

## Recurrent *Escherichia coli* Bacteremia

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***Escherichia coli* is the most common gram-negative organism associated with bacteremia. While recurrent *E. coli* urinary tract infections are well-described, recurrent *E. coli* bacteremia appears to be uncommon, with no episodes noted in multiple series of patients with gram-negative bacteremias. We report on 5 patients with recurrent bloodstream infections identified from a series of 163 patients with *E. coli* bacteremia. For each patient, the isolates from each episode were analyzed by pulsed-field gel electrophoresis (PFGE) and ribotyping and for the presence of *E. coli* virulence factors. For each of four patients, the index and recurrent episodes of bacteremia represented the same strain as defined by PFGE, and the strains were found to carry one or more virulence factors. The remaining patient, with two episodes of bloodstream infection separated by a 4-year interval, was infected with two isolates that did not carry any virulence factors and that were clonally related by ribotype analysis but differed by PFGE. All five patients had either a local host defense defect (three patients) or impaired systemic defenses (one patient) or both (one patient). Thus, recurrent *E. coli* bacteremia is likely to represent a multifactorial process that occurs in patients with impaired host defenses who are infected with virulent isolates.**

*Escherichia coli* is the species that most frequently causes gram-negative bacteremia. In numerous reports describing the clinical and microbiological aspects of this disease, the frequency and nature of recurrent bacteremia have not been addressed (8, 13, 22). Several studies suggest that bacterial factors may be predisposing factors to the persistence of virulent strains in patients or the environment. For example, isolates obtained in cultures of perineal samples from women with symptomatic urinary tract infections (UTIs) at various times posttreatment typically have the same O serotype as the prior urinary tract isolate (9). In an outbreak of urinary tract disease within a neonatal unit, the epidemic strain, a P-piliated *E. coli* serotype O6:K5 strain, was also cultured from the feces of the hospital staff (20). We recently observed that four of nine patients who failed therapy for UTIs had a recurrent episode with the original adhesin-positive strain of *E. coli*, as determined by analysis of the chromosomal DNAs of the isolates (11). Here we report on 5 patients with recurrent *E. coli* bacteremia identified during a prior study of *E. coli* sepsis in 163 patients at two hospitals (16) and discuss the patient and bacterial factors associated with recurrent disease.

### CASE REPORTS

**Patient 1.** A 52-year-old man presented in February 1987 to the Boston Veterans Affairs Medical Center (BVAMC) with a complaint of 2 weeks of fever, chills, generalized myalgias, and malaise. Three years previously, the patient was found to have adenocarcinoma of the ampulla of Vater and had undergone a partial small-bowel resection, partial pancreatectomy, and cholecystectomy. On admission, physical examination was remarkable only for a fever of 38.3°C. Blood cultures yielded *E. coli* isolates resistant only to tetracycline; a urine culture was negative. Liver function tests were within the

normal ranges. A chest radiogram and computed tomography (CT) scan of the abdomen were normal. No source of the bacteremia was determined. He was treated with ampicillin and gentamicin for 2 weeks, with clinical improvement, and was discharged.

In January 1991, he was admitted to another hospital with the acute onset of right upper quadrant pain, nausea, vomiting, and shaking chills. A CT scan of the abdomen revealed a 5-cm intrahepatic abscess, and the following day he was transferred to BVAMC. Cultures of blood yielded *E. coli* and *Clostridium perfringens*. The hepatic abscess was drained emergently under CT guidance; culture of the abscess fluid also yielded *E. coli* and *C. perfringens*. The *E. coli* isolate was resistant to ampicillin and piperacillin and was susceptible to tetracycline. The patient's hospital course was complicated by the development of disseminated intravascular coagulation, hemodynamic instability, and necrosis of numerous fingers and toes, requiring amputation. He was treated with ampicillin, gentamicin, and clindamycin for approximately 4 weeks and was discharged 5 months after admission. He was still alive 2 years after this second episode of bloodstream infection.

