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Review

Medical and economic impact of extraintestinal infections due to *Escherichia coli*: focus on an increasingly important endemic problem

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Abstract

Escherichia coli is probably the best-known bacterial species and one of the most frequently isolated organisms from clinical specimens. Despite this, underappreciation and misunderstandings exist among medical professionals and the lay public alike regarding *E. coli* as an extraintestinal pathogen. Underappreciated features include (i) the wide variety of extraintestinal infections *E. coli* can cause, (ii) the high incidence and associated morbidity, mortality, and costs of these diverse clinical syndromes, (iii) the pathogenic potential of different groups of *E. coli* strains for causing intestinal versus extraintestinal disease, and (iv) increasing antimicrobial resistance. In this era in which health news often sensationalizes uncommon infection syndromes or pathogens, the strains of *E. coli* that cause extraintestinal infection are an increasingly important endemic problem and underappreciated "killers". Billions of health care dollars, millions of work days, and hundreds of thousands of lives are lost each year to extraintestinal infections due to *E. coli*. New treatments and prevention measures will be needed for improved outcomes and a diminished disease burden.

Keywords: Extraintestinal *Escherichia coli* infections; Economics; Incidence of infection; Costs; Mortality; Antibiotic resistance; Sepsis; Urinary tract infection

1. Introduction

Although *Escherichia coli* is regarded by the public primarily as a cause of foodborne diarrheal disease, the diversity, frequency, potential severity, and economic impact of extraintestinal infections due to *E. coli* are as great as for any bacterial pathogen. Evolutionary forces have resulted in the selection of *E. coli* strains with contrasting infectious potentials. From a pathogenesis perspective, strains capable of causing intestinal disease are largely unable to cause extraintestinal disease, and vice versa. Over the past decade, the genetic basis for this clinical dichotomy has become increasingly well understood. The goal of this report is to provide a brief summary of the differences between strains of *E. coli* that cause extraintestinal versus intestinal disease, to describe the spectrum of extraintestinal infections caused by *E. coli*, to document (when possible) the frequency and economic impact of such infections, and to discuss the potential implications of increasing antimicrobial resistance and incidence of extraintestinal infections due to *E. coli*.

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2. Clinical categories of *E. coli*

Despite clinicians' familiarity with *E. coli* there is a general underappreciation of the significant genetic differences between different strains. These differences determine whether the strains are able to cause disease and, if so, whether they can cause gastroenteritis or extraintestinal infection. From a genetic and clinical perspective, *E. coli* strains of biological significance to humans can be broadly categorized as (1) commensal strains, (2) intestinal pathogenic (i.e. enteric or diarrheagenic) strains, and (3) extraintestinal pathogenic *E. coli* (ExPEC) [1].

2.1. Commensal E. coli

Commensal *E. coli* variants, which constitute the major portion of the normal facultative intestinal flora in most humans and other mammals, for the most part confer benefits to their hosts such as colonization resistance. These strains generally lack the specialized virulence traits that enable intestinal and ExPEC to cause disease within or outside of the gastrointestinal tract, respectively. However, commensal *E. coli* can participate in extraintestinal infections when an

Table 1
The pathogenic potential of different groups of *E. coli* strains for causing intestinal vs. extraintestinal disease [4–7]

Clinical syndrome	Commensal *E. coli*	ExPEC	Intestinal pathogenic *E. coli*
Uncomplicated UTI	Minor	Major	Non
Uncomplicated pyelonephritis	Minor	Major	Non
Catheter-associated UTI	Major/minor[a]	Major/minor[a]	Non
Complicated UTI	Major/minor[a]	Major/minor[a]	Non
Prostatitis	Minor	Major	Non
Spontaneous bacterial peritonitis	Minor	Major	Non
Abdominal abscess	Unknown	Unknown	Non
Biliary sepsis	Major	Minor	Non
Pneumonia	Minor	Major	Non
Neonatal meningitis	Minor[b]	Major	Non
Surgical wound infection	Unknown	Anecdotal	Non
Osteomyelitis	Unknown	Anecdotal	Non
Cellulitis/soft-tissue infection	Unknown	Unknown	Non
Myositis/fasciitis	Unknown	Anecdotal	Non
Pelvic inflammatory disease	Unknown	Unknown	Non
Sinusitis	Unknown	Unknown	Non
Brain abscess	Unknown	Unknown	Non
Endophthalmitis	Unknown	Unknown	Non
Community-acquired bacteremia	Minor[b]	Major	Non
Nosocomial bacteremia	Minor	Major	Non
Gastroenteritis	Non	Non	Major

Major, causative pathogen in the majority of cases; Minor, causative pathogen in the minority of cases; Anecdotal, causative pathogen in anecdotal cases, number of cases evaluated too small to reliably assess proportions; Non, not known to cause this syndrome; Unknown, unknown/not evaluated.

