Prehospital Delay in Sepsis Diagnosis: Current Evidence and Future Research Directions

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Section I: Background

Defining and identifying sepsis

Sepsis is a syndrome of life-threatening organ dysfunction due to a dysregulated immune response to acute infection [1]. While sepsis has been recognized as an entity for centuries, scientific understanding of its pathophysiology – and therefore its definition – has evolved substantially over the past 50 years. The concept of sepsis as a result not only of infection, but also of a patient's immune response to that infection, was developed in the early 1990s [2]. While the definition by Bone and colleagues in 1992 ('Sepsis-1' and 'Sepsis-2') identified features of hyperinflammation that were associated with sepsis, the Systemic Inflammatory Response Syndrome (SIRS) criteria, subsequent research has identified both hyper- and hypo-inflammatory components of immune response to infection that are now understood to be hallmarks of sepsis. Therefore the definition was revised in 2016 through an consensus-building process among a group of international experts to replace the concept of hyperinflammation with that of immune dysregulation which accompanies acute infection ('Sepsis-3') [1].

While the consensus definition of sepsis is a statement of sepsis physiology, there currently is no 'gold standard' test or singular clinical feature that allows for easy, accurate diagnosis of sepsis. Several clinical criteria for sepsis have been proposed, including criteria proposed by the Sepsis-3 Task Force. These clinical criteria rely upon a combination of physical exam features such as vital signs or mental status (e.g., the quick Sepsis-Related Sequential Organ Failure Assessment (qSOFA) score), and in some cases include results of laboratory tests or medication doses (e.g., the Sepsis-Related Sequential Organ Failure Assessment (SOFA) score or Universal Vital Assessment (UVA) score) [3-5]. As patients are required to meet only a portion of a given set of clinical criteria, and there is no single

reference set of criteria, there remains disagreement even among expert clinicians regarding whether specific patients are indeed septic [6, 7]. This diagnostic uncertainty is understandably magnified in settings with limited diagnostic information (e.g., inability to perform requisite laboratory testing), in situations with limited time for assessment (e.g., during emergency medical system (EMS) transport), or among patients or providers with limited familiarity with sepsis.

Sepsis is a syndrome, rather than a singular disease process, which can make diagnosis more challenging. While there is an advantage to identifying sepsis as a unifying common pathway for the purposes of epidemiology and management, it is also important to recognize that the multitude of pathogens, primary organ systems infected, presenting symptoms, and diverse systemic manifestations create a myriad of protean pathways to sepsis (Figure 1)[8]. This is relevant since the preceding infection and accompanying symptoms are more varied than for other conditions for which prehospital care and triage have been more successful (e.g., acute myocardial infarction (AMI) or stroke). While we acknowledge the variety of pathogens and infectious conditions that can lead to sepsis, the scope of this paper is largely restricted to their common pathway once organ dysfunction develops due to a dysregulated immune response. However, it is important to note that many of the current knowledge gaps and future research opportunities related to prehospital diagnostic delay in sepsis are related to the identification, monitoring, and care of patients with uncomplicated acute infection, in effect identifying and intervening with patients who are directly at risk of sepsis but are not yet (and ideally, never will be, septic).

Like any health condition, sepsis is defined by pathophysiology at the level of the individual, rather than by where that individual may be. Sepsis can develop and be diagnosed within the home or living

environment, in ambulatory care settings (i.e., primary or specialty care clinics or urgent cares), during emergency medical transport (e.g., in the ambulance), in the emergency department (ED), or in the hospital. Although the pathophysiology of sepsis may be the same regardless of patient location, the context is critical when considering content and quality of sepsis assessment, diagnosis, and management. Human, material, and informational resources differ between these care environments, and evidence from one setting cannot be readily extrapolated to others. While each location is unique, for the purposes of this paper we will separate them into prehospital, meaning any patient location outside of the hospital or ED (e.g., home, nursing facility, clinic, or EMS vehicle), and hospital (including ED) contexts. This paper focuses specifically on sepsis diagnostic delay in the prehospital setting, and as such does not review literature from ED or inpatient settings except when directly applicable to the prehospital environment.

For decades, research on sepsis diagnosis and management largely focused on patients in the hospital (a term which will henceforth be used to refer to patients in the ED or inpatient settings). This was likely driven by the fact that many patients with sepsis are seriously ill, thus meriting inpatient care. Additionally, sepsis diagnosis relies upon multiple data points, obtained through clinical exam or laboratory testing, many of which are not traditionally routinely available in the prehospital setting due to time, cost, or resource distribution. However, given the large burden of sepsis morbidity, mortality, and cost (described in detail below) and recognizing that sepsis stems directly from acute infection that, if promptly and appropriately diagnosed and treated may not develop into sepsis at all, the focus of sepsis research has increasingly moved beyond the walls of the hospital. The COVID-19 pandemic has perhaps accelerated this shift towards the diagnosis and treatment of acute infection (indeed, with the potential to develop into sepsis) in the prehospital

environment. The rapid development of research and interventional initiatives aimed at screening for and diagnosing COVID-19 has expanded our collective understanding of possibilities for patient- and family-centered identification and care of patients with acute infection in the prehospital space.

Sepsis epidemiology and burden on the US healthcare system

Worldwide, there are estimated to be 48.9 million incident sepsis cases each year, with 11 million associated deaths [9]. This represents nearly 20% of all global deaths as of 2017. Age-standardized incidence per 100,000 population is estimated to be 677.5 cases globally, and age-standardized mortality is estimated to be 148.1 per 100,000 population. Estimates for sepsis incidence among adults in the United States (US) range from 903,000 to 1.7 million, and adult sepsis-related mortality estimates range from 174,000 to 270,000 as of 2014 [9, 10]. Overall sepsis incidence for all ages in the US as of 2017 is estimated to be 1.08 million cases, with an age-standardized incidence rate of 254.9 cases per 100,000 population, and overall sepsis mortality is estimated to be 190,000 as of 2017, with an age-standardized mortality rate of 35.1 deaths per 100,000 population [9]. The most common underlying cause of sepsis worldwide each year is pneumonia, accounting for 16.4% of sepsis-related deaths among all age-groups in 2017. Other common underlying infectious causes include diarrheal diseases, urinary tract infections, intra-abdominal infections, diabetes-related infections, and meningitis.

Sepsis is associated with 2.9-16.7% of adult hospitalizations [11, 12] and 36.9-55.9% of inpatient deaths in the US each year, with variation in estimates across datasets and case definitions [12, 13]. This sums to a massive cost of human lives, resources, and healthcare spending. Sepsis is estimated to be the single greatest source of inpatient healthcare costs in the US, accounting for over $38 billion

in hospital expenses; this represents 8.8% of all US inpatient medical spending [14, 15]. Inpatient sepsis spending eclipses any other condition, and is substantially higher than other acute health conditions such as AMI ($14 billion), heart failure ($14 billion), respiratory failure ($9.2 billion), or stroke ($7.4 billion) [14].

While sepsis is a major public health challenge across the US, there is strong evidence that certain subgroups are at far higher risk than others. Among children, neonates are at highest risk for developing and dying from sepsis [9, 16-20]. Data of hospital discharges from the Healthcare Utilization Project demonstrate a 2019 septicemia incidence of 1,466 cases per 100,000 infants, which declines to an incidence between 32-64 cases per 100,000 children in age-groups from 1 to 17 years of age [21]. The data show that after childhood sepsis incidence steadily rises with increasing age, until there is a sharp increase in middle-to-later adulthood, ranging from 1,014-5,457 cases per 100,000 in the 45–64-year-old and $\geq$ 85 year-old age-groups, respectively [16, 21]. Indeed, more than half of all sepsis cases in the US occur among those ≥ 65 years [9]. Consistent with this increased incidence with older age, other medical risk factors for sepsis incidence and mortality in the US include frailty and multimorbidity, the presence of multiple chronic conditions [22, 23].

