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Frequency and Types of Healthcare Encounters in the Week Preceding a Sepsis Hospitalization: A Systematic Review

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OBJECTIVES: Early recognition and treatment are critical to improving sepsis outcomes. We sought to identify the frequency and types of encounters that patients have with the healthcare system in the week prior to a sepsis hospitalization.

DATA SOURCES: PubMed, Cumulative Index to Nursing and Allied Health Literature, Scopus, and the Cochrane Library.

STUDY SELECTION: Observational cohort studies of patients hospitalized with sepsis or septic shock that were assessed for an outpatient or emergency department encounter with the healthcare system in the week prior to hospital admission.

DATA EXTRACTION: The primary outcome was the proportion of patients with a healthcare encounter in the time period assessed (up to 1 week) prior to a hospitalization with sepsis.

DATA SYNTHESIS: Six retrospective observational studies encompassing 6,785,728 sepsis admissions were included for evaluation, ranging from a 263-patient single-center cohort to a large database evaluating 6,731,827 sepsis admissions. The average (unweighted) proportion of patients having an encounter with the healthcare system in the week prior to a sepsis hospitalization was 32.7% and ranged from 10.3% to 52.9%. These encounters commonly involved presentation or potential symptoms of infectious diseases, antibiotic prescriptions, and appeared to increase in frequency closer to a sepsis hospitalization admission. No consistent factors were identified that distinguished a healthcare encounter as more or less likely to precede a sepsis hospitalization in the subsequent week.

CONCLUSIONS: Patients that present to the hospital with sepsis are frequently evaluated in the healthcare system in the week prior to admission. Further research is necessary to understand if these encounters offer earlier opportunities for intervention to prevent the transition from infection to sepsis, whether they merely reflect the comorbidities of sepsis patients with a high baseline rate of healthcare encounters, or the declining trajectory of a patient's overall health in response to infection.

KEY WORDS: health services; hospitalization; infection; prehospital; sepsis; systematic review

Sepsis is responsible for one in five of all global deaths and is the leading cause of death in hospitalized patients (1–3). In addition to being the most common principal diagnosis for hospitalizations in the United States, sepsis costs an estimated $41.5 billion per year to the healthcare system (4). Early recognition and prompt antimicrobial therapy are well-recognized supportive measures for sepsis care (5–7). However, a recent medical record review-based analysis suggested that most sepsis-associated deaths are unlikely to be preventable through improvements in hospital-based care given that patients who die in the hospital from sepsis tend to present in extremis and/or have severe underlying comorbidities (8).

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Given that 80% of hospitalized patients with sepsis present from the community setting (9, 10), patient encounters with the healthcare system in the week(s) prior to a sepsis hospitalization (prehospital encounters) represent opportunities for early identification of the transition from infection to sepsis, more intensive monitoring in certain patients, and potential opportunities for intervention to reverse course. Estimating the overall proportion of patients with a prehospital "touch point," along with information about the healthcare setting and resulting clinical outcomes, is critical to inform potential interventions. Thus, we conducted a systematic review to elucidate the proportion of sepsis hospitalizations with a prehospital encounter, the healthcare settings where these encounters occurred, and resulting clinical outcomes.

METHODS

Our primary aim was to describe the proportion of patients that had an encounter with the healthcare system in the week prior to a sepsis hospitalization. According to various typologies of systematic reviews, this is best described as a systematic review of prevalence (11). Accordingly, we used the Condition, Context, Population framework as follows: population (patients with a sepsis hospitalization), condition or variable of interest (the event of a prehospital encounter with the healthcare system), and context (those patients assessed for a healthcare encounter within 1 week of hospital admission) (12).

Search Strategy

A systematic literature search was performed adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (13). In consultation with a medical librarian, we developed search strategies containing combinations of controlled vocabulary, title, and abstract keywords using Boolean operators. Studies were identified through comprehensive literature searches of the databases PubMed (PubMed.gov), Cumulative Index to Nursing and Allied Health Literature—CINAHL (EBSCO), Scopus (Elsevier), and the Cochrane Library (Wiley) from inception to June 9, 2021. Search strategies contained combinations of controlled vocabulary, title, and abstract keywords using Boolean operators. Full search strategies are included in **eTable 1** (http://links.lww.com/CCX/A914). The reference lists of included articles were also reviewed for relevant studies. Duplicates were removed using EndNote X9 (Clarivate Analytics, London, United Kingdom).

