14%) and K. pneumoniae (0.1% to 1.1%) (86, 92). The majority of ESBL-E recovered in Canada produced CTX-M β-lactamases (86, 90, 92, 113). Among E. coli, the CTX-M-15 ST131 clone
predominated, similar to worldwide reports of the dissemination of this successful clone (90, 92, 107).

1.3 Clinical challenges associated with ESBL-E

Severe ESBL-E infections (e.g. bacteremia) have been associated with a 1.9 fold increased mortality, 1.2 fold increased length of stay and 1.7 fold increased hospital costs (58, 58, 109). The primary issue associated with ESBL-E is multidrug resistance (MDR). β-lactams including 3rd generation cephalosporins (ceftriaxone or cefotaxime) or β-lactam/β-lactamase inhibitors (piperacillin-tazobactam) are the most common empirical antimicrobial agents used in hospitals for patients presenting with a severe infection or sepsis. These antimicrobial agents are ineffective in the treatment of severe ESBL-E infections, and inadequate antimicrobial therapy for these infections is considered an independent risk factor for mortality (45). This is particularly pertinent for the critically ill population in which every hour that the patient receives an inappropriate antibiotic is associated with an 7.6% increase in mortality (52).

MDR in ESBL-E also extends beyond the β-lactam class of antibiotics. ESBL-E are frequently resistant to alternative antibiotic classes such as fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole (97). With the changing epidemiology of ESBL-E from hospital associated infections (eg. TEM and SHV) to community associated infections (eg. CTX-M), the lack of active antimicrobial agents presents a further challenge (83, 98). Urinary tract infections represent the most common bacterial infection in adults with E. coli the predominant pathogen (72). The increasing prevalence of community acquired CTX-M E. coli creates treatment difficulties in outpatient clinics as there is often no oral option available.

Treatment options for ESBL-E are limited with carbapenems recommended as first line agents for severe infections (82). However, carbapenems are a class of antibiotics used as a last resort and increased use of this class may result in selective-pressure for the development and spread of carbapenem-resistant Enterobacteriaceae (CRE) (81).

1.4 Carbapenem-resistant Enterobacteriaceae

Carbapenem resistance due to the production of a carbapenemase enzyme was first identified in 1993 from a NMCa-producing Enterobacter cloacae (71). Since then, CRE have proliferated and disseminated worldwide (75). Similar to ESBL-E, carbapenemase encoding enzymes are plasmid
mediated and are categorized within Ambler Class A (Eg. *Klebsiella pneumoniae* carbapenemase, KPC), B (Eg. New-Delhi Metallo-β-lactamase-1, NDM-1) and D (Eg. Oxacillinase-48, OXA-48) (76, 102). Treatment options are limited for CRE since carbapenemases have the ability to hydrolyze penicillins, cephalosporins and carbapenems (102). In addition, the only active agents remaining are tigecycline and colistin as they also frequently carry multiple resistance genes for fluoroquinolones and aminoglycosides (13). Unfortunately, neither agent is ideal as colistin is associated with significant nephrotoxicity while tigecycline is associated with increased mortality and emerging resistance (11, 76, 115, 126).

The KPC enzyme is a serine β-lactamase and within the same Ambler class as the ESBL-E that will be discussed in this paper. It is primarily found in *K. pneumoniae* and less frequently in other *Enterobacteriaceae* (74). This enzyme was first identified in 1996 in North Carolina, USA. It has spread worldwide but is endemic in the northeastern USA, Israel and Greece (75). KPC’s have been sporadically recovered in Canada and have been associated with plasmids that are endemic in the USA (64).

In the last 5 years, there has been an alarmingly rapid dissemination of NDM-1-producing *Enterobacteriaceae* worldwide (75). Since being first isolated from a Swedish patient previously hospitalized in India in 2008 (127), the spread of NDM-1 has been associated with imported cases secondary to hospitalization or travel to an endemic area such as the Indian subcontinent (53, 96). Case reports of NDM-1-producing *Enterobacteriaceae* in Canada have also been imported (54, 70, 85, 88, 117). The prevalence of NDM-1 among *Enterobacteriaceae* in India is approximately 5-8% (76), and it appears to be pervasive in environmental reservoirs in India such as tap water and seepage water (122). In addition to its MDR profile, NDM-1 is carried on promiscuous plasmids that are able to transfer between *Enterobacteriaceae* as well as non-fermentative bacteria such as *Pseudomonas* spp., *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Achromobacter* spp., *Sutonella indologenes* and *Kingella denitrificans* (76, 122). NDM-1 has also been recovered from the highly successful and virulent clone of *E. coli* ST131 described previously (91).

In Canada, the prevalence of carbapenemase-producing *Enterobacteriaceae* is currently low (65). In this study of 20 hospitals across Canada in 2010, only 10 isolates out of 52,078 *Enterobacteriaceae* carried a carbapenemase gene (7 KPC, 2 NDM-1 and 1 SME-2). However,
continued surveillance and vigilance is required as evidenced by a recent outbreak of NDM-1-producing *K. pneumoniae* due to nosocomial transmission in a Canadian institution (60).

2 Preventing the transmission of ESBL-E

2.1 Epidemiology of *Enterobacteriaceae*

The family of *Enterobacteriaceae* are Gram negative bacilli that include hundreds of species including *Escherichia* spp. and *Klebsiella* spp (25). They can be found throughout the environment in soil, plants and water. These bacteria colonize the human gastrointestinal tract and are considered to be normal bacterial flora (25). ESBL-producing *Enterobacteriaceae* can also colonize the gastrointestinal tract without evidence of clinical infection. Patients can be colonized with ESBL-producing organisms for months to years (100, 123). Patient-to-patient transmission of ESBL-E occurs but *K. pneumoniae* appears to have a higher propensity to transmit than *E. coli* (32, 36). Transmission of these organisms between patients in a health-care facility is presumed to be secondary to direct or indirect contact. Direct contact refers acquisition of ESBL-E due to contact with fecally contaminated material. Indirect contact implies patient-to-patient transmission as a result of contaminated hands of health care workers (79).

An emerging modality of transmission of ESBL-E in hospitals is environmental reservoirs (12, 59). Sinks were found to be the environmental reservoir in our investigation of an outbreak of *Klebsiella oxytoca* at a Toronto area hospital. Ongoing transmission of ESBL-producing *K. oxytoca* occurred in the intensive care unit until intensified disinfection of sinks as well as structural sink modifications were implemented (59). Although sinks are traditionally associated with contamination due to *Pseudomonas aeruginosa* (22, 43), *Enterobacteriaceae* are increasingly recognized as potential and prolonged contaminants in sinks (60).

Specific patient populations are at increased risk for acquiring ESBL-E while admitted to hospital. Risk factors include a history of extended antibiotic courses (especially cephalosporins and fluoroquinololones), prolonged hospital stay, admission to the intensive care unit, underlying host factors (Eg. neutropenia, transplant recipients, neonates) and the presence of foreign devices (Eg. Foley catheter, central venous catheters, mechanical ventilators) (50, 77, 93-95). In non-hospitalized patients, risk-factors associated with ESBL-E included recent antibiotic use in the past 3 months, residence in a long-term care facility, recent hospitalization 3 months prior to a
positive culture, age ≥65 years, and male sex (3, 106). Due to the long carriage of ESBL-E in the gastrointestinal tract, community onset cases of ESBL-E infection were also associated with previous hospitalization in the preceding year (119). Although patients can present with ESBL-E cases in the community, the source of the ESBL-E in many cases can be from previous exposure to a health-care setting.

A history of travel is increasingly recognized as a risk-factor for becoming colonized (or infected) with MDR organisms (56). In highly endemic areas such as the Asia-Pacific region, 34% of *E. coli* and 22% of *K. pneumoniae* are ESBL-producers (44). As a result, in one study of Canadians travelling to Asia, 65% returned with stool positive for CTX-M-producing *E. coli*. International travel from all regions resulted in 14% of Canadian travelers returning to Canada with CTX-M-producing *E. coli* (87). As previously discussed, travel to endemic countries is also a potential risk factor for acquisition of CRE, particularly NDM-1-producing *Enterobacteriaceae* (53, 96).

2.2 Infection control interventions for ESBL-E in hospital

Routine practices are the basic fundamentals of infection control, regardless of the pathogen. One of the principles of routine practices is the proper and consistent practice of hand hygiene. Other components of routine practice include a risk assessment of potential exposures (Eg. blood, body fluids or non-intact skin), maintenance of the environment (Eg. cleaning and disinfection), administrative support (Eg. education, immunizations and staffing) and access to appropriate barrier equipment (80). The implementation of additional measures is pathogen and host dependent.

With respect to ESBL-E, there is no standardized practice for the use of additional precautions such as barrier precautions, isolation, cohorting and screening/surveillance. Recommendations by the Provincial Infectious Diseases Advisory Committee (PIDAC), which is an advisory committee to Public Health Ontario, suggest that infection control interventions for ESBL-E should be based on each hospital’s existing policy (79). Generalized standards are outlined by the Healthcare Infection Control Practices Advisory Committee (HICPAC), an advisory committee for the Centers for Disease Control and Prevention (CDC) (112). These recommendations are not specific for ESBL-E but include other MDR organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci
The limitation of generalized guidance is that the epidemiology of each organism, as well as transmissibility, is different. As a result, there was significant diversity in practices identified for ESBL-E in a survey of Ontario and Quebec hospitals. Approximately 22% of hospitals utilized contact precautions (gown and gloves) while a further 48% utilized contact precautions and isolation. The remainder of hospitals recommended no specific interventions for ESBL-E. Protocols for discontinuation of precautions for ESBL-E positive patients were equally as variable (67).

The emergence of CRE has prompted the release of specific infection control interventions to prevent the spread of these organisms by both the Public Health Agency of Canada (PHAC) and the CDC (15, 101). CRE is a significant concern to the public due to the lack of alternative antimicrobial agents available (75). They are also associated with poorer outcomes and mortality rates have been reported as high as 70% for invasive infections due to CRE (7, 66) However, the epidemiology of both ESBL-E and CRE should be similar as both are plasmid-mediated β-lactamases found in Enterobacteriaceae. The discordance in policies can be detrimental to the containment of both ESBL-E and CRE. As rates of ESBL-E increase, carbapenems will be relied upon as first-line empirical antibiotic treatment placing further selective pressure on the development of CRE (51).

2.3 Admission screening as an intervention to prevent nosocomial transmission of ESBL-E

Admission screening for ESBL-E refers to the practice of administering rectal swabs within 72 hours of admission to hospital to identify patients who are colonized with ESBL-E. For patients identified as ESBL-positive on admission, contact precautions and isolation can be implemented early in their hospital course, hopefully preventing the transmission of ESBL-E to other patients. Rectal colonization of ESBL-E can be an unrecognized reservoir of transmission, serving as a potential source of an outbreak (15, 112). In outbreaks of ESBL-E, admission screening as a component of the infection control interventions has been effective in aborting the outbreak (57, 63). Recent outbreaks of CRE have also included this intervention with success (5, 6, 110). The utility of admission screening in outbreaks of ESBL-E and CRE have been well described and included in the CRE guidelines published by the PHAC and CDC (15, 101). In non-outbreak situations, the indications are not clearly defined with a lack of well-designed prospective
studies, particularly for admission screening (28). In Canada, a previous Canadian Nosocomial Infection Surveillance Program (CNISP) survey reported that few hospitals (1/26) used admission screening for ESBL-E. The only centre performing admission screening limited the intervention to a transplant unit (78).

