Shetty Amith (Orcid ID: 0000-0001-7349-1128)

Macdonald Stephen (Orcid ID: 0000-0001-9921-4620)

Keijzers Gerben (Orcid ID: 0000-0003-1100-4552)

Sepsis in the emergency department – Part 2: Investigations and Monitoring

AUTHORS:

Amith Shetty

Stephen Macdonald

Gerben Keijzers

Julian Williams

Benjamin Tang

Bas De Groot

Kelly Thompson

John F Fraser

Simon Finfer

Rinaldo Bellomo

Jonathan Iredell

Corresponding Author:

Amith L Shetty

Centre for research in Critical Infection

Westmead Institute for Medical Research

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Westmead Hospital, University of Sydney

Author Manuscript

Abstract

Sepsis is characterised by organ dysfunction resulting from infection, with no reliable single objective test and current diagnosis based upon clinical features and results of investigations. In the ED, investigations may be conducted to diagnose infection as the cause of the presenting illness, identify the source, distinguish sepsis from uncomplicated infection (i.e. without organ dysfunction), and/or risk stratification. Appropriate sample collection for microbiological testing remains key for subsequent confirmation of diagnosis and rationalisation of antimicrobials. Routine laboratory investigations such as creatinine, bilirubin, platelet count and lactate are now critical elements in the diagnosis of sepsis and septic shock. With no biomarker sufficiently validated to rule out bacterial infection in ED, there remains substantial interest in biomarkers representing various pathogenic pathways. New technologies for screening multiple genes and proteins are identifying unique network 'signatures' of clinical interest. Other future directions include rapid detection of bacterial DNA in blood, genes for antibiotic resistance and EMR based computational biomarkers that collate multiple information sources. Reliable, cost-effective tests, validated in the ED to promptly and accurately identify sepsis, and to guide initial antibiotic choices, are important goals of current research efforts.

Overview

The focus of part-two of the three-part miniseries on sepsis in the Emergency department (ED) is on the role of investigations and monitoring in the diagnosis and risk stratification of patients presenting to the Australasian EDs with suspected sepsis.

Background

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection, and is characterised by the presence of suspected or proven infection accompanied by an increase in Sequential [sepsis-related] Organ Failure Assessment (SOFA) score of two points or more from

baseline.(1, 2) The current definition incorporating organ failure reflects a shift in focus from the physiological manifestations of infection, with sepsis previously defined as infection accompanied by two or more systemic inflammatory response syndrome (SIRS) criteria.

The in-hospital cohort at risk of death from sepsis includes patients recognised to have sepsis in the ED, those with evolving sepsis that is not evident at first assessment, and those developing nosocomial sepsis during hospital admission. Under the previous SIRS based sepsis definition, 1 in 8 patients admitted to the intensive care unit (ICU) with infection and organ dysfunction did not meet SIRS criteria.(3) SIRS-based screening algorithms used in Australia and overseas are far from ideal; one assessment demonstrated a positive predictive value of 71% and a negative predictive value of 55%.(4) Revised criteria based on the new sepsis definition are less sensitive, with around 4% of those who fall between the old and new definitions, that is, patients who satisfy the SIRS criteria but not the new SOFA criteria, dying soon after admission to hospital.(5) This is important because early identification facilitates earlier interventions including appropriate antibiotics which can be lifesaving; (6-8) whilst inappropriate broad-spectrum antibiotic use can be followed by increased severe antibiotic-associated complications such as *C. difficile* infection.(9) Early recognition of sepsis, exclusion of antimicrobial resistant (AMR) organisms as causation, and/or 'focusing' of antibiotic prescriptions will remain as high priorities in the future.

In the ED, clinicians regularly face the challenge of unwell patients with undifferentiated diagnoses (Figure 1). Investigations and monitoring conducted in the ED on patients with suspected sepsis based on clinical suspicion or screening algorithms may be divided into three broad categories:

- Confirmation of infection as the cause of illness e.g. procalcitonin, C-reactive protein (CRP)
- Identification of the causative pathogen and resistance patterns e.g. microbiological cultures, serology, nucleic acid amplification (NAA), in order to guide appropriate therapy
- Risk stratification for adverse outcomes e.g. lactate, markers of organ dysfunction, illness severity scores

Figure 1 Stepwise screening for Suspected Sepsis in the Emergency department - Screening tests including algorithms, diagnostic investigations and risk scores

