Screening for Extended-Spectrum $\beta$-Lactamase–Producing Enterobacteriaceae among High-Risk Patients and Rates of Subsequent Bacteremia

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Background. Bloodstream infections due to extended-spectrum $\beta$-lactamase (ESBL)–producing Enterobacteriaceae have associated with increased hospital costs, length of stay, and patient mortality. However, the role of routine patient surveillance for ESBL colonization in predicting related infection is unclear.

Methods. From 2000 through 2005, we screened 17,872 patients hospitalized in designated high-risk units for rectal colonization with vancomycin-resistant enterococci and ESBL-producing Enterobacteriaceae using a selective culture medium. In patients with a bloodstream infection due to ESBL-producing Enterobacteriaceae (ESBL-BI) during the study period, surveillance results were evaluated for evidence of antecedent ESBL-producing Enterobacteriaceae colonization.

Results. The rate of ESBL-producing Enterobacteriaceae colonization doubled during the 6-year study period, increasing from 1.33% of high-risk patients in 2000 to 3.21% in 2005. Among patients with ESBL-producing Enterobacteriaceae colonization, 49.6% also carried vancomycin-resistant enterococci. The number of ESBL-BIs increased 14-fold in 5 years, from 9 cases in 2001 to 40 cases in 2005. Of 413 patients colonized with ESBL-producing Enterobacteriaceae, 35 (8.5%) developed a subsequent ESBL-BI. Of concern, more than one-half of all ESBL-BIs occurred in patients who were not screened. These 56 patients received a diagnosis of ESBL-BI in the emergency department, when hospitalized in low-risk medical units, or at transfer from an acute or long-term health care facility.

Conclusions. Colonization with ESBL-producing Enterobacteriaceae is increasing at a rapid rate, and routine rectal surveillance for ESBL-producing Enterobacteriaceae may have clinical implications. However, in our experience, over one-half of patients with an ESBL-BI did not undergo screening through our current surveillance measures. As a result, targeted screening for ESBL-producing Enterobacteriaceae among additional patient populations may be integral to future ESBL-BI prevention and management efforts.

The production of extended-spectrum $\beta$-lactamases (ESBLs) among Enterobacteriaceae is an emerging problem. A recent US survey estimated that 3% of all Enterobacteriaceae produce ESBLs [1]. Data from the 1997–2003 Meropenem Yearly Susceptibility Test Information Collection Program suggest that 12.3% of Klebsiella pneumoniae, 7.5% of Escherichia coli, and 3.9% of Proteus mirabilis in North America harbor ESBLs [2]. The rate of increase in ESBL production among Enterobacteriaceae is even more worrisome. According to National Nosocomial Infections Surveillance data, >20% of Klebsiella isolates in intensive care units in the United States produced ESBLs in 2003, a 47% increase over the preceding 5 years [1].

The consequences of infection due to ESBL-producing Enterobacteriaceae (ESBL-E) are well known. Bloodstream infections due to ESBL-E (ESBL-BI) have led to increased length of hospital stay [3, 4], increased hospital costs [4], improper antibiotic use [5], and most notably, increased mortality [4–6]. Not surprisingly, prior colonization with an ESBL-E is a risk factor for ESBL infection [7–9]. However, the role of routine surveillance cultures as a means of screening for ESBL-E colonization among hospitalized patients is unclear.
Rectal surveillance cultures, together with isolation precautions and antibiotic-restriction measures, have been instrumental in ESBL outbreak management [6, 7, 10], but routine surveillance is costly and may not be effective in predicting clinical disease [11, 12].

In 2000, we expanded our vancomycin-resistant enterococci (VRE) rectal surveillance program in high-risk units to include screening for ESBL-E. To determine the prevalence of ESBL-E colonization among patients in high-risk units, the rate of ESBL-E colonization among patients with VRE, and the role of ESBL-E colonization in ESBL-BI, we reviewed and analyzed results for our institution (Northwestern Memorial Hospital [NMH]; Chicago, IL) for the period 2000–2005.