[a] Commensal and ExPEC are approximately 50% each in these clinical syndromes.

[b] Usually in compromised hosts.

aggravating factor is present, such as a foreign body (e.g. urinary catheter), host compromise (e.g. local anatomical or functional abnormalities such as urinary or biliary tract obstruction, or immunocompromise), or a high or a mixed bacterial species inoculum (e.g. with fecal contamination of the peritoneal cavity) (Table 1).

2.2. Intestinal pathogenic E. coli

Intestinal pathogenic strains of *E. coli* have evolved a special ability to cause gastrointestinal disease, including enteritis, enterocolitis, and colitis. Six pathotypes have been described to date [2]. Disease due to this group of pathogens occurs primarily in developing countries, with the exception of the enterohemorragic or Shiga toxin-producing strains of *E. coli*. Mere acquisition of these pathogens by the naïve host usually is sufficient for disease to ensue. Only extremely rarely are intestinal pathogenic strains responsible for infections outside of the gastrointestinal tract (Table 1) [3].

2.3. Extraintestinal pathogenic E. coli

The available studies of *E. coli* isolates from symptomatic infection of the urinary tract, bloodstream, cerebral spinal fluid [4,5], respiratory tract [6], and peritoneum (spontaneous bacterial peritonitis) [7] demonstrate that the majority of such isolates, as indicated by their functionally similar virulence factor profiles and clonal background, are distinct from commensal and intestinal pathogenic *E. coli* (Table 1). It has been recently proposed that these strains of *E. coli* be termed ExPEC, rather than uropathogenic *E. coli* (UPEC), sepsis associated *E. coli* (SEPEC), or neonatal meningitis associated *E. coli* (NEMEC), to reflect their ability to cause disease at multiple anatomical sites [1,8]. Evaluation of a limited number of strains has established that ExPEC are also capable of causing surgical wound infection, osteomyelitis, and myositis, but the number of cases evaluated to date is too small to reliably assess proportions [9]. Studies on the nature of *E. coli* strains responsible for other extraintestinal infections are in progress (Table 1).

ExPEC strains, like commensal *E. coli* (but in contrast to intestinal pathogenic *E. coli*), are often found in the normal intestinal flora and do not cause gastroenteritis in humans. Although acquisition of an ExPEC strain by the host is a prerequisite to subsequent ExPEC infection, it is not the rate-limiting step, which instead is entry of a colonizing ExPEC strain from its site of colonization (e.g. the colon, vagina, or oropharynx) into a normally sterile extraintestinal site (e.g. the urinary tract, peritoneal cavity, or lungs). ExPEC strains have acquired genes encoding diverse extraintestinal virulence factors that enable them to cause infections outside of the gastrointestinal tract, in both normal and compromised hosts [4,5]. These virulence genes are for the most part distinct from those that enable intestinal pathogenic strains to cause intestinal disease. From a pathogenesis perspective, this is a logical evolutionary development, since host environment and associated defense mechanisms differ substantially within versus outside of the gastrointestinal tract. Characteristic virulence traits that are present in most

ExPEC include various adhesins (e.g. P and type I fimbriae), factors to avoid or subvert host defense systems (e.g. capsule, lipopolysaccharide), mechanisms for nutrient acquisition (e.g. siderophores), and toxins (e.g. hemolysin, cytotoxic necrotizing factor 1). The genotypic and phenotypic characteristics of ExPEC have been recently reviewed [8].

