Control of an Outbreak of Infection Due to Extended-Spectrum \(\beta\)-Lactamase–Producing *Escherichia coli* in a Liver Transplantation Unit


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We report an outbreak of infection due to genotypically identical extended-spectrum \(\beta\)-lactamase–producing *Escherichia coli* among patients in a liver transplantation unit. Control of the outbreak was achieved by a combination of contact isolation, feedback on hand hygiene, and gut decontamination with an orally administered fluoroquinolone. These interventions led to abrupt curtailment of the outbreak.

More than 50 outbreaks of infection due to organisms that produce extended-spectrum \(\beta\)-lactamases (ESBLs) have been reported [1]. In some hospitals, initial outbreaks of infection have been supplanted by the endemicity of the ESBL producers [2–5]. This may lead to increased mortality rates for patients when antibiotics that are inactive against ESBL producers are used [6]. As a consequence, empiric therapy may change, leading to increases in antibiotic resistance in other organisms [2, 3].

Control of endemic ESBL producers is difficult and may only be possible after significant nursing and medical reorganization is done, at substantial financial cost [3, 4]. Therefore, control of the initial outbreak of ESBL producers in a hospital or a specialized unit of a hospital, is of critical importance.

We describe control of an outbreak of infection due to ESBL-producing *Escherichia coli* that occurred among patients in a liver transplantation unit. In the 2 years before the outbreak, <5 patients with ESBL-producing organisms had been identified per year in our acute-care hospital and an associated long-term care facility. Therefore, we applied strenuous efforts to halt the outbreak.

**Methods.** During February 1998, 2 cases of bacteremia due to ESBL-producing *E. coli* were observed among patients in the liver transplantation unit within a 9-day period. An investigation was conducted to assess the potential asymptomatic spread of the organism.

Culture was performed on rectal flora samples from all patients who were in the transplantation unit for at least 3 days, during the admissions of 2 patients with bacteremia. Including the 2 patients with bacteremia, 6 (67%) of 9 liver transplantation candidates and recipients in the liver transplantation unit were found to be colonized with ESBL-producing *E. coli*. Two patients were colonized with both ESBL-producing *E. coli* and *Klebsiella pneumoniae*. A liver transplantation candidate in an associated long-term care facility was also found to be colonized with ESBL-producing *K. pneumoniae*. Only 1 of the 6 carriers of ESBL-producing *E. coli* had received a cephalosporin in the 6 months before the outbreak.

The genotypic relationships of ESBL-producing isolates that were recovered from each patient were determined by pulsed-field gel electrophoresis. Every ESBL-producing isolate of *E. coli* was genotypically similar, implying horizontal transfer of the clone.

Each patient in the liver transplantation unit was housed in a single room that contained a sink and nonmedicated soap. Nursing and medical staff were stopped on leaving a patient’s room and were asked to participate in an “infection control” teaching exercise. The glove juice sampling procedure (performed by donning sterile gloves containing tryptic soy broth) was performed on each staff member [7]. A total of 9 (32%) of 28 nurses and 3 (23%) of 13 physicians had positive hand culture results. Culture yielded organisms such as methicillin-resistant *Staphylococcus aureus* \((n = 4)\) and vancomycin-resistant *Enterococcus* species \((n = 2)\), but no ESBL-producing *E. coli*.

Staff members with positive hand culture results were confidentially informed of their results and given instruction on the methods and importance of hand washing. The rates of positive results among staff members was disseminated to the group as a whole by means of in-service sessions. A hand washing campaign was introduced on the basis of feedback on the high rates of hand carriage of pathogenic organisms. Contact isolation (use of gloves and gowns for all patient contact and contact with the patient’s immediate environment) was introduced at the same time for all patients who were found to be colonized with ESBL-producing *E. coli*. Contact isolation was
continued for the duration of the patient’s admission and for all subsequent admissions.

With the aim of reducing fecal loads of ESBL-producing organisms, orally administered norfloxacin (400 mg q12h for 5 days) was given to all carriers of ESBL-producing organisms (with the exception of the second patient with bacteremia, who died). Use of cephalosporins was not restricted. For no patient could ESBL-producing organisms be cultured from stool samples collected 48–72 h after administration of the last dose of norfloxacin. Diminution of stool carriage of ESBL-producing organisms was transient; 2 (40%) of 5 patients again had cultures that were positive for ESBL-producing organisms at 14 days after the last dose of norfloxacin and 3 (60%) of 5 patients had positive culture results at 28 days after the last dose (table 1).

Results and discussion. No further cases of infection with ESBL-producing E. coli were identified among patients in the liver transplantation unit or anywhere else in the hospital for 2 years after the outbreak. In the course of subsequent hospitalizations of colonized patients during the 6 months after the E. coli outbreak, there were 11 isolates of gram-positive organisms (4 of which were ciprofloxacin resistant) and 3 isolates of gram-negative organisms (none of which were ciprofloxacin resistant). Two of the gram-negative infections were due to ESBL-producing K. pneumoniae in patients previously noted to have carriage of this organism (at 4 and 16 months after initial isolation of this organism from stool samples).