There are significant barriers to implementing routine screening within a hospital during periods without an active outbreak. The primary concern has been the effectiveness of this intervention in preventing nosocomial infection (27). In a prospective trial of admission screening to a transplant ward, 69 patients were found to be infected or colonized with an ESBL-producing organism. Analysis of these 69 isolates revealed 66 unique clones, and none of the patients who developed a clinical infection were due to patient-to-patient transmission. Based on this finding, the authors concluded that admission screening was ineffective in non-outbreak situations (27). However, 83% (57/69) of the isolates were Enterobacter spp. or Citrobacter spp. which confer resistance to β-lactams via chromosomally mediated AmpC. Due to this mechanism of resistance, these AmpC-producing organisms are less likely to be transmitted from patient-to-patient (47).

In institutions with a low prevalence of ESBL-E, screening may also be ineffective and inefficient (116). Only 0.45% of ICU admission rectal screens were positive for ESBL-E in this study of a non-endemic population. Of the imported cases who were admitted to the ICU with an ESBL-E clinical infection (19 patients), admission screens were negative for 9 of these patients (116). Screening populations at high risk for acquisition of ESBL-E has also been studied with limited success. During a 5-year study period, ESBL prevalence rates increased from 1.33% to 3.21%. Unfortunately, rectal screening also failed to identify more than half of patients that subsequently developed ESBL-E bloodstream infections. The targeted surveillance focused on the ICU, surgical wards, solid-organ transplant wards and hematology/oncology wards, suggesting screening a broader patient population would be required to identify the majority of carriers (103).

Contributing to the reported ineffectiveness of ESBL-E admission rectal screening is the test itself. Rectal swabs are limited by the quality of the specimen collected from the patient as well as the microbiology work-up for ESBL-E. Prospectively following patients with routine swabs over the course of admission identified patients who were intermittently colonized, which may
be secondary to the limits of detection of the rectal swab (123). In addition, implementing an admission screening program would require significant a financial commitment, estimated at $1,130,000 per year in a tertiary care hospital in Toronto (27). For non-endemic regions with low prevalence rates, this program may be cost inefficient as the vast majority of tests will be negative (116).

Despite the aforementioned issues, admission screening can potentially identify colonized patients on admission, enabling the implementation of infection control interventions, thereby reducing patient-to-patient transmission and lowering ESBL-E incidence. Although the frequency with which ESBL-E is transmitted from patient-to-patient within the healthcare setting is uncertain (and may vary for specific pathogens), it clearly does occur. In two related studies in the United States, person-to-person transmission of ESBL-producing *K. pneumoniae* and *E. coli* were documented in up to 52% and 13% of cases, respectively (32, 36). In a prospective study of admission screening for General Medicine patients in Israel, patients were screened on admission and every 2-3 days until discharge. Within a cohort of 167 patients, 21% who were initially negative on admission screen became colonized with ESBL-E during the course of their hospitalization (26). Finally, with the introduction of admission screening at a tertiary care facility in France, ESBL-E prevalence rates decreased from 5.5 cases per 1,000 patient-days to 1.9 cases per 1,000 patient days (118).

### 2.4 Predictive value of an ESBL-E admission screen on empirical antimicrobial therapy

A secondary benefit of ESBL-E admission screening would be the earlier recognition of patients colonized with ESBL-E. As outlined previously, patient outcomes for severe infections are significantly affected by the choice of antimicrobial agent and the time to administration of an effective antibiotic (45). Knowledge of the patient’s ESBL-E status may be beneficial in patients that subsequently develop an infection in hospital, as antibiotic coverage can be altered to cover ESBL-E. This has not been demonstrated in a prospective trial, but rates of progression from ESBL-E colonization to ESBL-E bloodstream infection have been reported between 8.5% to 15.4% (4, 103). With respect to clinical infections (from all sources), previously known colonized patients developed clinical ESBL-E infection in 25%-68% cases (17, 34).
3 Evaluation of ESBL-E admission screening in Toronto, Canada

There is a paucity of evidence with respect to the effectiveness of admission screening to prevent nosocomial ESBL-E transmission in non-outbreak acute care settings (28). Standardized guidelines have yet to be established for ESBL-E infection control interventions (79, 112).

We hypothesize that admission ESBL-E screening will reduce the rate of hospital-onset (nosocomial) ESBL-E cases in hospitals which screen for ESBL-E compared to hospitals which do not.

This study will attempt to describe the current state of ESBL-E in Toronto, Canada. The objectives of this study will be as follows:

1) To outline the current approach to infection control interventions of ESBL-E and CRE in Toronto.

2) To determine the incidence of ESBL-E in Toronto and analyze the susceptibility profiles of ESBL-E.

3) To study the effects of admission screening on hospital-onset ESBL-E by comparing rates of hospital-onset ESBL-E cases in hospitals which screen and hospitals which do not.
Chapter 2
Disparity in infection control practices for multidrug resistant Enterobacteriaceae

1 Prologue

Infection Prevention and Control (IPAC) programs are integral to patient care and safety in hospitals. The emergence of MDR organisms places further emphasis on implementing and maintaining effective measures to prevent the spread of MDR organisms in hospital. With the continued evolution of bacteria, hospitals are challenged by the changing epidemiology of infectious micro-organisms. ESBL-E and CRE are emerging MDR Enterobacteriaceae in which there is a lack of evidence for infection control interventions (28). With the worldwide dissemination of ESBL-E (75, 107), we sought to establish a baseline of infection control practices within Toronto hospitals in the absence of recommended guidelines for ESBL-E. The following Chapter was published ahead of print in the American Journal of Infection Control on February 24, 2012 (doi:10.1016/j.ajic.2011.11.008) (61).

2 Introduction

ESBL-E are globally endemic MDR organisms (38, 41, 44). CRE have also become a global concern. In Canada, the prevalence of ESBL-producing Escherichia coli is 4.1%, although higher rates have been reported from Ontario (6.3%) (113). Thus far, CRE are a rare occurrence in Canada but cases, as well as transmission, of both KPC and NDM-1 have been described (29, 54, 117).

Despite the urgency of this problem, there is uncertainty regarding the extent to which in-hospital transmission contributes to the overall incidence of ESBL-E compared to antibiotic use/overuse and/or community transmission (including potential food and water borne transmission) (31, 33). Without clear empiric evidence supporting specific infection control strategies, recommendations for ESBL-E are incorporated into general guidance on the control of resistant Gram negative organisms (111, 112). Although guidelines for the control of CRE
transmission have been issued by the CDC, PHAC, and others, it is not clear to what extent their recommendations have been implemented (13, 15, 39, 101).

We hypothesized that infection control practices for both ESBL-E and CRE vary widely between hospitals, even within a single healthcare system and a defined geographic area. To test this hypothesis, we conducted a survey of infection control practices for ESBL-E and CRE in hospitals in Toronto, Canada. Our results may have implications for the emergence of CRE in Canada, as a unified approach to CRE may be required to prevent or delay the emergence of CRE (31, 110).

3 Methods

As part of an ongoing study examining the incidence of ESBL-E colonization and infection in Toronto area hospitals, 15 hospitals participated in a survey to determine current infection control practices related to the control of ESBL-E and CRE (Appendix A). All academic hospitals participated, and community hospitals of varying sizes and geographic locations in Toronto agreed to participate. The survey gathered information on hospital characteristics and infection control practices including the use of active screening, contact precautions, isolation, cohorting and laboratory-based surveillance practices for ESBL-E and CRE identification (Appendix B). Contact precautions were defined as the use of gowns and gloves for patient contact. The survey was addressed to the professional most responsible for ESBL-E or CRE control at each institution. Research Ethics Board approval was obtained at all participating sites.

4 Results

Thirteen of 15 hospitals completed the survey between November 2010 and April 2011; two hospitals (C5 and C6) responded after the initial April 2011 deadline and completed the survey retrospectively. This was after the release of the PHAC guidance on control of CRE in Canadian healthcare settings in November 2010 (101). For academic hospitals (A1, A2, A3, A4, A5, A6), mean beds per hospital were 344 (range 136 – 460), mean admissions per year were 17,300 (range 4,531 – 26,317) and mean inpatient days per month were 10,655 (range 3,375 – 17,627). At community hospitals (C1, C2, C3, C4, C5, C6, C7, C8, C9), mean beds per hospital were 401 (range 208 – 703), mean admissions per year were 20,751 (range 11,713 – 45,285) and mean inpatient days per month were 10,618 (range 5,220 – 23,221). Respondents included infection
control professionals (8/15, 53%), infection control physicians (6/15, 41%), and a microbiologist (1/15, 7%).

While all hospitals described having written policies for Gram positive antibiotic resistant organisms (i.e. MRSA, VRE), fewer had policies for ESBL-E (67%, 10/15) or CRE (5/15, 33%) (Table 1). ESBL-E practices were based on: evidence (4 hospitals), local epidemiology (4 hospitals) or both (4 hospitals). The remaining hospitals based practices on peers (2 hospitals) or were unsure of their rationale (1 hospital). The rationale for CRE policies was not addressed as the recent release of Canadian guidelines afforded hospitals limited time to adjust their policies before responding to the survey.

**Table 1.** Infection control practices for ESBL–producing *Enterobacteriaceae* and carbapenem resistant *Enterobacteriaceae*.

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<tr>
<th></th>
<th>ESBL – E</th>
<th>CRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Academic (%)</td>
<td>Community (%)</td>
</tr>
<tr>
<td></td>
<td>N=6</td>
<td>N=9</td>
</tr>
<tr>
<td><strong>1. Written infection control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>policies</td>
<td>2 (33.3)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td><strong>2. Contact precautions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. All patients</td>
<td>3 (50.0)</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>b. Patients with increased risk of transmitting</td>
<td>3 (50.0)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td><strong>3. Private rooms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (33.3)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td><strong>4. Cohorting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 (83.3)</td>
<td>6 (66.7)</td>
</tr>
<tr>
<td><strong>5. Discontinuation of precautions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. After 1 negative specimen (from the original positive site)</td>
<td>1 (16.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>b. After 3 negative screens separated by 1 week</td>
<td>1 (16.7)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>c. Until discharge</td>
<td>4 (66.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>d. Not yet determined</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>6. Positives flagged in the clinical database</strong></td>
<td>2 (33.3)</td>
<td>6 (66.7)</td>
</tr>
<tr>
<td><strong>7. Admission screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. No screening</td>
<td>5 (83.3)</td>
<td>2 (22.2)</td>
</tr>
</tbody>
</table>
### Table 1: Infection Control Practices Surveyed

<table>
<thead>
<tr>
<th>Category</th>
<th>Hospital A2</th>
<th>Hospital B2</th>
<th>Hospital C2</th>
<th>Hospital D2</th>
<th>Hospital E2</th>
<th>Hospital F2</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Risk factor based screening</td>
<td>(16.7)</td>
<td>(55.6)</td>
<td>(40.0)</td>
<td>(33.3)</td>
<td>(44.4)</td>
<td>(40.0)</td>
</tr>
<tr>
<td>b. Universal screening</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>c. Not yet determined</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>d. Universal screening</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>e. Periodically on units with high incidence</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>f. Only in outbreak situations</td>
<td>5 (83.3)</td>
<td>6 (66.7)</td>
<td>11 (73.3)</td>
<td>4 (66.7)</td>
<td>1 (11.1)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>g. Not yet determined</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11.1)</td>
<td>1 (6.7)</td>
</tr>
</tbody>
</table>

Note: unless otherwise stated, the table refers to infected and colonized patients.