Social determinants of health (SDH) such as level of education, family income, and marital status are also associated with sepsis incidence and mortality in the US [24-26]. The associations between sepsis incidence and outcomes and race/ethnicity appears to be complex, with some research identifying that Black race/ethnicity is associated with increased incidence and worse outcomes, while other research has demonstrated lower hospitalizations [24, 27-30]. Some research has identified that other socioeconomic factors may mediate these racial disparities, which may also explain some of the

variation in results from different study populations [24, 30, 31]. Geography, including community features, rurality, and residence within a medically-underserved area are also associated with sepsis risk and sepsis mortality in the US [32, 33].

Section II: Prehospital Diagnostic Delay in Sepsis

Timely diagnosis of sepsis is critical to facilitate early treatment and improve outcomes. One of the only sepsis interventions which has repeatedly been shown to improve outcomes is early administration of appropriate antimicrobials. Although findings are mixed, several studies have found that that even 1-hour delay in antibiotic administration is associated with increased mortality [34-36]. As sepsis always evolves from an acute infection, it is the result of a predictable clinical trajectory; timely diagnosis and intervention at multiple points in this pathway has the potential to prevent sepsis from developing or to prevent poor outcomes once it does (Figure 2). This clinical trajectory is relevant to discussion of sepsis diagnostic delay generally, and specifically to prehospital diagnostic delay, as sepsis criteria arguably justifies urgent diagnosis and treatment of both non-septic infection and infection plus dysregulated immune response. Previous studies have demonstrated that timeliness of prehospital diagnosis and patient referral, with 'delay' broadly conceived and discussed further below, is associated with time to treatment and in some cases, with outcomes among patients hospitalized with sepsis [37, 38].

What amount of time defines clinically meaningful diagnostic delay in sepsis?

The current body of evidence provides rationale for setting the bar for diagnostic excellence for sepsis at producing a sensitive and specific result within 1 hour for sepsis and septic shock, with some rationale to liberalize this timeframe for less severely ill patients with sepsis and or uncomplicated

acute infection. We base this opinion given that the time scale defining *treatment* delay for sepsis and septic shock is generally accepted to be 1-3 hours, placing our proposed diagnostic window under this timeframe as well. This concept of the "golden hours" for treating sepsis is biologically plausible and has face validity by analogy to care of other acute conditions, such as AMI and stroke, with well-established diagnostic and treatment timeframes [39, 40]. Additionally, although early meta-analyses demonstrated inconclusive results [41], more recent large observational studies of sepsis and septic shock in the hospital setting provide evidence that there is a consistent, modest increase in mortality for every hour in delay of antibiotic administration [42, 43]. While these data have informed the development of professional society clinical care guidelines and the Centers for Medicare and Medicaid's core hospital quality care metrics [44, 45], it remains unknown whether the effect will carry over to the prehospital setting where the case-mix includes less severe forms of sepsis that may attenuate the impact of time-to-antibiotics on mortality. While a systematic review demonstrated evidence towards benefit of prehospital antibiotic administration [46], the one large randomized, controlled trial in EMS transport setting with approximately 37% of patients with non-severe sepsis and 81% of the control group subsequently receiving antibiotics within 3 hours of arrival to the ED did not demonstrate a difference in mortality [47]. While these lines of evidence provide some rationale for liberalizing the acceptable timeframe of diagnosis for less severe forms of sepsis above the 1-hour mark, an early and accurate diagnosis plausibly optimizes the treatment of infections while mitigating the risks of overuse of empiric antibiotic prescribing on individuals and the community.

What is the extent of prehospital diagnostic delay in sepsis?

The issue of diagnostic delay in sepsis is highly complex, particularly in the prehospital setting. To measure diagnostic delay, one needs to capture a time of onset and time of subsequent definitive diagnosis; however, neither parameter is currently reliably characterized or captured in sepsis. While the hospital setting provides parameters for capturing an onset time from recorded clinical data or administrative timestamps of presentation, in the prehospital setting it is difficult to define a specific transition point when an infection becomes sepsis. It is also difficult to define the time of definitive diagnosis, since microbiological cultures are often inconclusive and no 'gold standard' diagnostic test currently exists. While initiation of empiric antibiotic treatment has in some cases been utilized as a relevant and available surrogate timepoint, this obscures the ideal paradigm for testing that facilitates a rapid and accurate biologic diagnosis *before* treatment to optimize efficacy of individualized treatment and minimize harms of inappropriate treatment.

Within this conceptual framework, with the exception of the availability of prehospital testing for COVID-19, malaria, or a few other pathogens, it is reasonable to suggest that diagnostic delay is pervasive in most all cases of prehospital sepsis since pathogen, susceptibility, and dysregulated immune response are not reliably diagnosed before the appropriate initiation of treatment. This paradigm is particularly important in the prehospital setting, where the true goal is to diagnose and treat infections before they progress to sepsis. One recent study of sepsis-associated hospital deaths highlights this goal – among hospitalized septic patients who died during their hospital stay (74% of whom had sepsis upon admission) 88% of the deaths were deemed not preventable [48]. This, in part, supports the concept that sepsis is a critically late stage of illness along the spectrum of infection and that the goal for diagnostic excellence in the prehospital setting should be a paradigm of accurately diagnosing infection in its earlier stages.

While defining the extent of prehospital delay in sepsis is difficult, there is some literature describing the contexts of where prehospital sepsis may occur. A recent review systematically summarized healthcare encounters in the week preceding sepsis hospitalization across 6 studies (4 from US, 1 UK, and 1 the Netherlands) [49]. Collectively, 10.3%-52.9% of sepsis admissions had a healthcare encounter in the week preceding hospitalization [49]. The largest study of the group demonstrated that 60% of Medicare beneficiaries had a healthcare claim in the week before sepsis hospitalization, with 20% of the hospitalizations preceded by an outpatient claim and the rest comprised of home health, unskilled nursing assessments, and skilled nursing facility claims [50]. Additionally, this study further demonstrated that most of these encounters occurred a day before the sepsis admission [50]. Finally, an additional 10-15% of US Medicare beneficiaries had an inpatient claim in the week before admission [50]. Another study found that 45.5-52.9% of patients hospitalized for sepsis had a healthcare encounter in the preceding week, with increasing occurrence leading up to the day before admission and with concomitantly increasing proportions of encounters with diagnoses of infections (3.3% increase per day) and use of antibiotics (2.1% per day) [51]. A smaller, more detailed study demonstrated that 60.7% of sepsis admissions had a recent healthcare exposure: 24.2% had an outpatient encounter in the prior week and 42.5% received medical treatment such as an infusion, wound care, dialysis, or a procedure in the prior month [52].

In summary, while it is difficult to conceptually and practically describe the extent of diagnostic delay in prehospital sepsis, through these studies we gain some understanding of the relevant contexts for intervention. They demonstrate that while various healthcare settings often proximally precede hospitalizations for sepsis, high proportions of sepsis hospitalizations do not appear to have a

preceding healthcare encounter. Furthermore, the increasing pace and treatment intensity of outpatient encounters for sepsis leading up to admission lends support to the concept that the optimal parameters for time and accuracy of diagnostic tests in the prehospital setting are similar in scope and scale to those of the inpatient setting.

Section III: Approaches to Sepsis Diagnosis in the Prehospital Space

What is the current state of the art for diagnosing sepsis?