Study Selection and Outcomes of Interest

We included observational cohort studies of adult patients hospitalized with sepsis or septic shock, as defined by the specific study, who were assessed for an encounter with the healthcare system within 1 week of their sepsis hospitalization. Exclusion criteria included those encounters involving emergency medical services and ambulance transfer as the sole prehospital encounter, those solely involving nursing home or long-term care as prehospital encounter, and studies of pediatric patients. The primary outcome of interest was the proportion of patients with a sepsis hospitalization that had an encounter with the healthcare system in the week prior to their hospitalization. An encounter with the healthcare system for the purpose of this review was broadly defined as a physical visit or triage via telecommunication, regardless of which specific healthcare practitioner was involved. Secondary outcomes of interest included describing the specific healthcare settings that patients had encounters with (i.e., primary care, emergency department [ED]) and associated clinical outcomes such as requirement for intensive care, hospital mortality, and length of stay. Finally, where applicable, we evaluated whether there were any differences in patient comorbidities or overall patient outcomes between patients with and without a healthcare encounter in the week preceding their sepsis hospitalization. Two reviewers independently screened at the title and abstract level, followed by full article review of potentially eligible studies. Any discrepancies were resolved in consultation with a third reviewer. The protocol for the systematic review was registered on PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020216759).

Data Extraction and Risk of Bias Assessment

The following study characteristics were extracted from included studies: author, year, study design, source of population, presepsis admission healthcare exposure timeframe, patient comorbidities, methods for identifying sepsis admission, how presepsis hospital admission healthcare encounters were categorized, and sample size. Given that studies did not always share common

control groups and explored details of patients' healthcare encounters with a variety of different descriptors, other noteworthy findings were summarized at the discretion of the authors. Risk of bias was assessed by two independent reviewers using the Newcastle-Ottawa Scale for observational cohort studies (14). The primary outcome is described as a range along with an unweighted average due to one study contributing over 90% of the total sepsis hospitalizations evaluated.

RESULTS

Electronic database searching yielded 4,985 potential citations. Exclusion criteria were applied as noted in **Figure 1** to yield six studies for final inclusion, all published from 2018 to 2021 (9, 15–19). All six studies were retrospective, observational cohort studies and assessed as low risk of bias for cohort studies (**eTable 2**, http://links.lww.com/CCX/A914) (9, 15–19). Two studies were single center while the remaining four included large cohorts of multiple hospitals or national databases. Four studies from the United States evaluated any healthcare encounters available, while two focused on general practitioners and primary care in the Netherlands and United Kingdom healthcare systems, respectively (17, 19). A total of 6,785,728 sepsis hospitalizations were evaluated. Studies ranged in size from single-center cohorts of 263 patients to large insurance claims data including 6,731,827 sepsis admissions of Medicare beneficiaries (15, 17). *International*

