Patients at Risk of Invasive Extraintestinal Pathogenic *Escherichia coli* Disease: a Systematic Literature Review

Peter Hermans[1*] PhD; Marc Bonten[2] MD, PhD; Leonidas Georgalis[3] MSc; Anke L. Stuurman[3] MSc; James R. Johnson[4] MD; Stefan Gravenstein[5] MD, MPH; Patricia Ibarra de Palacios[6] MD; Thomas Verstraeten[3] MD; Jan Poolman[1] PhD

[1] Janssen Vaccines & Prevention B.V., Leiden, Netherlands; [2] Julius Center, UMC Utrecht, Utrecht, Netherlands; [3] P95 Pharmacovigilance and Epidemiology Services, Leuven, Belgium
[4] University of Minnesota, Minnesota, USA; [5] Brown University and Providence Veterans Administration Hospital, Rhode Island, USA; [6] Janssen Vaccines, Bern, Switzerland

**Presenting author*

BACKGROUND

- Extraintestinal pathogenic *Escherichia coli* (ExPEC) is a common Gram-negative bacterial pathogen that causes a variety of infections including urinary tract infection (UTI), blood stream infection (BSI), sepsis, meningitis and pneumonia; mortality rate due to ExPEC is increasing globally.[1]
- The most common ExPEC diseases are UTI and BSI (marked increase in incidence with age especially >50 years).[1]
- Several studies have found increasing invasive ExPEC disease (IED) rates associated with increased morbidity, mortality and costs.[2]
- IED prevention requires an understanding of its epidemiology and the population at increased risk for it. Several countries aim to introduce mandatory surveillance of *E. coli* BSI (EcBSI) to investigate factors responsible for its increase.[3]
- However, information regarding the epidemiology and people at increased risk of IED is relatively limited.

OBJECTIVES

Systematic literature review to describe IED epidemiology

- Identify patients at increased risk for IED, specifically EcBSI, by measuring
  - Proportional contribution of different primary sites of infection to EcBSI
  - EcBSI incidence by specific patient settings vs. the general population
  - Relative contribution of *E. coli* to BSI in specific patient subsets vs. general population

METHODS

Study design

- A systematic literature review was performed as follows:

Figure 1: Systematic literature review (January 2007 to March 2018)

#1 Terms for *E. coli*
ExPEC[tiab] OR "Extraintestinal Pathogenic *Escherichia coli*"[Mesh] OR "*E. coli*"[tiab] OR "*Escherichia coli*"[tiab] OR "*Escherichia coli*"[Mesh]

#2 Terms for invasive disease
bloodstream[tiab] OR bacteremia[tiab] OR bacteremic[tiab] OR bacteraemia[tiab] OR bacteraemic[tiab] OR bacteremia[Mesh] OR sepsis[tiab] OR septicaemia[tiab] OR septicemia[tiab] OR "septic shock"[tiab] OR sepsis[Mesh] OR invasive[tiab] OR urosepsis[tiab] OR systemic[tiab] OR (meningitis[tiab] NOT neonatal[tiab]) OR "septic arthritis"[tiab] OR osteomyelitis[tiab] OR empyema[tiab] OR peritonitis[tiab] OR encephalitis[tiab] OR hepatitis[tiab] OR pneumonia[tiab]

#3 Terms for case reports
"case report"[tiab] OR "case reports"[tiab]

Search String: #1 AND #2 NOT #3

Databases searched:
- MEDLINE (via PubMed)
- LILACS
- SciELO
- EMBASE

Inclusion criteria
- Includes patients aged ≥18 years
- Addresses IED or *E. coli* surgical site infections
- Provides data on IED incidence, proportion of disease attributable to *E. coli*
- Study conducted in Europe, United States, Canada, Japan, Australia, or New Zealand, and published on or after Jan 1, 2007
- Language: English, Dutch, French, Italian, Spanish, Portuguese

Exclusion criteria
Non-human studies, case reports, case series, intervention trial, reviews, and conference abstracts

