CONCISE COMMUNICATION

Uropathogenic Escherichia coli as Agents of Diverse Non–Urinary Tract Extraintestinal Infections

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Escherichia coli isolates from 3 consecutively encountered patients with serious, invasive, non–urinary tract extraintestinal infections (pneumonia, deep surgical wound infection, and vertebral osteomyelitis with associated epidural/psoas/fililicus abscesses) were characterized, using molecular methods, as to extended virulence genotype and phylogenetic background. All 3 isolates exhibited virulence genotypes and genomic profiles characteristic of specific familiar virulent clones of extraintestinal pathogenic E. coli (ExPEC), which traditionally have been regarded primarily as uropathogenic or as associated with meningitis. These included E. coli O1/O2:K1:H7, E. coli O18:K1:H7, and a recently described E. coli O11/O17/O77:K52: H18 clonal group (clonal group A). These findings demonstrate the extraintestinal pathogenic versatility of ExPEC clones, which supports the use of an inclusive designation for such strains and suggests the possibility of cross-syndrome protective interventions. They also provide novel evidence that multidrug-resistant epidemic clonal group A can cause extraintestinal infections other than uncomplicated urinary tract infections and can cause them in hosts other than young women.

As an extraintestinal pathogen, Escherichia coli is best known for causing urinary tract infection (UTI), bacteremia, and neonatal bacterial meningitis (NBM) [1, 2]. However, E. coli can also infect almost any anatomic site. The distinctive strains of E. coli responsible for most cases of UTI, sepsis, and NBM represent a limited number of virulent clones that are characterized by specific O:K:H serotypes and derive predominantly from E. coli phylogenetic group B2, as defined by multilocus enzyme electrophoresis, and, to a lesser extent, group D [1, 2]. They typically exhibit multiple specialized virulence-associated factors (VFs) that enable them to overcome or subvert host defense mechanisms, injure or invade host tissue, and stimulate a noxious inflammatory response, thereby causing extraintestinal disease [1, 2]. Recognition of the commonality among diverse virulent E. coli strains irrespective of clinical syndrome prompted the recent proposal of the inclusive term “extraintestinal pathogenic E. coli” (ExPEC) for such strains in place of traditional more restrictive terms, such as “uropathogenic E. coli” (UPEC), “sepsis-associated E. coli,” and “meningitis-associated E. coli” (MENEC) [2].

Whether the E. coli strains that cause extraintestinal infection syndromes other than UTI, bacteremia, and NBM are similar to the ExPEC that cause these more classic syndromes has been less studied. However, recent data suggest considerable commonality among urinary-source versus pulmonary-source E. coli bacteremia isolates [3] and among spontaneous bacterial peritonitis isolates versus classic ExPEC clones [4]. To provide further insights into this question, we extensively characterized 3 E. coli isolates from patients who had serious invasive extraintestinal infections other than UTI, bacteremia, and meningitis.

Subjects, Materials, and Methods

Strains and subjects. In October 2000, the Infectious Disease consultant (T.A.R.) at Erie County Medical Center (Buffalo, NY) identified 3 patients from whom E. coli was isolated from specimens other than urine, blood, cerebrospinal fluid, or surface swabs. Medical record review and bedside evaluation revealed that, according to standard clinical criteria, all 3 had a significant extraintestinal infection at the site that yielded E. coli. The clinical syndromes and associated specimen types included pneumonia (tracheal aspirate, blood culture), lumbar deep surgical wound infection (intraoperative...
missions, but the counts dropped to 1200 and 57,000 cells/mL. Chest auscultation revealed left posterior rales. The patient's condition deteriorated initially, requiring intubation and mechanical ventilatory assistance. Sputum Gram stain showed abundant neutrophils and many gram-negative bacilli. Imipenem and ceftriaxone were administered. Blood and sputum cultures yielded *E. coli* resistant to TMP-SMZ, ampicillin, and chloramphenicol and intermediate susceptible to piperacillin and ampicillin/sulbactam. Urine cultures were negative. Abdominal CT scanning revealed no intra-abdominal focus of infection. Ceftriaxone alone was used to complete a 14-day treatment course.

