Clinical Profile and Antimicrobial Susceptibility of Invasive Extraintestinal Pathogenic *Escherichia coli* Disease in Hospitalized Adults Aged ≥60 Years: EXPECT-2 Study

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KEY FINDINGS STATEMENTS

- The EXPECT-2 study prospectively enrolled hospitalized adults aged ≥60 years to characterize clinical profile of invasive extraintestinal pathogenic *Escherichia coli* disease also known as invasive *E. coli* disease (IED) and associated antimicrobial resistance (AMR) patterns
- Bacteremic IED was reported in 80.4% and nonbacteremic IED in 19.6% of patients (N=240)
- Sepsis was diagnosed in 72.1% and septic shock in 10.0% of patients
- By day 28 of IED diagnosis, 32.5% of patients were encountered in the emergency department (ED) and 11.8% in the intensive care unit (ICU); the in-hospital mortality rate was 4.6%
- 98.2% of *E. coli*-positive isolates were cultured from blood and/or urine
- Multidrug resistance (MDR) was detected in 34.8% of isolates. The observed AMR rates were 30.4% for trimethoprim–sulfamethoxazole, 22.1–24.1% for fluoroquinolones, and 4.3–16.4% for extended-spectrum cephalosporins

CONCLUSIONS

- Combining systemic inflammatory response syndrome (SIRS) or Sequential Organ Failure Assessment (SOFA) criteria with ≥1 *E. coli* isolate cultured from blood, urine, or an otherwise sterile body site can optimize diagnosis of IED
- More than one-third of *E. coli* isolates displayed MDR and more than two-thirds of IED patients developed sepsis
- The data warrant a need of effective immunization strategies to prevent severe forms of IED in older population

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Disclosures

JD, **JG**, **OG**, **MS**, **BS**, and **JP** are employees of Janssen, and may hold stock in Johnson & Johnson. **MB** discloses being an advisor/consultant for AstraZeneca, Janssen Pharmaceuticals, Janssen Vaccines, Merck, and Novartis. **JR-B**, **TV**, **CV**, **HG**, and **ME** have no conflicts of interest or relevant disclosures.

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INTRODUCTION

- Extraintestinal pathogenic *Escherichia coli* (ExPEC) can infect normally sterile body sites outside the gastrointestinal tract and cause a range of invasive diseases, including bloodstream infections, sepsis, and urosepsis[1,2]
- Invasive ExPEC disease, also known as invasive *E. coli* disease (IED), is defined as an acute illness consistent with systemic bacterial infection microbiologically confirmed by a positive *E. coli* culture from a normally sterile body site (including blood) or urine in patients with urosepsis and no other identifiable source of infection[2]
- The incidence of IED is increasing over time,[3-6] likely influenced by the widespread and increasing incidence of antimicrobial resistance (AMR) of pathogenic *E. coli* strains[6]
- *E. coli* resistance to antibiotics is common,[7] including those used for treating IED, such as extended-spectrum cephalosporins and fluoroquinolones[8]

OBJECTIVES

- The EXPECT-2 study (NCT04117113) characterized the clinical profile of IED and AMR patterns of causative *E. coli* isolates in hospitalized adults aged ≥60 years

METHODS

- EXPECT-2 was a prospective, multinational, observational study conducted in 8 hospitals in Japan (2 sites), United States, Canada, France, Germany, Italy, and Spain
- The study was conducted between October 22, 2019 and January 28, 2021
- Eligible patients were aged ≥60 years, hospitalized, and diagnosed with IED either as a cause for admission or developed during hospitalization
  - IED was defined by the presence of clinical criteria of an invasive bacterial infection* and the isolation of *E. coli* from blood or an otherwise normally sterile body site, and/or the isolation of *E. coli* from urine with no other identifiable source of infection
- Endpoint data (**Figure 1**) were collected on day 1 of IED diagnosis and at follow-up (day 28 or discharge, ie, whichever came first)
- *E. coli* isolates were identified in the study sites and confirmed by the central laboratory
  - Antimicrobial susceptibility testing was performed according to the broth microdilution assay per CLSI guidelines. Data were reported according to CLSI and EUCAST-established breakpoints

*The qSOFA score of ≥2, or an acute change in total SOFA score of ≥2 points from baseline consequent to the infection, or fulfilling ≥2 criteria of SIRS.