Confirmation of infection

Reliable timely identification of the causative organism is currently unavailable during ED assessment, and antibiotics have to be chosen based upon the clinical scenario (10, 11). Sepsis may develop in the absence of bacteraemia, and where present, confirmation of bacteraemia is limited by the suboptimal sensitivity of blood cultures in patients presenting with suspected infection (12). Using current techniques, blood cultures are negative in the majority of patients who develop sepsis thus, it is important that appropriate samples from other clinically relevant sites such as urine, sputum, cerebrospinal fluid, swabs of purulent material, or drained infected fluid are collected without significant delay and prior to initiation of antibiotics while awaiting the results. However, the causative organism may remain unidentified in up to 40% of cases of clinical sepsis(13). Thus in undifferentiated patients, confirming infection as the cause of deterioration takes priority to optimize decisions regarding timely interventions. Biomarkers may play a critical role in the diagnostic work up of patients suspected of having sepsis with potential impacts on ED workflows. The characteristics of an 'ideal' sepsis biomarker is summarised in table 1.

Table 1 Characteristics and impacts of ideal sepsis biomarker in ED (Adapted from Mally P et al)(14)

Biomarkers

C-reactive protein, Procalcitonin and Proadrenomedullin

C-reactive protein (CRP) and Procalcitonin (PCT) have been proposed as suitable biomarkers to discriminate viral from bacterial infection (15). Despite its widespread use, CRP is not accurate enough for this discrimination and cannot therefore be used in the ED or elsewhere for the decision to withhold or administer antibiotics (16-18). PCT is upregulated by pro-inflammatory mediators in response to bacterial infections and its production is inhibited by interferon- γ produced in response

to viral infections (19). Therefore, PCT may potentially differentiate between bacterial and viral infection. In the presence of sepsis, its plasma concentration increases and returns towards normal faster than white blood cell count and CRP, conferring a potential advantage over these for clinical decision making (20). A recent meta-analysis suggested a reduced risk of mortality and broad spectrum antibiotic use associated with the use of PCT based algorithms in different clinical settings (21). However, there are fewer data on use of PCT to guide the diagnosis of sepsis in ED, and thus PCT is not currently recommended to rule out sepsis in the ED (22) (Table 3). Future studies are required to investigate its potential to rule-in or rule-out sepsis.

Most biomarkers with potential to confirm bacterial infection have only been investigated in non-ED settings. The recent availability of commercial point-of-care PCT/CRP and Proadrenomedullin (ProADM) testing opens potential new avenues of enquiry about their specific role in bedside sepsis screening in ED. ProADM is a calcitonin peptide similar to PCT, functioning as a vasodilator with additional metabolic and immune modulating effects. Like PCT it is produced by the inflammatory response to bacterial infection. In an ED study of patients admitted with pneumonia, ProADM predicted mortality with similar accuracy to the pneumonia severity score, and was superior to PCT (23). In a study of patients with lower respiratory tract infections, a clinical algorithm using ProADM along with the CURB-65 score was superior for predicting mortality than CURB-65 alone (24).

Experimental biomarkers

Over 170 molecules have been investigated as potential sepsis biomarkers, including cytokines, cell surface markers, coagulation factors and acute phase reactants, but none have been found to be either sufficiently sensitive or specific for routine clinical use (25). As such, a detailed discussion of these is beyond the scope of this paper. A biomarker combination approach has been suggested as a solution to improve screening for bacterial sepsis (26) and may be a plausible approach for ED workflows while awaiting the advent of future panels of biomarkers. Rigorous evaluation of putative biomarkers is essential not only to ensure appropriate decisions are made regarding patient management, but also because they are expensive, and indiscriminate use will place a significant

financial burden on the healthcare system. Conversely, appropriate use of a valid biomarker may save money by reducing initiation and duration of antibiotic therapy and overall duration of in-hospital care.

Future Biomarkers – The ‘omics’.

The sequencing of the human genome in 2003 heralded a new era in science. This new phase is marked by the rapid emergence of “omics” sciences, including transcriptomics, proteomics and metabolomics (**Table 2**). Typically, this involves studying thousands of genes, proteins or metabolites simultaneously in the target tissue or organ. In sepsis research, this new approach has led to two key insights. First, sepsis, both its genesis and progression, is mediated by multiple immune pathways. This means that the treatment of sepsis is unlikely to be based on a “single cure” or a drug that targets only one single pathway. Secondly, the diagnosis of sepsis is unlikely to be based on the measurement of a single biomarker. In the future, sepsis biomarker panels including multiple such biomarkers representing different immune pathways will need to be validated and, if proven beneficial, made available for use in ED settings.