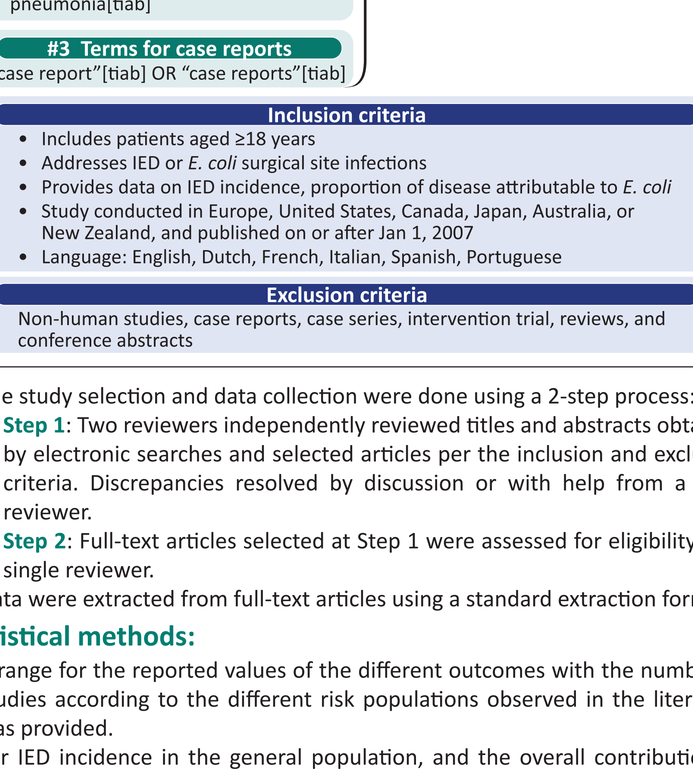
- The study selection and data collection were done using a 2-step process:
  - **Step 1**: Two reviewers independently reviewed titles and abstracts obtained by electronic searches and selected articles per the inclusion and exclusion criteria. Discrepancies resolved by discussion or with help from a third reviewer.
  - **Step 2**: Full-text articles selected at Step 1 were assessed for eligibility by a single reviewer.
- Data were extracted from full-text articles using a standard extraction format.

Statistical methods:

- A range for the reported values of the different outcomes with the number of studies according to the different risk populations observed in the literature was provided.
- For IED incidence in the general population, and the overall contribution of *E. coli* to BSI, DerSimonian meta-analysis[4] was performed and pooled effect estimates calculated using a random-effects model (R and/or SAS 9.4).

RESULTS:

Figure 2: PRISMA flowchart



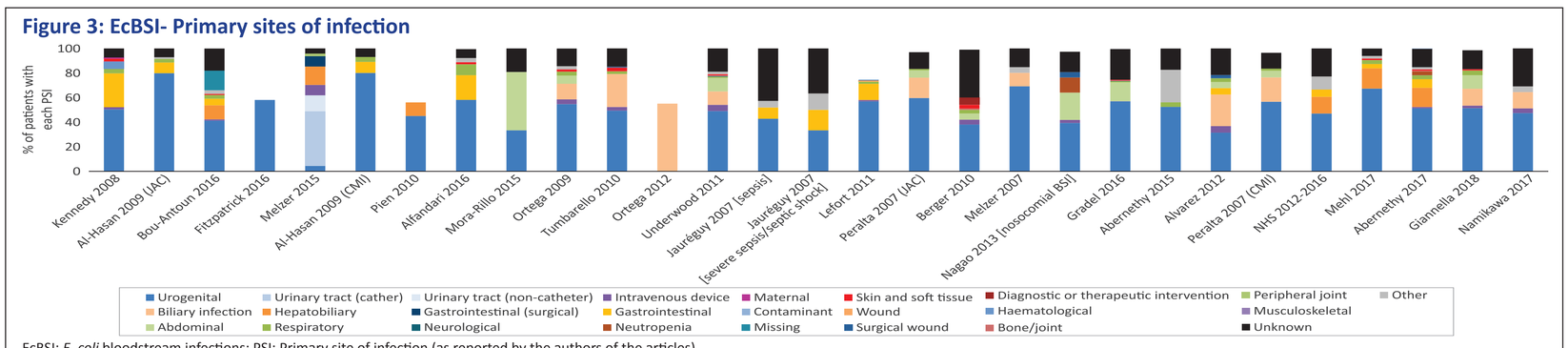
EcBSI: *E. coli* blood stream infection; ExPEC: Extraintestinal pathogenic *E. coli*