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; qSOFA, quick SOFA.

FIGURE 1: Study endpoints and associated endpoint measurements

Endpoint	Endpoint measurement
Proportion of bacteremic and nonbacteremic IED cases	**Bacteremic IED** was determined by isolation of *E. coli* from blood. **Nonbacteremic IED** was determined by isolation of *E. coli* from urine or an otherwise sterile body site
Proportion of IED by acquisition setting and source of infection	**Community-acquired:** Infection present without prior 3-month exposure in a hospital, doctor's office, clinic, home-care treatment **Hospital-acquired:** Infection during or after hospitalization that was not present or incubating >48 hours following admission **Healthcare-associated:** Infection present at hospital admission/ within 48 hours of admission in patients fulfilling additional criteria **Infection source:** Infectious focus within 30 days of IED
Clinical profile of IED	% of patients fulfilling clinical criteria of SIRS, SOFA, and qSOFA; % of patients presenting with sepsis and septic shock; % of patients with IED complications; outcome of IED by day 28 or at discharge
Medical resource utilization	% of IED patients with medical encounters in 28 days following IED diagnosis
Antimicrobial resistance of *E. coli* isolates	**Antibiotics of interest** were those deemed clinically relevant for treating IED[7]: Extended-spectrum cephalosporins (cefepime, ceftazidime, ceftriaxone), fluoroquinolones (ciprofloxacin, levofloxacin), and trimethoprim–sulfamethoxazole **Multidrug resistance (MDR)** was defined as acquired nonsusceptibility to ≥1 agent in ≥3 antimicrobial categories

RESULTS

Population

- 240 patients were enrolled (full analysis set [FAS]); 50.8% of patients were female, 76.6% were white (**Table 1**)

TABLE 1: Baseline characteristics of patients with IED, FAS

	All patients
Age at time of diagnosis, y, (n)	240
Mean (SD)	75.4 (8.58)
Median	75.0
Range (min, max)	(60, 97)
60−74	48.8%
75−84	32.9%
≥85	18.3%
Sex, (n)	240
Female	50.8%
Race, (n)	167
White	76.6%
African	4.2%
Asian	18.0%
Hispanic or Latino	0.6%
Indian	0.6%
History of UTI (previous 10 years), (n)	231
No UTI	64.1%
<2 years prior to enrollment	23.8%
≥2 years prior to enrollment	12.1%
History of IED (previous 10 years), (n)	222
No IED	84.7%
With IED	15.3%
Medication use (3 months prior to IED), (n)	240
Antibiotics	37.5%
Immunosuppressive therapy	24.2%

UTI, urinary tract infection.

IED characterization

- Bacteremic IED was reported in 80.4% and nonbacteremic IED in 19.6% of patients
- IED was community acquired in 50.4%, healthcare associated in 29.6%, and hospital acquired in 20.0% of patients
- The most common source of infection was the urinary tract (62.9%)

Clinical profile of IED

- **Table 2** summarizes the clinical profile of patients with IED
  - Sepsis and septic shock were diagnosed by the investigator in 72.1% and 10.0% of patients, respectively
- Complications were reported in 20.0% of cases; median duration was 4 days (interquartile range, 2–10)
  - The most common complication was kidney dysfunction (12.9%)

TABLE 2: Clinical profile of patients with IED, FAS

	All patients
FAS	240
Any general symptom of IED (malaise, fatigue, muscle pain, or chills)	59.2%
Any laboratory values indicating bacterial infection and/or sepsis	81.3%
Diarrhea	5.8%
SIRS evaluated	240
0 criteria	9.2%
≥1 criterion	90.8%
≥2 criteria	65.8%
≥3 criteria	30.8%
4 criteria	4.6%
SIRS criteria collected	
Tachycardia, (n)	237
Tachycardia (present)	59.1%
Tachypnea, (n)	164
Tachypnea (present)	35.4%
Abnormal temperature, (n)	233
Abnormal temperature (present)	57.5%
Leukocytosis, leukopenia, or bandemia, (n)	240
Leukocytosis, leukopenia, or bandemia (present)	53.8%
SOFA[a]	240
Score ≥2	60.4%
qSOFA	240
Score 0	66.3%
Score 1	24.2%
Score 2	9.6%
Score 3	0
Sepsis[b]	72.1%
Septic shock[b]	10.0%
UTI (any signs and/or symptoms)	50.4%

[a]Refers to a change in the total SOFA score from baseline. [b]Per investigator assessment.