Table 2 The application of "omics" science in the study of sepsis.

Identification of the likely causative pathogen

Blood cultures

Although results from blood cultures are not immediately available for decision making in the ED, microbiological cultures provide key information for diagnosis and antimicrobial prescribing. Blood cultures are an important investigation in patients with sepsis, but only a proportion of these will have organisms isolated directly from their blood. Blood cultures should be taken from all patients

with suspected sepsis depending on the clinical setting. The true positive yield from blood cultures is maximised by appropriate patient selection, aseptic collection technique and sampling prior to administration of antibiotics. Guidelines recommend obtaining a minimum of two sets of blood cultures (i.e. 40mls of blood in total) from two separate sterile sites.(33) False positive (contaminated) blood cultures result in overuse of antibiotics and increased costs of care.(34) Although some studies have challenged the use of blood cultures in community acquired pneumonia,(35) cellulitis,(36) and urinary tract infection,(37) most of these are retrospective. In view of the increasing risk of anti-microbial resistance and lack of clarity of initial ED diagnosis, currently it is recommended that blood cultures be obtained in these patients. The epidemiological and AMR data generated from cultured organisms are important for antibiotic guideline development and healthcare planning and should not be underestimated. Decision rules to guide which patients should have blood cultures collected may rationalise their use and improve utility.(38)

Techniques for rapid pathogen identification in blood

Bacterial DNA is commonly found in the blood in patients with sepsis or septic shock as a result of the primary illness and/or due to secondary bacterial translocation as a consequence of gut mucosal ischaemia.(39) An infection source may continually seed the blood with bacteria which die in the bloodstream,(40) products from recently killed cells may stimulate release of inflammatory mediators,(41) and/or reticuloendothelial clearance of such products may be impaired.(42) Healthy animal models clear small intravenous inoculates of *E. coli* in 9 minutes without specific therapy (42) and most people undergoing major dental surgery clear asymptomatic bacteraemia (primarily viridans streptococci) within an hour.(43) The lethality of meningococcal disease in children rises with the density of the bacteraemia at presentation,(46) and antibiotic-sensitive *staphylococcus aureus* bacteraemia which is still detectable by culture after 48 hours of optimal therapy is associated with increased risk of metastatic infection and death.(47) The association between bacteraemia and ongoing bacterial DNA detection of other pathogenic and gut mucosal agents in blood with adverse outcomes in sepsis needs further investigation.

With available technology identification of the likely responsible organism through bacterial DNA detection techniques can be made in less than 6 hours but the cost-effectiveness of comprehensive large platforms is debateable (44) (45) and commercial realities have made some of these non-viable.(46) The argument for a clear decision point associated with definite mortality or cost reduction has not yet been made.

The potential for quantitative bacterial DNA detection assays to demonstrate benefit (e.g. in triaging high-risk vs low-risk groups) has not been evaluated although intuitively they seem likely to have value. Similarly, a reliable bacterial DNA detection tool to recognise/ exclude antibiotic resistance (and thereby improve prescribing) is not currently available, although this also seems likely to have value in the future.(47) Appropriate targeting of the transmissible AMR gene pool could permit prediction of antibiotic resistance in major Gram-negative agents of septic shock (e.g. *Escherichia coli* and *Klebsiella pneumoniae*) with high negative predictive values (>99.5%).(48, 49)

Risk stratification for adverse outcomes

Markers of organ or tissue dysfunction

The Sepsis-3 definition uses the SOFA score as the criterion standard (1, 50). Acute renal failure is a common complication of sepsis, and elevation of serum creatinine is one component of the SOFA score. However, there is a delay between onset of renal injury and creatinine elevation that may not peak for several days. Neutrophil Gelatinase Associated Lipocalin (NGAL) has been evaluated as a biomarker of early acute renal injury in a variety of illnesses including sepsis (51). Other components of the SOFA score which are routinely measured in ED practice include bilirubin and platelet count. Calculation of the SOFA respiratory component requires arterial blood gas (ABG) analysis to evaluate the PaO₂/FiO₂ ratio. ABG analysis is not routinely conducted in ED patients with suspected sepsis, though past studies have suggested the calculation of SpO₂/FiO₂ (peripheral saturations) may be used as a surrogate in the calculation of SOFA score (52), thus obviating the need to conduct a

routine ABG on all suspected sepsis patients. In patients undergoing an ABG, the calculation of the CO₂ GAP, (difference between the arterial PCO₂ and end-tidal CO₂) has been shown to correlate better than the Alveolar-arterial gradient with the physiological dead space and risk for adverse outcomes and thus should be considered.(53) Future analysis of such physiological biomarkers in sepsis are warranted.