Other authors have used restriction of third-generation cephalosporins to control endemic infection due to ESBL producers [3]. This approach has been effective, albeit at the cost of losing an entire class of antibiotics. Given the lack of association in our center of the use of third-generation cephalosporins with the development of colonization with ESBL-producing organisms, we believed that restriction of this antibiotic class would not be an effective mode of control. Although continued use of third-generation cephalosporins may have contributed to selective pressure that promoted ESBL production, the use of third-generation cephalosporins among patients in the liver transplantation unit was so low that the effect of restriction of this antibiotic class was thought to be negligible.

Our hospital serves as a national referral center for liver transplantation candidates in the Veterans Affairs health care system. Therefore, it is most likely that the ESBL producer was introduced to the liver transplantation unit by a patient who was referred from another hospital. In view of our fears of the chronic therapeutic problems of ESBL-producing organisms becoming endemic (particularly in the liver transplantation and intensive care units), we sought to apply aggressive measures for the control of infections with ESBL-producing organisms. Although we believed that contact isolation might decrease the opportunity for patient-to-patient transmission of ESBL-producing organisms, we were concerned by the lack of complete effectiveness of this measure, as demonstrated elsewhere [4]. Even during the outbreak, patients in the liver transplantation unit had been accommodated in private rooms.

We therefore chose to complement the use of contact isolation with 2 additional infection control measures. First, we demonstrated to our hospital staff that they were capable of transmitting pathogenic organisms from patient to patient via their hands. That 32% of nurses and 23% of physicians had hand carriage of a pathogenic organism was a graphic reinforcement of the need for improved hand washing practice. However, no staff member carried ESBL-producing E. coli. Therefore, although we could not prove transmission of the ESBL-producing organisms via the hands of our staff members, the high rates of hand carriage of other organisms strongly suggested that poor hand washing practices had been important in causing the outbreak. Transmission of ESBL-producing organisms from a common environmental source is extremely rare [1], and no changes in procedure were made that would have altered such transmission. No ESBL producers were found in 36 environmental sites sampled in the liver transplantation unit. Therefore, even in the absence of documented hand carriage, transmission of the outbreak strain by hands is the most

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<tr>
<th>Table 1. Orally administered norfloxacin (Nfx) produced a temporary reduction in rectal carriage of ESBL-producing organisms.</th>
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<td>Organism</td>
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<td>ESBL + Escherichia coli&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>ESBL + Klebsiella pneumoniae&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>Note</sup>. ESBL, extended-spectrum β-lactamase.

<sup>a</sup> A total of 6 patients were carriers of ESBL-producing E. coli; index patient 2 died before receiving norfloxacin therapy, and 1 patient died on day 12 after completion of norfloxacin therapy.

<sup>b</sup> A total of 3 patients were carriers of ESBL-producing K. pneumoniae.
logical means of patient-to-patient transmission of such organisms.

A weakness of our study was that we did not observe the hand washing practices of staff members and therefore could not demonstrate that providing staff with feedback on rates of carriage of hand flora improved performance of hand washing. However, unobtrusive observation was impossible, given the location of sinks within each patient’s room in the liver transplantation unit.

The second component of our intervention was administration of norfloxacin to carriers of ESBL-producing E. coli. Our rationale was that norfloxacin may be able to reduce the fecal load of ESBL-producing E. coli and, therefore, the quantity of such organisms on the patient’s skin. We found that for all carriers who were given norfloxacin, ESBL-producing organisms were not detectable in stool samples obtained 2–3 days after the completion of norfloxacin treatment. We suspect that the diminished quantity of organisms in carriers decreased the chance that a health care worker would acquire an ESBL-producing organism from the skin of his or her patients.

To our knowledge, no other groups have used norfloxacin to aid in the control of outbreaks of infection due to ESBL-producing organisms. The advantages of norfloxacin include its ready availability and ease of administration to ambulatory patients compared with the “slurries” associated with other orally administered antibiotics. However, we noted that stool carriage of ESBL-producing organisms was again detectable at 2 days to 2 weeks after discontinuation of norfloxacin. Clearly, orally administered norfloxacin cannot be considered as a means of permanently eradicating carriage of ESBL-producing organisms. We administered norfloxacin for only 5 days; longer-term administration of the antibiotic may have produced more prolonged periods of suppression of growth in stool, but we doubt whether it would induce permanent loss of stool carriage. Regardless, our aim was only to reduce stool carriage of ESBL-producing organisms during the intense outbreak period.

It should be noted that ~15%–30% of ESBL-producing organisms [5, 8] are resistant to quinolones and therefore are unlikely to be suppressed by use of norfloxacin prophylaxis. In addition, the use of quinolone prophylaxis carries with it the danger of quinolone resistance in both gram-positive and gram-negative organisms. We did not demonstrate quinolone resistance in the recurrent isolates of ESBL-producing organisms. In conclusion, we do not believe that decolonization with norfloxacin should be attempted in settings where ESBL-producing organisms are endemic but should be formally evaluated in the control of outbreaks of infection.

References