1. Hospital C7 utilized contact precautions and isolation for infected, but not colonized patients.
2. Hospital A2 cited point prevalence surveys periodically on all units and if a new colonized patient was identified.

Table 1 summarizes the infection control practices of hospitals surveyed. Eight hospitals initiated contact precautions for all identified ESBL-E patients, while 7 instituted precautions only for patients/situations thought to be a high risk for transmission. This was defined as fecal/urinary incontinence, diarrhea or draining wounds (4 hospitals), ICU patients (2 hospitals) or ICU patients with one of the aforementioned risk factors (1 hospital). Three methods of admission screening were reported: no screening, risk-factor based and universal. Among hospitals instituting screening, 7 of 8 were from the community. Risk factors used for screening by each hospital are listed in Table 2. International hospitalization was cited as a risk factor by all 6
hospitals. All 8 hospitals conducting screening utilized rectal swabs with some also performing urine culture (1/8) or wound (3/8) and invasive device (3/8) swabs.

**Table 2.** Risk factors considered in hospitals utilizing risk factor based admission screening.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A2</td>
</tr>
<tr>
<td>Admission to a unit or service</td>
<td>X¹</td>
</tr>
<tr>
<td>Previous ESBL-E or exposure to ESBL-E</td>
<td>X⁷</td>
</tr>
<tr>
<td>Previous hospitalization</td>
<td>X¹³</td>
</tr>
<tr>
<td>Previous hospitalization outside of Canada</td>
<td>X¹⁹</td>
</tr>
<tr>
<td>Resident of a long-term care facility or rehabilitation centre</td>
<td>X²⁵</td>
</tr>
<tr>
<td>Patient at increased risk of environmental contamination</td>
<td>X³¹</td>
</tr>
</tbody>
</table>

¹ ICU/NICU, medical ward or surgical ward with risk factors (hospitalized within 2 years, transferred from a nursing home or previous history of an antibiotic resistant organism)

² ICU

³ ICU or NICU

⁴ Incontinent of stool, diarrhea and draining wounds

The practice variation is only partially appreciated by reviewing individual control strategies separately; if one considers infection control ‘bundles’, the true extent of variation in practice for ESBL-E can be better appreciated as 8 different approaches were used at the 15 surveyed hospitals (Figure 1).
Figure 1. Diversity in infection control practices for ESBL-producing *Enterobacteriaceae* in Toronto, Canada.

Similarly, there were a broad range of practices for CRE. However, in general, hospitals appeared more likely to utilize contact precautions for all patients, isolate colonized/infected patients, and maintain precautions until discharge for patients with CRE as compared to ESBL-E (Table 1). Seven hospitals performing admission screening for ESBL-E also adopted admission screening for CRE, largely from the same specimens, while the remaining hospital (C6) performing screening for ESBL-E had yet to develop protocols for screening of CRE. Hospital A3 did not screen for ESBL-E but adopted CRE screening, although only for patients returning from endemic areas.

Routine point prevalent surveys were infrequently performed for either ESBL-E or CRE and were used primarily for case finding during identified outbreaks rather than for routine surveillance.
All laboratories serving the 15 surveyed hospitals tested for and reported the presence of KPC-producing *Enterobacteriaceae* and 14 of 15 reported the capability to identify NDM-1 producing *Enterobacteriaceae*.

5 Discussion

Despite growing concerns regarding the spread of ESBL (e.g. CTX-M-15 (21)), serine carbapenemases (e.g. KPC (74)) and metallo-β-lactamases (e.g. NDM-1 (53)), the optimal method to prevent nosocomial spread of these organisms is unknown. During outbreaks, infection control intervention ‘bundles’ and coordinated efforts at regional and national levels have been shown to be effective (110). However, less is known about the appropriate approach to controlling ESBL-E in non-outbreak settings (28), while the economic and resource implications of implementing such policies are considerable (20, 27).

Harris et al. suggested that in the absence of empiric evidence, decisions regarding the use of screening or contact precautions for the control of drug-resistant Gram negative bacteria should be based on the relative proportion of resistance attributable to person-to-person transmission compared to the proportion resulting from antibiotic use on an organism specific basis (33). Transmission of ESBL *K. pneumoniae* and *E. coli* has been demonstrated (32, 36, 83). While there is less experience with CRE, the expected mode of transmission should be similar as both are plasmid-encoded β-lactamases in *Enterobacteriaceae*. The primary difference between ESBL-E and CRE is clinical – for patients with severe infections due to CRE, available antibiotic therapy may be sub-optimal and mortality higher (66).

In a 2002 survey of Ontario hospitals, 70% of respondents required contact precautions for some or all patients colonized with ESBL-E and 48% required isolation as compared to 100% and 60% in this survey (67). Similarly, in a 2007 survey of Canadian hospitals, only 1 of 26 hospitals performed universal or risk-factor based screening for ESBL-E as compared to 53% in our survey (78). Although these surveys are not directly comparable, they demonstrate the potential for variation in infection control practices for ESBL-E across geographical regions while suggesting an evolution towards a more standardized approach, at least for contact precautions.

Point prevalence surveys are recommended by the CDC and PHAC, if an unrecognized case of CRE was discovered on retrospective review of microbiology records over the previous 6 – 12
months (15, 101). The variability seen in implementation of prevalence screens may be reflective of the relatively low incidence of CRE in Toronto (29, 113, 117). However, our survey demonstrates that adoption of these new guidelines is still in its early stages, with 2 community hospitals not planning to perform prevalence screening and 1 with protocols still to be determined.

Based on the clinical importance of MDR, particularly to carbapenems, it appears rational to take an early and coordinated approach to prevent CRE from becoming endemic (13, 110). Guidelines for CRE appear to be moving in this direction, as European guidelines recommend active surveillance, while Canadian and US guidelines suggest surveillance to detect asymptomatic patients when hospital transmission is identified (13, 15, 101). While our survey confirms that many hospitals are implementing these approaches, practices continue to vary widely and fall short of complete implementation at most facilities.

Our study has several limitations. It was conducted in a single geographic area and its generalizability may be limited. However, 15 diverse academic and community hospitals participated and the response rate was high. Our results demonstrate the potential for widespread practice variation even within a single healthcare system and geographic area when evidence and guidelines are lacking. The study results, particularly for CRE, must be interpreted cautiously as the study was conducted only shortly after Canadian guidance for CRE was released and hospitals may be in the process of developing or modifying their practices with respect to CRE. Finally, due to the low prevalence of CRE in Toronto, there is limited experience managing CRE infected/colonized patients from an infection control perspective and approaches are likely to change as institutions begin to face more clinical cases.

Although ESBL-E emerged over 25 years ago, a lack of evidence and evidence-based guidelines has led to a diverse range of infection control practices that may in part be responsible for the increasing incidence of ESBL-E. This is particularly concerning in the face of the threat of CRE and pan-drug resistant Gram negative bacteria. Guidance for CRE in Canada has recently been developed, but the document cites a lack of evidence in important areas such as active screening and discontinuation of contact precautions (101). Research is urgently needed to identify the optimal infection control approaches to control both ESBL-E and CRE transmission; while this evidence base evolves, it may be prudent to take a coordinated approach to controlling CRE.
Chapter 3
Decreased susceptibility to non-carbapenem antimicrobials in extended-spectrum \( \beta \)-lactamase producing \textit{Escherichia coli} and \textit{Klebsiella pneumoniae} in Toronto, Canada

1 Prologue

After establishing the diversity in practice for ESBL-E, the focus shifted to determining the burden of hospital-onset (nosocomial) ESBL-E in Toronto. Variation in practice may be partially responsible for an ongoing increase in ESBL-E incidence, as resistance that develops at hospitals where screening is not used may then enter the community or be transferred to other facilities that do screen; conversely, isolated hospitals that screen incur significant financial costs without the benefit of a broadly effective control program. In addition, the susceptibility profile of the ESBL-E was studied to determine the extent of non-susceptibility expressed by ESBL-E beyond \( \beta \)-lactamases. The results presented in the following Chapter were published ahead of print by Antimicrobial Agents and Chemotherapy on April 16, 2012 (doi:10.1128/AAC.00260-12) (62).

2 Introduction

MDR \textit{Enterobacteriaceae} have become a global concern. Increasing incidence of ESBL-E may be attributable, in part, to the successful clonal dissemination of the CTX-M-15 plasmid worldwide (21, 107). CRE are also emerging across the globe (30, 53, 74). Low prevalence rates (4.1\%) of ESBL-producing \textit{E. coli} have been described in Canada, predominantly due to CTX-M \( \beta \)-lactamases (113), and only sporadic cases of imported CRE have been reported (64, 113).

Infections due to ESBL-E are associated with increased morbidity, mortality, length of hospital stay and cost (58). Therapeutic alternatives for ESBL-E are limited with increasing resistance to non-\( \beta \)-lactam antibiotics (40, 41) resulting in a high likelihood of inappropriate initial empirical therapy (45). Carbapenems continue to be the treatment choice for severe infections due to ESBL-E (83), but resistance to these agents is also emerging (53, 74).
3 Methods

In light of these concerns regarding ESBL-E, a retrospective review of incidence rates and susceptibility profiles for ESBL-E was conducted in 11 large hospitals (five academic and six community) in Toronto, Canada from 2005 to 2009. Participating hospital characteristics have been previously described in Chapter 2. Hospital A6 was excluded as it is primarily an outpatient facility. Hospitals C5, C6 and C7 were excluded as they were unable to extract the required data from the hospital information system. All ESBL-producing Ambler Class A Escherichia coli and Klebsiella pneumoniae clinical isolates were included. Susceptibility testing was performed utilizing VITEK2 (bioMérieux, St. Laurent, Quebec) in 10 hospitals and Phoenix2 (Becton Dickenson, Mississauga, Ontario) in the remaining hospital. Isolates intermediate or resistant to a 3rd generation cephalosporin (cefpodoxime, ceftriaxone or ceftazidime) were confirmed as ESBL-E with double disk diffusion testing as per the 2009 Clinical and Laboratory Standards Institute (CLSI) standards (18). Mean incidence rates were calculated after each site was adjusted per 1,000 inpatients-days. Only the first clinical isolate from any one patient was included. Isolates were defined as nosocomial if they were identified from cultures obtained 3 or more days after admission to hospital in patients without a prior specimen yielding ESBL-E. Statistical analysis was performed utilizing the chi-squared test or the chi-squared test for trend, as well as a multivariate analysis (SAS 9.2, Cary, North Carolina).

4 Results

Overall incidence of ESBL-E per 1,000 inpatient-days increased as follows: 0.12 in 2005, 0.28 in 2006, 0.29 in 2007, 0.35 in 2008 and 0.47 in 2009. Incidence rates stratified by organism are shown in Figure 2. There were 1,994 ESBL-E isolates over the 5 years: 1,736 E. coli and 258 K. pneumoniae. Isolates were most commonly from a urinary source (74.1%), but also recovered from blood (12.0%), respiratory tract (5.2%), wound (4.6%), abscess/fluid (2.7%) and other sources (1.4%).
Figure 2. Overall and nosocomial incidence of ESBL-producing *Enterobacteriaceae* clinical isolates between 2005 – 2009.