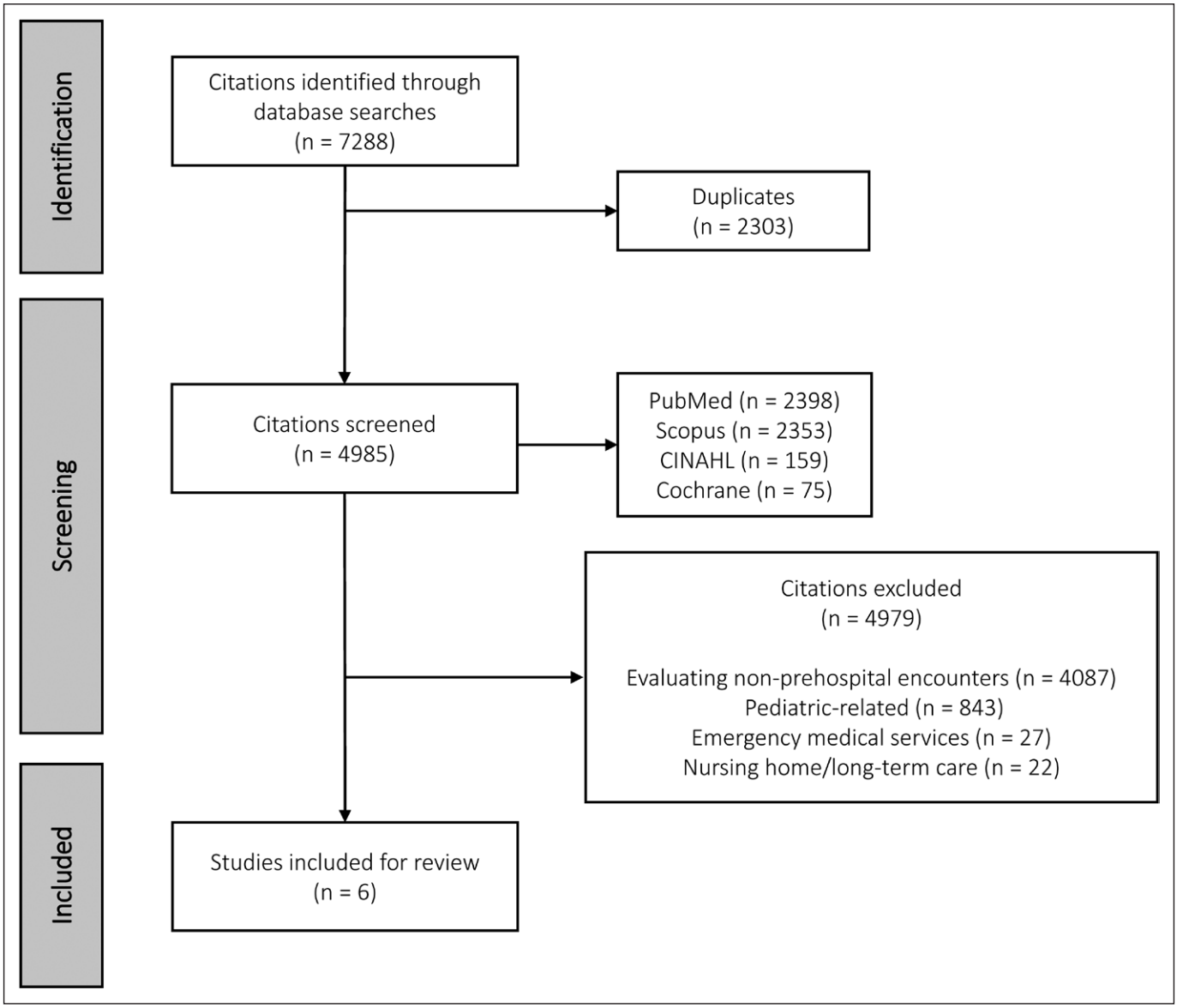

Figure 1. Study inclusion and exclusion. CINAHL = Cumulative Index to Nursing and Allied Health Literature.

Classification of Diseases, 9th Revision and 10th Revision codes were primarily used to identify sepsis hospitalizations in all but one of the included studies (17). The timeframe assessed for a healthcare encounter prior to admission was up to 7 days in three of the studies (9, 15, 16), up to 3 days prior to admission in two of the studies (17, 19), and within 1 calendar day in a single study (18). Classification schemes for the healthcare encounters assessed varied across studies but typically included assessment of primary care, specialty care, or ED in some combination (and not always together). Patients with sepsis hospitalizations tended to be elderly (median age in 70s) and frequently had several comorbidities as described in **eTable 3** (http://links.lww.com/CCX/A914), particularly diabetes, pulmonary, vascular, and kidney disease.

Regarding the primary outcome of the systematic review (**eTable 4**, http://links.lww.com/CCX/A914), an average (unweighted) of 32.7% (range, 10.3–52.9%) of patients admitted with sepsis or septic shock had an encounter with the healthcare system in the week prior to a sepsis hospitalization (**Fig. 2**). When considering the average (unweighted) proportion reported by the time frame for observation before the sepsis hospitalization, the results were: 7-day preadmission window (35.4%), 3-day preadmission window (38.5%), and 1-day preadmission window (10.3%). Although these visits could have occurred in the week prior to admission, several studies noted these visits increasing closer to the day of the sepsis hospitalization, including the day of admission (15, 16).