Since sepsis is one point on a continuum of severity that begins with an infection, we find it useful to describe the landscape of diagnosing infection and sepsis within three broad categories: 1) early clinical warning scores that can help identify patient populations appropriate for further testing; 2) rapid, sensitive screening tests for sepsis; and 3) specific confirmatory and susceptibility tests for infectious pathogens. After reviewing the literature for each category, we will synthesize them into a conceptual framework for the diagnosis of infection and sepsis along the healthcare trajectory from prehospital to hospital.

Provider clinical diagnosis

First, we consider clinicians' abilities to diagnose sepsis. A retrospective analysis of 249 critically ill patients in 2019 highlighted the challenges of clinical diagnosis by demonstrating that there was not robust agreement between admitting physicians' initial impression and 3 sets of expert reviewers (kappa range 0.58-0.68) [7]. One prospective study of ED patients with sepsis demonstrated poor recognition, with general practitioners and EMS providers identifying 31.6% and 41.4% of sepsis patients respectively [53]. Moving further up the chain of care, in a retrospective study of patients subsequently determined to have sepsis, EMS personnel only recognized 13.7% of cases [54]. Finally,

in the ambulatory care setting, in a prospective study of 357 in-home care visits for acutely ill adults with fever, primary care providers' perceived probability of sepsis within 72 hours had a reasonable predictive capacity (area under the receiver operating characteristic curve (AUROC) 0.73) [55]. One reason this study may have had increased accuracy above the more acute care settings was that the in-home care visit was prompted by a telephone triage system already identifying signs and symptoms of infection, and in the acute care settings more patients are in extremis for a variety of other reasons, making distinction of underlying causes potentially more challenging.

We identified a few small but important qualitative studies focused on understanding patient- and provider-level factors associated with delayed presentation to the hospital with sepsis. Most of this literature focuses on EMS providers. One Swedish study identified themes pertaining to how EMS providers assess patients with sepsis [56]. They found that factors such as previous experience and the patient's severity of illness played a role in prehospital patient assessment. We identified one study focused on cancer patients with neutropenic sepsis which assessed prehospital interactions with multiple types of providers and settings [57]. Although the study was small and had a limited patient population, the help-seeking experiences of these patients sheds light on potential future research pathways for improved sepsis diagnosis in the prehospital non-EMS space. This study found several potentially modifiable factors delaying patients' presentation to the hospital, including mixed messages from providers on urgency of presentation to the hospital, inconsistent messaging about possibility of sepsis in the absence of fever, and discharge from a care setting where diagnostic testing was performed but treatment was not initiated. Some studies have described the characteristics of outpatient clinical encounters, such as those in primary care offices, that immediately precede sepsis hospitalizations [58]. Future mixed-methods or qualitative studies aimed

at understanding providers' clinical reasoning and diagnostic approaches in these settings would be helpful.

Several studies have attempted to improve clinician diagnosis of sepsis in the prehospital setting through educational or other quality improvement efforts [59]. One group implemented a prehospital EMS-based sepsis screening and alert protocol, training 300 providers over a 12-month period [60]. In a retrospective pre-post assessment, they found that sepsis recognition by EMS providers improved from just 12% before implementation to 59% ($p<0.001$). While observational studies have linked prehospital sepsis diagnosis to earlier ED administration of antibiotics, this is one of the few studies to link improved prehospital sepsis diagnosis to treatment, reporting that septic patients identified by the EMS providers received earlier antibiotics in the ED (28 min vs 52 min, $p=0.02$) [53].

Clinical scores

Clinical scoring systems have been developed and used for multiple purposes in the care of patients with sepsis or who are at high risk for sepsis. These have largely been developed within the inpatient care space, using clinical data from hospitalized patients, though several have been validated in prehospital settings. There are three primary ways the scores have been used, irrespective of the purpose for which they were originally developed; most of the scores discussed here have been subsequently tested for multiple purposes beyond their initial design. Therefore, we will review the literature summarizing uses for which scores have been tested, not limiting our review to original intent.

First, some scores are used as 'early warning scores' (EWS) to alert providers of the potential worsening clinical condition of their patient, regardless of whether that worsening is due to sepsis or a non-sepsis condition. We consider a paper to be testing EWS if the score is applied to patients with undifferentiated illness or infection without limiting the study population to those already diagnosed with sepsis. EWS may be helpful in identifying prehospital patients in need of further evaluation, or for the purposes of cohort enrichment for high-risk individuals in research studies. Second, some scores are used as clinical markers of acute inflammation (e.g., the SIRS criteria, used in Sepsis-1 and Sepsis-2) or acute organ dysfunction presumed due to dysregulated immune response (e.g., the SOFA or qSOFA scores, used in Sepsis-3) accompanying suspected or confirmed infection, to identify patients likely to be septic (we will call these 'sepsis identification scores'). These are helpful when considering scores to aid in the diagnosis of sepsis. Third, some scores have been used to predict poor outcome (e.g., mortality) among specific populations of patients, including patients already diagnosed with sepsis (we will call these 'prediction scores'). These might be helpful in measuring severity of illness at time of presentation for adjustment in research analyses, or for use as more proximate markers in the testing of interventions. It is important to note that features associated with mortality may or may not be associated with likelihood of having sepsis itself[8].

It is important to note that there is some epistemological overlap between these categories. As EWS are meant to predict clinical deterioration, tests of association in these studies use markers of worsening or poor status (e.g., intensive care unit (ICU) transfer, need for organ support interventions, or death) as outcomes. Likewise, some studies have used scores with the intention of identifying patients likely to be septic, from among those with suspected or confirmed infection, using mortality or other markers of poor clinical status as an outcome in tests of association [61, 62].

This follows the logic that, as sepsis is defined as life-threatening organ dysfunction due to dysregulated immune response to acute infection, patients with sepsis are more likely to have their 'life threatened' than those without sepsis. We will consider those studies with the stated intent of identifying patients likely to be septic in the second category, 'sepsis identification scores.' As this paper is focused on the prehospital diagnosis of sepsis, we will primarily focus on the second category – prehospital use of sepsis identification scores as a clinical indicator of inflammation or acute organ dysfunction to 'complete' the diagnosis of sepsis among patients already suspected or confirmed to have infection, with a brief review of the prehospital literature pertaining the sepsis in the other two categories (EWS and prediction scores).

There are multiple observational studies on the use of EWS among patients with suspected infection both within and outside of the hospital. One of the largest of these, using prospectively collected data from 773,477 patients admitted to non-ICU wards of 28 hospitals in the US, found that the National Early Warning Score (NEWS) had the highest discrimination for mortality vs the Modified Early Warning Score (MEWS), Between the Flags (BTF) score, qSOFA score, or SIRS criteria [63]. The largest interventional study implementing an EWS also used NEWS [64]. This study reports on the implementation of NEWS across an entire health system – the National Health Service for the West of England, including EMS and non-hospital-based clinics, at the time of referral from the community into the acute healthcare system in patients with suspicion of sepsis. An interrupted time series analysis demonstrated a reduction in mortality among patients with suspected sepsis which was not seen in other areas of England, without an associated increase in admissions.

Several ‘sepsis identification scores’ have been evaluated for prehospital use, primarily in the EMS setting [65]. One large study compared 14 different EMS-based scoring systems in a retrospective cohort validation study [66]. This included over 130,000 adult patients who were transported by ambulance and diagnosed with an infection in the ED, and scores were calculated using prehospital data. The outcome of interest was presence of inpatient sepsis criteria (ED diagnosis of infection plus ICD codes or vital signs consistent with organ dysfunction). Overall, the authors found that the Critical Illness Prediction (CIP) score, NEWS, and qSOFA score had good predictive ability for sepsis diagnosis. A smaller retrospective study of prehospital qSOFA found that it had high specificity (94%) but low sensitivity (43%) for sepsis when using discharge diagnosis as the outcome of interest [67]. Other studies have shown similarly low sensitivity and high specificity of prehospital qSOFA for inpatient sepsis [68]. Additional studies have also identified prehospital NEWS, or a slightly modified version termed NEWS2, as having good sensitivity and specificity for inpatient Sepsis-3 criteria [69].