Figures 3 and 4 describe the susceptibility profile of *E. coli* and *K. pneumoniae* over time. Declining susceptibility to piperacillin-tazobactam in *E. coli* (p<0.001) and *K. pneumoniae* (p=0.01) was observed. With respect to *E. coli*, susceptibility to non-β-lactam agents was stable except for improved susceptibility to aminoglycosides (gentamicin and amikacin p<0.001; tobramycin p=0.002). For *K. pneumoniae*, susceptibility rates decreased for ciprofloxacin (p<0.001) and nitrofurantoin (p<0.001) over the course of the study.
Figure 3. Susceptibility profile of ESBL-producing *Escherichia coli* recovered over a 5 year period.
Figure 4. Susceptibility profile of ESBL-producing *Klebsiella pneumoniae* recovered over a 5 year period.

Both of these agents (ciprofloxacin and nitrofurantoin) were also found to have reduced susceptibilities in non-nosocomial settings and community hospitals (Table 3). This study identified 3 carbapenem resistant *E. coli*: 1 in 2008 and 2 in 2009. Multivariate analysis adjusting for date of culture, nosocomial status and hospital type did not differ from the univariate analysis. In addition, resistance to ≥3 non-β-lactam antimicrobial classes occurred in 30.2% of *E. coli* and 40.5% of *K. pneumoniae*, and did not change significantly over time.
Table 3. Comparison of susceptibility rates in *Escherichia coli* and *Klebsiella pneumoniae* with respect to nosocomial status and hospital type.

<table>
<thead>
<tr>
<th></th>
<th>Nosocomial</th>
<th>Non-Nosocomial</th>
<th>P-value</th>
<th>Academic</th>
<th>Community</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>12.6% (76/601)</td>
<td>10.7% (106/995)</td>
<td>0.26</td>
<td>11.8% (109/927)</td>
<td>10.9% (73/669)</td>
<td>0.66</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>49.1% (295/601)</td>
<td>54.7% (525/960)</td>
<td>0.04</td>
<td>52.5% (487/927)</td>
<td>52.5% (333/634)</td>
<td>0.96</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>33.4% (189/566)</td>
<td>33.4% (292/874)</td>
<td>0.96</td>
<td>37.1% (343/925)</td>
<td>26.8% (138/515)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amikacin</td>
<td>95.8% (588/614)</td>
<td>98.0% (982/1002)</td>
<td>0.01</td>
<td>97.1% (898/925)</td>
<td>97.3% (672/691)</td>
<td>0.96</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>36.9% (222/601)</td>
<td>33.4% (319/955)</td>
<td>0.17</td>
<td>31.5% (292/925)</td>
<td>38.5% (243/631)</td>
<td>0.005</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>83.9% (468/558)</td>
<td>83.2% (754/906)</td>
<td>0.80</td>
<td>83.1% (765/921)</td>
<td>84.2% (457/543)</td>
<td>0.63</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>60.4% (252/417)</td>
<td>58.2% (291/500)</td>
<td>0.53</td>
<td>60.4% (460/762)</td>
<td>61.9% (86/139)</td>
<td>0.81</td>
</tr>
<tr>
<td>Meropenem</td>
<td>99.6% (272/273)</td>
<td>100.0% (447/447)</td>
<td>0.80</td>
<td>99.8% (515/516)</td>
<td>100.0% (204/204)</td>
<td>0.63</td>
</tr>
<tr>
<td>Imipenem</td>
<td>99.5% (366/368)</td>
<td>100.0% (517/517)</td>
<td>0.34</td>
<td>99.8% (482/483)</td>
<td>99.8% (401/402)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>K. pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>34.3% (59/172)</td>
<td>19.5% (15/77)</td>
<td>0.03</td>
<td>33.0% (65/197)</td>
<td>17.3% (9/52)</td>
<td>0.04</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>36.9% (62/168)</td>
<td>37.3% (28/75)</td>
<td>0.94</td>
<td>35.0% (69/197)</td>
<td>45.7% (21/46)</td>
<td>0.24</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>28.6% (46/161)</td>
<td>27.1% (19/70)</td>
<td>0.75</td>
<td>25.0% (49/196)</td>
<td>45.7% (16/35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Amikacin</td>
<td>92.9% (158/170)</td>
<td>97.4% (76/78)</td>
<td>0.95</td>
<td>94.9% (186/196)</td>
<td>92.3% (48/52)</td>
<td>0.70</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>22.0% (37/168)</td>
<td>16.0% (12/75)</td>
<td>0.36</td>
<td>21.3% (42/197)</td>
<td>15.2% (7/46)</td>
<td>0.47</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>29.1% (46/158)</td>
<td>7.4% (5/68)</td>
<td>&lt;.001</td>
<td>25.0% (49/196)</td>
<td>6.7% (2/30)</td>
<td>0.05</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>42.3% (60/142)</td>
<td>38.0% (19/50)</td>
<td>0.72</td>
<td>39.6% (72/182)</td>
<td>70.0% (7/10)</td>
<td>0.12</td>
</tr>
<tr>
<td>Meropenem</td>
<td>100.0% (73/73)</td>
<td>100.0% (35/35)</td>
<td>0.99</td>
<td>100.0% (83/83)</td>
<td>100.0% (25/25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Imipenem</td>
<td>100.0% (105/105)</td>
<td>100.0% (41/41)</td>
<td>0.99</td>
<td>100.0% (127/127)</td>
<td>100.0% (19/19)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

5 Discussion

We report a 4-fold increase in overall incidence and a 2-fold increase in nosocomial incidence of ESBL-E over a 5 year period in Toronto, Canada. Previous Canadian surveillance in 2000 identified 0.3% of *E. coli* and 0.7% of *K. pneumoniae* as ESBL-producers (68). Between 2007 – 2009, estimated national prevalence of ESBL-producing *E. coli* was reported to be 4.1%, and
stable over the 3 year study period (113). Concurrently, studies in Calgary have described increasing rates of ESBL-producing *K. pneumoniae* (0.1% to 1.1%) and *E. coli* (0.3% to 14%) in the past decade (86, 92). This underscores the importance of understanding local epidemiology, particularly for antimicrobial susceptibility, as local geographic changes may not be apparent in larger surveillance studies.

ESBL-E are associated with a delay in administration of active antimicrobial agents (120), a risk factor for mortality due to ESBL-E infection (45). Over the 5 year study, the majority of agents had stable susceptibility profiles. Aminoglycoside susceptibility improved among *E. coli*, although about one-third of isolates remained resistant to gentamicin and tobramycin. Reduced ciprofloxacin susceptibility was observed in *E. coli* (12.8%), similar to rates reported in Canada and worldwide (40-42, 113). However, *K. pneumoniae* susceptibility to ciprofloxacin (28 - 36%) were significantly higher in other Canadian centres than observed in this study by 2009 (9.0%) (86, 121). More concerning was the frequent occurrence of multi-class resistance among ESBL-E. Use of alternative agents such as piperacillin-tazobactam have been assessed (104), but *in vitro* susceptibility testing is required as decreasing susceptibility was observed over the course of this study. In patients with severe sepsis where ESBL-E is considered the probable organism, empirical treatment with carbapenems is warranted. However, dependence on carbapenems will increase the selective pressure for carbapenem resistance. Resistance was rare in Toronto in 2009, but several recent case reports suggest that CRE incidence may be increasing (54, 117).

Although for *K. pneumoniae* there was a trend towards reduced susceptibility among non-nosocomial isolates to ciprofloxacin, TMP-SMX and nitrofurantoin, there was no difference in the susceptibility to these oral agents in nosocomial and non-nosocomial *E. coli* isolates. Susceptibility profiles within academic and community institutions were generally indistinguishable. This may be due to the community introduction and spread of CTX-M β-lactamase-producing *E. coli* in Canada (90, 92, 98). The lack of difference between nosocomial and non-nosocomial isolates poses challenges in treatment of severe community acquired infections where ESBL-E is a potential pathogen.

There are limitations to this study as antimicrobial susceptibility testing was based on 2009 CLSI standards with higher cephalosporin breakpoints. Although both 3rd generation cephalosporin intermediate and resistant isolates were confirmed with phenotypic testing in this study, ESBL-E
with low level ceftazidime resistance could have been missed (37). As a result, ESBL-E incidence rates may have been underestimated. Also, given the retrospective nature of the study, nosocomial and non-nosocomial isolates were stratified by a pre-determined definition. Without correlation with the clinical history, these isolates are ‘probable’ rather than ‘confirmed’ nosocomial isolates.

Increasing rates of ESBL-E, especially in non-nosocomial patients, presents therapeutic challenges due to low susceptibility to non-β-lactam antimicrobials. In addition, non-nosocomial ESBL-E were associated with lower susceptibility to the limited oral agents remaining for ESBL-E, particularly *K. pneumoniae*. Fluoroquinolones should be avoided in patients with suspicion for an infection due to ESBL-E due to the very low rates of susceptibility to ciprofloxacin observed in both *E. coli* and *K. pneumoniae*. 
Chapter 4

Active admission screening to reduce nosocomial transmission of extended-spectrum $\beta$-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*

1 Prologue

In the analysis of ESBL-E in Toronto, we have established that there is currently no uniform approach to the infection control of ESBL-E in local academic and community hospitals. Over the same time period, both the incidence of total and nosocomial ESBL-E clinical isolates were rising. The increasing incidence of ESBL-E and the diversity in practice provided an opportunity to compare the effects of screening in one geographical centre. The results of the study below provide important information on the epidemiology of ESBL-E in Canadian hospitals and the utility of admission screening both for identifying patients at risk of infection with ESBL-E and for reducing the incidence of hospital-acquired ESBL-E infection. The study also provides preliminary evidence to guide those developing guidelines for the control of both ESBL-E and CRE given that the same organisms (i.e. *Enterobacteriaceae*) and resistance mechanisms (i.e. plasmid-encoded $\beta$-lactamases) are involved.

2 Introduction

The proliferation of antibiotic resistant organisms is emerging as a public health crisis (46). ESBL-E have disseminated throughout the world, largely due to the success of the CTX-M ST131 clone (21, 107). While carbapenems are recommended for treatment of severe ESBL-E infections (83), resistance has been increasingly reported worldwide (54, 64, 75). The rapidly changing epidemiology of MDR *Enterobacteriaceae* places increased emphasis on the prevention of transmission, though guidance for ESBL-E are only included in the general protocols for MDR Gram negative organisms (112). In the absence of guidelines for ESBL-E, infection control practices were found to be diverse (61, 67). Specifically with respect to admission rectal screening, 53% of hospitals implemented a form of admission screening,
including 6 performing risk-factor based screening and 2 utilizing universal admission screening (61).

Admission rectal screening as a means to control ESBL-E transmission continues to be controversial due to its associated costs and perceived ineffectiveness (20, 27). The variations in practice seen in Toronto area hospitals provided an opportunity to compare outcomes between hospitals that do and do not perform admission rectal screening for ESBL-E colonization. We hypothesized that hospitals conducting admission screening for ESBL-E colonization would have lower rates of hospital-associated ESBL-E transmission than hospitals that do not perform such screening.