That ExPEC are the major cause of most (and perhaps all) varieties of extraintestinal infection due to *E. coli* is an important concept. It implies that if preventive measures (e.g. vaccination) or therapies could be developed to specifically target the ExPEC fraction of the *E. coli* population, this could have a major beneficial impact on extraintestinal infections due to *E. coli*. For example, a vaccine strategy that leads to the development of bactericidal or interfering antibodies directed against ExPEC-specific virulence factors has the potential to prevent infections due to ExPEC without perturbing the commensal strains of *E. coli* that make up an important component of the normal intestinal flora. The medical and financial ramifications of preventing extraintestinal *E. coli* infection are unquestionable, when the extent of the problem is fully recognized, as discussed below.

3. Extraintestinal infection syndromes due to *E. coli*: frequency and estimated costs

E. coli is the most common enteric Gram-negative species to cause extraintestinal infection in the ambulatory, long-term-care, and hospital settings [10–13]. The diversity and the medical and economic impact of extraintestinal *E. coli* infections are evident from a review of the following specific syndromes. It is important to note, however, that data reported below have been generated primarily from studies based in the US and Europe. The extent to which this data can be extrapolated to other countries is unknown. Clearly, costs will be health-care-system dependent. Additional data, in particular from developing countries, would be desirable.

3.1. Urinary tract infection

The urinary tract is the most frequent extraintestinal site infected by *E. coli*. Urinary tract infection (UTI) is a common infection in ambulatory patients, accounting for 1% of ambulatory care visits in the US, and is second only to lower respiratory tract infection among infections responsible for hospitalization [14,15]. From both clinical and economic points of view, UTI is best considered by clinical syndrome within the context of specific hosts (Fig. 1). *E. coli* is the single most prevalent pathogen for all (UTI syndrome)–(host group) combinations. Estimates of frequency and related costs are available for three specific UTI syndromes: uncomplicated cystitis, uncomplicated pyelonephritis, and catheter-associated UTI.

E. coli causes 85–95% of episodes of uncomplicated cystitis in premenopausal women [14,15]. The estimated total number of cases of uncomplicated cystitis per year is 6–8 million in the US and 130–175 million globally. In the US uncomplicated cystitis is responsible for an estimated 1 billion dollars of direct health care costs annually [16–18]. Furthermore, each episode results in a mean of 2 restricted-activity days and 6 symptom days [19]. Because of this, since women now constitute nearly 50% of the work force, cystitis results in considerable additional indirect costs.

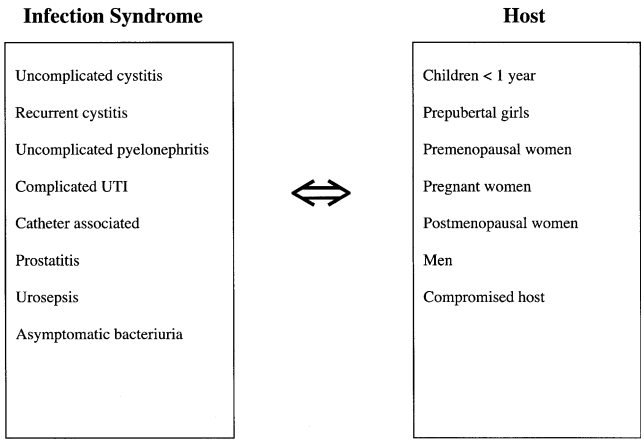

Fig. 1. Infections of the urinary tract are best considered within the context of specific clinical syndrome and host combinations. The box on the left lists the various clinical syndromes due to infections of the urinary tract. The box on the right lists the various hosts infected. A given clinical syndrome may affect some or many different hosts.

E. coli causes over 90% of cases of uncomplicated pyelonephritis in premenopausal women [20]. An estimated 250 000 cases of pyelonephritis occur each year in the US, 100 000 of which require hospitalization [21,22]. Based on population ratios (US population 286 million, global population 6.2 billion) this would translate into an estimated 5.4 million cases worldwide per annum. In the US the mean direct cost per cure is approximately $700 [20]. Therefore, in the US alone, the estimated *E. coli*-associated costs for pyelonephritis are 175 million dollars per year.

An estimated 1–1.5 million episodes of catheter-associated UTI [23] occur annually in the US, with an associated treatment cost of $676 per episode [24,25]. *E. coli* accounts for 25–35% of episodes. Thus, the estimated direct health care cost in the US associated with catheter-associated UTI due to *E. coli* is 170–350 million dollars per annum.

