Peer reviewed article

Surveillance of Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* in a Swiss Tertiary Care Hospital

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Summary

Background: Extended spectrum beta-lactamase producing enterobacteriaceae (ESBL-E) are increasing worldwide, but there is sparse data on patient-to-patient transmission and the prevalence among risk groups in Switzerland. A prospective, observational cohort study was performed to: 1) assess the prevalence of ESBL-E at admission among at-risk groups; 2) evaluate nosocomial cross-transmission in acute care (ACF) versus long-term care facilities (LTCF); and 3) evaluate prevalent mutations of the detected beta-lactamase genes.

Methods: Predefined risk groups were screened either on admission or after having been in contact with index patients diagnosed with ESBL-E by clinical cultures. Three patient categories were distinguished: patients previously known to be ESBL-E carrier (category I); patients transferred from countries with known high ESBL-E prevalence and thus at risk for ESBL-E carriage (category II); and roommates of index patients (category III).

Results: A total of 93 patients with ESBL-E were identified: Sixty-two percent (31/50) of category I patients were positive when screened upon rehospitalisation (category I); eighteen percent (22/124) of category II patients; and eight out of 177 category III patients (4.5%) of which five showed identical ESBL-E strains or shared the same beta-lactamase gene as their index cases. The incidence density of transmission was 0.9/1000 exposure-days, with more transmissions in ACF than in LTCF (4.2 vs 0.4/1000 exposure days). CTX-M-15 was the predominant beta-lactamase gene (60%) among the index patients.

Conclusions: The prevalence of ESBL-E carriage among patients coming from regions with endemic rates or those previously identified as carriers is high; on-admission screening should be considered for these high risk populations. Documented nosocomial ESBL-E transmission was low.

Key words: extended-spectrum-beta-lactamase; contact isolation; cross-transmission; epidemiology; antimicrobial resistance

Introduction

The incidence of extended spectrum β-lactamase producing enterobacteriacae (ESBL-E) has increased worldwide since their first description two decades ago [1, 2]. A recent survey in the US estimated that 6% of all *Escherichia coli* and 12% of all *Klebsiella* spp. isolates produce ESBL [3, 4]. The European rates are higher, but show a variation between 2.7% and 30% for *E. coli* [4]. There is no published epidemiological data for ESBL-producers in Switzerland. However, in 2008 the Sentinel Surveillance of Antibiotic Resistance in Switzerland (www.antibioticresistance.ch) found third generation cephalosporin resistance among 4.2% of tested *E. coli* and among 4.1% of *Klebsiella* spp, which may be considered as a surrogate marker for the real prevalence of ESBL-producing enterobacteriacae.

Infections by ESBL-strains cause increased morbidity and mortality warranting adequate ESBL-E surveillance [5]. Early detection of ESBL-producing pathogens is considered important in order to implement efficient infection control measures and to select appropriate antimicrobial treatment regimens [6]. However, universal screening at admission is neither feasible nor effective [7]. Thus, a practical definition of at-risk

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groups would be of use. However, only few studies have systematically evaluated ESBL-E carriage among defined high-risk patients [2, 8].

In our institution, the rate of ESBL-producing isolates has increased from 0.07% to 2.3% among *E. coli* and from 1.5% to 5.7% among *Klebsiella* spp between 1998 and 2005, respectively. We therefore performed a prospective observational cohort study to: 1) assess the prevalence of ESBL-E at admission among at risk groups; 2) evaluate nosocomial cross-transmission in acute care (ACF) versus long-term care facilities (LTCF); and 3) evaluate prevalent mutations.

Methods

Setting

The study was conducted at the University of Geneva Hospital (HUG), a 2167-bed tertiary care hospital with 48 000 annual admissions representing 750 000 patient-days, and more than 5000 antimicrobial susceptibility assays for enterobacteriaceae. The institution consists of acute care facilities (ACF) offering all medical specialities of a tertiary care centre as well as long-term care facilities (LTCF) for the elderly and patients requiring chronic care [9].

Study design

A prospective, observational cohort study was performed between May 2006 and December 2006 using two ESBL-E surveillance methods: 1) prospective surveillance of all clinical ESBL-E isolates based on an electronic alert system; and 2) targeted screening of defined risk groups.

ESBL screening

According to our study objectives, patients eligible for ESBL screening were divided into three categories: category I: a history of known ESBL colonisation/infection at HUG before current hospitalisation; category II: member of a predefined group considered to be at risk for ESBL-E carriage: 1) direct repatriation from a hospital abroad (except emergency transfers from neighbouring France); 2) history of hospitalisation or medical treatment abroad within the last 30 days; and 3) residents of countries known to have a high ESBL-E prevalence in the community; category III: patients sharing a room or hospitalised in the proximity of an index case newly diagnosed with ESBL-E in clinical cultures (= new index patient).