3 Methods

3.1 Study sites and settings

This is a retrospective cohort study of 12 hospitals in Toronto, Canada, with data collected from 2005 to 2009. Baseline characteristics of the study hospitals are described in Table 4. Hospitals that did not perform admission screening included A1, A3, A4, A5, C1 and C8. Among screening hospitals, 4 conducted risk-factor based screening (A2, C3, C4, C5) and 2 conducted universal screening (C2, C9). Risk-factors incorporated into the screening protocols varied at each hospital, but a history of travel to an endemic country was considered in the 4 risk-factor based screening hospitals. Other risk factors included previous ESBL-E colonization/infection (A2), previous hospitalization (A2, C5), transfer from a long-term care facility (C5), admission to a specific ward (intensive care unit (A2, C3, C4, C5), neonatal intensive care unit (A2, C5), general medicine (A2) or general surgery (A2) or increased risk of environmental contamination such as diarrhea or draining wound (C3, C4)). Screening practices were in place at all screening hospitals prior to the start of the study period; no non-screening hospitals had previously had an admission screening program. All screening strategies were combined together for the analysis of screening hospitals as the total screens per 1,000 admissions were comparable. Hospitals A6, C6 and C7 were excluded as described in Chapter 3.3.
Table 4. Characteristics of non-screening and screening hospitals.

<table>
<thead>
<tr>
<th>Hospital Characteristics</th>
<th>Non-Screening Hospital (N=6)</th>
<th>Screening Hospital (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient Days per Month:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11,842</td>
<td>9,205</td>
</tr>
<tr>
<td>Median</td>
<td>11,437</td>
<td>9,327</td>
</tr>
<tr>
<td>Range</td>
<td>7,369 – 14,627</td>
<td>5,220 – 12,492</td>
</tr>
<tr>
<td><strong>Mean Admissions per Year:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19,605</td>
<td>18,567</td>
</tr>
<tr>
<td>Median</td>
<td>21,270</td>
<td>18,055</td>
</tr>
<tr>
<td>Range</td>
<td>9,882 – 26,317</td>
<td>13,188 – 25,875</td>
</tr>
<tr>
<td><strong>Mean Number of Beds:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>395</td>
<td>376</td>
</tr>
<tr>
<td>Median</td>
<td>421</td>
<td>382</td>
</tr>
<tr>
<td>Range</td>
<td>260 – 460</td>
<td>227 – 510</td>
</tr>
<tr>
<td><strong>Number of ESBL-E Clinical Isolates</strong></td>
<td>1,357</td>
<td>731</td>
</tr>
<tr>
<td><strong>Number of ESBL-E Bloodstream Infections</strong></td>
<td>175</td>
<td>77</td>
</tr>
<tr>
<td><strong>Number of Positive ESBL-E Rectal Screens</strong></td>
<td>N/A</td>
<td>1,887</td>
</tr>
</tbody>
</table>

**Infection Control Practices**

- **Contact Precautions for all ESBL-E**
  - 50.0% (3/6) for non-screening hospitals, 66.6% (4/6) for screening hospitals.
- **Private Room**
  - 33.3% (2/6) for non-screening hospitals, 66.6% (4/6) for screening hospitals.
- **Cohort**
  - 83.3% (5/6) for non-screening hospitals, 33.3% (2/6) for screening hospitals.
- **Precautions implemented for the duration of admission**
  - 50.0% (3/6) for non-screening hospitals, 16.6% (1/6) for screening hospitals.
- **ESBL-E flagged in electronic clinical database**
  - 33.3% (2/6) for non-screening hospitals, 66.6% (4/6) for screening hospitals.

**Clinical Isolates Positive for ESBL-Producing Organism**

- **Escherichia coli**
  - 80.3% (1,131) for non-screening hospitals, 87.4% (639) for screening hospitals.
- **Klebsiella pneumoniae**
  - 14.8% (209) for non-screening hospitals, 8.1% (59) for screening hospitals.
- **Klebsiella oxytoca**
  - 1.2% (17) for non-screening hospitals, 4.5% (33) for screening hospitals.

**Culture Site**

- **Urine**
  - 72.6% (985) for non-screening hospitals, 75.6% (553) for screening hospitals.
- **Blood**
  - 12.9% (175) for non-screening hospitals, 10.5% (77) for screening hospitals.
- **Respiratory**
  - 6.0% (81) for non-screening hospitals, 4.5% (33) for screening hospitals.
- **Wound**
  - 4.1% (56) for non-screening hospitals, 5.9% (43) for screening hospitals.
- **Abscess**
  - 3.3% (45) for non-screening hospitals, 1.8% (13) for screening hospitals.
- **Other**
  - 1.1% (15) for non-screening hospitals, 1.6% (12) for screening hospitals.

* The other 3 non-screening hospitals discontinued precautions after 1 negative specimen from the original site (1 hospital) or after 3 negative screening samples each separated by 1 week (2 hospitals). For the other 5 screening hospitals, 3 discontinued after 3 negative
screening samples each separated by 1 week and 2 had no written protocols established for discontinuation of precautions.

Although infection control strategies varied at all 12 hospitals, practices were largely similar between screening and non-screening hospitals although use of a private room for ESBL-E colonized/infected patients was more common in screening hospitals (4/6 vs. 2/6) (Table 4). Of note, although 2 screening and 3 non-screening hospitals did not routinely use contact precautions for all ESBL-E colonized/infected patients, contact precautions were used at all 5 hospitals for ESBL-E patients at increased risk of transmission (e.g. incontinent or draining wound).

3.2 Definitions

The primary analysis compared screening and non-screening hospitals, with incidence of hospital-onset ESBL-E per 1000 patient days as the primary outcome. Patients were considered to have hospital-onset ESBL-E if an ESBL-E was identified from a clinical specimen obtained >72 hours after admission without any prior cultures yielding ESBL-E. Clinical cultures positive within 72 hours of admission were defined as community-onset ESBL-E. The results of admission screening specimens were not used in this definition to ensure that the definitions could be applied identically at both screening and non-screening hospitals.

We also examined the ratio of hospital-onset cases to community-onset cases. This ratio provides a crude estimate of the number of nosocomial transmissions that resulted per ESBL-positive patient admitted. Finally, we also compared the incidence of hospital-onset bacteremias between screening and non-screening facilities and re-analyzed all of the data separately for E. coli and K. pneumoniae.

A secondary analysis was conducted focusing only on the 6 screening hospitals. For these hospitals, admission screening results allowed for re-classification of hospital-onset cases as follows: hospital-onset cases with negative admission screens (confirmed nosocomial cases); hospital-onset cases with positive admission screens (colonized on admission); and hospital-onset cases without an admission screen performed (probable nosocomial cases). This subgroup analysis allowed us to evaluate the accuracy of the hospital-onset classification in identifying hospital transmission of ESBL-E. It also allowed measurement of the undetected ratio, which is the ratio of patients identified only via admission screening compared to all patients identified as
ESBL-E positive via admission and/or clinical cultures. The undetected ratio estimates the proportion of patients that would not be identified as ESBL-E colonized in hospitals without an admission screening program (6).

3.3 Patient population

Adult patients with a clinical culture and/or an admission rectal screen positive for an Ambler Class A ESBL-producing *Escherichia coli, Klebsiella pneumoniae* and *Klebsiella oxytoca* were included. Only the first clinical isolate and admission screen for each patient was included.

3.4 Microbiology

Clinical isolates were worked-up utilizing conventional microbiology techniques. Admission screens were plated onto MacConkey cefpodoxime (2µg/mL) agar. Clinical isolates intermediate or resistant to a 3rd generation cephalosporin (cefpodoxime, ceftriaxone or ceftazidime) or colonies with growth on the MacConkey cefpodoxime agar were confirmed as ESBL-producers with the double disk diffusion test (ceftriaxone, ceftazidime and aztreonam plus/minus clavulanic acid and cefoxitin) (18).

3.5 Statistics

Data were exported from the laboratory informatics system of all hospitals, merged and stored in a Microsoft Excel 2007 (Redmond, Washington) database. Analysis was conducted using SAS Version 9.2 (Cary, North Carolina). Crude case numbers at all facilities were adjusted for patients days and incidence rates presented as cases per 1000 inpatient days.

For the primary analysis comparing the incidence of hospital-onset ESBL-E between screening and non-screening hospitals, a negative binomial model was developed with the number of hospital-onset ESBL-E cases per facility as the outcome, offset by the natural logarithm of patient days. The impact of screening strategy was evaluated using the model after adjustment for the year of data collection and incidence of community-onset cases.
4 Results

4.1 Hospital characteristics

Over the 5 year study period, there were 3,975 patients admitted with an ESBL-E clinical culture (2,088) or admission rectal screen (1,887). Table 4 describes the characteristics of screening and non-screening hospitals. The median rate of admission screening at the 6 screening hospitals was 550 per 1000 admissions (range: 266-872).

4.2 Primary analysis – comparison of hospital-onset rates between non-screening and screening hospitals

In the first year of the study (2005), the incidence of hospital-onset cases was higher at non-screening hospitals as compared to screening hospitals (0.098 vs. 0.034 per 1,000 inpatient days). This difference was apparent in all study years, although the incidence at both non-screening and screening hospitals rose over time (Figure 5). By 2009, the incidence of hospital-onset ESBL-E in non-screening and screening hospitals was 0.184 vs. 0.097 per 1,000 inpatient days. This effect was seen for both E. coli (2005: 0.073 vs. 0.031 per 1,000 inpatient days; 2009: 0.14 vs. 0.069 per 1,000 inpatient days) and K. pneumoniae (2005: 0.025 vs. 0.003 per 1,000 inpatient days; 2009: 0.044 vs. 0.019 per 1,000 inpatient days). In contrast, the rate of community-onset ESBL-E was similar in screening and non-screening institutions throughout the study period (Figure 6), and for both organisms. The hospital-onset to community-onset ratio was higher for the non-screening hospitals (0.88 vs. 0.45). This effect was seen when stratified by organism as well: E. coli (0.74 vs. 0.39) and K. pneumoniae (2.26 vs. 1.76).

In the negative binomial model, screening hospitals had a 49.1% (p<0.001) reduction in hospital-onset cases compared to non-screening hospitals.
Figure 5. Incidence of hospital-onset cases of ESBL-producing *Enterobacteriaceae* in non-screening compared to screening hospitals.
Figure 6. Incidence of community-onset cases of ESBL-producing *Enterobacteriaceae* in non-screening compared to screening hospitals.

Analysis of hospital-onset bloodstream infections also demonstrated higher rates for non-screening hospitals as compared to screening hospitals (0.02 vs. 0.006 per 1,000 inpatient days) (Figure 7). Total incidence of bloodstream infections is presented in Table 4.
Figure 7. Incidence of hospital-onset ESBL-producing *Enterobacteriaceae* bacteremia in non-screening compared to screening hospitals.

4.3 Secondary analysis – evaluation of screening hospitals

Both the absolute number of positive admission screens for ESBL-E and the proportion of screens that were positive increased over the 5 year study period (Figure 8). At the 6 screening hospitals, total positive screens per year rose from 122 (1.3 per 1,000 admissions) in 2005 to 765 (6.9 per 1,000 admissions) in 2009.
*Only includes Hospitals A2, C5 and C9 as the total number of annual ESBL-E rectal screens from all years were unavailable at the other 3 screening hospitals.

**Figure 8.** Incidence and percentage of positive ESBL-producing *Enterobacteriaceae* admission rectal screens.

The percentage of patients (14-22%) with ESBL-positive rectal screen on admission and a concurrent or subsequent ESBL-E clinical isolate was stable (Table 5). The undetected ratio in screening hospitals was 72.2% (*E. coli* = 73.6% and *K. pneumoniae* = 64.4%) and stable across the 5 year study. For those with a positive admission screen and no clinical isolate within 72 hours of admission, 5.1% (113/2235) subsequently had a clinical isolate (median = 11 days after admission, range = 4 – 137 days). Six patients (0.3%) developed a bloodstream infection after a positive admission ESBL screen (median = 10.5 days after admission, range = 4 – 27 days).
Table 5. Distribution of patients with positive admission ESBL-producing *Enterobacteriaceae* rectal screening.