3.2. Abdominal and pelvic infection

The abdomen/pelvis is the second most frequent extraintestinal site for infections due to *E. coli*. A large variety of clinical syndromes occur in this location, including acute peritonitis secondary to fecal contamination, spontaneous bacterial peritonitis, dialysis-associated peritonitis, diverticulitis, appendicitis, intraperitoneal or visceral abscesses (hepatic, pancreatic, splenic), infected pancreatic pseudocysts, septic cholangitis and/or cholecystitis, and pelvic inflammatory disease. *E. coli* can be isolated either alone or, as often occurs, with other facultative and/or anaerobic members of the intestinal flora. Specific data are not available for intra-abdominal and pelvic infections regarding overall in-

fection rates, the proportion of episodes in which *E. coli* is isolated, or associated costs. However, considering the frequency of these infections, the common participation of *E. coli*, and the multiple interventions and prolonged hospital stays often necessary for successful management, the cost of intra-abdominal/pelvic infections due to *E. coli* is undoubtedly substantial.

3.3. Pneumonia

E. coli is not usually regarded as a significant cause of pneumonia. Indeed, enteric Gram-negative bacilli account for only 2–5% of community-acquired pneumonia episodes, in part because in healthy hosts they colonize the oropharynx only transiently and in only a minority of individuals. In contrast, oral colonization with *E. coli* and other Gram-negative bacilli increases with severity of illness and antibiotic use. As a result, Gram-negative bacilli are a substantially more common cause of pneumonia among residents of long-term-care institutions [26] and are the most frequent cause (60–70%) of hospital-acquired pneumonia, particularly in post-operative patients and in the intensive care unit [23,27–29]. Regardless of the host, pneumonia due to enteric Gram-negative bacilli is a serious disease, with high crude (20–60%) and attributable (10–20%) mortality rates [30,31].

An estimated 300 000 cases of nosocomial pneumonia occur annually in the US. Although significant institutional variation occurs, *E. coli* is generally the third or fourth most commonly isolated enteric Gram-negative bacillus in nosocomial pneumonia, accounting for 5–8% of episodes in both the US and European-based studies [23,29,32,33]. Nosocomial pneumonia prolongs hospitalization by a mean of 5.9 d and adds an estimated $5000 in costs per episode [31,34]. Therefore, the total annual associated cost of nosocomial pneumonia in the US is an estimated 1.5 billion dollars per year, with estimated *E. coli*-associated costs of 75–120 million dollars per annum.

3.4. Surgical site infection

Approximately 34 million surgical procedures are performed annually in the US. As a result of these procedures, 300 000–800 000 surgical site infections occur per annum [35]. Surgical site infection is associated with a 2–2.5-fold increase in the 6-month mortality rate [36,37]. *E. coli* is the fourth most common organism implicated in surgical site infections, accounting for 8% of the total [29]. Surgical site infection results in a mean increase of 10.2 d of hospitalization and an added cost of $4000–5000 per patient [37,38]. Therefore, the total estimated associated costs of surgical site infection in the US is 1.2–4.0 billion dollars per year, with the estimated *E. coli*-associated portion being 94–252 million dollars per annum.

3.5. Meningitis

E. coli is one of the two leading causes of neonatal meningitis (along with group B *Streptococcus*), causing 20–40% of an estimated 400 cases annually in the US [39,40]. However, the number of cases of *E. coli* meningitis may be increasing due to the increased use of ampicillin designed to reduce the vertical transmission of group B S*treptococcu*s. Although this strategy has been effective in decreasing the prevalence of group B streptococcal infections, a concomitant increase in infections due to *E. coli* (85% were ampicillin resistant) has been observed [41]. Case fatality rates range from 25% to 40% and 33% to 50% of survivors develop neurological sequelae [39,42,43]. Other than in neonates, *E. coli* meningitis occurs predominantly in the setting of disruption of the meninges due to surgery or trauma, or in the presence of cirrhosis where presumably the meninges are seeded from poorly cleared portal-source episodes of bacteremia [44]. No cost data are available for these infections, but the prolonged hospitalizations they commonly entail and the extensive supportive and rehabilitative care that often is needed even after the infection is cured doubtless result in substantial direct costs despite the modest number of cases.