The types of visits were categorized and reported differently among the included studies. Liu et al (16) observed primary and specialty care visits as well as ED and urgent care visits. By design, Loots et al (17) only observed encounters in the general practitioner cooperative and Cecil et al (19) only evaluated primary care encounters. The study by Buchman et al (15) categorized visits as office/outpatient versus nursing facility, with established office/outpatient visits of 15 or 25 minutes most commonly billed. Fay et al (9) noted a relatively similar exposure to primary care, specialty care, and ED or urgent care visits prior to the sepsis hospitalization but did note that patients older than 65 years old tended to be seen in primary or specialty care, while younger patients tended to be seen in urgent care centers or EDs. By design, Miller et al (18) limited evaluation to outpatient providers within the health system of interest.

Descriptive statistics on clinical outcomes are reported in eTable 4 (http://links.lww.com/CCX/A914). Two studies assessed mortality differences between patients with and without healthcare encounters before their sepsis hospitalizations and observed in unadjusted analyses numerically higher mortality in

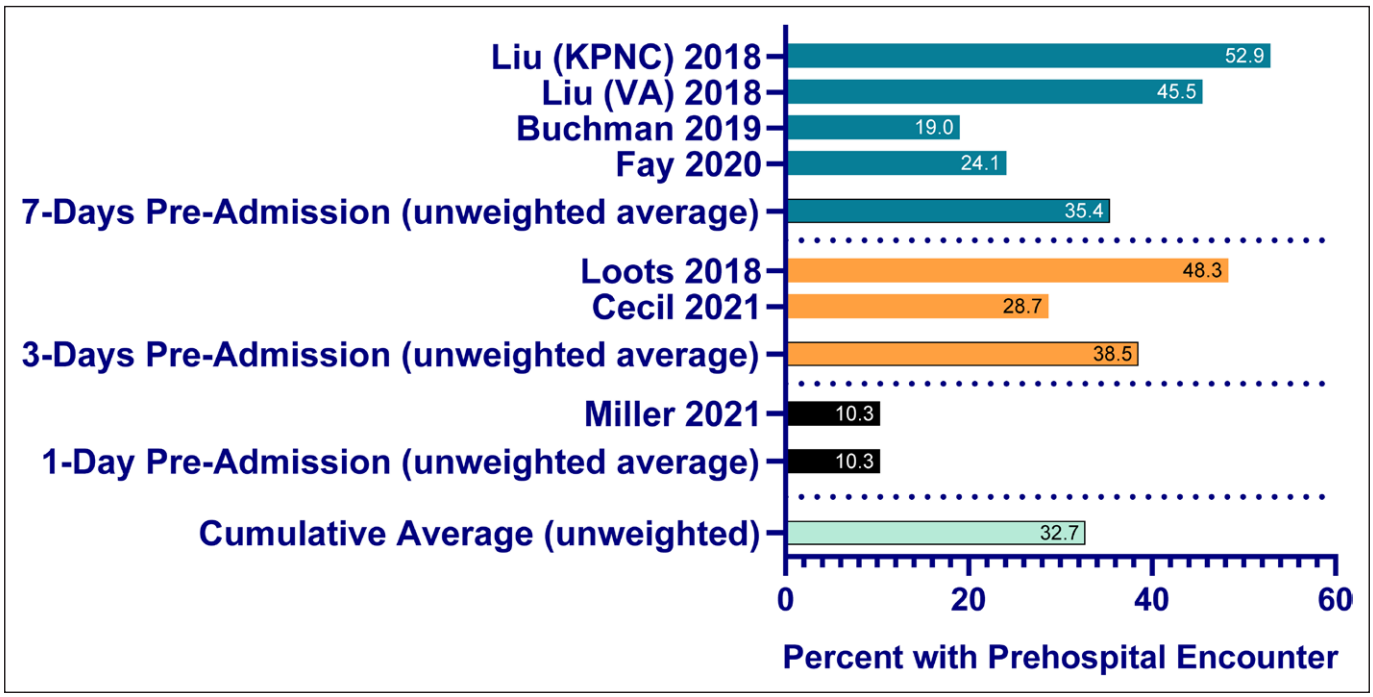

Figure 2. Prehospital encounters by study. KPNC= Kaiser Permanente Northern California; VA=Veterans Health Administration.

patients with a healthcare encounter prior to their sepsis hospitalization (16, 17). In the same comparisons, hospital lengths of stay were not meaningfully different between patients with and without a healthcare encounter before their sepsis admission (16, 17).

