Received: 4 January 2024 | Revised: 15 March 2024 | Accepted: 19 March 2024

DOI: 10.1111/acem.14914

Academic Emergency Medicine

RESEARCH LETTER

Atypical symptoms in emergency department patients with urosepsis challenge current urinary tract infection management guidelines

Brett Biebelberg[1] | Iain E. Kehoe[1] | Hui Zheng PhD[2] | Abigail O'Connell[1] | Michael R. Filbin MD[1] | Thomas Heldt PhD[3] | Andrew T. Reisner MD[1]

[1]Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

[2]Massachusetts General Hospital Biostatistics Center, Harvard Medical School, Boston, Massachusetts, USA

[3]Institute for Medical Engineering and Science and Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

Correspondence
Andrew T. Reisner, Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA 02114, USA.
Email: areisner@mgh.harvard.edu

Funding information
Nihon Kohden Corporation; CRICO Risk Management Foundation; MIT-MGH Strategic Grand Challenge Partnership

The Infectious Diseases Society of America (IDSA)'s guidelines for managing asymptomatic bacteriuria (ASB) advise against antimicrobial treatment for potential urinary tract infection (UTI) except when patients have localizing genitourinary (GU) symptoms, fever, or hemodynamic instability.[1] For patients lacking specific UTI signs and symptoms, including older patients with acute mental status changes or falls, they advise close observation instead of antibiotics. The authors of the IDSA guidelines classified the strength of their recommendations as "strong" while simultaneously categorizing the quality of the underlying evidence for these recommendations as "low" or "very low" (per the GRADE framework) due to reliance on studies limited by setting, sample size, and confounding effects.[1,2] The Choosing Wisely campaign—an effort to combat unnecessary tests and treatments—draws on these recommendations, similarly advising against urine testing and treatment, even in the presence of delirium, unless there are localizing urinary symptoms.[3]

At the same time, the Surviving Sepsis Campaign emphasizes early recognition and antibiotic treatment of sepsis.[4] Up to 80% of patients with sepsis receive initial care in the emergency department (ED), and urosepsis represents a common form.[5] Prior reports on ED sepsis presentation describe that many patients lack hemodynamic instability on presentation,[6,7] and many septic patients do present with acute confusion.[4] Given the Surviving Sepsis Campaign's continued recommendation of prompt administration of antibiotics for the treatment of sepsis, and the lack of any clinical data from EDs cited in the IDSA guidelines, we explored the presenting symptoms of a cohort of ED patients with urosepsis. We hypothesized there may be a subset of patients at risk of delayed antibiotic treatment under the IDSA guidelines.

In this letter, we report a secondary analysis of a data set of adult sepsis patients treated in the ED of an urban academic medical center from April 1, 2014, to March 31, 2016. The study protocol was approved by our institutional review board with a waiver of informed consent. The data set included all ED patients meeting sepsis criteria based on the CMS Severe Sepsis and Septic Shock (SEP-1) definition.[8] Additional details about this database have been reported.[6] The original data set also contained a set of control, non-septic patients randomly selected from the same time interval who had vital sign abnormalities (qSOFA positive, systolic blood pressure [SBP] < 100 mm Hg, or shock index >1 [SBP < heart rate]), for use as a comparator to the septic cohort.[9]

All data were sourced retrospectively from the hospital's medical record electronic data warehouse. Presenting symptoms were abstracted by two trained reviewers who independently evaluated portions of the ED clinical notes (triage note as well as nursing and providers' initial documented patient histories) and completed a

Supervising Editor: Brigitte M. Baumann

TABLE 1 Univariable screen and multivariable regression investigating factors associated with urosepsis.