Many studies of prehospital clinical scores for sepsis tested ‘prediction scores.’ These studies, mostly performed in the EMS setting but some in ambulatory care settings, limit their study population to those diagnosed with sepsis at the hospital level and test the association between prehospital score values and patient outcomes, such as hospital or 28-day mortality. We identified studies on shock index variation, qSOFA, SIRS, and MEWS, among others [67, 70-73]. As these are less relevant to the issue of prehospital sepsis diagnosis but perhaps more pertinent to triage, adjustment for severity of illness in research, or as proximate endpoints in therapeutic trials, we will not further describe these studies.

Wearable devices

Wearable health monitoring devices (or simply 'wearable devices') represent an emerging technology with multiple different modalities that have potential application to infectious diseases and sepsis [74]. Wearable devices can capture a wide range of biologic data, including non-invasive monitoring of blood pressure, respiratory rate, pulse oximetry, temperature, body posture, fall detection, activity, and levels of consciousness. A recent systematic review of 34 studies of remote monitoring devices in chronically critically ill patients concluded that there remain issues related to practical utilization of devices and data processing, and there are currently insufficient data regarding their role within home-based management models [75]. More specific to acute infection, a 2022 systematic review summarized data from 12 studies describing performance of many commercially available sensors for detecting COVID-19 infection [76]. Several studies retrospectively assessed a range of physiologic parameters such as heart rate, respiratory rate, skin temperature, sleep, and activity, and some included additional symptom questionnaires with several achieving high diagnostic accuracy for COVID-19 (>90% specificity, >80% sensitivity) [76]. One provocative study among participants enrolled in a healthy behaviors platform that monitors data from commercially-available wearable devices conducted surveys regarding Influenza-like illness symptoms and outcomes every two weeks [77]. Among the >15,000 participants who reported an Influenza-like illness, 18.8% sought medical attention, and 0.4% were hospitalized. This study demonstrates a proof-of-principle for platforms that could connect wearable sensor data to periodic questionnaires to collect data on infections, timing, physiologic effects, and outcomes [77]. Despite these interesting studies, a 2021 systematic review of 18 studies of remote monitoring of chronic diseases through primary care clinics highlighted some of the difficulties in scaling up the information into feasible clinical workflows [78]. Additionally, consideration of the potential exacerbation of structural inequalities in diagnostic

excellence with the use of new and expensive technologies must be a part of any future work in this area.

Laboratory tests for sepsis-associated dysregulated immune response

In this section we describe available and emerging tests for identifying sepsis-associated dysregulated immune response. While these tests may not identify a specific pathogen, in patients with signs of organ dysfunction their goal is to help determine if the cause is infectious and thus to inform the next steps of diagnostic testing and clinical management. Additionally, in patients with signs or symptoms of acute infection, these tests may help identify dysregulated immune response and thus complete the diagnosis of infection. This section will focus on studies of biomarkers' utility in the diagnosis of sepsis, rather than prognostic performance among those already diagnosed.

A host of biomarkers have been examined for diagnostic value in sepsis, but the most literature exists for C-reactive protein (CRP), a non-specific marker of systemic inflammation, and procalcitonin (PCT), another acute phase reactant which is more specifically increased in inflammation from bacterial than viral infections. A 2018 meta-analysis demonstrated the moderate diagnostic accuracies of PCT (summary sensitivity 0.80; specificity 0.77) and CRP (summary sensitivity 0.80; specificity 0.61) for sepsis [79]; however, most of this literature was developed in hospitalized patients and their performance may be attenuated in the prehospital setting where prevalence and pre-test probability for infection and sepsis are lower. One pragmatic, prospective study of CRP and PCT in the prehospital setting examined 357 primary care home visits to develop and validate a sepsis diagnostic model [55]. In these adults with acute illness with clinical symptoms of infection triaged telephonically for an in-home assessment, 9 clinical parameters (age, temperature, systolic blood

pressure, oxygen saturation heart rate, respiratory rate, altered mental status, rapid progression, and rigors) and three biomarkers (CRP, PCT, and lactate) were examined against a diagnosis of sepsis within 72 hours adjudicated by three expert panels. This study demonstrated that a model including 6 clinical parameters had a moderate diagnostic accuracy (C-statistic 0.80; sensitivity range 18%-100%, and specificity range 2%-98% at different model cut-off points) that was not improved by inclusion of any of the biomarkers [55]. A different study incorporating several additional biomarkers, however, found substantial improvement in identification of community-onset sepsis over a clinical risk score alone [80]. This prospective cohort study of adult patients at risk of sepsis who were transported by EMS used presence of clinical criteria for sepsis early in the hospital course as the outcome (defined using Sepsis-3 criteria of SOFA score >2 plus suspected infection). Using blood samples collected at the time of prehospital (EMS) intravenous catheter placement, they measured several biomarkers: IL-6, IL-10, TNF, CRP, procalcitonin, troponin, and lactate. They first used a clinical risk score based on prehospital vital signs, finding that the AUROC was 0.59. This improved to 0.79 when adding a 'best performing panel' of IL-6, TNF, troponin, and lactate ($p<0.01$).

While there may still be a role for these biomarkers for the prehospital diagnosis of sepsis when used in a multi-test platform, there are emerging technologies that have additional promise. A 2020 narrative review summarizing the preceding decades' progress demonstrated 9 biomarkers with better diagnostic value than either or both CRP or PCT [81]. Again, these candidate biomarkers (thromboelastometry lysis index, decoy receptor 3, PLA2-II, Hepcidin, sCD163, CD64, serum amyloid A, heparin-binding, DLL1) were studied in hospitalized patients and many were assessed for their prognostic and severity classification characteristics rather than to a gold standard sepsis diagnosis [81].

In addition to individual biomarkers, there has been promising work in examining the RNA transcriptome of blood samples to uncover signatures that may identify infectious inflammation. Several such signatures such as the FAIM3/PLAC8 ratio, sNIP score, Bauer Gene expression, Sepsis Meta Score, and SeptiCyte Score, have been discovered and explored in initial clinical samples [82-89]. Two studies have compared three of the RNA transcript signatures, Sepsis Meta Score, SeptiCyte Score, and FAIM3:PLAC8 ratio, in retrospective clinical samples. One study of 61 blood samples from critically ill patients on mechanical ventilation showed that while all three scores demonstrated differences between sepsis and non-sepsis patients, the Sepsis Meta Score performed best (AUROC 0.80, compared to 0.69 and 0.68 for FAIM3:PLAC8 and SeptiCyte Lab, respectively) [83]. Another study examining 39 clinically and methodologically distinct cohorts of publicly-available banked gene expression samples demonstrated the best performance from the Sepsis Meta Score across two sets of clinical comparisons: 1) comparing sepsis with SIRS/trauma patients (Sepsis Meta Score AUROC 0.82, compared to 0.78 and 0.73 for the FAIM3:PLAC8 and SeptiCyte Lab, respectively); and 2) comparing sepsis/acute infection with healthy controls (Sepsis Meta Score AUROC 0.96 compared to 0.94 and 0.71 for the FAIM3:PLAC8 and SeptiCyte Lab, respectively) [86]. Among these tests, at the time of writing the SeptiCyte Lab (Immunexpress Inc., Seattle, WA) is the only one with FDA approval [90].