<table>
<thead>
<tr>
<th>Year</th>
<th>% Colonized (with no concurrent or subsequent clinical culture)</th>
<th>% with subsequent isolate &gt;72 hours after admission</th>
<th>% with concurrent non-nosocomial isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 (n=122)</td>
<td>82.8%</td>
<td>5.7%</td>
<td>11.5%</td>
</tr>
<tr>
<td>2006 (n=341)</td>
<td>78.3%</td>
<td>9.4%</td>
<td>12.3%</td>
</tr>
<tr>
<td>2007 (n=387)</td>
<td>85.8%</td>
<td>3.6%</td>
<td>10.6%</td>
</tr>
<tr>
<td>2008 (n=620)</td>
<td>85.0%</td>
<td>4.7%</td>
<td>10.3%</td>
</tr>
<tr>
<td>2009 (n=675)</td>
<td>86.3%</td>
<td>4.1%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Total (n=2235)</td>
<td>84.4%</td>
<td>5.1%</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

Table 6 analyzes the screening status of all patients with an ESBL-E clinical culture admitted to a hospital performing admission screening. In these hospitals, there were 79 patients with a confirmed nosocomial isolate, including 8 bloodstream infections, distributed over the course of the study. Positive clinical cultures were identified within this group a median of 27 days after admission (range=4–148 days) while confirmed nosocomial bloodstream infections occurred a median of 26 days after admission (range=4–37 days). At the 6 screening hospitals, 46.5% of isolates defined in the primary analysis as hospital-onset cases could be re-classified as colonized on admission cases based on a positive admission screen result.

Table 6. Results of admission screens in patients with a positive clinical culture at the 6 screening hospitals.

<table>
<thead>
<tr>
<th>Admission screen status</th>
<th>Clinical cultures first positive &gt;72 hours after admission (N=243)</th>
<th>Clinical cultures positive at admission (N=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission screen positive</td>
<td>113 (46.5%) (colonized at admission)</td>
<td>235 (48.8%) (community-onset)</td>
</tr>
<tr>
<td>Admission screen negative</td>
<td>79 (32.5%) (confirmed nosocomial)</td>
<td>33 (6.8%) (false negative)</td>
</tr>
<tr>
<td>Admission screen not done</td>
<td>51 (21.0%) (probable nosocomial)</td>
<td>214 (44.4%) (missed by screening algorithm)</td>
</tr>
</tbody>
</table>

With respect to community-onset cases, 44.4% of patients with an ESBL-E clinical culture obtained <72 hours after admission were not screened for colonization at admission despite screening hospitals attempting to target patients at risk for ESBL-E. Hospital C3 and C4 had the
highest rates of community-onset cases (54.0% and 60.5%) who were not screened. The remaining screening hospitals had rates ranging from 23 – 36%. This included both universal screening hospitals and 2 risk-factor based hospitals (A1, C5). In addition, admission rectal screening was negative in 12.3% (33/268) of patients with an ESBL-E positive clinical isolate within 72 hours of admission.

5 Discussion

Admission screening for an antimicrobial resistant organism is of value if identifying colonized patients can prevent the nosocomial transmission of the particular organism. Unlike organisms such as MRSA and VRE, there is almost no direct evidence of the effectiveness of screening as part of a transmission control program for ESBL-E, particularly in non-outbreak situations (28). Additionally, there is controversy with regards to the transmissibility of ESBL-E (27, 32, 36), the influence of patient-to-patient transmission versus antibiotic selective pressure (33), the impact of local endemicity of ESBL-E (116) and the sensitivity of the screening test (123). The epidemiology of transmission may also differ between organisms within the family Enterobacteriaceae, with E. coli more associated with community acquisition and Klebsiella spp. more likely a result of hospital transmission (99). In-hospital transmission has been demonstrated for E. coli and K. pneumoniae (32, 36), and has resulted in outbreaks of ESBL-E in which interventions including active screening appeared to assist in outbreak control (57, 63). In our study, K. pneumoniae had a higher ratio of hospital-onset to community-onset cases, supporting the findings of other studies that K. pneumoniae may be more transmissible in hospitals than E. coli (32, 36, 86, 92). Overall, hospitals performing admission screening had rates of hospital-onset cases that were 49.1% lower than hospitals that did not perform screening.

The effectiveness of a surveillance program is in part dependent on the “undetected ratio”, describing the proportion of patients potentially at risk of transmitting that would not be identified by monitoring clinical cultures alone (33). In the management of a CRE outbreak, active surveillance was implemented with an initial undetected ratio of 55.7% increasing to 92.5% at the end of the outbreak (6). Over 5 years, the undetected ratio in Toronto was 72.2%, similar to a prospective study on active surveillance of ESBL-E for ICU admissions (35). A higher ratio - that is, a method for identifying a larger proportion of patients from whom transmission would occur - would be ideal, but may be difficult to attain in non-outbreak
settings. However, the undetected ratio of 0.72 achieved by screening hospitals in Toronto indicates that identifying all ESBL-E positive patients may not be necessary in non-outbreak settings. The 6 screening hospitals in our study had a lower ratio of hospital-onset to community-onset cases suggesting early identification and initiation of infection control practices reduces nosocomial transmission. In non-screening hospitals, precautions are initiated after detection of a clinical isolate, which may result in a delay of almost 2 weeks, as the median time from admission to clinical isolate was 11 days.

For screening hospitals in Toronto, 44% of patients presenting to hospital with a community-onset clinical ESBL-E isolate were not screened. Hospital R2 and R3 had the highest rates, as they primarily screened ICU admissions. Similarly, almost half of patients with ESBL-E bloodstream infection were not screened in a prospective study screening high risk patients which included critical care, solid-organ transplant and hematology/oncology wards (103). Universal screening was similar to R1 and R4, potentially since these 2 risk-factor based screening programs targeted a broader patient population. Accurately identifying patients at risk of ESBL-E (or CRE) will be complicated by the fact that traditional risk factors for carriage of an antibiotic resistant organism such as previous hospitalization, previous admission to an intensive care unit or transfer from another health care facility may miss a significant proportion of the increasingly common community-associated CTX-M strains, as well as those associated with travel (56, 87). Similarly, although hospitalization is a risk factor for CRE, it is clear that NDM-producing Enterobacteriaceae are circulating in the community in the Indian subcontinent (76, 122), and potentially in non-endemic countries such as Canada (54, 60, 73). Adding questions about recent travel to screening algorithms may improve ESBL-E and CRE detection rates, but the effectiveness of this addition has not been tested, and would significantly complicate the admission screening process. This difficulty with identification of risk factors for ESBL-E suggests universal admission screening may be necessary to capture all asymptotically colonized patients, but is a significantly more expensive program for most hospitals.

Among patients colonized with ESBL-E at admission, the majority will not develop ESBL-E infections during their admission. The risk of such patients developing an infection in our study was lower (at 5.1%) than that reported by others. Progression to ESBL-E bloodstream infection has been reported in 8.5% to 15.4% of ESBL-E colonized patients (4, 103), while development
of a clinical infection of any source occurred in 25 – 68% of cases (17, 34). Our lower risk of infection likely occurred because our study population included 4 of 6 hospitals in which admission ESBL-E screening extended beyond the ICU, resulting in a colonized population at lower overall risk of infection. Development of an ESBL-E clinical isolate can be dependent on numerous clinical factors and prediction of a subsequent ESBL-E clinical culture should not be solely based on admission status.

There are several limitations to this study. It was a retrospective review and with some data not available for study including total admission screens tested in 3 screening hospitals from 2005 – 2007 and ESBL-E cases at 1 screening hospital in 2005. However, the effect was found to be consistent in subsequent years with data from all 12 hospitals. We also used a pre-defined definition for hospital-onset cases. Almost half of the hospital-onset isolates represented late detection of a community-associated infection. However, this definition was the only definition that could be applied consistently at both screening and non-screening hospitals. Mixing cases that were hospital and community-onset would bias the analysis towards the null hypothesis and suggests that our result may underestimate the impact of screening. In addition, there may have been systematic differences between screening and non-screening hospitals, such as hospital type (academic vs. community), infection control strategies other than screening for ESBL-E and infection control standards (eg. Hand hygiene rates). The majority of screening hospitals (5/6) were community hospitals, whereas academic hospitals accounted for 4/6 of non-screening hospitals. Stratifying hospitals by hospital type and screening practice revealed similar results (data not shown), but interpretation was limited due to the small sample size in subsets. Other interventions for ESBL-E were similar among both cohorts (Table 4).

Our data suggests that control programs that include admission screening for ESBL-E have contributed to lower rates of hospital-onset ESBL-E cases in Toronto, including bloodstream infections. Active screening does impart a significant financial commitment, previously estimated between $1,130,000 per year in a tertiary care hospital (27). Further cost-analysis studies will need to be conducted, taking into account the potential savings from decreasing transmission, both from a financial and public health perspective. Prospective studies investigating admission screening are needed for ESBL-E. The results can also provide guidance on CRE admission screening since both resistance mechanisms are plasmid mediated and likely to be transmitted similarly. With an increasingly scarce selection of effective antimicrobials
targeting ESBL-E, attention must shift towards the optimization of infection control practices to prevent the spread of multidrug resistant *Enterobacteriaceae*. 
Chapter 5
Discussion, Conclusion and Future Directions

1 Discussion

Healthcare associated infections estimated in the United States in 2002 accounted for 4.5% of all infections, or 1.7 million affected patients. This translated into approximately 99,000 deaths attributable to hospital acquired infections and $6.5 billion in economic cost (124). There is a lack of evidence for infection control interventions, especially for emerging MDR Enterobacteriaceae (28, 101, 112). The prevention of healthcare associated infections should be a priority given its impact on patient safety and the delivery of quality care. The World Health Organization believes that up to 50% of hospital acquired infections can be prevented with implementation and adherence of the standards of practice for infection control (124).

Beyond the intervention of admission screening, the prevention of hospital acquired infections, including ESBL-E, is based upon a multi-faceted and multi-disciplinary approach. It is essential to reinforce the foundations of infection control such as hand hygiene, education (both for patients and healthcare workers) and surveillance. For the infection control program as a whole, as well as individual interventions, success is dependent on numerous variables including buy-in from hospital leaders, sufficient financial and human resources, efficient microbiology laboratory services and compliance from frontline healthcare workers (112). As described in the management of an outbreak of ESBL-producing K. oxytoca, a coordinated effort by the IPAC team, the microbiology laboratory, environmental services and antimicrobial stewardship was necessary to manage and resolve the outbreak (59). Experience in the past decade suggests that cooperation and coordination should be extended past individual hospitals to regional or national IPAC programs (110).

One intervention, in isolation, will not eliminate hospital acquired ESBL-E, but can help contribute to minimizing its dissemination. In our study, hospital-onset ESBL-E clinical isolates were found to be an increasing burden in Toronto, with varied infection control practices for ESBL-E. This provided an opportunity to study the epidemiology of ESBL-E in a setting in which different practices for infection control had been established for a long period of time.
Over the 5 year study period, we identified a reduction in hospital-onset infections in hospitals performing admission rectal screening. This effect was identified when stratified according to clinical isolate, bloodstream isolates, *E. coli* and *K. pneumoniae*. The reduction seen in screening hospitals may have been underestimated, as almost half of the hospital-onset cases identified at screening hospitals were ESBL-E admission screen positive. In contrast, community-onset rates were similar in both cohorts.