Clinical outcome

- By day 28 of IED diagnosis, 85.8% (206/240) of patients were discharged, 9.6% (23/240) were still hospitalized, and 4.6% (11/240) had died

Medical resource utilization

- 70.4% of patients had a medical encounter in 28 days following IED diagnosis
  - The most common medical encounter setting was ED (32.5% [55/169])
  - ICU encounters were reported in 11.8% (20/169) of patients with IED

Microbiological characterization

- The number of samples yielding *E. coli* was 334 (N=238 patients with IED)
  - 62.6% samples originated from blood, 35.6% from urine, and 1.8% from other sites
- *E. coli* was the only detected pathogen in 82.6% of samples (276/334) and was detected alongside other pathogens in 17.4% of samples (58/334; 55 samples from bacteremic IED)
  - The most common other pathogens were *Enterococcus faecium* (22.4% [13/58]), *Enterococcus faecalis* (12.1% [7/58]), and *Klebsiella pneumoniae* (10.3% [6/58])

AMR of *E. coli* isolates

- Resistance rates were 30.4% for trimethoprim–sulfamethoxazole, and ranged between 22.1–24.1% for fluoroquinolones, and 4.3–16.4% for extended-spectrum cephalosporins; 34.8% of isolates displayed MDR (**Table 3**)
- MDR rates were similar between isolates from bacteremic vs nonbacteremic patients

TABLE 3: Resistance levels of *E. coli* isolates collected from IED patients

	All IED[a]
FAS	238
Number of *E. coli* isolates with antimicrobial susceptibility test performed	299
Number and percentage of *E. coli* isolates resistant to a given antibiotic[b,c]	
Amikacin	0.7%
Ampicillin	56.2%
Ampicillin/Sulbactam	18.7%
Aztreonam	9.0%
Cefazolin	18.7%
Cefepime	5.7%
Ceftazidime	4.3%
Ceftriaxone	16.4%
Ciprofloxacin	24.1%
Colistin	1.0%
Gentamicin	11.0%
Levofloxacin	22.1%
Minocycline	6.0%
Piperacillin/Tazobactam	1.7%
Tetracycline	30.4%
Tigecycline	0.3%
Tobramycin	10.0%
Trimethoprim–Sulfamethoxazole	30.4%
E. coli isolates resistant to ≥1 antibiotic in ≥1 drug class	62.2%
E. coli isolates resistant to ≥1 antibiotic in ≥2 drug classes	45.5%
E. coli isolates resistant to ≥1 antibiotic in ≥3 drug classes (MDR)	34.8%

[a]Microbiology data were available for 238 patients due to an accidental loss of sample (n=1) and a negative *E. coli* re-identification result (n=1). [b]Denominator is the total number of *E. coli* isolates with antimicrobial susceptibility tests performed. [c]A patient may have ≥1 isolate test result.

LIMITATIONS

- A selection bias in countries where informed consent (IC) was required cannot be ruled out
  - The IC requirement might have biased the enrollment towards less severe cases and contributed to the mortality rate of 4.6%, which is lower to that reported in the literature[9-11]
- Nonrandom selection of study sites might have introduced systematic measurement errors
- Difficulties to clinically identify nonbacteremic cases coupled with nonrandom site selection might have resulted in the lower identified percentage of nonbacteremic cases
- The case definitions of UTI and IED might have not been accurately and consistently applied in the assessment of patient medical history
- The lack of data about prior hospitalizations at sites other than the participating hospitals might have contributed to the overestimation of community-acquired infections

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