**Case subject 2 (strain 186).** A 79-year-old woman with Alzheimer-type dementia was admitted with a 2-week history of progressive lower back pain, lower extremity weakness, and frequent falls. She denied fevers, chills, and other constitutional symptoms. She appeared comfortable but was lethargic. Vital signs were normal. Spinal tenderness was present from L2 through S1. Motor strength was markedly diminished in both lower extremities.

The patient's WBC count was 18,700 cells/μL, with 65% segmented neutrophils and 14% band forms. The erythrocyte sedimentation rate was 65 mm/h, and the level of C-reactive protein was 8.6 mg/dL (normal, 0.1–0.5 mg/dL). Spinal CT and magnetic resonance imaging disclosed an extensive, destructive osteomyelitis and discitis of L3–L5, with associated epidural abscess and compression of the thecal sac. Bilateral psoas and iliacus abscesses were present, as were scattered gas collections anterior to L3–L5 and within the spinal canal. Blood cultures and pus from the epidural space, obtained by CT-guided aspiration, yielded a fully susceptible *E. coli*. Urine culture test was negative. Intraoperative drainage and lavage, spinal decompression, and debridement of necrotic tissue and bone were performed, and bone grafts were placed. Ceftriaxone was administered intravenously for 6 weeks, with a satisfactory clinical response.

**Case subject 3 (strain 185).** A 50-year-old man without underlying medical conditions was admitted because of a 1-week history of a draining lumbar surgical wound. Three weeks previously he had undergone posterior spinal decompression and fusion, with implantation of hardware and bone and fat grafts, for spinal stenosis and degenerative disk disease. Ten days later he developed purulent drainage from the wound without fever or chills. Outpatient cephalaxin therapy had no effect. The patient appeared comfortable and was afebrile. The lumbar incision was partially dehisced and drained pus. The WBC count was 8500 cells/μL (81% neutrophils).

Surgical exploration of the wound revealed no superficial evidence of infection, but it did reveal abundant pus within the deeper layers down to the level of the implanted hardware. The dura, bone, and fat grafts were intact, and the hardware was stable. The surgical site was aggressively lavaged, drains were placed, and the wound was closed. Intraoperative cultures grew fully susceptible *E. coli*. Drains were removed 2 days later. Ciprofloxacin (intravenous followed by oral) was administered for 12 weeks total. The patient had an excellent outcome, with no evidence of relapse 2 years later.

**Virulence genotypes.** By multiplex PCR, the 3 patients' *E. coli* isolates each contained multiple putative ExPEC VFs in patterns suggesting membership in specific classic virulent clones (table 1). The VF profile of strain 184 (from case subject 1) suggested 2 closely related clonal groups from *E. coli* phylogenetic group D (i.e., the O15:K52:H1 clonal group [11, 12]
Table 1. Extended virulence genotypes and serotypes of selected extraintestinal *Escherichia coli* clinical isolates.

| Strain, serotype | Reference | Source | Group | papA allele | papG allele | sfa/foc | sfaS | iha | fim | bly | cnf1 | icedA | intA | ireN | fyuA | ireA | kpsMT group | kpsMT II | kpsMT III | H7 | fliC | cvaC | traT | ibeA | iss | ompT | malX |
|------------------|-----------|--------|-------|-------------|-------------|--------|------|-----|-----|-----|-----|-------|------|-----|------|-----|--------|---------|----------|---|-----|------|------|-----|-----|------|-----|-----|-----|
| 184, NA          | Present   | Pneumonia | D     | 16          | II          | +      | +    | +   | +   | +   | +   | +     | +    | +   | +    | +   | +      | +       | +         | + | +   | +    | +    | +   | +   | +    | +   | +   | +   |
| UMN26, O17:K52:H18 | [10]    | Cystitis | D     | 16          | II          | +      | +    | +   | +   | +   | +   | +     | +    | +   | +    | +   | +      | +       | +         | + | +   | +    | +    | +   | +   | +    | +   | +   | +   |
| 185, NA          | Present   | Wound   | B2    | 10          | III         | +     | +    | +   | +   | +   | +   | +     | +    | +   | +    | +   | +      | +       | +         | + | +   | +    | +    | +   | +   | +    | +   | +   | +   |