As a single retrospective study, further evidence is necessary given the controversy regarding the potential benefits of screening. Two significant impediments to utilizing screening routinely in hospitals are efficacy and cost. While the efficacy of screening continues to be debated, the cost of screening is an objective barrier to implementation. Admission screening imposes additional costs on the hospital in the form of additional equipment requirements (eg. rectal swabs, gowns and gloves), human resources (eg. nursing staff collecting the samples), room/bed spacing issues (eg. increased requirement for private rooms for isolation) and microbiology workup. In total, this has been estimated to be in excess of $1 million per year at a single institution in Toronto (27). With costs of the program taken in isolation, if transmission of ESBL-E does not occur as suggested in Gardam et al.’s (2002) study, screening would not be a financially viable option. However, accounting for the potential benefit from preventing the spread of ESBL-E could be cost effective given the significant financial impact of infections due to a MDR Gram negative organism. MDR Gram negative infections are significantly more costly ($80,500 USD) compared to susceptible Gram negative infections ($29,600 USD) (24). From the public health perspective, preventing the development of an endemic focus of ESBL-E (and CRE) in Canada is paramount, since there are fewer and fewer active antimicrobial agents against ESBL-E and CRE.

ESBL-E are not the only MDR pathogen that healthcare facilities need to account for. MRSA, VRE and *Clostridium difficile* are some of the epidemiologically significant micro-organisms that require additional precautions beyond routine protocols, including isolation in private rooms (112, 114). Particularly for older healthcare facilities and hospitals, there is additional strain on room availability due to the need for all patients colonized or infected with these organisms to be isolated. This presents a practical limitation of attempting to perform admission screening for ESBL-E as there may not be enough single rooms to isolate all patients colonized or infected. In addition, for ESBL-E positive patients in appropriate precautions, older hospital design and
construction can also facilitate unsafe practices. We recently described an outbreak of ESBL-producing *K. oxytoca* in which the source was likely hand-washing sinks in the ICU. Contamination of the sinks was potentially secondary to healthcare workers disposing of patient bodily fluids in the hand-washing sinks. Due to the older design, there was no alternative sink in the patient’s room, and transporting potentially contaminated bodily fluids through the ward to the disposal area was also sub-optimal (59). Hospital design is a significant contributor to potential transmission of MDR organisms, and is a key component of IPAC programs (114). The role of the environment is increasingly being recognized as a hidden reservoir for transmission of MDR organisms. A significant burden of environmental contamination can circumvent the effectiveness of a screening program, as ongoing nosocomial transmission may result despite identifying and isolating all patients colonized/infected with ESBL-E (59). Active participation of IPAC in the design and construction of new hospitals, as well as upgrades for older facilities, is important to ensure that newer facilities are equipped to accommodate (and reduce) the increasing burden of MDR organisms.

In the interim, in the absence of an evidence-based approach to ESBL-E (28), decisions regarding infection control of ESBL-E must be made. Ideally, all patients infected or colonized with an MDR organism, including ESBL-E, with a potential to transmit should be in precautions. However, with financial and functional restraints, resources must be allocated to the most efficacious interventions. *Enterobacteriaceae* are transmitted via the fecal-oral route, but the propensity of different genera to transmit is poorly defined. In two related studies in the United States, person-to-person transmission of ESBL-producing *K. pneumoniae* and *E. coli* were documented in up to 52% and 13% of cases, respectively (32, 36). ESBL-producing *K. pneumoniae* which possessed TEM and SHV β-lactamases were predominantly hospital-associated infections in the 1990’s (9, 83, 84). With the emergence of CRE, KPC-producing *K. pneumoniae* outbreaks have frequently been reported (5, 6, 48, 66, 110). Meanwhile, the epidemiology of ESBL-producing *E. coli* can be diverse and may be different for TEM and SHV compared to CTX-M. As with *K. pneumoniae*, hospital outbreaks have been associated with TEM and SHV-producing *E. coli* (108). CTX-M β-lactamase-producing *E. coli*, which has become the predominant ESBL-E worldwide, are primarily associated with community-onset cases rather than hospital-onset cases (107). While hospital-onset CTX-M-producing *E. coli* infections occur (55, 99, 125), analysis of CTX-M-producing *E. coli* isolated >48 hours after
admission (ie. Hospital-onset) in Spain found that the isolates were clonally unrelated by PFGE (105). As K. pneumoniae have often been implicated as a hospital-associated organism compared to E. coli (99), a potential compromise for hospitals initiating screening and isolation of ESBL-E would be to focus their efforts on ESBL-producing K. pneumoniae. Further study of this strategy would be required. In our study, reductions in hospital associated ESBL-E isolates were identified for both genera. If hospitals were to adopt this strategy, ongoing surveillance of ESBL-producing E. coli would be needed to monitor for the development of clonal outbreaks.

Continued molecular characterization of ESBL-producing E. coli would also be needed to follow the epidemiology within each institution.

Another consideration that requires further investigation are the plasmid-mediated AmpC-producing E. coli and K. pneumoniae. AmpC β-lactamases are chromosomally expressed on Enterobacteriaceae such as Serratia marcescens, Providencia stuartii, Morganella morganii, Citrobacter spp., Enterobacter spp. and Hafnia alvei, in which patient-to-patient transmission is limited for these organisms (47, 69). Chromosomally mediated AmpC has also been identified in E. coli, but both E. coli and K. pneumoniae can also acquire plasmids which contain the AmpC gene (47). The extent to which plasmid mediated AmpC-producing E. coli and K. pneumoniae can be transmitted in hospital is poorly defined. However, with the ampC gene on a transposable element, it theoretically has the potential to transmit similar to the ESBL-E possessing Class A β-lactamases. The usefulness of distinguishing AmpC from ESBL-producing E. coli and K. pneumoniae is an important issue to resolve, particularly with respect to the clinical microbiology laboratory. Laboratories in Toronto currently follow the CLSI standards from 2009 which suggest confirmation of all 3rd generation cephalosporin resistant E. coli and K. pneumoniae (18). The most recent CLSI guidelines have lowered the breakpoints for cephalosporins in an attempt to capture ESBL-E without the need for confirmation (19). There is a caveat that confirmation can still be performed for epidemiological purposes. As laboratories start to transition to the new guidelines, IPAC programs will need to work closely with Microbiology to determine the extent to which 3rd generation cephalosporin resistant Enterobacteriaceae will be worked-up in the laboratory.

Incidence of ESBL-E in Canada is currently low (113), but increasing rates of ESBL-E have been reported in other Canadian centres (86, 92) similar to our study. These are significant pathogens with limited treatment options. The Infectious Diseases Society of America considers
ESBL-producing *K. pneumoniae* one of the 5 most important MDR pathogens, as it is a significant contributor to hospital associated infections (8). Preventative measures should be a priority for hospitals in an attempt to contain the spread of ESBL-E, and delay the development of an endemic focus of CRE in Canada. However, the optimal evidence-based method for ESBL-E prevention is not known. In the era of pan-resistant organisms, hospitals must focus their attention on infection prevention and control as antibiotics alone are insufficient to eradicate these increasingly prevalent MDR organisms.

2 Conclusion

In our multi-centre study of ESBL-E in Toronto hospitals, significant variation in practice for the infection prevention and control of ESBL-E was identified. Admission screening was evenly divided between those that screen (8/15) and those that do not (7/15). Over this same time period, rates of ESBL-E in Toronto increased 4-fold while nosocomial rates increased 2-fold. The ESBL-E isolates were resistant to multiple classes of antimicrobials, with rates of susceptibility to ciprofloxacin lower than expected (12.8% of *E. coli* and 9.0% of *K. pneumoniae*). Focusing specifically on admission screening, we found that hospitals which conducted admission screening had 49.1% fewer hospital-onset ESBL-E compared to hospitals which do not screen. This was also observed in the analysis of *E. coli*, *K. pneumoniae* and bloodstream infections, while incidence of community-onset ESBL-E were similar in both cohorts. These findings suggest that admission screening programs can be effective in reducing nosocomial transmission of ESBL-E.

3 Future Directions

Prospective studies on active admission screening for ESBL-E are needed. Many aspects of the epidemiology of ESBL-E are still unknown, such as organism specific transmissibility (*E. coli* compared to *Klebsiella* spp.) and plasmid mediated transmissibility (Class A compared to AmpC). Implementing screening into hospitals presents an additional challenge, and prospective cost-benefit analyses of admission screening are needed which look beyond the actual costs of the intervention. Further study is also needed into the potential for risk-factor based compared to universal screening, as universally admission screening may be impractical for hospitals to implement. In addition, admission screening followed by isolation and contact precautions creates a need for guidelines around discontinuation of these precautions. To date, there is also a
lack of evidence in this area as well (101). Admission screening has the potential to be an integral component for the prevention of nosocomial transmission of ESBL-E but more well-designed and prospective studies are needed to confirm the results of our retrospective multi-centre study.
References


79. Ontario Agency for Health Protection and Promotion, Provincial Infectious Diseases Advisory Committee. 2011. Annex A: Screening, testing and surveillance for antibiotic-
resistant organisms (AROs). 3rd ed. 


113. **Simner, PJ, Zhanel, GG, Pitout, J, Tailor, F, McCracken, M, Mulvey, MR, Lagace-Wiens, PR, Adam, HJ, Hoban, DJ, Canadian Antimicrobial Resistance Alliance (CARA).**


Appendices

Appendix A. List of participating hospitals.
A1 – St. Michael’s Hospital
A2 – Mount Sinai Hospital
A3 – Sunnybrook Health Sciences Centre
A4 – Toronto General Hospital
A5 – Toronto Western Hospital
A6 – Princess Margaret Hospital
C1 – North York General Hospital
C2 – Toronto East General Hospital
C3 – The Scarborough Hospital, General Campus
C4 – The Scarborough Hospital, Birchmount Campus
C5 – Lakeridge Health
C6 – Markham-Stouffville Hospital
C7 – William Osler Health Centre
C8 – Credit Valley Hospital
C9 – Southlake Regional Health Centre
Appendix B. Survey of infection control practices for extended-spectrum β-lactamase-producing Enterobacteriaceae and carbapenem resistant Enterobacteriaceae.

Please have this survey completed by the Infection Control professional or other member of the infection control team most responsible for the control and prevention of ESBL-producing organisms. For some questions, input from your local microbiology laboratory may also be appropriate. This survey should take approximately 20 – 30 minutes.