Other notable findings we observed in our review of included studies that were not reported consistently or easily quantified are summarized in **Table 1**. Of the two studies investigating antibiotic use prior to admission, antibiotic use was noted to increase in the days leading up to a sepsis hospitalization and up to 73.4% of patients had received antibiotics in the 30 days prior (9, 16). Documentation of infectious disease diagnoses or symptoms ranged from 27.0% to 80.5% (16, 18). Loots et al (17) found that 43% of patients were not suspected of having an infection in their presepsis hospitalization healthcare encounter. This group of patients, compared with their counterparts that had infection recognized and treated, were older, had more comorbidities, and experienced greater mortality during sepsis hospitalization. The study by Buchman et al (15) was the only study to include a comparator group of nonsepsis hospitalizations and noted that although the specific diagnoses and patterns of claims leading up to admission were generally unable to discriminate a sepsis hospitalization, that sepsis patients were more likely to have office visits of intermediate complexity (19% versus 15%), require skilled and/or unskilled nursing services, or have an inpatient claim in the week prior.

The only study to evaluate granular details of prehospitalization healthcare exposure, such as vital signs and potential organ dysfunction, was the single-center study by Miller et al (18). Notably, in that study, which considered only clinic visits the day of or day prior to hospitalization with sepsis, 65.2% of patients had abnormal vital signs and/or a quick Sequential Organ Failure Assessment (qSOFA) score greater than or equal to 1 (18, 20). While more than half of the patients (52.5%) had progressed in their illness severity by the

TABLE 1.
Other Notable Findings

References	Noteworthy Findings
Liu et al (16)	Primary and specialty care visits increased the week leading up to admission (16.2% of Kaiser Permanente Northern California and 23.0% of Veterans Affairs patients seen on the day of admission)
	The use of antibiotics increased steadily in the 7 d prior to sepsis hospitalization, and 27.0–34.2% of patients with a presepsis encounter had ≥ 1 acute infection diagnosis
Loots et al (17)	No significant differences between characteristics of patients with and without general practitioner encounter before sepsis hospitalization
	43% of patients with a general practitioner encounter not suspected of having infection. These patients tended to be older, and mortality rates nearly three times higher than those patients initially suspected of infection in the general practitioner encounter
Buchman et al (15)	The pattern of claims in the week prior to hospitalization were indistinguishable between patients with a sepsis and nonsepsis hospitalization, however, those patients with a sepsis admission were more likely to have diagnosed fever, conditions predisposing to infection or infection in the past year
	Patients with a sepsis admission were 2.8 times more likely to have claims for services in nursing facilities in the week prior to hospital admission compared with patients without a sepsis admission
Fay et al (9)	For patients ≥ 65 yr, a visit to primary care or outpatient medical specialist was the most common outpatient medical encounter. For patients ≤ 64 yr ED and urgent care visits were more common. 73.4% of patients receiving prehospital medical treatment within 30 d of admission were receiving antibiotics
Cecil et al (19)	A 5-min increase in consultation time was associated with a reduction in odds of self-referral for emergency hospital admission for sepsis (odds ratio, 0.91; 95% CI, 0.85–0.96)
Miller et al (18)	In clinic, 65.2% of patients had abnormal vital signs and/or quick Sequential Organ Failure Assessment score ≥ 1
	Infectious symptoms documented in 80.5% of patients
	62.7% of patients referred directly to the ED

ED = emergency department.

time they reached the ED/hospital, a relatively large proportion of patients (34.7%) presented with normal vital signs and a qSOFA score of 0, despite 68.3% reporting symptoms that could signify infection (18).

DISCUSSION

In this systematic review, we identified six retrospective cohort studies that reported on healthcare encounters in the week preceding hospitalizations for sepsis. The primary finding is that healthcare encounters in this week were common, occurring in approximately one out of every three sepsis admissions on average, with an increasing frequency closer to the day of admission. Documentation of infectious diagnoses in these prehospital encounters was variable but was as high as 80% in one study (18), and antibiotics were commonly prescribed. However, in another study, 43% of patients were not suspected of having infection in their prehospital encounter, and these patients experienced greater mortality during their sepsis hospitalization (17). Overall, our findings support the notion that there may be ample opportunities to improve sepsis outcomes through earlier identification, triage, and treatment in the prehospital setting.