METHODS

Study patients and sample collection. NMH is an 825-bed academic medical center in Chicago, Illinois. At NMH, all adult patient care rooms are single-occupancy rooms. The medical intensive care unit consists of 23 beds. The surgical intensive care unit contains 12 beds; critically ill gastrointestinal surgery, orthopedic surgery, and solid-organ transplantation patients are treated in this unit. The solid-organ transplant unit contains 30 beds, and the hematology/oncology unit contains 60 beds. For the purposes of this study, patients hospitalized in these 4 units are defined as high-risk patients.

As part of the infection-control program at NMH, high-risk patients are routinely screened for VRE and ESBL-E colonization. From 2000 through 2003, rectal surveillance cultures were performed weekly for all high-risk patients. In an effort to control an increase in VRE incidence and transmission, the hematology/oncology unit started screening patients weekly and at unit admission in 2003; for the same reason, the medical intensive care unit adopted this practice in 2004.

Rectal cultures are performed by registered nurses or patient care technicians for each unit. In patients with thrombocytopenia (defined as a platelet count <50 platelets/μL), a perianal culture or stool culture is performed instead. Each rectal swab (or stool) specimen is simultaneously evaluated for the presence of VRE and ESBL-E using a selective culture medium. Of note, patients with rectal cultures positive for VRE are flagged in the computerized surveillance database, facilitating the use of contact precautions upon readmission to the hospital. As a result, VRE-positive patients may not undergo routine rectal culturing on subsequent hospital admissions.

Microbiologic methods. A single rectal swab specimen is collected from each patient. To detect the presence of VRE and/or ESBL-E, the swab specimen is plated onto a selective medium of 5% sheep’s blood agar containing vancomycin (10 μg/mL), amphotericin B (2 μg/mL), ceftazidime (2 μg/mL), and clindamycin 1 μg/mL (VACC). The VACC plate, initially constructed in the NMH microbiology laboratory [13], is now acquired through a commercial vendor (Remel). All catalase-negative, gram-positive cocci on VACC plates are identified to the species level using Vitek-2 (bioMérieux). Traditional manual biochemical methods are used for identification when Vitek-2 results are indeterminate. Susceptibility testing of these isolates is performed via agar dilution according to Clinical Laboratory Standards Institute guidelines [14] or, more recently, via Vitek-2. Enterococcus faecalis and Enterococcus faecium with a vancomycin minimum inhibitory concentration (MIC) ≥6 μg/mL are categorized as VRE.

All oxidase-negative, gram-negative bacilli from VACC plates are evaluated for ESBL production. From January 2000 through August 2001, ESBL production was confirmed by agar dilution using ceftazidime and ceftazidime-clavulanic acid alone. In September 2001, ESBL confirmation by agar dilution with ceftazidime and cefotaxime (with or without clavulanic acid) was initiated according to Clinical Laboratory Standards Institute guidelines [14]. Because of greater ease of operation, ESBL production has been confirmed via the double disk diffusion method, in accordance with Clinical Laboratory Standards Institute guidelines, since 2004 [14]. Of note, at NMH, Clinical Laboratory Standards Institute guidelines are also applied to non–E. coli, non-Klebsiella species, and non- Proteus species in which the phenotype suggests the presence of an ESBL. Isolates confirmed to be ESBL-E are processed by Vitek-2 for species-level identification. Complete antibiotic susceptibility profiles for VRE and ESBL-E isolates from rectal surveillance cultures are not performed routinely.

All gram-negative bacilli obtained from blood cultures are processed by Vitek-2 for species-level identification and antibiotic susceptibility testing. Traditional manual biochemical methods are used when Vitek-2 results are indeterminate.

Database construction and statistical methods. Surveillance data are entered routinely into a Microsoft Excel spreadsheet (Microsoft). For each patient screened from 2000 through 2005, this surveillance database contains the date of surveillance culture, patient care unit, and culture result with species-level identification. The database is constructed for an ESBL-BI database, containing the date of bacteremia, patient care unit, and species-level identification, and antibiotic susceptibility profile.