- Of the 386 articles included in qualitative synthesis, 153 did not identify potential risk factors for EcBSI.

Proportional contribution of different primary sites of infection to EcBSI

- Most common primary site for infection was urogenital (range from included articles: 31%-80%, n=28 [no. of articles reporting the finding]) followed by hepatobiliary (11%-16%, n=6), gastrointestinal (4%-28%, n=12), and abdominal (5%-48%, n=10). (Fig 3)
- Urogenital source of infection was more common in women (1.25 to 1.5-fold higher than men, n=3).

Figure 3: EcBSI- Primary sites of infection

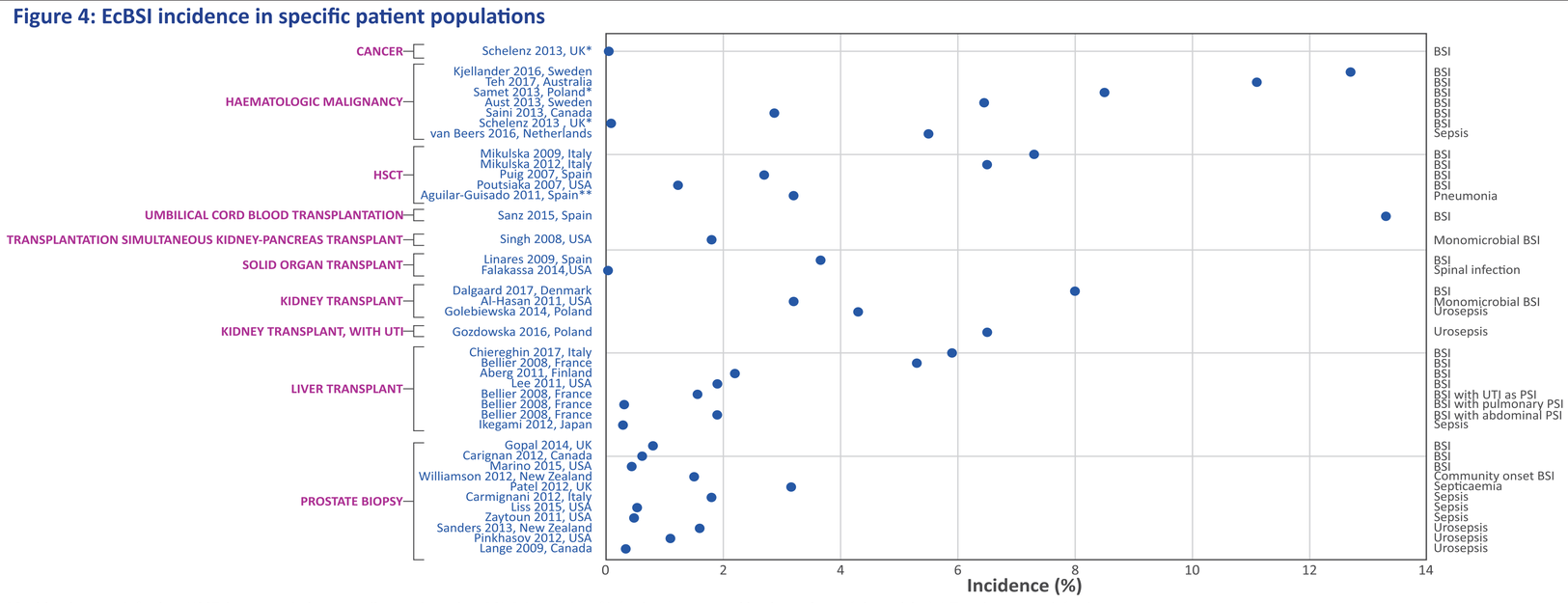


EcBSI: *E. coli* bloodstream infections; PSI: Primary site of infection (as reported by the authors of the articles)