The SeptiCyte family of tests represent an ongoing pipeline of development. The SeptiCyte Lab test described above examines a signature of 4 RNA transcripts (CEACAM4, LAMP1, PLAC8, and PLA2G7), and has undergone additional pragmatic, prospective validation. While it has demonstrated an AUROC range of 0.82-0.89, with a sensitivity ranging from 0.92-0.97 and negative predictive value of

0.89, this work has been done in critically ill patients and therefore may not reflect performance in the prehospital setting [91, 92]. From this, Immunexpress, Inc. created a two RNA transcript (PLAG27 and PLAC8) test, integrated into an automated platform requiring 2 minutes of handling time and 60 minutes to result (SeptiCyte RAPID), which was approved by the FDA in 2021 [93, 94]. More recent studies describe the development novel RNA signatures for distinguishing viral from bacterial infections [95-97] and for diagnosing viral and bacterial infections in the ED, with a prospective validation study achieving an AUROC of 0.95 in a cohort of adults presenting to the ED with fever [98].

Confirmatory tests for infectious pathogens

In some scenarios, diagnostic tests confirming infection with a specific pathogen can be concurrent or precede the progression to sepsis. This may happen in more indolent infections whose trajectories may permit early diagnosis utilizing traditional clinical history and physical examination and testing such as chest radiograph, urinalysis, culture, or white blood cell count. Additionally, the development and dissemination of rapid, reliable, in-home COVID-19 testing is an exemplary model for what technology and implementation can look like in rapidly diagnosing specific pathogen infection before progression to sepsis in the prehospital space.

While microbiological culture has long held the role of an imperfect gold standard for diagnosing many types of infection, there are evolving and increasingly available molecular technologies that may more rapidly identify pathogens and perform antibiotic susceptibility testing. At present, the time-to-result, narrow applicability to specific specimens (i.e., blood for blood stream infections), and required equipment places these emerging technologies beyond readiness for immediate prehospital

testing for sepsis [99-102]. However, they represent an essential part of the entire conceptual framework of responsibly targeting earlier, effective treatment of prehospital infections. Specifically, the non-culture-based technologies to confirm pathogens and antibiotic susceptibilities will be essential components of antimicrobial stewardship programs that effectively, appropriately, and rapidly de-escalate or discontinue antibiotics started in the prehospital setting to reduce patient harm from side effects, costs, and community harm of increasing antimicrobial resistance [103-110].

Section IV: A Socioecological Approach to the Causes, Context, and Prevention of Prehospital Sepsis Diagnostic Delay

Limited data exist on the causes of prehospital sepsis diagnostic delay, particularly outside of EMS settings, and this is currently a major research gap. Some data exist on sepsis disparities, briefly discussed in Section I, above, which could serve as important preliminary insights to inform future research on the role of diagnostic delay in contributing to these disparity conditions. Additional limited data are available on diagnostic delay in specific infectious conditions from which inferences may be drawn. We conceive of the causes and context – and therefore prevention – of prehospital sepsis diagnostic delay through the framework of the socioecological model (Figure 3). Socioecological models recognize that individuals are situated within the multi-layered environments and communities around them, and that forces and processes within those layers contribute to individual-level health outcomes [111]. These five layers are 1) the individual themselves, including biological and social risk factors for sepsis; 2) interpersonal relationships and interactions; 3) organizations with which individuals may interact; 4) their physical and social communities; and 5) society-level values, policies, and other broad social factors that impact health and equity in health status.

Individual

While there are sparse data on the magnitude of prehospital diagnostic delay and its contribution to health disparities, we hypothesize that there are likely disparities in sepsis-related diagnostic excellence – just as there are disparities in sepsis incidence and outcomes – according to individual-level SDH [112]. Potential factors in need of further study include level of education, cultural or ethnic identity, health literacy, primary language and / or English language proficiency, housing stability, substance use, or insurance status [113, 114]. In addition to the plausible but currently unexamined relationships between prehospital diagnostic delay and SDH, there are also several personal health features that are known to carry an increased risk for, or expedited timeline of progression to, sepsis. These health features, including very young or older age, frailty, immune suppression, genetic characteristics, certain medical comorbidities, multimorbidity, and health behaviors (hygiene, illicit drugs, tobacco, alcohol) should be examined in future research as potential characteristics for enrichment of diagnostic efficiency.

Interpersonal

At the interpersonal level, interactions with one's community, including family, friends, social or news media, religious groups, or cultural community could impact knowledge of sepsis and response to early symptoms. While we were unable to identify data on the role of culture and community in prehospital diagnostic delay of sepsis, this association has been described for specific infectious conditions within and outside of the US, such as COVID-19, diarrheal diseases, or malaria. Public health information campaigns, community events, and media stories focused on sepsis have been one approach to increasing awareness of what sepsis is and how to recognize it. The spread of

medical information – and misinformation – through communities, especially via social media, has been a major challenge during the COVID-19 pandemic in the US. Future research on the impact of interpersonal information exchange on sepsis awareness, diagnostic timing, and outcomes will be important.

Beyond these community-based interpersonal interactions that influence health-related knowledge, beliefs, and behaviors, the nature and content of interactions with healthcare providers could also impact diagnostic delay in sepsis. Given the predictable trajectory of sepsis developing from an acute infection, there are potential opportunities to prevent it through appropriate diagnosis and treatment of the preceding infection or patient education, and future research is needed to better understand the role of primary care or specialty health care clinics, telehealth services, patient-health team communication via phone or online platforms, and the role of non-physician or clinic-based healthcare providers such as pharmacists or home-health care providers [115, 116]. This vein of research should include studies specifically focused on further understanding and improvement of provider-patient or provider-family member communication. These interactions are almost certainly impacted by external forces such as structural racism, ageism, gender bias, or ableism, though very little is known about how and to what extent these forces impact diagnostic excellence. Additionally, when considering patient populations who are unable to directly communicate with providers, such as infants and children, important work focused on improving third-person communication and sepsis diagnosis remains to be done.

In addition to research focused on understanding the role of interpersonal interactions between patients and healthcare providers, future work is needed to understand how best to implement

programs aimed at educating clinicians and improving medical decision-making related to sepsis. While in Section III, above, we reviewed previous studies aimed at educating clinicians about sepsis, data on the efficacy of such programs have been mixed. Potential future avenues of implementation or education-based research could focus on more effective training modalities such as virtual reality-based simulation or 'point of decision making' education informed by approaches such as choice architecture.

Organizational

In addition to the impact of interpersonal relationships and interactions between individuals on the sepsis continuum (at risk, with an uncomplicated infection, or with sepsis), the structure, resources (including human resources and diagnostic system capabilities), and accessibility of health-related organizations within which these interactions take place may also impact prehospital diagnostic delay. Two predominant types of these organizations are EMS systems and non-EMS healthcare systems outside of hospitals, including clinics, free-standing urgent care facilities, telehealth systems, home health systems, or EDs. At this organizational level, data on the causes and prevention of prehospital diagnostic delay in sepsis are largely limited to EMS systems. Although sepsis represents an overall small fraction of EMS encounters in the US, the EMS system has thus far been the primary focus of efforts to understand and improve diagnostic delay in the prehospital space. We hypothesize that there may be several reasons for this. First, sepsis research has traditionally had an approach and perspective that centers medical providers, rather than patients and communities. EMS systems are the predominant health system in the prehospital space, and therefore a natural area of focus with this approach. Future patient- and community-focused research may uncover alternative venues for the study and improvement of diagnostic delay in sepsis. Second, given evidence that early,

appropriate administration of antibiotics is one of the most critical hospital-based interventions to improve outcomes in sepsis, a natural extension of this may be to try to move the process of diagnosis – and antibiotic delivery – earlier, into the prehospital space. While non-EMS healthcare systems may play an important role in this, the majority of research we identified remained focused on EMS organizations as the venue for this endeavor. Thus far, there is not consistent evidence that delivery of antibiotics or IV fluids by EMS providers improves sepsis-related morbidity or mortality, but important questions remain. One such potential avenue of future research may be the use of community paramedicine or 'hospital at home' programs to improve care of patients with uncomplicated acute infection (therefore perhaps preventing some sepsis cases entirely) and more closely monitor these patients for sepsis onset.