There are several ways in which prehospital healthcare encounters could potentially prevent sepsis admissions or mitigate the risk of poor outcomes. First, for patients who are already exhibiting concerning physiologic signs, facilitating triage to the hospital could improve time to antibiotics, resuscitation, and other critical supportive care. For patients not requiring immediate hospitalization but who are identified as high risk of clinical deterioration, telemedicine follow-up may offer a convenient opportunity for closer monitoring the potential progression from infection to sepsis. Second, outpatient healthcare encounters offer an opportunity to educate patients and caregivers on the signs and symptoms of sepsis. This education could draw from established materials such as the "Get Ahead of Sepsis" campaign from the Centers for Disease Control and Prevention and empower patients to seek urgent medical care early when signs of sepsis do develop (21). Finally, additional laboratory testing in the outpatient setting may help with additional risk-stratification and screening. Point-of-care C-reactive protein, procalcitonin, or lactate levels have also been proposed to help potentially identify those patients with infection at risk of progressing to sepsis in the community setting, although the benefit of such testing in nonhospitalized patients warrants further study (17, 22–24). Urinary biomarkers may hold promise in detecting organ injury from sepsis, as the urinary product of tissue inhibitor of metalloproteinase-2 × insulin-like growth factor binding protein 7 (NephroCheck Astute Medical, Inc., San Diego, CA) may help detect sepsis-related kidney injury in patients with infection (but not meeting sepsis criteria) nearly 1 day prior to traditional criteria of serum creatinine and urine output being met (25). Additional point-of-care technologies are also in development for molecular and immune-based diagnostics (26). Given the relative lack of distinguishing features that we observed in this review of patients seen in the healthcare system that would predict risk of a sepsis hospitalization in the next week (aside from potentially older age and multiple comorbidities—certainly not an uncommon combination), novel approaches to improve risk-stratification for progression from infection to sepsis in the outpatient setting are urgently needed.

Although the strategies detailed above may hold promise, given our findings that one in three patients encounter the healthcare system prior to a sepsis hospitalization, there are several factors to consider that might limit the potential impact of prehospital care on sepsis outcomes (27). Patients admitted with sepsis are more likely to have chronic conditions and may therefore have more routine visits and interaction with the healthcare system in general. Furthermore, given that the number of encounters in the week prior to sepsis hospitalization increased closer to the date of hospital admission (and several studies indicate that many outpatient encounters occurred on the day of admission to the hospital), it is possible the care that was delivered was entirely appropriate. Indeed, several studies from our review indicate a number of patients admitted to the hospital the day of their encounter with the healthcare system (16–18). As no studies have critically evaluated the appropriateness of care delivered in these visits prior to a sepsis hospitalization, it is premature to attribute to clinician treatment patterns. Indeed, an intense focus on preemptively treating sepsis in outpatient visits could unintentionally lead to increased prescribing of inappropriate antibiotics when an estimated one-third of antibiotic prescriptions may already be inappropriate (27, 28).

Patient factors and preferences may affect their threshold to seek additional medical attention even when prompted by outpatient providers. The extent to which patient-controlled factors about seeking additional medical attention is also unknown. For example, qualitative interviews with neutropenic septic patients revealed denial of symptoms to avoid hospital admission in some cases, while others reported perception of mixed messages from healthcare providers regarding the symptom severity threshold to go to the hospital (29).

More broadly, the degree to which sepsis hospitalizations are truly preventable even with better care in the preceding week remains unclear. In the medical record review-based study that assessed the preventability of inhospital deaths, most patients who died from sepsis had severe underlying comorbidities such as progressive cancer, including 40% who would have qualified for hospice at the time of admission (8). The study by Buchman et al (15) noted that patients with sepsis admissions tended to have more claims for fever, conditions predisposing to infection, and infections in the prior year, suggesting that the sepsis admission may be the culmination of more chronic infection, debilitation, or immune dysregulation. This concept is supported by the strong link between frailty and elderly patients treated for infections (30) and also by the findings from studies in our review that observed patients with a healthcare encounter prior to their sepsis hospitalization experienced higher mortality once they were hospitalized compared with those without a healthcare encounter in the week prior to sepsis hospitalization. Distinct trajectories into sepsis have been successfully identified based on healthcare use in the previous year (low, rising, and high use) and are strongly associated with 90-day mortality (31). The elder risk assessment score has also been shown to predict critical illness in the next 2 years in elderly outpatients (32). Accordingly, the specific actions that could be taken at a healthcare encounter must be put into context of the patient's overall health trajectory.