For bloodstream infection analysis, the ESBL-BI database was compared with the surveillance database. Each patient with an ESBL-BI was categorized as ESBL-BI/screened or ESBL-BI/not-
screened on the basis of the presence or absence of surveillance cultures in the 12 months preceding bacteremia. ESBL-BI/ESBL-E screened patients were further categorized as either ESBL-BI/screen-negative (if the results of surveillance cultures obtained within 12 months were negative for an ESBL-E) or ESBL-BI/screen-positive (if the results of surveillance cultures obtained within 12 months were positive for an ESBL-E).

Statistical analyses were performed on surveillance and ESBL-BI data using SAS software, version 9.1 (SAS Institute). For each year of the study period, each patient was counted once in analysis. Trend analysis for the 6-year study period was performed using the Cochrane-Armitage test.

RESULTS

From 1 January 2000 through 31 December 2005, 17,872 patients were screened for VRE/ESBL-E colonization at NMH. This represents 88.8% of eligible patients (i.e., patients hospitalized in high-risk units). Among screened patients, the rate of rectal colonization with ESBL-E doubled during the study period, increasing from 1.33% in 2000 to 3.21% in 2005 ($P < .001$) (figure 1). This increase was largely attributed to increased colonization with ESBL-producing Enterobacter cloacae and Klebsiella species (K. pneumoniae and Klebsiella oxytoca). Rates of colonization with ESBL-producing Enterobacter cloacae also increased significantly during the study period. Individually, statistically significant increases in the rate of colonization with ESBL-producing P. mirabilis, Providencia stuartii, and Citrobacter koseri were noted. Aggregate data suggest that colonization rates with all non–E. coli, non–Klebsiella species, and non–E. cloacae Enterobacteriaceae increased significantly, from 0.30% of patients in 2000 to 0.74% in 2005 ($P = .002$) (figure 1). Colonization with >1 species of ESBL-E was also increasingly common during the study period, increasing from 10 patients in 2000 to 27 patients in 2005.

By patient care unit, rates of ESBL-E colonization were most marked in the medical intensive care unit. In 2005, 7.08% of medical intensive care unit patients were ESBL-E colonized, a 224% increase from 2000 (figure 2). Statistically significant increases in colonization were also noted in the hematology/oncology and solid-organ transplant units. In contrast, although the rate of ESBL-E colonization in the surgical intensive care unit increased from 2.54% to 3.47% during the 6-year study period, this increase did not reach statistical significance.

The number of cases of ESBL-BI increased >4-fold in 5 years, from 9 cases in 2001 to 40 cases in 2005. Overall, 102 patients with an ESBL-BI were identified. Although annual ESBL-BI rates among colonized patients varied during the study period (range, 2.9%–14.1%), no trend was apparent. Of 413 patients colonized with an ESBL-E, 35 (8.5%) developed a subsequent bloodstream infection. Of note, these ESBL-BI/screen-positive patients accounted for only 34.3% of all ESBL-BI cases (figure 3). Few (10.8%) of the ESBL-BIs occurred among patients who were screen-negative, but more than one-half (54.9%) of ESBL-BIs occurred among patients who were not screened for ESBL-E colonization. Many of these ESBL-BI/not-screened patients were identified in the emergency department (29.6%) or at

Figure 1. Percentage of screened patients colonized with an extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-E), by species, 2000–2005. Cochrane-Armitage test for linear trend suggests an increase in colonization with any ESBL-E ($P < .05$). Patients colonized with >1 species of ESBL-E were counted once for each species (bar) but only once for any ESBL-E (line), accounting for the difference in height between bar and line graphs. Other ESBL-E include Citrobacter species, Providencia stuartii, Proteus mirabilis, Enterobacter aerogenes, and Serratia marcescens.
Figure 2. Percentage of screened patients colonized with an extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-E), by patient care unit, 2000–2005. HEME/ONC, hematology and oncology unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; SOT, solid-organ transplant unit.

transfer from an outside facility (12.5%). An additional 42.9% of ESBL-BI/not-screened patients were located in other patient care units where ESBL-E screening is not performed, such as the neurosurgical, cardiothoracic, and vascular surgery intensive care units (17.9%) and general medical units (25.0%).