Screening consisted of a rectal swab. Patients in categories I and II were screened within 48 hours of admission. Category III patients were screened as soon as a new index case was identified. Isolates from roommates and their index patients were further evaluated for clonal relatedness using PFGE and genotyping of the beta-lactamase gene. Patient-to-patient transmission was defined as time overlapping and identification of a similar PFGE pattern and/or the same beta-lactamase gene.

Microbiological analyses

The chromID ESBL medium (bioMérieux, Lyon, France) used in this study contains cefpodoxime, an antibiotic recognised as being the marker of choice for this resistance mechanism. ESBL confirmation was performed using a combination of four disks: cefotaxime versus cefotaxime/clavulanate and ceftadizime versus ceftadizime/clavulanate, as described in the CLSI guidelines (www.clsi.org) [10, 11]. ESBL was declared as present whenever the inhibition zone around the disk containing clavulanate was at least 5 mm larger than that of the disk containing the same cephalosporin but without clavulanate. Genomic strain typing was carried out by PFGE according to established protocols. Banding patterns were analysed using the BioNumerics software (Applied Maths, Kortrijk, Belgium); discrimination of closely-related strains was performed as described [12].

The genes bla_{TEM}, $bla_{\text{CTX-M}}$ bla_{OXA} and bla_{SHV} were detected by PCR using specific primers [13, 14]. Following analysis of PCR amplification with the BioAnalyzer 2100 (Agilent), amplicons were purified and sequences determined by direct sequencing of PCR products (Applied Biosystems 3130 XL DNA analyser; Applied Biosysems, Foster City, USA). The nucleotide and deduced protein sequences were analysed with specifically developed software using information from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

ESBL Surveillance

Surveillance of ESBL-positive patients was conducted by a trained infection control nurse. Incidence density was defined as all newly detected ESBL-E cases (colonised and infected) per 1000 patient days. Colonisation pressure was defined as the proportion of ESBL-E-positive patient days per 100 patient days. The rate of ESBL-E transmission was expressed as an incidence density per 1000 exposure patient days.

Infection control measures

All category I patients were placed in preemptive contact isolation and three consecutive screening swabs at a one week interval were performed. Contact isolation measures were not suspended until three consecutive negative rectal swabs were obtained. In case of a positive test result, infection control measures were maintained until discharge without further screening. Category II and III patients were placed in contact isolation as soon as a positive ESBL-E test result was reported.

Statistical analysis

Categorical variables were compared using the χ^2-test; continuous variables were summarised as means or medians where appropriate and compared by the Wilcoxon rank sum test. A p-value <0.05 (two-sided) was considered statistically significant. All statistical analyses were conducted using Stata 10.0 (Stata Corporation, College Station, Texas; USA).

Results

A total of 30 221 admissions occurred during the eight-month-study period, during which 351 patients were screened for ESBL-E. Of these, 32 (9.1%) were found to be infected with ESBL-E (median age [interquartile range IQR]: 68 [51–81] years; 21 [68%] were male). The incidence density was 0.7 new ESBL-E cases per 1000 patient days, with a corresponding incidence of 0.10 per 100 admissions.

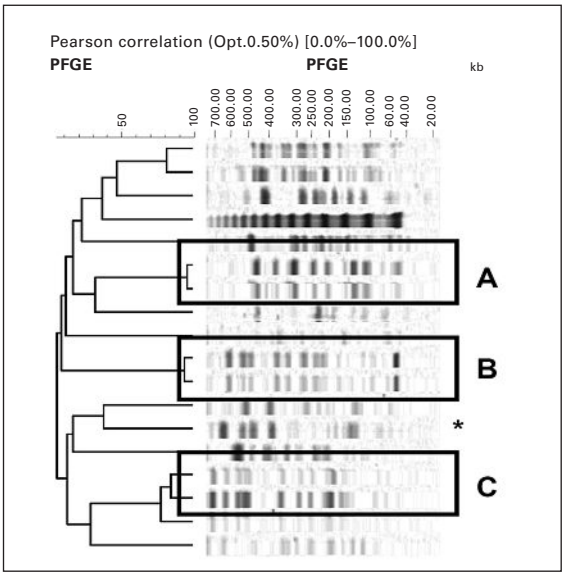

Figure 1

Pulsed-field gel electrophoresis (PFGE) of isolates from ESBL-E index cases and roommates that shared the same clone and had a temporal overlap during hospital stay at the University of Geneva Hospital, Switzerland.

ESBL-E strains from index patients and their roommates were genotyped using PFGE. This figure shows the banding pattern of ESBL strains found among roommates and their respective index case. Three identical roommate-index pairs (A-C) could be identified. Further analysis revealed a chromosomally encoded beta-lactamase for this strain (*) [35].