Lactate

Measurement of serum lactate concentration is recommended by the Surviving Sepsis Campaign (SSC) guidelines as a marker of illness severity, for prognostication and for monitoring response to treatment (54). Lactate ≥ 2 mmol/L is a component of the revised definition of septic shock (1) (along with refractory hypotension), while some investigators have found lactate ≥ 4 mmol/L indicates a significantly increased mortality risk even in the absence of hypotension (55). ED clinicians need to appreciate that in a patient with suspected infection an isolated lactate ≥ 4 mmol/L, but without refractory hypotension, is associated with a 1.7 times greater risk of death compared with refractory hypotension with lactate < 4 mmol/L. Lactate “clearance” is also associated with improved outcome (56), and this has been proposed as a resuscitation target (57). However, this is a misnomer because decrease or increase in lactate is only a measure of production relative to removal (not clearance). Moreover, the evidence supports the view that attempting to increase “clearance” does not have a sound mechanistic or physiological basis, and does not confer any outcome benefit. (58) Whilst lactate is not a component of SOFA or the recently promulgated qSOFA scores, a recent study in a retrospective cohort of ED patients with suspected sepsis from multiple sites in Australia and the Netherlands suggests that adding lactate (at a cut-off ≥ 2 mmol/l) improves the diagnostic accuracy of the qSOFA score(59). In light of this, and the widespread availability of lactate in point of care blood gas measurements, lactate (venous or arterial) should be measured in all patients presenting to the ED with suspected sepsis.

Monitoring of patients with sepsis (in ED and beyond)

Risk stratification and monitoring of ED patients with sepsis is important for optimal management, resource allocation and appropriate disposition to a general ward, the ICU or discharge. As previously outlined, a proportion of patients admitted with suspected infection develop or are diagnosed with organ dysfunction later in their hospital stay, often in less-monitored areas, and this is associated with higher risk for adverse outcomes.(60-62) Illness severity scores may be used as a suitable method for the ongoing monitoring of patients for high care needs,(63, 64) but significant variations in severity score performance have been reported in the past.(65, 66) and has been discussed in first article in this miniseries. (67)

The implementation of integrated electronic medical records (iEMR) including real-time monitoring systems are suitable for automated risk scoring and identifying patients at-risk.(68) The adoption of an increase of two or more SOFA points defining the organ dysfunction component of sepsis and the qSOFA risk score presents a unique opportunity for uniform monitoring systems to track these changes through iEMR and physiologic monitoring. The concept of generating computational sepsis biomarkers combining continuous physiological data coupled with machine learning and data mining methods presents unique opportunities for the future.(69)

Several non-invasive monitoring techniques measuring tissue oxygenation (70, 71) or cardiac output (72) have been investigated as tools for identifying patients at risk of adverse outcome but none have been extensively validated to date. Dynamic monitoring and trends analysis rather than static SIRS thresholds in the ED may help identify high risk patients prior to visible clinical deterioration.(73, 74) Age-based and risk-strata based SIRS and biomarker level cut-offs developed and constantly validated by artificial intelligence systems have the potential to aid clinicians in early identification of deteriorating patients.(75)