Characteristics	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
Age (each decade)	1.48 (1.32–1.68)	<0.01	1.57 (1.32–1.86)	<0.01
Report of fever or fever at triage	11.51 (7.41–17.87)	<0.01	16.35 (8.81–30.35)	<0.01
Report of confusion or triage GCS < 15	1.80 (1.21–2.67)	<0.01	2.93 (1.57–5.46)	<0.01
GU localizing symptoms or abd pain	2.54 (1.71–3.78)	<0.01	3.61 (1.96–6.65)	<0.01
Hypoxia (triage SpO_2 < 95%)	4.05 (2.54–6.44)	<0.01	1.44 (0.72–2.88)	0.31
Triage SBP (each 10 mm Hg)	0.87 (0.81–0.94)	<0.01	0.84 (0.76–0.93)	<0.01
Triage RR (each five respirations)	1.72 (1.36–2.15)	<0.01	1.48 (1.07–2.06)	0.02
Nausea or vomiting	1.32 (0.87–2.02)	0.20	0.79 (0.41–1.53)	0.49
Shortness of breath	0.82 (0.48–1.39)	0.45	0.73 (0.33–1.64)	0.45
Diarrhea	2.50 (1.44–4.33)	<0.01	2.73 (1.20–6.24)	0.02
Number of major comorbidities	1.59 (1.40–1.80)	<0.01	1.42 (1.17–1.72)	<0.01
Fatigue/malaise/weakness/lethargy	3.29 (2.20–4.92)	<0.01	3.18 (1.85–5.47)	<0.01

Note: C-statistic for multivariable regression = 0.91.

Abbreviations: abd, abdominal; GCS, Glasgow Coma Scale; GU, genitourinary; RR, respiratory rate; SBP, systolic blood pressure.

standardized data entry form. The reviewers were blinded to the clinical assessments, plans, details of ED management, diagnostic findings, and final diagnosis. Septic and nonseptic cases were evaluated in a random order. Fever as a symptom included subjective or measured fever reported by the patient or temperature greater than or equal to 100.4°F measured at triage. GU symptoms were those classically associated with a GU disease process: hematuria, cloudy urine, increased urinary frequency, dysuria, back pain, flank pain, or GU pain. The fatigue/malaise/weakness/lethargy symptom complex also included dizziness, near syncope, and lightheadedness.

Next, reviewers were unblinded, reviewed the remainder of the ED and hospital documentation, and abstracted whether an acute infection warranting treatment was documented in the hospital admission note. If yes, reviewers also documented which infection source, e.g., urinary, was diagnosed. For every subject, the coding of each reviewer was compared, and any disagreements were resolved by majority vote in a review session that included a third (physician) reviewer.

In this novel secondary analysis, we hypothesized that some patients with urosepsis would present atypically, without meeting the IDSA criteria for treatment. We characterized the presenting symptoms for that subset of septic patients diagnosed with a urinary source, i.e., the urosepsis cohort. We also hypothesized that presenting characteristics of urosepsis patients would differentiate them from the randomly selected cohort of ED patients with abnormal vital signs. Regression analysis was performed to evaluate which symptoms were discriminatory, using SAS Version 9.4 (SAS institute). As investigational predictors, we analyzed all symptoms that had a prevalence of ≥15% in the urosepsis cohort.

From the original data set, we identified 123 patients with urosepsis (SEP-1 criteria for sepsis with a diagnosed urinary source of infection). Their median (IQR) age was 70 (61–82) years old and 86% were white non-Hispanic. A total of 56% were admitted to an ICU and mortality was 13%. Their presenting characteristics were as follows:

- At triage: 22% had an initial SBP < 90 mm Hg and 29% had GCS < 15;
- 64% had report of prior fever or had measured fever at triage;
- 44% had report of localizing GU symptoms; and
- 28% had "atypical" symptoms, i.e., no report of fever, no triage fever, and no report of GU symptoms.

Additional characteristics of those urosepsis patients with atypical symptoms were notable for the following:

- Median (IQR) triage SBP was 105 (127–82) mm Hg;
- 59% had documented fatigue/weakness;
- 55% had report of confusion or GCS < 15 at triage;
- 31% had report of both fatigue and confusion; and
- Diagnostically, 82% had leukocytosis (WBC > 11×10^9/L), 54% had hyperlactatemia (lactate > 4 mmol/L), and 43% had both.