EcBSI incidence in general population and specific patient populations

- EcBSI incidence in the general population was 47.9/100.0 person-years. A high level of heterogeneity (Q=15434.4, p-value=0, I^2=100%) was observed.
- This incidence was highest in association with haematological malignancy with chemotherapy (0.1%-13%, n=6), solid organ transplant (0.3%-8%, n=12), stem cell transplant (1%-7%, n=4), and prostate biopsy (0.5%-1.5%, n=5).

Figure 4: EcBSI incidence in specific patient populations

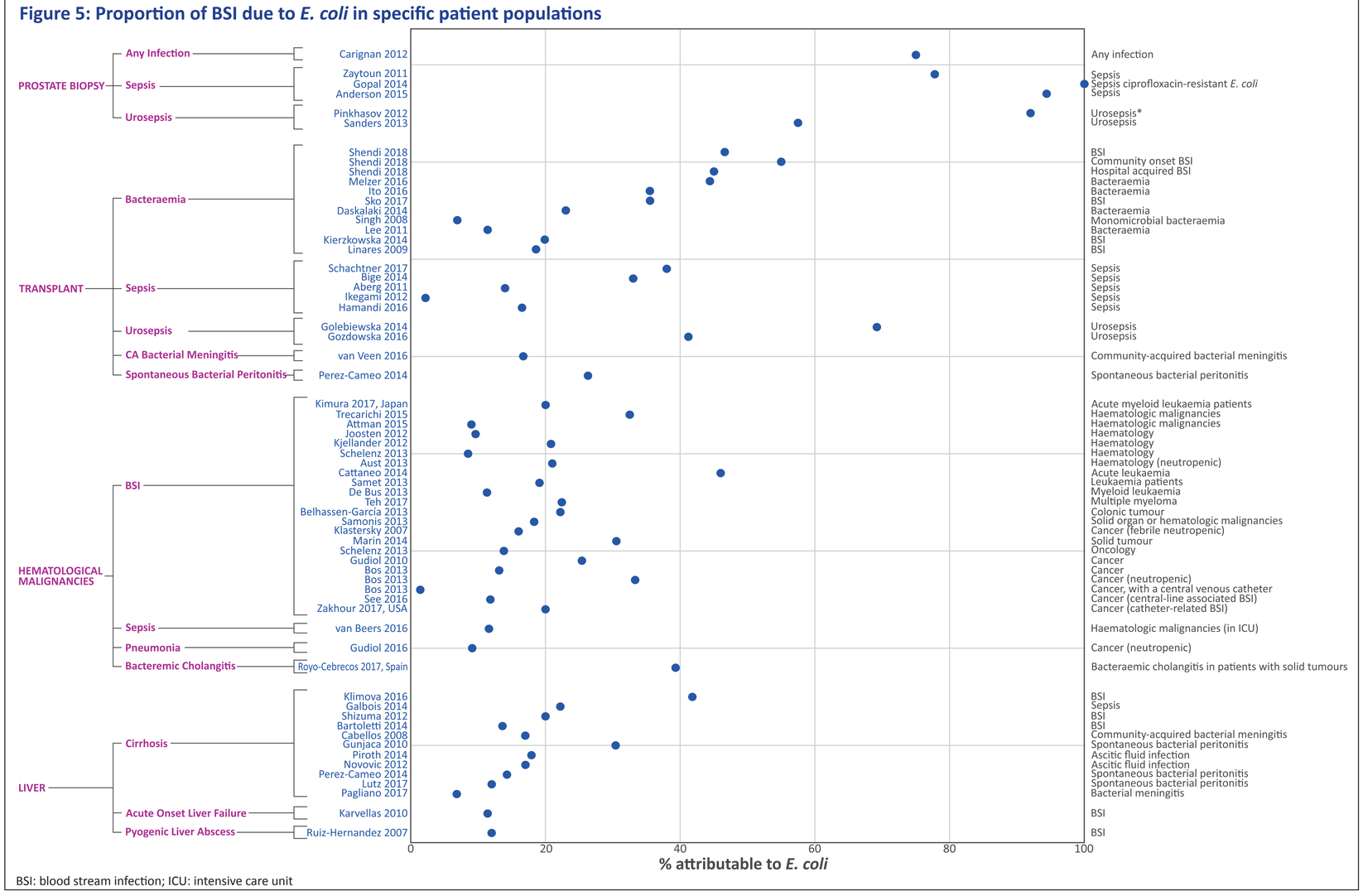


BSI: blood stream infection; HSCT: hematopoietic stem cell transplantation; PSI: Primary site of infection (as reported by the authors of the articles); UTI: urinary tract infection

Proportion of BSI due to *E. coli* in general population and specific patient populations

- The overall contribution of *E. coli* to BSI in the general population was 25%. A high level of heterogeneity (Q=5186.4, p-value=0, I^2=100%) was observed.
- In articles identifying BSI in specific patient populations, the contribution of *E. coli* was highest following prostate biopsy (58%-100%, n=5, for sepsis only), in transplant patients (7%-69%, n=9), patients with haematological malignancies (9%- 46%, n=11), and patients with liver cirrhosis (14%-42%, n=4).

Figure 5: Proportion of BSI due to *E. coli* in specific patient populations



BSI: blood stream infection; ICU: intensive care unit

CONCLUSIONS

- We found that the urogenital system is the most common primary site of infection in patients with IED, specifically EcBSI.
- Patients at highest risk for EcBSI were patients undergoing prostate biopsy, immunocompromised patients, and patients with cancer.
- Additional research is needed to better define high-risk groups for IED.