**Patient 2.** A 39-year-old man was admitted to BVAMC in April 1987 with fever to 39°C and lethargy. Two years previously he had been found to have adenocarcinoma of the esophagus; he received radiation therapy to the thorax, and chemotherapy with 5-fluorouracil, adriamycin, and methotrexate. One month previously the patient had been admitted to BVAMC with a complaint of dysphagia; endoscopy was complicated by esophageal perforation necessitating thoracotomy for repair. The postoperative course was unremarkable and he was discharged. Two weeks previously he was admitted to BVAMC with a complaint of posterior thoracic pain. A radiogram of the lumbar and thoracic spine revealed an erosive lesion at the second and third lumbar vertebrae that crossed the disk space. The patient refused any further studies and was discharged.

Upon readmission in April 1987, a CT scan of the thorax and abdomen revealed a paraaortic and paraspinous abscess. Anti-

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biotic therapy with oxacillin and gentamicin was instituted. Blood cultures obtained on admission yielded *E. coli* resistant only to tetracycline. Two weeks later the patient agreed to drainage of the abscess; cultures yielded *Candida albicans*, *Enterococcus fecalis*, and coagulase-negative staphylococci. His antibiotic therapy was changed to piperacillin and amikacin. Repeat aspirations 2 and 3 weeks after the initial drainage procedure yielded similar culture results. The patient refused antifungal therapy or surgical intervention. He received 6 weeks of antibiotic therapy and was discharged.

He was readmitted in November 1987 with a 3-day history of fevers to 38.8°C, chills, diaphoresis, and increasing back pain. A bone scan revealed increased uptake at the second lumbar vertebra; a CT scan of the abdomen revealed paracural and soft-tissue thickening in the area of the former paraspinal abscess, a pericardial effusion, and new paraaortic adenopathy. A chest radiogram revealed a right pleural effusion but was otherwise unremarkable. Cultures of blood and sputum samples obtained on admission yielded *E. coli* isolates susceptible to all antibiotics tested. He was treated with penicillin, gentamicin, and metronidazole for 1 week. The patient died 8 months later, and an autopsy revealed widely metastatic adenocarcinoma of the gastroesophageal junction; no residual abscess was noted.

**Patient 3.** A 53-year-old man was admitted to BVAMC in April 1988 with the acute onset of nausea and vomiting. He had a history of ethanol abuse and cirrhosis complicated by recurrent episodes of variceal bleeding and ascites. On admission he was febrile to 39.2°C. Blood cultures yielded *E. coli* resistant to ampicillin, tetracycline, and chloramphenicol and with intermediate resistance to cephalothin and piperacillin; cultures of the urine, sputum, and ascitic fluid samples were negative. After 7 days of antimicrobial therapy with cefotetan, the patient left the hospital against medical advice. He was readmitted a week later with fever. Although cultures of the blood, urine, and sputum were negative, recurrent infection was suspected; he was treated with cefotetan for 2 weeks and was discharged.

One day later the patient was readmitted with fever to 39.7°C. Blood cultures yielded *E. coli* and *Lactobacillus casei*; cultures of urine and ascitic fluid samples were negative. The antimicrobial susceptibilities of the *E. coli* isolate were similar to those of the prior isolate, except for complete resistance to piperacillin and cephalothin. An echocardiogram revealed a calcified aortic valve without vegetations. He was treated with ceftriaxone and penicillin for 4 weeks and was discharged.

He was readmitted 5 days after discharge with fever to 39.6°C. Cultures of blood yielded *E. coli* isolates with the same antimicrobial susceptibilities as the second bloodstream isolate; urine and peritoneal fluid cultures were negative. A CT scan of the abdomen, an indium-labeled leukocyte scan, a gallium scan, and a repeat echocardiogram revealed no apparent focus of infection. Pyelephlebitis was suspected, but angiography was not performed. The patient was again treated with ceftriaxone for 4 weeks. The patient had no further episodes of bacteremia but remained hospitalized because of complications related to cirrhosis and died 3 months after admission. No autopsy was performed.

**Patient 4.** A 61-year-old man was admitted to BVAMC in February 1991 with a complaint of right heel pain and the inability to bear weight on his right foot secondary to vascular insufficiency of the right lower extremity. The patient had received a cadaveric renal transplant 1 month earlier. A preoperative culture of urine had yielded *E. coli* isolates susceptible to all antibiotics tested, and the infection was not treated. On admission he was febrile to 39.4°C; cultures of

blood and urine yielded *E. coli* isolates with the same antibiotic susceptibilities as the previous isolates. He was treated with aztreonam for 2 weeks. The day after antibiotics were discontinued the patient had recurrent fever to 38.6°C; cultures of blood and urine were again positive for *E. coli* isolates with susceptibilities identical to those of isolates in the prior cultures. He was again treated with aztreonam for 2 weeks. There were no further episodes of recurrence; 1 year later he was alive and well.