Community

There is mixed evidence on whether features of communities in which one lives, such as healthcare access and quality, community poverty levels, rural location, or distance to care, impact sepsis incidence and mortality [26, 32, 33, 117-123]. A recent national sample of over 900 US adults found no significant association between home-to-hospital distance and severity of illness upon presentation or 30-day mortality related to sepsis, suggesting that there are other features of healthcare access and quality that may be more impactful on disparities in sepsis incidence and outcomes across communities [124]. Limited data exist exploring the mechanisms by which these community features may impact sepsis risk or examining the relationships between community-level features and individual-level social and medical risk factors for sepsis. We hypothesize that economic factors, social cohesiveness, transportation quality and availability (including roads or geographic considerations), and other factors may contribute to disparities in sepsis incidence and outcome via

differences in prehospital diagnostic excellence, including delay, and these features will be important avenues of future research.

There are specific community-level considerations for individuals living in skilled nursing facilities or other quasi-medical or assisted care settings such as adult family homes or senior communities [125, 126]. While limited data currently exist on the degree and prevention of diagnostic delay in these settings, given the prevalence of high-risk comorbidities among residents of such communities (e.g., frailty, chronic inflammatory conditions, diabetes, chronic indwelling catheters, etc.), we propose that future research on prehospital diagnostic delay in sepsis should prioritize these populations.

Society

Lastly, elements of the society in which one lives, including public health policies such as state-level sepsis mandates, healthcare financing and insurance systems, health services priorities, or social forces such as racism, xenophobia, attitudes towards minoritized communities such as immigrants, indigenous persons, or religious minorities may further impact prehospital sepsis diagnostic delay. While multiple potential mechanistic pathways for this exist, this area of research remains undeveloped [127]. We identified one research protocol which aims to implement a community coalition-based intervention to better equip health systems and the communities they serve to mitigate structural racism, and to measure the impact of the intervention on racial inequities in sepsis outcomes, including time to diagnosis and treatment initiation [128]. This implementation study is promising, and future work specifically addressing the relationships between society-level forces and diagnostic delay in sepsis is needed. Future research on diagnostic excellence in sepsis must explicitly

focus on reducing inequities; one way to achieve this will be to ensure that studies engage diverse populations in the design, testing, and implementation of interventions.

Section V: Research Priorities

The two fundamental challenges in prehospital sepsis diagnostic delay are that currently there is: 1) no available test to diagnose the dysregulated immune response of sepsis inside the 60-minute timeframe to guide treatment decisions; and 2) no validated way to measure or define diagnostic delay in sepsis. Precocious interventions that promote earlier treatment without such validated diagnostics or without understanding of where in the illness timeline such interventions are most effective may have unintended consequences of antibiotic over-prescribing, risking harmful side effects to the individual and increased antimicrobial resistance within communities. On the other hand, given the urgent public health imperative of sepsis, approaches that await an ideal and universally operational definition of diagnostic delay for intervention may also fall short. Therefore, our overall assessment is that 1) advancements in diagnostic test development will need to engage industry partnerships with the resources for scalable production before implementation, and 2) feasible next-step research directions will balance the discovery and benchmarking of impactful definitions of diagnostic delay with science aimed at improving outcomes.

We conceive of the next steps in research aimed at improving diagnostic excellence in sepsis and reducing prehospital diagnostic delay within a framework of broad patient- and family-centered research questions (Table 1 and Figure 2). Each of these broad questions has multiple specific knowledge gaps. Future research to address these priority areas may use a variety of methodologic approaches, interventions, or data sources. Overall, major recommended approaches to future

research in this space include: the use of qualitative methods to improve understanding of human factors pertaining to prehospital providers' decision-making and patient-centered identification of sepsis; application of machine learning or other advanced technologies to support all elements of diagnostic excellence, including timeliness; efforts to improve understanding of, and to reduce, disparities in prehospital diagnostic delay; engaging in research across the 5 layers of the socioecological framework rather than focusing solely on individuals or healthcare organizations; focus on participants across a range of sepsis risk levels (e.g., healthy individuals enrolled in wearable health device tracking platforms, those with frailty and chronic comorbidities enrolled in home healthcare or a medical home, or those with new outpatient antibiotic prescriptions for an acute infection); and use of implementation science methodologies to advance knowledge while igniting change. Below, we have outlined some examples of potential research initiatives, incorporating our major research questions with this overall paradigm. For each initiative, we highlight the socioecological level(s) of focus, relevant conceptual framework, potential approach(es), and broadly categorized potential data sources.

1. Deploy a smartphone patient-centered application combining periodic surveys and wearable device information to define diagnostic delay, discover and assess early warning scores, and implement interventions

a. *Socioecological level* – Individual

b. *Conceptual framework* – Development of user-driven research outside of healthcare encounters is relevant in the prehospital space, captures broad and generalizable at-risk cohorts, and reduces recall and selection biases.

c. *Potential approach* – Patient-centered and user-driven app to assess timing of onset, severity, and risk at baseline and at app-prompted follow-up. Such a system could use manual entry of information by users or in conjunction with wearable monitors that extract and subsequently track this information as a patient-triggered event. Integrate device and survey data with machine learning algorithms for ongoing predictive improvement and A/B testing for improved app performance.

d. *Potential data sources* – Partner with mobile app development or wearable device companies.

2. **Implement patient-centered strategies within a healthcare system's patient portal and/or mobile app infrastructure to support infection and sepsis recognition and triage**

a. *Socioecological level* – organizational

b. *Conceptual framework* – The spectrum of conditions from infection to sepsis is common, often non-specific, and yet requires early recognition and appropriate triage. Stepwise triage starting from automated patient portal questionnaires to tele-medicine encounters can track onset, severity, and patients' timed trajectories and outcomes within a single network with the added value of setting up next steps for intervention.

c. *Potential approach* – Retrospectively, can examine patient portal and ambulatory healthcare encounters of cases of subsequent sepsis requiring hospital care compared to randomly sampled matched controls of all patient portal encounters. Prospectively, could design a healthcare network patient portal care pathway that incorporates known chronic patient information and acute care surveys to develop and train predictive models driving triage prompts for subsequent telemedicine encounters and outcomes tracking. Enrollment can be patient-initiated or prompted by new outpatient encounter or antibiotic prescription for acute infection.

d. *Potential data sources* – Partner with integrated healthcare systems with currently existing patient web portals and/or mobile applications.

3. **Implement a patient-centered home healthcare-based intervention for diagnosing and triaging infection and sepsis in high-risk cohorts**

a. *Socioecological level* – organizational

b. *Conceptual framework* – Early research and implementation effectiveness may be optimized in populations with highest risk and within already-existing healthcare infrastructure of medical home, home health, paramedicine, hospital-at-home, assisted living and rehabilitation facilities, and/or posthospital discharge programs.

c. *Potential approach* – Incorporate EWS calculations with automated prompts to healthcare providers triggering reassessment with patient-centered trajectory and outcomes tracking. Initial observational phases validating process could lead to pre-/post or cluster stepped wedge trial designs, grouped by systems or practice groups within a network that can pragmatically roll out and assess various components of the intervention by comparing group-level sepsis hospitalizations. Alternative or complementary qualitative research could focus on elucidation of human factors such as decision-making and cognitive approaches to patient signs and symptoms to improve identification of patients likely to be septic.

d. *Potential data sources* – Partner with home healthcare companies or healthcare organizations with a strong medical home model in order to capture data at all points along the spectrum from early acute infection to development of sepsis.