References:
1. Poolman JT, et al. J Infect Dis. 2016; 213(1):6–13.
2. Russo TA and Johnson JR. Microbes Infect. 2003; 5(5):449-56.
3. Williamson DA, et al. BMC Infect Dis. 2013; 13:385
4. DerSimonian R, Laird N. Controlled Clinical Trials. 1986; 7(3):177-88.

Acknowledgements:
Sonia Philipose, PhD (SIRO Clinpharm Pvt. Ltd., Thane, India) provided writing assistance and Bradford Challis, PhD (Janssen Global Services, LLC) provided editorial assistance for the development of this poster.

Disclosures:
Marc Bonten has received grants from Crucell/Janssen and is consultant to Crucell/Janssen. All funds go to the UMC Utrecht. James Johnson has received grants from Achaogen, Allergan, Melinta, Merck, Syntiron, and Tetraphase; is a consultant to Crucell/Janssen and Syntiron; has a NIH grant subcontract with IDGenomics; and has patent applications for tests to detect *E. coli* strains. Stefan Gravenstein has received grant and contract support from Pfizer, Sanofi Pasteur, and Seqirus; he is a consultant/advisory or data safety monitoring board member for the American Geriatrics Society, Gerontological Society of America, Healthcentric Advisors, Longeveron, Merck, Novartis, Novavax, Pfizer, Janssen, and Johnson & Johnson; and a speaker for Gerontologic Society for America, GlaxoSmithKline, Pfizer, Sanofi Pasteur, Seqirus. Thomas Verstraeten, Anke Stuurman, Leonidas Georgalis are consultants to Janssen Vaccines. Peter Hermans and Jan Poolman are employed with Janssen Vaccines & Prevention B.V., Leiden, Netherlands and Patricia Ibarra de Palacios is employed with Janssen Vaccines, Bern Switzerland. They may hold stock or stock options in Johnson & Johnson.

The study was funded by Janssen Infectious Diseases and Vaccines, Leiden, Netherland.