3.6. Additional infections

E. coli is capable of causing infection in nearly every organ and anatomical site. Other extraintestinal infections that can be caused by *E. coli* include infections of ulcers due to pressure or ischemia (particularly in diabetics or other hosts with neurovascular compromise), cellulitis, burn wound infections, osteomyelitis (via contiguous spread or hematogenously; particularly of vertebral bodies), orthopedic device-associated infection, and myositis/fasciitis [9,45–49]. *E. coli* occasionally causes complicated sinusitis and rarely causes endocarditis, vascular graft infection, endophthalmitis or brain abscesses. Reliable frequency data and cost figures are unavailable for these infections.

3.7. Bacteremia

E. coli bacteremia can result secondarily from any of the above primary sites of infection, from percutaneous intravascular devices, or from the increased intestinal mucosal permeability that occurs in neonates and accompanies neutropenia, chemotherapy-induced mucositis, trauma, and burns. In studies from all continents *E. coli* accounts for 17–37% of clinically significant blood isolates, with isolates originating in the community versus hospital being roughly equal [10,11,23,50–58].

3.8. Sepsis

Isolation of *E. coli* from a blood culture is almost always clinically significant, and typically is accompanied by sepsis syndrome, severe sepsis (sepsis-induced dysfunction of at

least one organ or system), or septic shock [59]. Septicemia was the 10th ranked cause of mortality in the US in 2000 and was responsible for 1.3% of deaths overall [60]. A recent study, based on the US data, estimated that 751 000 cases of severe sepsis occurred in 1995. With the observed 28.6% associated mortality rate [61], this translates into an estimated 215 000 deaths. Among the 15 leading causes of death in the US since 1950, the largest increase in death rate has been due to septicemia, increasing 38-fold (i.e. from 0.3 in 1950, to 11.5 in 2000, per 100 000 US standard population) [40,60]. Estimated hospitalization rates for septicemia in Medicare beneficiaries have also increased dramatically, from 90 965 in 1986 to 219 350 in 1997 (a 241% increase) [10]. The incidence of severe sepsis and its associated mortality has been projected to increase in coming years by 1.5% per annum [61].

Although associated mortality overestimates true attributable mortality, in the context of sepsis this difference may be less than one might predict. In the recent study by Angus et al. [61], the associated mortality for severe sepsis in patients with and without underlying co-morbidity was 31.8% and 25%, respectively. Since the latter value derives from hosts without co-morbid conditions that could confound the association of sepsis with mortality, it probably approximates the true attributable mortality due to sepsis. These data thus strongly suggest that most of the mortality associated with severe sepsis is actually due to sepsis itself and not to co-morbidities.

In 1997, approximately 219 350 hospitalizations for septicemia were estimated to cost Medicare 1.8 billion dollars in hospitalization costs alone [10]. The true cost is acknowledged to be significantly higher, since neither pre-hospital and post-hospital costs, nor costs for physician services in hospital, were included. In 1997, a total of 773 530 cases of severe sepsis were estimated to occur nationwide [61]. Therefore, extrapolation of estimated Medicare costs for septicemia would yield a conservative estimate of 6.5 billion dollars per annum. A considerably higher estimate is provided by Angus et al., who calculated the average cost per case of severe sepsis to be $22 100 (in 1995). This projects to an annual US cost for all-cause sepsis of 16.7 billion dollars [61].

By using the conservative estimate that *E. coli* causes 17% of cases of severe sepsis [10,23,50], severe sepsis due to *E. coli* would be associated with an estimated 40 000 deaths in 2001, and an estimated 1.1–2.8 billion *E. coli*-associated direct health care dollars per annum in the US alone.