4. **Implement outpatient provider-focused intervention to improve sepsis diagnostic excellence**

a. *Socioecological level* – interpersonal, organizational

b. *Conceptual framework* – Automated prompts to providers may promote fatigue, disrupt busy workflow, and promote inappropriate compensatory practices. However, data on choice architecture show that interventions to support decision-making may be helpful. Additionally, periodic individualized performance reports with group-level comparisons on various facets of performance around sepsis prevention and antibiotic prescribing may promote self-reflection and improvement.

c. *Potential approach* – Providers receive periodic reports on individual and group-level metrics on their patient panels' distribution of sepsis risk, antibiotic prescribing, and incidence of urgent care and higher-level care for infections and sepsis with additional optional prompts to explore their own cases that progressed. Before-after study designs to assess provider-level risk-adjusted outcomes.

d. *Potential data sources* – Partner with primary and relevant specialty care clinics (e.g., geriatrics, nephrology, infectious diseases, etc.), preferably those with provider feedback reporting or machine learning-guided clinical decision support programs already deployed for other conditions. Will need to consider balance between patient panel or practice size (perhaps smaller with subspecialty clinics than in primary or urgent care settings) and density of high-risk patient populations (may be higher in some subspecialty clinics such as geriatrics or oncology).

5. **Implement ambulatory pharmacy intervention to inform and intervene on progression from infection to sepsis in prehospital setting**

a. *Socioecological level* – organizational

b. *Conceptual framework* – Patients with outpatient antibiotic prescriptions hypothetically represent a study population at high risk for developing sepsis who may also be more invested in participating in a web- or smart phone-based tool that assesses symptom onset, medication adherence, and tracks progression towards sepsis.

c. *Potential approach* – Web- or smartphone-based survey system prompted at pharmacy for those with new outpatient antibiotic prescriptions which captures baseline information on onset of symptoms, severity score assessments, provides prompts for adherence, assesses improvement at periodic intervals, and tracks self-reported outcomes at 1-week with machine learning algorithms for ongoing predictive improvement. Could integrate A/B algorithms or qualitative research methods for user-experience improvement.

d. *Potential data sources* – Partner with major chain pharmacies that have a pre-existing mechanism of patient outreach and reminders (such as text message-based refill requests) and/or retail clinics that are located within pharmacy locations.

6. **Assessment and improvement of sepsis diagnosis by emergency medical providers**

a. *Socioecological level* – interpersonal, organizational

b. *Conceptual framework* – At time of EMS transport many patients are already at an acute phase of illness, making the distinction between sepsis and other causes of extremis difficult yet necessitating urgent triage and treatment. Most prior literature in this space assesses providers' and EWS' ability to prognose poor outcomes rather than specifically diagnose sepsis compared with a gold standard of retrospective clinical adjudication.

c. *Potential approach* – Pre/post, interrupted time series, or cluster randomized designs of EMS providers' assessment of probability of sepsis, implementing some combination of training and EWS

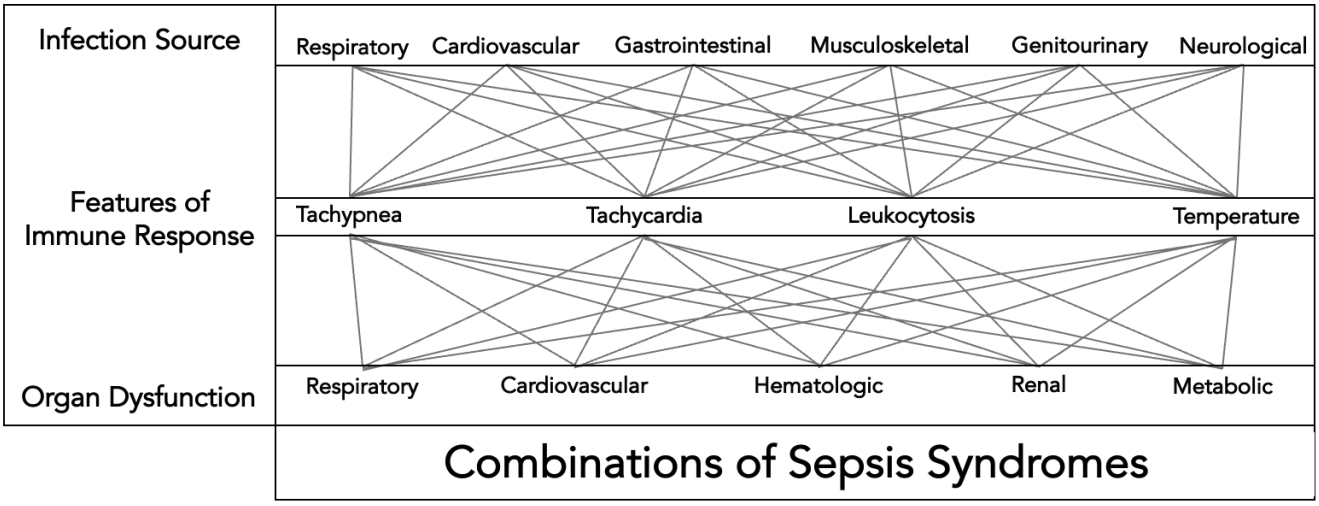
or laboratory testing deployments. Ideally would use mixed methods, integrating qualitative or implementation science methodologies. Additionally, could deploy machine learning-based prompts within the prehospital space as EMS clinicians capture clinical data.

d. *Potential data sources* – Would ideally partner with a large integrated EMS covering an entire region.

In summary, sepsis is a major health problem in the US, and widening the aperture of research and improvement efforts to include a patient-centered focus on diagnostic delay in the prehospital setting has the potential for a large positive impact on public health. However, understanding of sepsis in the prehospital context is limited and informed mostly by extrapolation of inpatient data. Furthermore, there are fundamental challenges in studying sepsis in the prehospital space. First, it is a heterogeneous syndrome for which it is difficult to define and capture a starting point for which to start the clock in measuring diagnostic delay. Second, there are not currently any widely available gold standard diagnostic tests that can provide a result within the timeframe for needed treatment decisions to define the endpoint for diagnostic delay. While such tests may be on the horizon, next steps for studying prehospital diagnostic delay in sepsis can apply existing technologies (e.g., wearable devices, smartphones, electronic health systems' patient portals) amongst populations of varying levels of sepsis risk to develop new knowledge identifying useful timepoints for defining delay in conjunction with building implementation infrastructure for future work to understand the multi-level causes for delay, its impact on outcomes, and how it may be improved upon.

Figures and Tables

Figure 1. A multitude of pathogens, primary organ systems infected, and diverse systemic manifestations create thousands of protean pathways to sepsis.



Limited examples of primary infectious sources, features of immune response, and sites organ dysfunction are depicted. These are not meant to represent an exhaustive list of potential combinations, but rather to illustrate the concept of heterogenous pathways to sepsis. Figure edited from Kempker et al [129].