Table 3 Brief overview of specific biomarkers discussed in the review

Summary

The ED diagnosis of sepsis involves a two-step process for screening based on risk factors in patients in whom there is clinical suspicion of infection, and subsequent confirmation of organ dysfunction based on clinical parameters and laboratory results. Similarly, confirmation of infection is based upon clinical features, often supported by radiological and laboratory testing. To date, no single biomarker or monitoring measure has been able to distinguish infection from non-infectious causes of illness, bacterial from viral causes of infection, and sepsis from uncomplicated infections. No fool-proof screening method for sepsis currently exists, however a number of investigations have proven utility to assist risk stratification and decision making at the bedside, and the subsequent management of the patient with sepsis. Research to investigate clinical screening tools, incorporating clinical variables and biomarkers specific to the ED setting is required to improve diagnostic accuracy. The aim is improving outcomes for patients with sepsis while minimising the harms of over diagnosis and overuse of antibiotics. Heterogeneity, complex pathophysiology, multiple aetiologies and phenotypic variations in sepsis presentations demand a unique approach to screening and diagnosis. Understanding the dynamic and often insidious progression of sepsis requires ongoing vigilance and monitoring of patients including those without evidence of organ dysfunction on initial assessment. Clinicians should embrace and work flexibly with emerging technologies to design better systems for identification, and continue research into investigations that will improve the diagnosis of sepsis in ED patients.

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Theme	Description	Impact on ED workflow
Identify aetiology of sepsis	Able to differentiate the causes of sepsis such as viral, bacterial or fungal	Therapeutic intervention selection
High sensitivity	Ability to rule out sepsis when test is negative (nearing 100%)	Antibiotic prescription decisions
High specificity	Ability to confirm sepsis reliably when sepsis is present (> 85%)	Reduce inappropriate interventions and refocus attention on alternative causes for critical illness
Rapid timely results	Results available within 60 minutes (point of care)	Reduce treatment delays
Technology readily available and standardized	Assays and technology with scientific and technical validation	Clinician and institution trust

Table 1 Characteristics and impacts of ideal sepsis biomarker in ED (Adapted from Mally P et al)(14)

	Definitions	Examples
Transcriptomics	The study of all RNA transcripts produced by the genome in a population of cells, including mRNA and non-coding RNAs.	RNA microarray Next-generation RNA sequencing(27-29)
Proteomics	The study of an entire set of proteins that are produced in a population of cells.	Protein microarray Mass spectrometry(30, 31)
Metabolomics	The study of a full collection of all metabolites produced by cells, tissue or organs.	Mass spectrometry derived methods(32)

Table 2 The application of "omics" science in the study of sepsis.

Test	Origin/ Mechanism	Relevance to ED sepsis workflow	Future Direction
Lactate	Stress hyperlactatemia (76) due to production secondary anaerobic glycolysis induced by hypoperfusion/ hypoxia, aerobically by adrenergic stimulation as part of a stress response to critical illness	Biochemical marker with significant evidence to date supporting risk stratification role in suspected sepsis patients in ED (77) (78).Not sensitive or specific for sepsis (79).	Role of addition to existing and novel screening tools to flag patients with suspected sepsis for adverse outcomes Further evidence needed to support role of lactate clearance in management of sepsis(54)
C-reactive protein (CRP)	Produced by hepatocytes, predominantly under transcriptional control by the cytokine IL-6	Nonspecific biochemical marker of inflammation. Sensitive marker for infection but non-specific in presence of other inflammatory causes. May not be elevated early in	Focused prospective evaluation of specific cut-off values in screening for sepsis in undifferentiated ED patients

		course of illness.	
Procalcitonin (PCT)	Produced by thyroid C-cells as precursor of calcitonin, an acute phase protein secreted by several tissues in response to various endogenous and exogenous stimuli such as cytokines and lipopolysaccharide, acting as a chemo-attractant factor on blood monocytes	Modest sensitivity/ specificity and likelihood ratios for bacterial sepsis(80). Some data to suggest levels track with severity of sepsis (81). Superior to CRP in diagnosing bacterial infections(82).	Prospective evaluation of point of care (POC) PCT and potential cut-offs embedded in sepsis screening algorithms in ED amongst undifferentiated suspected sepsis patients
Proadrenomedullin(proADM) and Mid-regional proADM	Calcitonin peptides similar to PCT, vasodilators with additional metabolic and immune modulating effects; produced by the inflammatory response to bacterial infection	Sensitive markers for sepsis and other inflammatory conditions. Some data supporting combination use with PCT in diagnosis and prognosis of sepsis(26, 83)	Prospective evaluation of combination algorithms with specific cut-off levels for use as screening tools in ED

Table 3 Brief overview of specific biomarkers discussed in the review

screening image hires.tiff

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Author/s:

Shetty, A;Macdonald, SPJ;Keijzers, G;Williams, JM;Tang, B;De Groot, B;Thompson, K;Fraser, JF;Finfer, S;Bellomo, R;Iredell, J

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