Hospital: ___________________
Date Completed: _______________

BACKGROUND
1) Please indicate your role within infection control and/or microbiology
   □ Infection Control professional
   □ Infection Control physician
   □ Microbiologist
   □ Other

2) For each of the following organisms, please indicate if your facility has a written infection control policy outlining your approach to the control of the indicated organism
   □ Methicillin Resistant Staphylococcus aureus (MRSA)
   □ Vancomycin Resistant Enterococcus (VRE)
   □ Extended-spectrum β-lactamase producing organisms (ESBL Class A)
   □ AmpC producing organisms (AmpC)
   □ Carbapenemase producing Enterobacteriaceae
      □ Klebsiella pneumoniae carbapenemase (KPC)
      □ New Delhi Metallo-β-lactamase 1 (NDM-1)
   □ Clostridium difficile (C. diff)

3) Do you feel that your hospital’s approach to ESBL Class A is
   □ Evidence and guideline based
   □ Evidence based but not based on guidelines
   □ Based primarily on local epidemiology (i.e. incidence of ESBL Class A in your community or facility)
   □ Based on what other local hospitals are doing
   □ Not sure

4) When did your institution initiate and implement infection control policies for the indicated organism?
   □ Methicillin Resistant Staphylococcus aureus (MRSA) - ________________
   □ Vancomycin Resistant Enterococcus (VRE) - ________________
   □ Extended-spectrum β-lactamase producing organisms (ESBL Class A) - ________________
   □ AmpC producing organisms (AmpC) - ________________
   □ Carbapenemase producing Enterobacteriaceae - ________________
      □ Klebsiella pneumoniae carbapenemase (KPC) - ________________
      □ New Delhi Metallo-β-lactamase 1 (NDM-1) - ________________
5) Why did your institution institute new infection control policies for the organisms indicated?
   □ Evidence and guideline based
   □ In response to an outbreak
   □ Increasing incidence of the indicated organisms on routine surveillance
   □ Other: ____________________

6) Complete the following demographic information for your institution:
   □ Number of Beds = ________
   □ Distribution of Beds
     • Private Rooms = ________  
     • Shared Rooms (Double) = ________  
     • Shared Rooms (Quadruple) = ________  
     • Shared Rooms (> Quadruple) = ________  
   □ Number of admissions per year = ____________  
   □ Average inpatient days per month = ____________  
   □ Average length of patient stay (hospital wide) = ____________

PRECAUTIONS UTILIZED

7) Does your facility use strategies (e.g. contact precautions, screening, isolation) for the control of ESBL Class A organisms other than routine practices for all colonized or infected patients?
   □ Yes (continue with question 8)
   □ No (proceed to question 11)

8) What precautions does your institution use for ESBL Class A organisms?
   □ contact precautions (gloves and gown in addition to routine practices)
   □ other (please specify) ___________________________

8A) Are these contact precautions used for:
   □ all patients infected or colonized with an ESBL Class A organism?  
   □ only patients at increased risk of transmitting the ESBL Class A?

8B) If your facility applies contact precautions selectively (i.e. only to high risk patients), how is risk defined [check all that apply]:
   □ patients with diarrhea
   □ patients with draining wounds
   □ patients with urinary incontinence
   □ patients with fecal incontinence
   □ other (please specify)_________________________

9) Are patients infected or colonized with an ESBL Class A placed in isolation (i.e. a private room)
   □ Yes

□ Clostridium difficile (C. diff) - ____________
10) Can patients infected or colonized with an ESBL Class A be cohorted?
   □ Yes
   □ No

11) Does your facility use strategies (e.g. contact precautions, screening, isolation) for the control of AmpC organisms other than routine practices for all colonized or infected patients?
   □ Yes (continue with question 12)
   □ No (proceed to question 15)

12) What precautions does your institution use for AmpC organisms?
   □ contact precautions (gloves and gown in addition to routine precautions)
   □ other (please specify) ___________________________

12A) Are these contact precautions used for:
   □ all patients infected or colonized with an AmpC organism?
   □ only patients at increased risk of transmitting an AmpC organism?

12B) If your facility applies these contact precautions selectively (i.e. only to high risk patients) then how is risk defined [check all that apply]:
   □ patients with diarrhea
   □ patients with draining wounds
   □ patients with urinary incontinence
   □ patients with fecal incontinence
   □ other (please specify) ___________________________

13) Are patients infected or colonized with an AmpC organism placed in isolation (i.e. a private room)?
   □ Yes
   □ No

14) Can patients infected or colonized with an AmpC organism be cohorted?
   □ Yes
   □ No

15) Does your facility use strategies (e.g. contact precautions, screening, isolation) for the control of CRE organisms other than routine practices for all colonized or infected patients?
   □ Yes (continue with question 16)
   □ No (proceed to question 20)

16) What precautions does your institution use for CRE organisms?
   □ contact precautions (gloves and gown, in addition to routine practices) in a single room only
   □ contact precautions (gloves and gown, in addition to routine practices) in any available room (can be multi-bed room)
   □ other (please specify) ___________________________
16A) Are these contact precautions used for:
- [ ] All patients infected or colonized with a CRE organism
- [ ] Only infected patients
- [ ] Only patients at increased risk of transmitting CRE

16B) If your facility applies contact precautions selectively (i.e. only to high risk patients), how is risk defined [check all that apply]:
- [ ] patients with diarrhea
- [ ] patients with draining wounds
- [ ] patients with urinary incontinence
- [ ] patients with fecal incontinence
- [ ] other (please specify)__________________________

17) Are patients with either infected or colonized with CRE placed in isolation (i.e a private room) or only infected patients?
- [ ] Infected
- [ ] Colonized
- [ ] Both

18) Can patients infected or colonized with CRE (same species) be cohorted?
- [ ] Yes
- [ ] No

19) Can patients infected or colonized with CRE (different species – eg. *E. coli* and *K. pneumoniae*) be cohorted?
- [ ] Yes
- [ ] No

**APPROACH TO SURVEILLANCE**

20) What type of laboratory-based admission surveillance/screening does your hospital do for ESBL Class A?
   - [ ] None
   - [ ] Universal screening of all admissions
   - [ ] Selective screening of high risk admissions
     - [ ] If selective screening, please define ‘high risk admissions’
       - __________________________________________________________

21) What specimens are used for screening? [CHECK ALL THAT APPLY]
   - [ ] Rectal swab
   - [ ] Perianal swab
   - [ ] Urine culture for all patients
   - [ ] Urine culture if foley
   - [ ] Wound swab (if present)
22) If a patient in a multi-bed room is identified as ESBL Class A positive, what follow-up is done for roommate contacts?
   - No follow-up
   - Contacts are identified and screened for ESBL Class A carriage once
   - Contacts are identified and screened for ESBL Class A carriage twice, one week apart
   - Other (please specify) ____________

23) Does your hospital ever do point prevalence surveys for ESBL Class A? (SELECT ALL THAT APPLY)
   - Never
   - Only if there is an outbreak
   - If a new colonized patient is identified
   - Periodically on all units
   - Periodically for units with high risk patient populations (e.g. ICU, heme/onc)
   - Periodically for units with a high incidence of ESBL Class A infection
   - Other (please specify) ____________

24) What type of laboratory admission screening/surveillance does your hospital do for AmpCs?
   - None
   - Universal screening of all admissions
   - Selective screening of high risk admissions
     - If selective screening, please define ‘high risk admissions’
       - ________________________________

25) What specimens are used for screening for AmpC? [CHECK ALL THAT APPLY]
   - Rectal swab
   - Perianal swab
   - Urine culture for all patients
   - Urine culture if foley
   - Wound swab (if present)
   - Device swab (if present)
   - Other ______

26) If a patient in a multi-bed room is identified as AmpC positive, what follow-up is done for roommate contacts?
   - No follow-up
   - Contacts are identified and screened for AmpC carriage once
   - Contacts are identified and screened for AmpC carriage twice, one week apart
   - Other (please specify) ____________

27) Does your hospital ever do point prevalence surveys for AmpC organisms? (SELECT ALL THAT APPLY)
☐ Never
☐ Only if there is an outbreak
☐ If a new colonized patient is identified on the unit
☐ Periodically on all units
☐ Periodically for units with high risk patient populations (e.g. ICU, heme/onc)
☐ Periodically for units with a high incidence of AmpC infection
☐ Other (please specify) _______________

28) What type of laboratory-based admission surveillance/screening does your hospital do for CRE?
   . ☐ None
   ☐ Universal screening of all admissions
   ☐ Selective screening of high risk admissions
     • If selective screening, please define ‘high risk admissions’
       ○ _______________________________________________________________________

29) What specimens are used for screening? [CHECK ALL THAT APPLY]
   ☐ Rectal swab
   ☐ Perianal swab
   ☐ Urine culture for all patients
   ☐ Urine culture if foley
   ☐ Wound swab (if present)
   ☐ Device swab (if present)
   ☐ Other ______

30) If a patient in a multi-bed room is identified as CRE positive, what follow-up is done?
   . ☐ No follow-up
   ☐ Roommate contacts are identified and screened for CRE once
   ☐ Roommate contacts are identified and screened for CRE carriage twice, one week apart
   ☐ Ward prevalence screens once
   ☐ Ward prevalence screens weekly for 2 weeks
   ☐ Ward prevalence screens weekly for 3 weeks
   ☐ Other (please specify) ___________

31) Does your hospital ever do ‘routine’ (i.e. not due to a known exposure or positive case) point prevalence surveys for CRE? (SELECT ALL THAT APPLY)
   . ☐ Never
   . ☐ Only if there is an outbreak
   . ☐ If a new colonized patient is identified
   . ☐ Periodically on all units
   . ☐ Periodically for units with high risk patient populations (e.g. ICU, heme/onc)
   . ☐ Periodically for units with a high incidence of ESBL Class A infection
   . ☐ Other (please specify) ___________

DISCONTINUATION OF PRECAUTIONS
32) If your hospital puts patients with ESBL Class A colonization or infection in contact precautions and/or isolation, what criteria are used to remove precautions?

- Precautions are continued until discharge
- Precautions are removed with one negative specimen from the site originally positive
- Precautions are removed when screening specimens are negative once
- Precautions are removed when screening specimens are negative twice, one week apart
- Precautions are removed when screening specimens are negative three times, each one week apart
- Other (please specify) ___________________

33) Does your hospital ‘flag’ ESBL Class A colonized or infected patients in the patient care system in order to initiate precautions on readmission?

- Yes
- No

34) Does your hospital routinely try to decolonize patients colonized with ESBL Class A?

- Yes
- No

35) If your hospital puts patients with AmpC colonization or infection in contact precautions and/or isolation, what criteria are used to remove precautions?

- Precautions are continued until discharge
- Precautions are removed with one negative specimen from the site originally positive
- Precautions are removed when screening specimens are negative once
- Precautions are removed when screening specimens are negative twice, one week apart
- Precautions are removed when screening specimens are negative three times, each one week apart
- Other (please specify) ___________________

36) Does your hospital ‘flag’ AmpC colonized or infected patients in order to initiate precautions on readmission?

- Yes
- No

37) Does your hospital routinely decolonize patients colonized with AmpC?

- Yes
- No

38) If your hospital puts patients with CRE colonization or infection in contact precautions and/or isolation, what criteria are used to remove precautions?

- Precautions are continued until discharge
- Precautions are removed with one negative specimen from the site originally positive
- Precautions are removed when screening specimens are negative once
- Precautions are removed when screening specimens are negative twice, one week apart
- Precautions are removed when screening specimens are negative three times, each one week apart
- Other (please specify) ___________________
39) Does your hospital ‘flag’ CRE colonized or infected patients in the patient care system in order to initiate precautions on readmission?
   □ Yes
   □ No

MICROBIOLOGY

40) Does your microbiology laboratory differentiate between ESBL Class A *E. coli* or *Klebsiella* and AmpC *E. coli* or *Klebsiella*?
   □ Yes
   □ No
   □ Not sure

41) Do ESBL surveillance cultures report the presence of SPICE organisms?
   □ Yes
   □ No

42) Does your microbiology laboratory report the presence of a carbapenemase producing *Enterobacteriaceae*?
   □ *Klebsiella pneumoniae* carbapenemase (KPC)
   □ New Delhi Metallo-β-lactamase 1 (NDM-1)
   □ Neither