**NOTE.** *cdtB*, cytolethal distending toxin; *cnf1*, cytolethal necrotizing factor 1; *cwaC*, colicin V; *fim*, type 1 fimbriae; *fliC*, flagellin; *fyuA*, yersiniabactin receptor; *hly*, hemolysin; *ibeA*, invasion of brain endothelium A; *iha*, putative adhesin–siderophore; *ireA*, siderophore receptor; *ireN*, siderophore receptor; *iss*, increased serum survival; *iatA*, aerobactin receptor; *kpsMT*, group II and group III capsule synthesis; *K1*, K1 *kpsMT* II variant; *malX*, marker for pathogenicity island from strain CFT073; *NBM*, neonatal bacterial meningitis; *ompT*, outer membrane protease T; *osteö.*, vertebral osteomyelitis with multiple abscesses; *papA*, P fimbrial structural subunit, with alleles F7–1–F16; *papG*, P fimbrial adhesin molecule, with alleles I, II, and III; *sfa/foc*, S and F1C fimbriae; *sfaS*, S fimbrial adhesin; *traT*, serum-resistance associated; *UTI*, urinary tract infection.

*a* Present of trait; —, absence of trait. All isolates were negative for *focG* (F1C fimbriae), *afa/dra* (Dr-binding adhesins), *bmaE* (M fimbriae), *gafD* (G fimbriae), and *rfc* (O4 lipopolysaccharide synthesis).

*b* Full O:K:H serotypes not available (NA) and O typing results uninformative for strains 184, 185, and 186. RS218 and IHE3034 represent the OMP pattern 6 and 9 subclones, respectively, of *E. coli* O18:K1:H7 [9].

*c* *E. coli* phylogenetic group A, B1, B2, or D.

*d* Isolates positive for *papA* or *papG* were also positive for *papC* and *papEF*. 
Figure 1.  A. Phylogenetic analysis of selected extraintestinal *Escherichia coli* isolates. Randomly amplified polymorphic DNA (RAPD) profiles, as generated using (separately) decamer primers 1247, 1254, 1281, 1283, and 1290 (shown in computer reconstruction), were subjected to cluster analysis according to the unweighted pair-group method with averaging to derive the dendrogram. Strains from the *E. coli* Reference collection are identified in parentheses as to phylogenetic group. Reference clinical isolates RS218 (*E. coli* O18:K1:H7; neonatal meningitis) [9], 31/P (*E. coli* O15:K52:H1; urinary tract infection) [10], and 135 (*E. coli* clonal group A; cystitis) [13] represent their respective clonal groups. The cluster of marker lanes (molecular weight, MW) reveals the degree of variability inherent in gel electrophoresis and image analysis, independent of amplification.  

B. Comparative RAPD analysis of selected *E. coli* isolates, using oligomer OPG13. Each isolate from the present study matches a reference isolate from a patient with cystitis (UMN26, from *E. coli* clonal group A: O17:K52:H18 [13]), neonatal meningitis (RS218: *E. coli* O18:K1:H7 [9]), or urosepsis (H15: *E. coli* O2:K1:H7 [5]). Of the 2 reference *E. coli* O18:K1:H7 neonatal meningitis isolates, strain 185 more closely resembles RS218 (outer membrane protein [OMP] profile 6 subclone) than it does IHE3034 (OMP-9 subclone) [9]. Lanes 1 and 9, 250-bp marker.

and the recently described TMP-SMZ–resistant clonal group A [CGA] [10, 13]). The VF profile of strain 185 (from case subject 3) suggested that the OMP-6 subclone of *E. coli* O18:K1:H7, which is from phylogenetic group B2, is a prominent cause of both uncomplicated cystitis in women and NBM and includes archetypical strains NU14 (cystitis) and RS218 (NBM) [8, 9, 14]. The VF profile of strain 186 (from case subject 2) suggested the O1/O2:K1:H7 clonal group, also from phylogenetic group B2, which is a prominent cause of pyelonephritis and urosepsis [5, 15].