**Patient 5.** A 72-year-old man was admitted to the Long Beach, California, Veterans Affairs Medical Center (LVAMC) in December 1990 with nausea, vomiting, epigastric pain, and a fever of 37°C. He had a history of paraplegia secondary to myelopathy at T10-11 from arachnoiditis associated with spinal anesthesia in 1943. He had multiple urinary tract infections in the past; because of urinary incontinence he wore a condom catheter. A blood culture obtained at the time of admission yielded *E. coli* isolates resistant to ampicillin, gentamicin, trimethoprim-sulfamethoxazole, and tobramycin as well as coagulase-negative staphylococci; a culture of urine yielded multiple bacterial organisms that were not further identified. He was treated with cefazolin for 15 days but continued to have fevers. A urine culture of urine at the end of therapy yielded *Pseudomonas aeruginosa*; a culture of blood was negative. He was treated with gentamicin and piperacillin for 10 days. Five days after completing therapy, he again became febrile. Cultures of blood and urine yielded *E. coli*. The urine isolate had antibiotic susceptibilities identical to those of the index blood isolate, while the blood isolate was additionally resistant to cefazolin. Radiologic evaluation with a gallium scan, CT scan, bone scan, and a magnetic resonance image of the spine revealed a paraspinal abscess and osteomyelitis at T10-11. The patient refused biopsy at that time. He was treated with amikacin and ceftazidime for 5 weeks. A needle biopsy of the thoracic spine was then performed. Histologic evaluation was negative for malignant cells; a specimen sent for culture yielded no growth. The patient was treated orally with ciprofloxacin for 4 months with no further evidence of infection. He was still alive 1 year later.

## MATERIALS AND METHODS

**Bacterial isolates.** Isolates of *E. coli* were obtained from routine patient blood cultures submitted to the clinical microbiology laboratories at BVAMC and LVAMC. At each institution, *E. coli* isolates from distinct episodes of bloodstream infection during the study period were collected prospectively. Bloodstream isolates of *E. coli* cultured within a 2-week interval were considered to represent the same episode of bacteremia.

**Genotypic analyses.** For each isolate, whole cellular DNAs from the bacteria were prepared and digested with *EcoRI* (New England Biolabs, Beverly, Mass.) (18). Dot blots and Southern transfers of *EcoRI*-digested DNA transferred to nylon membranes were prepared as described previously (15, 16). DNA homologous to the adhesins *pap* (which encodes for P pili), *sfa* (S pili), *afa* (afimbrial adhesin AFA), and *bma* (M adhesin) and the *E. coli*  $\alpha$ -hemolysin *hly* were detected by probing the dot blots as described previously (16). Detection of aerobactin was performed by probing the dot blots with the 6.9-kb *EcoRI*-*BamHI* fragment of pABN1, which spans the entire aerobactin operon (pABN1 was kindly supplied by Stephen Opal) (5). Polymorphisms associated with the *E. coli* ribosomal operon (ribotypes) were detected after probing the Southern blots with the 7.5-kb *BamHI* fragment of pC6, which contains the entire *rrnB* ribosomal operon (15). For pulsed-

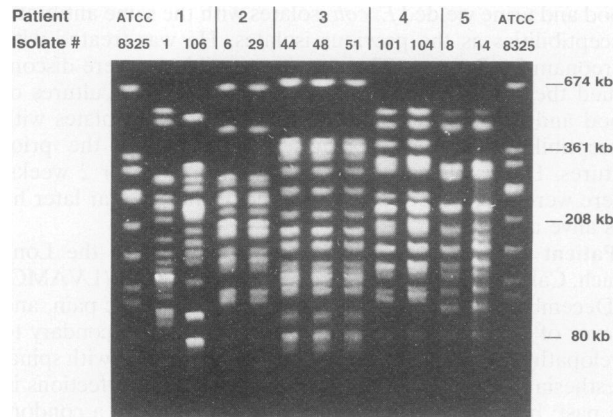


FIG. 1. PFGE to resolve *Xba*I restriction fragments of whole chromosomal DNAs of the isolates from five patients with recurrent *E. coli* bacteremia. The isolates from patients 2 to 5 had indistinguishable PFGE patterns or differed by a single band (patient 5, ~200 kb) and were considered to have relapsing infections with the same strain, whereas the two strains from patient 1 differed by PFGE and were considered to represent different strains.