The original data set also included 576 randomly selected ED patients without sepsis whose primary pathologies spanned toxicologic, cardiac, respiratory, gastrointestinal, vascular, and traumatic diagnoses. Substantial additional details about the urosepsis cohort and the nonseptic cohort are available in the Data S1 on our lab GitHub website.[10] The urosepsis cohort was compared with the randomly selected cohort of patients with abnormal vital signs (Table 1).

In this retrospective analysis of an ED cohort of urosepsis patients, we found that 28% presented with atypical symptoms that did not meet IDSA symptom criteria for antibiotic treatment. Nearly all these patients had either fatigue/weakness or confusion. Advanced age and comorbidities were the other significant factors that helped distinguish urosepsis patients from the random control group. Nearly all had either leukocytosis or hyperlactatemia. Only 22% of ED urosepsis patients had frank hypotension at triage. Although these findings arose from a small cohort, they suggest that early detection and treatment of high-mortality UTI may require

sending urinalyses and initiating antibiotics even in patients without fever or localizing symptoms. This is especially true in the presence of fatigue or confusion, the most common presenting symptoms in urosepsis patients with atypical symptoms.

The IDSA guidelines state that any bacteriuria should be considered asymptomatic "irrespective of the presence of pyuria" and advise against antimicrobial treatment *unless* there is fever or localizing GU symptoms, even if older or confused. Furthermore, the guidelines express uncertainty regarding whether older patients with acute confusion should receive antibiotics *even if febrile*, stating that that "[i]t is *unknown* whether antimicrobial therapy for ASB in patients with delirium is beneficial when fever or other systemic signs of infection are present *and no other localizing source of infection is apparent* [emphasis added]." The IDSA guidelines advise that patients with ASB, including those with acute mental status changes, should be observed, although details are not provided for how to safely observe such patients. The IDSA acknowledges that their practice recommendations are based on "very low-quality evidence." There were no ED studies cited in these recommendations.[1]

Our analysis suggests that the 2019 IDSA guidelines, though well intentioned in the effort to avoid antibiotic overuse, may be too narrow in the ED setting where strict adherence could result in a sizable minority of urosepsis patients failing to receive timely antibiotics. Indeed, we found that fatigue/weakness had a comparable association with urosepsis as localizing GU symptoms did and is therefore important to consider in ED patients (fatigue/weakness OR 3.18 vs. GU symptoms/abdominal pain OR 3.61). Clinicians should balance the priority of antibiotic stewardship with a sufficiently high index of suspicion for sepsis even in patients who present without classic symptoms, especially in patients with mild vital sign abnormalities and/or lab abnormalities consistent with systemic infection. The ideal UTI management guidelines would include clear and safe recommendations for identifying and treating atypical presentations of UTI before patients develop hemodynamic instability and high-mortality sepsis.

There are key limitations to this report. First, findings came from a moderate-sized cohort from a single center. Second, sepsis diagnosis was based in part on billing codes in accordance with SEP-1, which may reflect subjective diagnostic judgment of clinicians and billing staff; therefore, some misclassification between the sepsis and the control cohorts is possible. Third, symptoms were based on what was charted in the triage note, provider note, and initial ED nurse note, which are subject to errors in charting or chart review (mitigated in part by the aforementioned process of multistep, multi-reviewer blinded chart review).

Treatment guidelines would benefit from more data from the ED setting, where the majority of urosepsis patients initially present. Future studies should evaluate the significance of atypical symptoms in the diagnosis of UTI to optimize early detection and prevention of urosepsis. Doing so, with data from ED patients, could help define best practices for when to send urinalysis in the ED, when to give antibiotics for abnormal urinalysis in the ED, and how to best observe patients with atypical UTI symptoms and abnormal urinalyses such that they do not necessarily progress to hemodynamic instability before meeting criteria for antibiotics.