Table 1

Category II: screening upon admission in predefined risk groups.

Risk groups	Positive	Negative	Total	Prevalence
Patients repatriated from a hospital abroad	6[1]	27	33	18%
Patients hospitalised abroad <4 weeks prior to current hospitalisation	4[2]	11	15	27%
Residents of countries known to have high ESBL-E prevalence	12[3]	64	76	16%
Total	22	102	124	18%

Epidemiologic characteristics of patients with positive findings:
[1] Transfer from hospitals in: Egypt, Iran, Morocco, Czech Republic, Sudan, Venezuela; emergency transfers from neighbouring France were excluded.
[2] Countries where treatment or hospitalisation took place: Algeria, India, Tunisia, Morocco.
[3] Countries of origin: Dominican Republic, Hong Kong, Nepal, Libya, Mauritania, Benin, Thailand, Algeria, Nicaragua.

Table 2

Characteristics of cross-transmission pairs analysed by pulse-field gel electrophoresis (PFGE) and molecular gene determination.

Pairs	Facility	Microorganism	Identical PFGE pattern	β-lactamase gene analysis	TEM-type	CTX-M-type	SHV
A	ACF[2]	*E. cloacae*	Yes	nd[1]	–	3	–
B	LTCF[3]	*K. pneumoniae*	Yes	Yes	–	15	–
C	LTCF[3]	*K. pneumoniae*	Yes	Yes	–	15	5
D	ACF[2]	*E. coli*	No	Yes	–	15	–
E	ACF[2]	*E. coli*	No	Yes	116	15	–

[1] Strain from roommate not available for beta-lactamase gene analysis
[2] ACF: Acute care facility
[3] LTCF: Long-term care facility

The distribution of the 93 patients among predefined risk categories was: 31 (33.3%), category I; 22 (23.7%), category II; and 8 (8.6%), category III. Thirty-two index patients (34.4%) were identified during the hospital stay by clinical cultures. The distribution of isolated pathogens with ESBL was: 58 (62.4%) *E. coli*; 30 (32.3%) *K. pneumoniae*; 2 (2.1%) *Enterobacter cloacae*; 2 (2.1%) *Morganella morganii*; and 1 (1.1%) *Citrobacter* spp.

On admission screening

Category I: Thirty-one patients (62%) were persistent ESBL-E carriers with a median ESBL-E carriage [IQR] of 151 days [79–358] prior to readmission. The longest duration of known ESBL carriage before readmission was two years. Category II: Of 124 patients screened in category II, 22 (18%) were found to be colonised with ESBL-E (table 1).

Contact tracing

The electronic alert system identified 32 ESBL-E index cases with 26 urine cultures, three with blood cultures, and three with other clinical samples. Of 177 roommates screened, eight (4.5%) were found to be positive for ESBL-E. None of these roommates had been screened on admission because of the absence of a high-risk profile.

Genotyping

Three roommates were found with similar PFGE-types as their index cases (*K. pneumoniae* [2] and *E. cloacae* [1]) (fig. 1). Two of the three shared the same beta-lactmase genes (table 2). An additional two roommates were found with different PFGE-types but identical beta-lactamase genes as their index case (table 2). CTX-M-15 was the predominant beta-lactamase type (9/15 [60%]). Four *K. pneumoniae* isolates harboured bla_{SHV} 5 and this gene was shared by one index patient with one of his roommates.

Patient-to-patient transmission

A total of 31 out of 32 index patients and 177 roommates were included in this analysis. One index patient had no roommates. Eight exposed patients were found to be colonised with ESBL-E; five had either identical PFGE patterns with their index patient (n = 3) or shared the same beta-lactamase genes (n = 2). Only these five strains were considered to represent nosocomial cross-transmission. The overall ESBL-E transmission rate was 0.9/1000 exposure days. More transmissions were detected in ACF than in LTCF (4.2 vs 0.4/1000 exposure days), although exposure time was shorter (median days [IQR]: 7 [4–15] vs 20 [13–33]; p <0.001) and the colonisation pressure lower (0.6% vs 2.2%, respectively). Roommates with ESBL-E colonisation showed longer exposure times compared to roommates without ESBL-E colonisation (medians [IQR]: 18 [2–23] days and 7 [4–13] days; p = 0.03).

Discussion

Our study shows that ESBL-E are more frequently found in predefined patient groups at high risk for ESBL-E carriage. Most patients (62%) formerly known to be ESBL-E carriers were still positive at readmission. The median time span between last and current confirmation of ESBL-E was almost five months, although there was considerable variation of the time lag between first and last isolation of ESBL-E. Thus, it may be justified to place known ESBL-E-carriers in preemptive contact isolation at admission. Most ESBL-E strains harboured the CTX-M 15 beta-lactamase gene which has become the most common type in Western Switzerland [15].

