

Debate & Analysis

Urosepsis:

a growing and preventable problem?

INTRODUCTION

Public Health England data show a significant and important rise in hospital admissions and mortality rates for *Escherichia coli* (*E. coli*) bacteraemia over the last 12 years in England, Wales, and Northern Ireland, particularly in older patients. Although the cause is not established, some commentators have suggested that it might be due to delayed or inadequate treatment of urinary tract infections in primary care, possibly as a result of antimicrobial stewardship initiatives.

Providing evidence to establish the cause of the problem is a clear research priority. Here we discuss current *E. coli* bacteraemia admissions data, work in progress to investigate the rise, and future actions needed to establish whether primary care clinicians are indeed well placed to tackle this growing problem.

PREVALENCE AND TREATMENT IN SECONDARY CARE

E. coli bacteraemia is the most common cause of sepsis in England, with 30-day all-cause mortality of 18%. Mandatory surveillance of *E. coli* bacteraemia hospitalisation in England was initiated in 2011, following increases identified by Public Health England in voluntarily reported data. Surveillance confirmed that, between April 2012 and April 2017, the annual rate of *E. coli* bacteraemia hospitalisation increased by 22%, from 60.4 to 73.9 reports per 100 000 population.¹ To address this, the UK government aims to reduce the prevalence of health care-associated gram-negative bacteraemia by 50% by the year 2021.² *E. coli* is a particular focus of this aim given that it was aetiological in 54% of all gram-negative bacteraemia in 2016.³

Secondary care treatment for sepsis typically includes broad-spectrum antibiotics.⁴ Antibiotic use contributes to the development of antibiotic resistance, which has detrimental effects both to individual patients and society as a whole. The European Antimicrobial Resistance Surveillance Network (EARS-Net) showed that the invasive *E. coli* infections resistant to third-generation cephalosporins, aminoglycosides, and fluoroquinolones increased markedly between 2006 and 2009.⁵

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COMMUNITY-ACQUIRED INFECTIONS

Studies consistently show that a large proportion of UK *E. coli* bacteraemia hospitalisations result from community-acquired infections. The most common mode of entry of *E. coli* into the bloodstream is via the urinary tract ('urosepsis'), accounting for 47% of infections.⁶ A 2014 UK Government Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (ARHAI) sentinel surveillance study by Abernethy *et al* reported data from 1731 hospitalisations across 35 NHS trusts, aiming to identify risk factors for development of *E. coli* bacteraemia.⁷ Of particular relevance to primary care, the study estimated that 68% of cases were community acquired (positive blood culture obtained 0–1 day after admission), with almost 20% resistant to at least one antibiotic. Half of patients had been seen in either a community or secondary care healthcare setting in the 30 days prior to hospitalisation.

An earlier study conducted by Imperial College London and Public Health England of 19 914 *E. coli* bacteraemia cases between 2011 and 2012⁸ was consistent with the Abernethy *et al* study — around 68% were thought to be community acquired. Similarly, the NHS improvement plan for reducing gram-negative bloodstream infections reports that around three-quarters of *E. coli* bacteraemia occurs before admission to hospital.⁹

COMMUNITY-BASED INTERVENTIONS

Despite awareness of increasing incidence for the last 12 years, little headway has been made in understanding the cause of, or tackling the rise in, *E. coli* bacteraemia admissions. So, with primary care prevention in the spotlight, what can we do?

A 2014 ARHAI report suggested risk factors for *E. coli* bacteraemia included dehydration and repeated urinary tract infections (UTIs) treated by suboptimal community antibiotic prescribing.¹⁰ It stated that analysis showed that 'only a small proportion of infections were related to urinary catheterisation'. Although the report does not give more detail, we postulate that there are complex and potentially conflicting reasons why community prescribing may be inadequate:

- 1) too much treatment may be given (there is evidence that antibiotics can predispose to UTI);¹¹
- 2) treatment may be delayed;
- 3) antibiotics used may be too narrow spectrum (antimicrobial resistance point-of-care testing could be beneficial here); or
- 4) clinicians may fail to recognise infection is in the upper urinary tract and use an antibiotic suitable for lower, not upper, UTI.

In general, studies conclude that community-based interventions — particularly better use of urinary catheters, and improved antibiotic management — could help to reduce *E. coli* bacteraemia admissions.

In thinking about pathways to infection, it is important to consider the potential for interventions across the entire chain of infection. The most common reservoir for *E. coli* infection in humans is the gut. Acquisition is also possible from food or environmental sources, and hence infection could possibly be reduced by good food hygiene and handwashing, though evidence for this is currently lacking. As the mode of entry into the bloodstream is

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most commonly via the urinary tract, good catheter management and hygiene may help to prevent infection.

PRIMARY CARE RESEARCH

A first step for primary care research could be identification of modifiable risk factors, with a standard starting point being a systematic literature review. We conducted a thorough scoping review. Our MEDLINE search identified approximately 2600 articles. We screened 400 titles and abstracts, identifying seven broadly relevant papers and one systematic review. Studies were all conducted in secondary care, and did not provide evidence of modifiable risk factors for admission with urosepsis, suggesting the need for further, empirical primary care-based research.

Next, we sought to identify in-progress primary care studies by searching research registries. We identified a study by Paul Aylin *et al* at Imperial College using Clinical Practice Research Datalink data to report associations between primary care factors and hospitalisations for *E. coli* bacteraemia in older patients who consult primary care with symptoms of UTI.

The work being undertaken by Aylin *et al* will provide important preliminary data to improve understanding of the role of primary care clinicians in reducing *E. coli* bacteraemia. It may provide foundations for a large primary/secondary care observational cohort study. In theory, if risk factors for urosepsis in the community can be identified, along perhaps with risk factors for the antibiotic susceptibility/resistance status of the pathogen, then it should be possible to develop primary care interventions to improve the targeting of the ‘right antibiotic to the right patient at the right time’ — thereby reducing urosepsis.

However, it is important to bear in mind the scale of the problem faced by individual clinicians. Weekly incidence of urinary infection/cystitis in practices is 30/100 000,¹² translating to 156 episodes per year in a practice of 10 000, and this is likely to be underestimated given Read coding inconsistencies. Although *E. coli*

septicaemia is a growing problem, annual incidence in England remains relatively low at 74/100 000. As we have discussed, half of these events are precipitated by UTI, for which half of patients present to primary care prior to admission. Thus, for a practice of 10 000 patients, the potential for intervention is around one or two events each year (out of at least 150 UTI presentations).

SUMMARY

In summary, there is currently little evidence to support action to reduce *E. coli* bacteraemia by primary care clinicians, and such evidence will take time to gather. In the meantime, it is too early to lay the responsibility for mitigating this problem solely at the feet of primary care. Until evidence is established, we need to continue our work with colleagues in secondary care and public health to promote good hygiene practices, good catheter management, and the prudent use of broad-spectrum antibiotics.

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