AUTHOR CONTRIBUTIONS

Study concept and design (Brett Biebelberg, Michael R. Filbin, Thomas Heldt, Andrew T. Reisner), acquisition of the data (Brett Biebelberg, Iain E. Kehoe, Abigail O'Connell, Andrew T. Reisner, Michael R. Filbin, Thomas Heldt), analysis and interpretation of the data (Brett Biebelberg, Iain E. Kehoe, Hui Zheng, Michael R. Filbin, Thomas Heldt, Andrew T. Reisner), drafting of the manuscript (Brett Biebelberg, Iain E. Kehoe, Andrew T. Reisner), critical revision of the manuscript for important intellectual content (Hui Zheng, Abigail O'Connell, Michael R. Filbin, Thomas Heldt), statistical expertise (Brett Biebelberg, Hui Zheng, Andrew T. Reisner), and acquisition of funding (Michael R. Filbin, Thomas Heldt, Andrew T. Reisner).

FUNDING INFORMATION

This investigation was supported in part by the MIT–MGH Strategic Grand Challenge Partnership (to Andrew T. Reisner, Michael R. Filbin, and Thomas Heldt) and by grants from the CRICO Risk Management Foundation (to Andrew T. Reisner, Michael R. Filbin) and Nihon Kohden Corporation (to Andrew T. Reisner, Michael R. Filbin, and Thomas Heldt). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

Investigators Andrew T. Reisner, Michael R. Filbin, and Thomas Heldt hold a patent related to sepsis patient management (#WO2016133928A1), which has been licensed to the Nihon Kohden Corporation. The other authors declare no conflicts of interest.

ORCID

Brett Biebelberg https://orcid.org/0000-0001-7630-3807
Iain E. Kehoe https://orcid.org/0000-0002-0834-5076

REFERENCES

1. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):1611-1615. doi:10.1093/cid/ciz021
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
3. Memari M, Mendoza MA, Shukla B, O'Rourke P. Things we do for No reason™: obtaining urine testing in older adults with delirium without signs or symptoms of urinary tract infection. *J Hosp Med*. 2021;16(9):557-559. doi:10.12788/jhm.3620
4. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. doi:10.1097/CCM.0000000000005337
5. Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. Early care of adults with suspected sepsis in the emergency department and out-of-hospital environment: a consensus-based task force report. *Ann Emerg Med*. 2021;78(1):1-19. doi:10.1016/j.annemergmed.2021.02.006

6. Filbin MR, Lynch J, Gillingham TD, et al. Presenting symptoms independently predict mortality in septic shock: importance of a previously unmeasured confounder. *Crit Care Med*. 2018;46(10):1592-1599. doi:10.1097/CCM.0000000000003260
7. Filbin MR, Thorsen JE, Lynch J, et al. Challenges and opportunities for emergency department sepsis screening at triage. *Sci Rep*. 2018;8(1):11059. doi:10.1038/s41598-018-29427-1
8. Partnership for Quality Measurement. Severe Sepsis and Septic Shock: Management Bundle. Battelle Memorial Institute. Accessed December 1, 2021. https://p4qm.org/measures/0500
9. Koch E, Lovett S, Nghiem T, Riggs RA, Rech MA. Shock index in the emergency department: utility and limitations. *Open Access Emerg Med*. 2019;11:179-199. doi:10.2147/OAEM.S178358
10. Biebelberg B. GitHub repository for atypical symptoms in emergency department patients with urosepsis challenge current UTI management guidelines. GitHub. Accessed December 28, 2023. https://github.com/mgh-cdtl/Atypical-symptoms-in-ED-patients-with-urosepsis-challenge-current-UTI-management-guidelines/tree/main

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Biebelberg B, Kehoe IE, Zheng H, et al. Atypical symptoms in emergency department patients with urosepsis challenge current urinary tract infection management guidelines. *Acad Emerg Med*. 2024;00:1-4. doi:10.1111/acem.14914