Our ESBL-E incidence rate parallels findings of a recent three-year study from Germany (0.12 new cases / 1000 patient days) [16]. While the high rate of colonised patients remaining ESBL-E positive at readmission confirms findings by Kola et al. (70%), lower ESBL-E colonisation rates were found in the US [8, 16].

Risk factors for ESBL-E carriage have been widely described in the literature [17–22]. Our predefined screening criteria based on previous findings and set up for admission screening confirmed that certain patient groups are at higher risk of ESBL-E-carriage upon admission. This observation is consistent with other reports describing high ESBL-E rates among patients repatriated from countries with high ESBL-E prevalence [23–26].

Five potential cross-transmission events were documented between 31 index cases and their 177 roommates. While on the index case level this number seems high (5/31; 16%), the incidence density of ESBL-E transmission was low (0.9 per 1000 exposure days) if exposure time is taken into consideration. The likelihood of nosocomial cross-transmission of ESBL-E is highly debated in the literature. PFGE-confirmed ESBL-E transmissions in the ICU are rare events, especially for ESBL-producing *E. coli* [27, 28]. Hence, some authors speculate that the increase of ESBL-producing *E. coli* is not related to cross-transmission [2], since horizontal transmission of ESBL-producing *E. coli* is rare outside an outbreak situation [6, 29]. However, patient-to-patient transmission was considered important for *K. pneumoniae* acquisition [27]. Transmission of extended beta-lactamase genes through mobile genetic element-encoded resistance may occur even if PFGE patterns appear polyclonal [30]. Thus, PFGE analysis might underestimate the true rate of ESBL-transmission, which may be far more important for *E. coli* than for other *Enterobacteriaceae*.

The incidence density of confirmed cross transmission events in our study was higher in the ACF than in the LTCF although the exposure time in the LTCF was higher. This is somewhat unexpected and not easily explained. However, a possible explanation may be the frequent sharing of toilets, since most toilets are shared by many patients in our institution. We thus consider the ACF more at risk for direct patient-to-patient transmission than the LTCF where patients are more bed-ridden and equipped with personal toilets. Furthermore, patients in the ACF are exposed to more interventions accumulating more opportunities for hand hygiene and thus are more at risk for ESBL-transmission. Further studies will have to confirm this hypothesis. Ideally, such studies should include environmental sampling.

Nosocomial ESBL-E-control is still a matter of debate. Certain authorities advocate screening on admission, contact isolation for positive patients and the introduction of good antibiotic stewardship [31–33]. However, others have raised concerns about the efficiency of such measures in the light of an important community reservoir. At present, there is insufficient data to justify a complete abandon of infection control measures in the hospital, given that ESBL-E may cause serious infections and adverse outcomes [5, 8]. We did not perform universal ESBL-E-screening at admission but we placed all new ESBL-E cases in contact isolation and implemented preemptive isolation among category I patients. By doing so, contact precautions were established in almost 100% of cases. To reduce the need for contact precautions among patients in LTCFs, surveillance cultures may be performed from time to time [34]. A matter of debate is whether screening should be performed while patients are treated with antibiotics or not, since several agents may select for ESBL-E (penicillins, cephalosporins) thus increasing the sensitivity of screening or result in a false negative test results (carbapenems). Furthermore, there is no evidence on the optimal time interval between the screening tests. Future studies on this topic are needed.

Our study has limitations. The sample size was small and only selected patients were included in the study. Since we did not perform universal admission screening, the rate of ESBL-E colonisation is likely to be underestimated. However, clinical samples positive with ESBL-E were reported efficiently through our electronic surveillance system. Beta-lactamase gene analysis was performed only for the group of index cases and their roommates. Since the index cases did not belong to any other risk group for ESBL-E-carriage, our findings most likely reflect the situation in the greater Geneva area. However, the potential introduction of other ESBL-E-genes could not be addressed. Furthermore, we focussed on ESBL-producing microorganisms only albeit enterobacteriaceae may harbour additional mechanisms of resistance.

In conclusion, the incidence density of ESBL-E cross-transmission and colonisation in a non-outbreak situation is still low. Transmission occurs at least as frequently in the ACF as it does in the LTCF. ESBL-E-screening among predefined risk

groups such as known ESBL-E-carriers or patients admitted from areas of high ESBL-prevalence could be potentially useful. Similar to other Swiss regions and other European countries, CTX-M 15 was the predominant beta-lactamase gene identified among the isolates obtained from hospitalised patients with clinical ESBL-E infection.

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