Simultaneous screening for ESBL-E and VRE allowed us to calculate co-colonization rates among high-risk patients. ESBL-E strains were isolated from 413 screened patients. Of these ESBL-E–colonized patients, 205 (49.6%) were co-colonized with VRE. Of co-colonized patients, 161 (78.5%) carried vancomycin-resistant E. faecium, 27 (13.2%) carried vancomycin-resistant E. faecalis, and 17 (8.3%) carried all 3 organisms (ESBL-E, vancomycin-resistant E. faecalis, and vancomycin-resistant E. faecium). Co-colonized patients represented 10.6% of all VRE-colonized patients (205 of 1939 patients).

Of 413 ESBL-E–colonized patients, 54 (13.1%) underwent screening at a subsequent hospital admission during the study period. Forty (74%) were readmitted to the hospital and screened within 1 year after the initial positive culture result was obtained, and 15 (37.5%) were still ESBL-E colonized. The remaining 14 ESBL-E–colonized patients (26%) were readmitted to the hospital and screened >1 year after the initial positive culture result was obtained, and only 2 (14.3%) had positive results when screened again. Thus, of those colonized patients who had multiple surveillance cultures performed during the study period, only one-third (17 patients) were repeatedly ESBL-E positive.

DISCUSSION

To our knowledge, this 6-year database is the largest record of routine surveillance for ESBL-E colonization in the United States. In addition, this collection of data for nearly 18,000 patients reflects a high rate of capture (88.8%). Similar studies of screening for multidrug-resistant organisms cite capture rates of 80%–83% [9, 15, 16]. ESBL-E surveillance cultures among patients in intensive care units have proven to be even more difficult to obtain [9].

In our study, the increasing prevalence of ESBL-E among high-risk patients mirrors a national increase in ESBL production among Enterobacteriaceae [1]. Of interest, increased rates of ESBL-E colonization were attributable, in part, to non–E. coli, non–Klebsiella isolates, most notably E. cloacae. Among 21 non–intensive care unit study sites, Moland et al. [17] identified ESBL production in >14% of E. cloacae and ~9% of Serratia marcescens isolates. In addition, among all isolates tested, 2.8% of non–E. coli, non–Klebsiella species Enterobacteriaceae were ESBL positive. Our findings support these results, suggesting that increased ESBL-E colonization rates in the intensive care unit and elsewhere reflect increased ESBL production among non–E. coli, non–Klebsiella isolates.

Significant increases in ESBL-E colonization rates were noted among patients in the solid-organ transplant unit and the hematology/oncology unit. Aside from outbreak evaluations, rates of ESBL-E colonization in these patient populations have not, to our knowledge, been reported previously. Not surprisingly, the most significant rate increase was observed among patients in the medical intensive care unit. Risk factors for ESBL-E colonization are well-established and are common among patients hospitalized in medical intensive care units; they include prolonged hospital stay [18], bladder catheterization, arterial catheterization [19], severe underlying disease, congestive heart failure, and malignancy [20, 21].
Existing data on VRE and ESBL-E co-colonization rates among high-risk patients are limited. In patients hospitalized in the surgical intensive care unit and the medical intensive care unit, Harris et al. [16] demonstrated that 11% of VRE-positive patients carried an ESBL-E strain. The same study [16] indicated that, among patients colonized with an ESBL-E strain, 47% were VRE positive. Our results, which include data for patients in the solid-organ transplant unit and in the hematology/oncology unit, parallel these findings (10.6% of VRE-positive patients carried an ESBL-E strain, and 49.6% of patients colonized with an ESBL-E strain were VRE positive). Because shared risk factors for VRE and ESBL-E colonization exist, such as advanced comorbid disease, colonization pressure, length of hospitalization, and prolonged antibiotic exposure [16], a simultaneous increase in VRE and ESBL-E prevalence was perhaps inevitable.