Our study has several strengths, including a comprehensive literature search, appraisement, and reporting according to PRISMA guidelines (13). In addition to summarizing the findings, we have also suggested future paths for research given the infancy of this particular area of research. Our systematic review also has limitations. Despite the global burden of sepsis, the number of included studies was small and limited to retrospective, observational designs. Most studies defined sepsis hospitalizations using administrative claims data, which are known to have limited accuracy relative to medical record review. Different methods of sepsis identification among included studies may have significantly influenced the empiric cohorts identified in studies. In particular, explicit sepsis diagnoses tend to have high specificity but low sensitivity and are biased toward more severely ill patients, while implicit definitions that rely on infection and organ dysfunction codes have better sensitivity but lower specificity and identify less ill patients (33–36). Administrative claims data were also primarily used for classifying health encounters in the week prior to sepsis hospitalization, which provides limited detail on the nature of these visits, including vital signs and changes from a patient's baseline. Although no particular pattern of comorbidity diagnoses emerged in patients seen in the healthcare system that may go on to be admitted for sepsis in the next week, risk and protective factors studied were limited. Further, only a single study identified in our review (15) included a nonsepsis hospitalization comparator group. Although prospective studies in this area would also carry significant challenges, the retrospective cohort designs of these studies beginning with sepsis hospitalizations and looking back likely create challenges of identifying patterns of illness or other presenting features that would signal a risk of a sepsis hospitalization in the pending days from a healthcare encounter, or in other words, an interventional action. Studies evaluated varying time periods before a sepsis hospitalization (7-, 3-, and 1-d), which may have influenced the frequencies observed and the opportunity to identify any potentially modifiable factors (particularly for patients with a healthcare encounter that were immediately referred for hospitalization). This aspect may have introduced heterogeneity into the estimate of encounter frequencies, patient characteristics, and the search for risk factors. Statistical tools to provide a summary estimate for the findings in this type of systematic review continue to evolve (12). We used an unadjusted average for our primary analysis due to over 90% of sepsis hospitalizations identified from a single study (15) but recognize that interpretation of this estimate is hindered by the lack of comparator groups in many studies, the fact that not all studies assessed the same presepsis hospitalization healthcare encounters for inclusion (e.g., some were limited to primary

care only), and important differences among studies such as healthcare systems, countries, mechanisms of sepsis identification, and time periods of evaluation before hospitalization. Indeed, the study with the smallest observation window (1-d) reported the lowest proportion of encounters (18). A shorter time window such as 1-day prior may be best at detecting early sepsis, while a longer time period such as 7 days may be more appropriate for the examination of the transition from infection to sepsis. Our review only included studies with a maximum time window of 7 days prior to admission, but a longer evaluation period such as 4 weeks prior may also give important insights into patients' care leading up to a sepsis hospitalization. Importantly, the role of socioeconomic factors (including income, education, and distance to a healthcare provider) remains understudied in detecting patients at risk of progressing from infection to sepsis. For example, lack of insurance may deter patients from seeking initial or follow-up care and is associated with organ dysfunction and mortality in community-onset sepsis (37). Finally, we limited our systematic review to adult patients. The experiences and encounters of pediatric patients with the healthcare system prior to a sepsis hospitalization are likely very different.

As critical care continues to evolve as a subspecialty of medicine, research and practice have moved beyond the walls of the ICU. The last decade has seen increased focus and understanding of postintensive care syndrome and the study of patients' subsequent trajectories (38). By approaching investigations from the prehospital side of the healthcare spectrum and studying the development of sepsis, the potential exists for better diagnostics and novel interventions to be developed that improve patient outcomes by preventing hospital admissions in many cases or facilitating earlier hospital admission for those who need it. Future studies should assess in more granular detail the nature of prehospital outpatient encounters and the appropriateness of clinicians' actions, and ideally, well-designed randomized controlled trials should be conducted to rigorously test the impact of potential sepsis prevention interventions in the outpatient setting.

CONCLUSIONS

In this systematic review, 32.7% of patients on average (range, 10.3–52.9%) have an encounter with the healthcare system in the week prior to a sepsis hospitalization. These may present opportunities to improve early sepsis care or potentially prevent the transition from infection to sepsis.

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