From a global perspective, The World Health Organization's report regarding the leading infectious causes of death worldwide in 1999 is informative [62]. Although two of the infections listed (i.e. acute respiratory tract infection and acquired immunodeficiency syndrome) in some instances cause sepsis, sepsis per se did not appear on the list. Differentiating sepsis-associated mortality from mortality caused by an infection at a defined anatomical location may be difficult if not impossible. Nonetheless, it is important to acknowledge sepsis as a distinct, infectious clinical entity. A sepsis-specific therapy has recently been approved in the US [50], and additional sepsis-specific therapies are in development. Therefore, regardless of whether sepsis is primary or secondary, its prevalence, associated mortality, and economic consequences warrant individual recognition. If the US data on sepsis-associated mortality are extrapolated worldwide, sepsis-associated mortality would supplant acute lower respiratory infections (3 963 000 estimated deaths per annum) as the number one infectious cause of death (4 950 000 estimated deaths per annum). Sepsis-associated mortality due to *E. coli* (using the conservative estimate of *E. coli* causing 17% of sepsis cases [10,23,50]) would be ranked seventh overall (868 000 estimated deaths per annum). This calculation assumes that sepsis-associated mortality is uniform among all pathogens. This may not be the case, since some studies have suggested a higher sepsis-associated mortality with *Pseudomonas* and/or *Candida* than with other pathogens. Nonetheless, these figures leave little doubt that the global burden of *E. coli* sepsis-associated deaths is substantial.

Table 2
Estimated frequency and associated annual costs in the US of selected extraintestinal infection syndromes due to *E. coli*

Infection syndrome	Estimated frequency of cases	Estimated direct costs (US dollars)
Uncomplicated cystitis in premenopausal women	6–8 million	1 billion
Uncomplicated pyelonephritis	250 000	175 million
Catheter associated UTI	250 000–525 000	170–350 million
Pneumonia	14 100–23 400	80–133 million
Surgical site infection	24 000–64 000	94–252 million
Sepsis	127 500	1.1–2.8 million

4. Future prospects: no relief in sight

Perhaps one of the reasons why extraintestinal *E. coli* infections have not traditionally commanded a level of attention commensurate with their contribution to infectious morbidity, mortality, and costs (Table 2) is that in the past these strains have typically been highly antibiotic susceptible, hence readily eradicated with antibiotic therapy. Unfortunately, this situation has changed as of late. Antimicrobial resistance has increasingly developed among *E. coli* strains causing UTI in the US, particularly to trimethoprim-sulfamethoxazole (TMP-SMX), which until recently was the drug of choice for uncomplicated cystitis in many locales [20,63,64]. The recent epidemic of TMP-SMX resistance has been shown to involve virulent clones of ExPEC and otherwise healthy hosts [65]. Although continued empiric use of TMP-SMX predictably will result in ever diminishing cure rates, a wholesale switch to alternative agents (e.g. fluoroquinolones) predictably will accelerate the widespread emer-

gence of resistance also to this antimicrobial class, as has already occurred in some areas [66]. Considering the high incidence of cystitis, and the absence of equally effective or adequately studied therapeutic alternatives for fluoroquinolone-resistant strains, such a development predictably will have significant economic implications.

In addition, a significant minority of extraintestinal *E. coli* isolates from long-term-care facilities and hospitals in the US and Europe already have acquired resistance to extended spectrum beta-lactamases and/or fluoroquinolones, rendering them quite challenging to treat [67]. Considering the inherent pathogenicity of many extraintestinal *E. coli* isolates, such strains that have acquired substantial antimicrobial resistance capabilities will potentially expand their present clinical niche to increasingly compete with *Enterobacter* species, *Pseudomonas*, and other resistant Gram-negative bacilli as significant causes of a variety of nosocomial infections. Furthermore, the incidence of serious extraintestinal infection due to *E. coli* increases with age [10,61]. As the proportion of elderly patients increases in the US and other developed countries, so likely will the number of extraintestinal *E. coli* infections.

The combination of increasing numbers and increasing antimicrobial resistance predictably will make the future management of extraintestinal *E. coli* infections more challenging and costly than ever. Both new treatments and new primary and secondary prevention measures will be needed for improved outcomes and a diminished burden of extraintestinal disease due to *E. coli*. Possibilities include (1) ExPEC-specific vaccines [68,69], (2) diminishing vaginal colonization, a predisposing factor for UTI, by avoidance of spermicide-based contraception or, for post-menopausal women, topical estriol therapy [70], (3) prevention of intestinal or vaginal colonization by identifying and avoiding relevant reservoirs and transmission pathways for ExPEC [8], or (4) diminishing vaginal or intestinal colonization by treatment with adhesin receptor analogues [71,72]. Progress toward these important goals can only occur if the problem is first recognized to exist, such that appropriate resources can be dedicated to finding the needed solutions. Extraintestinal *E. coli* infections are increasing in frequency and becoming more difficult to treat. Thus they represent a growing problem that requires more attention than ever before.

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