It is clear that patients with ESBL-E rectal colonization are at increased risk of ESBL-E infection [22]. Christiaens et al. [23] found that 69% of ESBL-E–colonized patients also had clinical ESBL-E isolates, compared with only 12% of noncolonized patients. However, the role of surveillance cultures in predicting infection has not been elucidated. Recently, Ben-Ami et al. [24] demonstrated that 4 patients with ESBL-E rectal colonization (15.4%) developed subsequent ESBL-BI. In our study, 35 (8.5%) of the colonized patients developed a subsequent ESBL-BI, suggesting that routine surveillance for ESBL-E may have clinical implications.

On the other hand, more than one-half of ESBL-BIs occurred in patients who were not screened for ESBL-E colonization. Some of these ESBL-BI/not-screened patients were hospitalized in patient care units that do not undergo routine surveillance. However, an additional 20% of ESBL-BI/not-screened patients presented to the emergency department with bacteremia. Several authors have demonstrated that ESBL production among Enterobacteriaceae in the community and long-term health care facilities is increasing [24, 25]. The ESBL-BI cases diagnosed in the emergency department may reflect this trend. As a result, future screening efforts may need to target patients in long-term health care facilities (or even at-risk outpatients).

Few ESBL-E–colonized patients were culture positive in a subsequent year (17 patients). As a result, the steady increase in annual ESBL-E colonization rates was not attributable to readmission of known ESBL-E carriers. In this study, only one-third of colonized patients who underwent repeat screening were found to be ESBL-E positive according to subsequent culture results. A recent 3-year surveillance study suggests that, in the absence of effective antimicrobial therapy, nearly 70% of colonized patients remained ESBL-E positive when subsequently screened [26]. We did not assess therapeutic implications in our patient population, but the relatively low rate of ESBL-E recovery on subsequent culturing suggests that many factors, including antibiotic therapy, may play a role in the clearance of colonization. The low recovery rate on repeat screening of known ESBL-E carriers may also reflect the limited sensitivity of rectal culture for ESBL-E surveillance.

Several additional factors may have led to an underestimation of ESBL-E colonization rates. First, VACC plates were not impregnated with an enriched media. Second, VACC plates were formulated with ceftazidime (2 μg/mL), a concentration that may have inhibited the growth of some ESBL-E (e.g., cepotax-
images). Third, ESBL confirmation methods changed in 2001 and again in 2004 to reflect Clinical Laboratory Standards Institute guidelines; early estimates of ESBL-E prevalence may have been limited by methodology. As a consequence, the increase in colonization rates seen during the study may have been magnified by later, more sensitive detection techniques. Finally, ESBL-E screening measures are dictated by the prior VRE status of the patient. Patients who are previously flagged as VRE positive may not undergo further surveillance testing, and as a result, VRE and ESBL-E co-colonization rates may be underestimated. Despite these limitations, we found a significant increase in the rate of ESBL-E colonization among high-risk patients. Although we did not analyze patient-specific data or surveillance culture costs, future efforts to address these factors could determine the full clinical and economic implications of this trend.

In conclusion, ESBL-E colonization among high-risk patients is increasing at a rapid rate and doubled at our institution within a 6-year period. Increases in the rate of colonization are attributable, in part, to increased ESBL production among non–E. coli, non–Klebsiella species Enterobacteriaceae. One-half of ESBL-E–colonized patients also carry VRE, suggesting that shared risk factors are involved in acquisition. Of concern, the number of cases of ESBL-BI is also increasing, especially in the emergency department and in non–high-risk units. Although one-third of ESBL-BIs occurred among ESBL-E–colonized patients, more than one-half of ESBL-BI patients were not screened through our current surveillance measures. A cost-benefit analysis of ESBL-E surveillance is indicated to determine the usefulness of current practice and the need for an expanded surveillance program in the future.

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References