field gel electrophoresis (PFGE), whole chromosomal DNA in agarose was digested with *Xba*I and the restriction fragments were separated in a CHEF DRII apparatus (Bio-Rad, Richmond, Calif.) with  $0.5 \times$  TBE buffer at 200V and 15°C for 22 h and pulse times from 1 to 40 s with linear ramping (18).

## RESULTS

The patients described in detail here were identified as part of a previously reported analysis conducted at BVAMC and LVAMC to determine the roles of virulence factors in *E. coli* bacteremia (16). At BVAMC, 119 episodes of *E. coli* bacteremia occurred in 113 patients from January 1988 through December 1991. At LVAMC, 51 episodes occurred in 50 patients from January 1991 through December 1991. Among

the 163 patients at the two hospitals, 5 (3%) patients had recurrent bacteremia.

For each patient with multiple episodes of bacteremia, the isolates from each separate episode were compared by PFGE and ribotyping and for the presence of the *E. coli* virulence operons *pap*, *sfa*, *afa*, *bma*, *hly*, and *aer*. For each of four patients (patients 2 to 5), the index isolate and the subsequent isolate(s) were considered to represent the same strain on the basis of genotypic analysis. For each of three patients (patients 2 to 4), the PFGE patterns of paired isolates were indistinguishable, and for one patient (patient 5), the patterns differed at a single band (~200 kb) (Fig. 1). The isolates from these four patients were positive for one or more virulence factors (Table 1); the index and recurrent isolates from each patient carried the same virulence factors. For each of these four patients, the ribotypes of the index and recurrent isolates were identical (patients 2 to 4) or differed by a single band (patient 5), which is consistent with a single genetic event (Fig. 2). PFGE or ribotype patterns differing by only a single band shift are consistent with two independent isolates of the same strain (17). For the remaining patient (patient 1), the index and the subsequent bloodstream isolates represented different strains, as indicated by the PFGE analysis. Neither isolate carried any of these virulence factors; however, they were genetically related, as indicated by ribotypes that differed by a single band shift. Thus, in each of four patients, the multiple episodes of bacteremia represented relapsing disease, i.e., recurrence with the same strain, and the isolates were positive for one or more virulence factors, while the fifth patient had multiple episodes of bloodstream infection with genetically related strains that lacked such factors and that represented reinfection.

Multiple patient factors were examined for their roles in predisposing to the patients recurrent infection. Defects in local host defenses were present in four patients: one with abnormal biliary drainage following a Whipple procedure (patient 1), one with vertebral adenocarcinoma (patient 2), one with abnormal urinary tract drainage status post renal transplantation (patient 4), and one with abnormal clearance mechanisms because of neurologic deficits (patient 5). Defects in systemic host defenses were present in two patients, one

TABLE 1. Genotypic and serotype characterizations among the isolates from five patients with recurrent *E. coli* bacteremia

Patient no. <sup>a</sup>	Isolate no.	Date of isolation (mo/day/yr)	PFGE pattern <sup>b</sup>	Ribotype <sup>c</sup>	O serotype <sup>d</sup>	Virulence factors <sup>e</sup>
1	1	2/24/87	a	G.1	8	None
	106	1/10/91	b	G	85w	None
2	6	4/5/87	c	E	1	<i>pap</i> , <i>aer</i>
	29	11/13/87	c	E	1	<i>pap</i> , <i>aer</i>
3	44	4/6/88	d	D	18	<i>pap</i> , <i>sfa</i> , <i>hly</i> , <i>aer</i>
	48	5/9/88	d	D	18	<i>pap</i> , <i>sfa</i> , <i>hly</i> , <i>aer</i>
	51	6/30/88	d	D	18	<i>pap</i> , <i>sfa</i> , <i>hly</i> , <i>aer</i>
4	101	12/20/90	e	I	18	<i>pap</i> , <i>sfa</i> , <i>hly</i>
	104	1/3/91	e	I	18	<i>pap</i> , <i>sfa</i> , <i>hly</i>
5	8	12/24/90	f	I	Neg	<i>pap</i> , <i>sfa</i> , <i>hly</i>
	14	1/21/91	f.1	I.2	18	<i>pap</i> , <i>sfa</i> , <i>hly</i>

<sup>a</sup> Patients 1 to 4 were treated at BVAMC; patient 5 was treated at LVAMC.