Figure 2. Sepsis Trajectory and Future Directions for Investigation

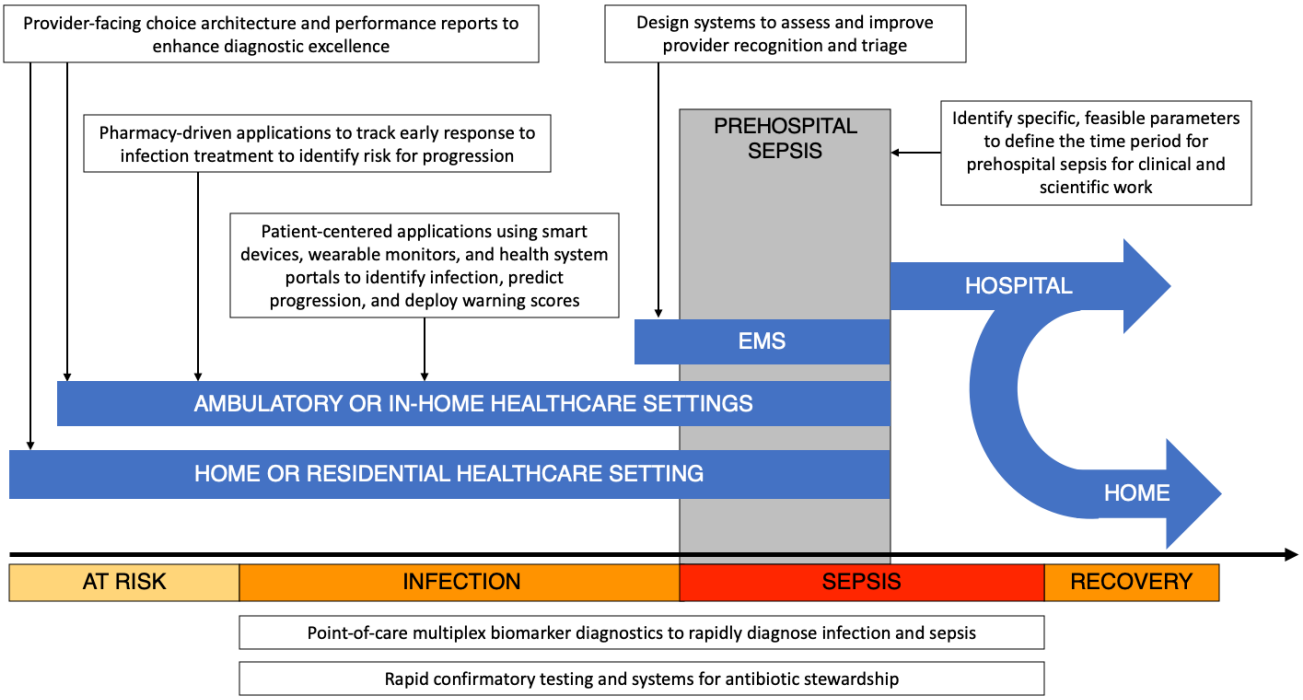
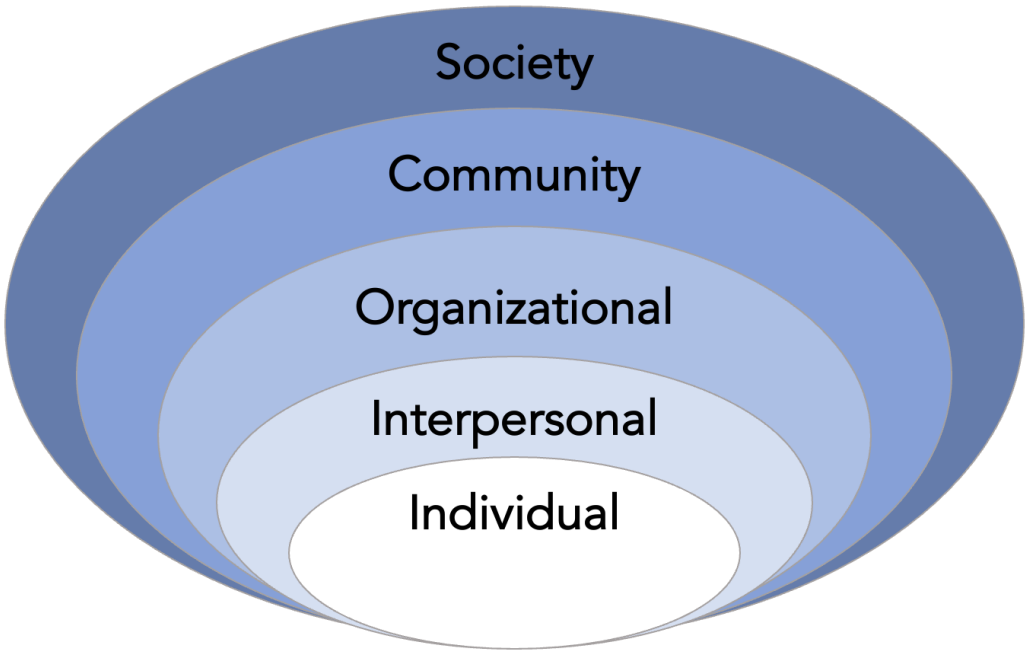


Figure 3. A classic socioecological model (Panel A) with examples of potential factors contributing to prehospital delay in sepsis diagnosis, and to disparities in this delay (Panel B).

Panel A.



Panel B.

Table 1. Broad research questions for next steps of understanding and improving the incidence, diagnosis, and outcomes of prehospital sepsis.

How do we define diagnostic delay in sepsis in the prehospital domain and how does such delay affect a primary proximal outcome of higher-level* of care visits for sepsis? **Knowledge gap:** While there are many critical research questions regarding the prevalence of diagnostic delay, the impact of delay on outcomes, the landscape of healthcare information and encounters that intersect patient trajectories, and socioeconomic disparities, these cannot be approached until there is a way to measure the time from onset of infectious symptom to progression to sepsis.
What is the accuracy of EMS providers for diagnosing and distinguishing sepsis amongst a broad cohort of patients in transport with signs of systemic inflammation and can this be modified by educational initiatives, early warning scores, and point-of-care testing? **Knowledge gap:** Much of the literature in this space assesses ability of warning scores to predict poor outcomes in patients retrospectively adjudicated to have sepsis rather than ability of providers to *diagnose* sepsis for appropriate early treatment.
How well can early warning scores completed at home, manually or in conjunction with wearable devices, predict subsequent diagnosis of infection requiring treatment and higher-level of care visits for sepsis? **Knowledge gap:** Current literature suggests that those arriving to the hospital with sepsis are either not having prior ambulatory healthcare encounters, having these encounters within just a few days of hospitalization, or arriving at a severity beyond which poor outcome is preventable. This suggests we need to understand whether patient-driven modalities in the prehospital space can diagnose and prognose infections at earlier time-points in the illness course. Additionally, the impact of individual-level features such as language, financial status, and health literacy on diagnostic delay or use of patient-facing interventions is a major current knowledge gap.
Can a healthcare system's patient portal be used in conjunction with provider-driven telemedicine encounters to diagnose, triage, and track time from early infection to resolution or progression necessitating higher-level care and can this be modified by focused training, early warning scores, and point-of-care testing? **Knowledge gap:** How can we improve patient education, interpersonal communication, and organization-level resources and approaches to reduce diagnostic delay? Little is currently known about how to empower individuals, improve organizations, and strengthen the link between them, and whether doing so would minimize delays.
Can a pharmacy-driven approach identify those with prehospital infections prescribed treatment capture diagnostic delay, predict progression, and assess outcome of progression to necessitating higher-level care for sepsis? **Knowledge gap:** The role of outpatient pharmacists or pharmacy organizations in sepsis prevention and diagnosis is currently unknown. Given that sepsis develops from infections, some of which may be treated with outpatient antibiotics or inappropriately self-managed with over-the-counter medications, there may be an opportunity to strengthen the link between outpatient providers, pharmacies, and individuals.
Can emerging technologies utilizing multiplex biomarker signatures for identifying sepsis among critically ill be applied to lower severity patient populations in the prehospital setting to identify infections and predict those likely to progress to sepsis?

Knowledge gap: There are emerging platforms with FDA approval for diagnosis sepsis in the ICU, and such approaches may eventually have utility and feasibility in the prehospital space, but these research directions will necessitate early partnership with industry resources for cost and scalability. Feasibility and clinical practicality are important considerations.

*With the term 'higher-level' care we refer to urgent care visits, ED, or hospitalizations

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