**Phylogenetic analysis and O antigens.** Composite RAPD analysis supported these inferences regarding the isolates’ clonal origins (table 1 and figure 1). In the UPGMA-based tree, isolates 185 and 186 were placed together with NBM isolate RS218 (O18:K1:H7; group B2) in a cluster that also contained ECOR 62 (O2:K1; group B2) (figure 1A). In contrast, isolate 184 was
placed as the nearest neighbor to CGA reference strain 135 (group D) within a larger cluster that also contained representatives of the O15:K52:H1 clonal group and ECOR strains 44 and 46 (group D; figure 1A). RAPD analysis using oligomer OPG13 was confirmatory and demonstrated strain 185 to be a member of the OMP 6 subclone of E. coli O18:K1:H7 (figure 1B). O serotyping was uninformative (table 1).

Discussion
We provide evidence from a detailed pathotypic and phylogenetic analysis of E. coli isolates from 3 adults with serious non–urinary tract, nonmeningeal extraintestinal infections that such infections can be caused by the same virulent E. coli strains that classically cause UTIs, NBM, and sepsis. This demonstrates the pathogenic versatility of such virulent E. coli clones and, hence, urges the use of an inclusive designation, such as ExPEC, rather than the more restrictive conventional terms UPEC and MENEC [2]. It also suggests the future possibility of protecting against multiple E. coli extraintestinal syndromes by using anti-VF interventions that may have been devised to prevent a specific clinical syndrome (e.g., UTI or meningitis) [9].

CGA, which, unlike most ExPEC clonal groups (group B2–derived), derives from phylogenetic group D [13], may account for 34%–50% of TMP-SMZ–resistant E. coli from women with uncomplicated cystitis and pyelonephritis [10, 13]. Case subject 1, who was infected with strain 184, provides novel evidence suggesting that this clonal group can also cause serious non–urinary tract extraintestinal disease (e.g., pneumonia and gram-negative sepsis) and is not confined to healthy women. This case also adds the northeastern United States to CGA’s known geographic range, which previously was shown to include the West Coast, and the midwestern, south central, and southeastern United States [10, 13]. Consistent with previous data associating CGA with TMP-SMZ resistance, the CGA isolate from the present study was TMP-SMZ–resistant and caused pneumonia in a patient who was taking prophylactic TMP-SMZ at the time of the infection episode.

Commonality among so-called “uropathogenic” and “meningitis-associated” E. coli has been documented previously, most notably with respect to the group B2–derived O18:K1:H7 clonal group, as represented by archetypal strains NU14 and RS218 [8, 9, 14]. Our findings with respect to strain 185 (from case subject 3) add a new clinical syndrome (i.e., deep surgical wound infection) to the known repertoire of the O18:K1:H7 clonal group. Of note, data shown elsewhere have suggested that members of this clonal group can also cause urosepsis [5] and spontaneous bacterial peritonitis [4].

The group B2–derived O1/O2:K1:H7 clonal group is a prominent cause of pyelonephritis and sepsis [1, 5, 15]. Case subject 2 (strain 186) demonstrates that such strains can also cause severe invasive soft-tissue infections and osteomyelitis in the absence of concurrent UTI. This patient’s vertebral osteomyelitis threatened spinal instability, the epidural abscess threatened permanent neurologic damage, and the psoas and iliacus abscesses threatened progression to overt sepsis had they not been promptly diagnosed and aggressively treated.

A limitation of the present study is the small sample size, which renders the findings largely anecdotal. However, we consider it significant that the 3 isolates, which were not selected on the basis of bacteriological characteristics but rather as having been isolated from patients with serious non–urinary tract extraintestinal infections, all proved to be members of notorious virulent clones of ExPEC. That O serotyping did not confirm the inferred clonal associations is noncontributory because, as documented elsewhere, O, K, H, and F antigen determination can be insensitive, irreproducible, and laboratory dependent [6, 7, 12]. The lower bound of the 95% confidence interval around the observed proportion of 3/3 is 29%, which indicates that at least 29% of non–urinary tract extraintestinal infection isolates are likely to be ExPEC. Future analysis of larger study populations will help refine this estimate.

In summary, we provide evidence that serious invasive extraintestinal E. coli infections other than the classic syndromes of UTI, bacteremia, and neonatal meningitis are often caused by E. coli strains similar to those that cause these more characteristic E. coli–associated syndromes. These findings invite reconsideration of the traditional nomenclature used to describe such strains and suggest the possibility of the development of broadly applicable cross-syndrome protective interventions.

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References
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