<sup>b</sup> PFGE pattern designations indicate similarities and differences among isolates in this report.

<sup>c</sup> Ribotype pattern designations correspond to designations assigned during the analysis of all 170 isolates in the series (16).

<sup>d</sup> O serotype designations include those with weak agglutinations (w) and nonagglutinating strains (Neg); serotyping was performed for all 170 study isolates (18a) by Richard Wilson, *E. coli* Reference Laboratory, Pennsylvania State University, State College.

<sup>e</sup> The presence of virulence factors was determined by probing for nucleotide sequences within each operon (16). The virulence factors of isolates that were probe negative for all of the virulence operons are listed as none.

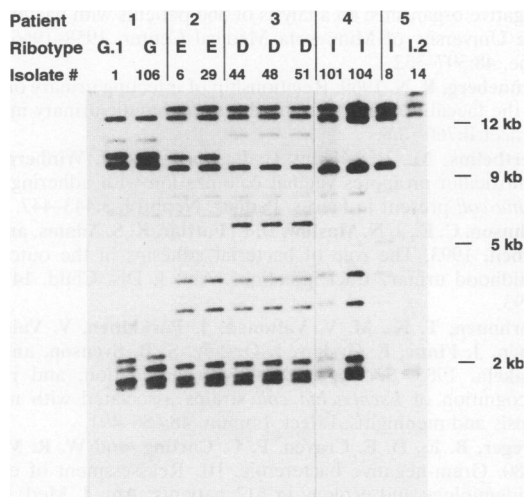


FIG. 2. Polymorphisms associated with the ribosomal operon (ribotypes) after *EcoRI* digestion of chromosomal DNAs of the isolates from five patients with recurrent *E. coli* bacteremia. The isolates from patients 2 to 4 had identical ribotypes, whereas the isolates from patients 1 and 5 differed by one and two bands, respectively, which is consistent with genetically related strains. For patient 5, one of the bands representing a doublet at 9 kb appears as a singlet at 9 kb and two new bands at 18 and 3 kb, which is consistent with a new *EcoRI* restriction site in one of the 9-kb fragments. The isolates from patients 4 and 5 were run in a second gel; the isolates from each patient appear in adjacent lanes of the same gel.

with cirrhosis (patient 3) and one receiving immunosuppressive agents to prevent rejection of a renal transplant (patient 4). Thus, local defense system defects were present in four patients and systemic defects were present in two patients; both types of defects were present in one patient.

## DISCUSSION

Recurrent bacteremia caused by *E. coli* was not mentioned in several large series of *E. coli* bacteremias (8, 13, 22), and recurrent infection with *E. coli* involving other sites has been reported in only a few studies. A recent study by Johnson et al. (11) examined the isolates from 35 children with *E. coli* UTIs, of whom 9 failed therapy. Five of these nine patients were reinfected with new strains, as determined by PFGE. Thus, in certain clinical situations, recurrent disease may represent reinfection (i.e., recurrence with a second strain) rather than relapse (i.e., recurrent disease with the index strain).

The pathogenesis of recurrent bacteremia may involve host factors that impair bacterial clearance, i.e., abnormalities of local or systemic host defense mechanisms or bacterial factors that confer a survival advantage (e.g., adhesins that facilitate mucosal colonization). Of the five patients described here, each had one or more identifiable defects in local or systemic host defense mechanisms. In addition, the organisms from all four patients with multiple episodes of bacteremia caused by a single strain had bacterial factors that have been associated with invasive infection (4, 12, 16).

Defects in local host defenses are known to be predisposing factors to the development of infection. For example, vesicoureteral reflux, renal scarring, benign prostatic hypertrophy, and the presence of urinary drainage devices are predisposing factors to upper UTI and bacteremia (2, 14), and endotracheal intubation, acute cholecystitis, and surgical procedures have been implicated in the development of *E. coli* bacteremia from

other primary foci (16). Additionally, in our prior study (16) we observed that defects in systemic host defenses associated with impaired leukocyte function, e.g., advanced liver disease, renal failure, and immunosuppressive therapy for renal transplantation, were independently associated with the development of *E. coli* bacteremia.

Although *E. coli* bacteremia is associated with significant mortality (13), none of the five patients reported here died as a result of acute sepsis, and only one patient died during any of the hospitalizations related to an episode of bloodstream infection. This is consistent with the observation that the mortality associated with gram-negative bacteremia correlates primarily with the presence of comorbid illnesses (13, 16).

Bacterial adhesins and hemolysin have been implicated in the pathogenesis of acute *E. coli* infections (2, 4, 12, 16). In particular, the adhesins *pap*, *sfa*, and *afa* have been associated with acute UTI and bacteremia (2, 4, 16), and *sfa* has been associated with neonatal meningitis (12). The presence of hemolysin may result in the increased virulence of adhesin-positive strains (21). In addition to conferring a colonization advantage, P-piliated and hemolytic strains of *E. coli* may inhibit normal leukocyte killing of the bacteria (7, 19). Four of the five patients reported here were infected with adhesin-positive strains, suggesting that these virulence factors may also contribute to strain persistence and relapsing infection.

Similar conclusions have been suggested in studies of non-bloodstream infections. Each of the four patients with relapsing UTI described by Johnson et al. (11) were infected with *pap*-positive isolates. Tullus et al. (20) described an outbreak of UTI among patients in a neonatal unit caused by a P-piliated strain of *E. coli* which persisted within the feces of patients and hospital staff after resolution of the outbreak. Since each patient from the current study who had recurrent bacteremia from a persistent focus was also infected with an adhesin-positive isolate, such strains may have a selective survival advantage in a protected focus. Of interest, treatment with the beta-lactam antibiotic amoxicillin has been reported to promote vaginal colonization with P-piliated *E. coli* in primates (10). All of the patients in the present study received antibiotics of the same class.

The patient with an abnormal biliary tract anatomy who had two episodes of bacteremia separated by 4 years was infected with different isolates, as indicated by PFGE. However, the two isolates had related ribotypes and electrophoretic types (data not shown). Isolates that have common ribotypes have been demonstrated to be genetically related; isolates that differ by a single band, which is consistent with a single genetic event, are considered to be represented by genetically related lineages (3, 17). PFGE has been shown to be superior to either multilocus enzyme electrophoresis or ribotyping for discriminating between unrelated isolates of *E. coli* (1). In a study of stool colonization of a single individual whose stools were cultured repeatedly over an 11-month period, multiple distinct strains of *E. coli* (as determined by multilocus enzyme electrophoresis) were detected at least once, but only two strains were resident in the bowel over the entire sampling time (6). Since the strains of *E. coli* resident in the bowel are relatively stable over prolonged periods, it is likely that the two episodes of bacteremia represent independent events resulting from genetically related bowel flora. Although these strains were adhesin negative, the same ribotype was detected in 11 other isolates (only one of which was adhesin positive; none were hemolysin positive) from epidemiologically unrelated patients at LVAMC and BVAMC. Thus, isolates with this genetic lineage may have increased capacities for invasion and persistence

resulting from the presence of factors other than bacterial adhesins.

In conclusion, although recurrent *E. coli* bacteremia is uncommon, we observed that in most such patients, recurrent sepsis represented relapsing infections caused by the index strain. On clinical review, these patients typically had anatomic defects associated with abnormal local host clearance mechanisms, systemic immune defects associated with impaired leukocyte function, or both types of defects. In addition, most isolates that caused recurrent bacteremia carried one or more adhesin operons. We conclude that patients with recurrent *E. coli* bacteremia be considered as subjects of investigations of such host and bacterial factors. Appropriate management for the prevention of further recurrences might include treatment directed at the comorbid host pathology, prolonged courses of antibiotics, and possibly, specific regimens designed to eradicate the virulent strain from the commensal flora.

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