Personalizing sepsis care

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Keywords: Sepsis, personalized medicine, precision medicine, biomarker, theranostic

Keypoints:

• While sepsis represents a syndrome of organ dysfunction related to a dysregulated host response to infection, it covers a wide range of causative microorganisms and sites of infection in heterogenous patient populations with differing comorbidities, clinical features, illness severity and outcomes

• A ‘one-size-fits-all’ approach, adopting a rigid, homogenized treatment approach, is unlikely to offer optimal care to an individual patient

• Biological signatures are increasingly being unravelled that can identify subsets of septic patients who may either respond positively or negatively to therapeutic interventions.

• Rapid access to such biomarker information will allow identification of suitable patients and titration of therapy to optimal effect

Abstract

Sepsis describes a broad-based umbrella syndrome covering many infectious agents, affecting various sites in patients of differing age, sex and co-morbidity, and resulting in variable degrees and combinations of organ dysfunction. Protocolized care with rigid goals may suit populations, assuming the often evidence-lite recommendations are indeed beneficial, but not necessarily the individual patient. A personalized approach to management is thus rational and likely preferable. Other than clinical heterogeneity, a range of biological signatures exist in sepsis, and these fluctuate over the disease course. There is some commonality that can help to differentiate sepsis from similar clinical pictures from non-septic inflammatory insults. Conversely, subsets of septic patients can display distinct biological signatures that may potentially be used to identify suitability for different treatments, and titration to optimal effect.

Protocols, guidelines and process of care

The term 'Evidence-based guidelines' first appeared in press in a series of articles in JAMA in 1990.[1] These papers differentiated between guidelines based upon consensus, evidence, outcomes and preference, and proposed that evidence-based should take precedence over the other forms. Sackett later described Evidence-based Medicine as "*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.*" [2] Crucially, he continued *"Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients."*

Eddy promoted this personalised, educational, bedside-based philosophy, coining the description of "Evidence-based individual decision-making (EBID)".[3] He contended that EBID should be undertaken "b*y individual physicians, using implicit and personal methods, to make decisions about individual patients and directly determine their care*." He distinguished EBID from Evidence-based Guidelines where generic guidelines and other policies address the needs of institutions and groups of people and thus affect individual patients indirectly. He argued that "*guidelines need to be tailored to individual cases, and EBID improves physicians' ability to do this. Many problems fall through the cracks of guidelines, and EBID is the only way to get evidence-based medicine to them. Physicians work on guideline teams, and the educational approach of EBID enables them to be better participants. EBID also helps physicians understand the rationale for evidence-based guidelines, which greatly improves their acceptance, especially when the evidence contradicts a time-honored practice".*[3]

Evidence-based guidelines have been incorporated into clinical practice within critical care, in particular, the management of sepsis and septic shock within the Surviving Sepsis Campaign guidelines.[4-7] However, these have perhaps not taken sufficient note of Sackett's and Eddy's strictures that individual expertise be brought to bear to guide management of the individual patient. Didactic recommendations suit populations but may not be best suited to the individual. While aiming to raise mediocre or poor practice and offering a framework for management, especially among practitioners who may be inexperienced in dealing with critically ill patients, there is a significant risk that strict adherence to guidelines may, in some cases, detract from best care. This is particularly pertinent when the bulk of recommendations are based on a poor evidence base and, often, a weak strength of recommendation as full consensus could not be achieved among the Guidelines Committee members. Strict blood pressure targets, fluid resuscitation volumes and duration of

antibiotic therapy are examples of rigid directives being applied to patients and situations where a more tailored approach is likely preferable.

Guidelines should perhaps be differentiated from protocols. While protocols may be viewed as mandatory, guidelines can be perceived as advisory. A protocolized approach can be reasonably applied to processes of care that should happen automatically. This includes, for example, a daily methodical clinical examination, daily review of drug chart and fluid balance, good infection control practices, and an individualized management plan reviewed at least daily. On the other hand, advisory guidelines should incorporate Eddy's EBID dictum, as described above. This allows the clinician to be aware of the wider evidence base and follow appropriate general recommendations. Yet it still permits a more flexible management approach that varies according to the patient's age, comorbidities, condition (cause of sepsis and affected organs), and initial response to treatment.

Individualized physiological endpoints

As with any critically ill patient, septic or otherwise, one size does not – should not – fit all. Didactic treatment endpoints and management strategies will serve a general population but not necessarily an individual. Thus, a hypertensive patient may benefit from a higher targeted blood pressure in sepsis.[8] However, in other patients, a lower-than-recommended mean blood pressure (e.g. 55-60 mmHg) may still be compatible with adequacy of tissue perfusion, thereby avoiding unnecessary and potentially deleterious vasopressor therapy (or high dosing). Avoidance of a rigid mindset and a stepwise evaluation of the adequacy of tissue perfusion at different pressures are key to a likely more beneficial individualized approach. Similarly, fluid resuscitation should not involve fixed volume administration as patients will vary markedly in requirements.[10] Some may require much less than 30 ml/kg

over the first few hours of sepsis presentation, especially in the presence of significant sepsis-induced myocardial depression as this may be compromised further by unnecessary fluid. Some patients may require very little fluid resuscitation if the pathophysiology relates more to loss of vascular tone rather than hypovolaemia. Careful, titrated fluid administration, assessing incrementally the impact of smaller fluid boluses on tissue perfusion, is a more physiologically appropriate strategy that should avoid fluid overload.

Key to a personalized approach is adequate monitoring of circulatory, respiratory and metabolic variables. This will enable optimization of the circulation, gas exchange, fluid status and metabolic status to suit the patient and their baseline physiological status, however this should not be a short-term strategy delivered at the expense of long-term detriment. For example, increasing minute ventilation will generally improve oxyhaemoglobin levels and carbon dioxide clearance, but this should not be at the cost of a significantly increased risk of barotrauma. Current technology is still however limited in terms of the ability to gauge cellular distress accurately at the bedside. Plasma lactate levels are frequently used but lack both sensitivity and specificity as markers of organ hypoperfusion.[11] An important factor is that the plasma level represents the balance between production and utilization. Excess production may be counterbalanced by large-scale utilization of lactate as an important fuel source for varied organs such as brain, heart, liver and kidney; lactate levels may thus remain within the normal range despite significant organ compromise. Indeed, septic, fluid-resuscitated, normotensive patients in multi-organ failure had similar mortality rates irrespective of their lactate level.[12]

Sepsis – an umbrella syndrome

Sepsis requires a definition that captures the essence of the condition and embraces both the pathophysiological basis and the clinical manifestation. In addition, there needs to be accompanying clinical criteria that allow operationalization of the definition to enable consistency for the purpose of improved epidemiology, research and coding. The new version of the international sepsis definitions – 'Sepsis-3' were published in 2016.[13] These update the current concept of sepsis as a dysregulated host response to infection that leads to life-threatening organ dysfunction. As a failing of previous definitions, strict descriptors of organ dysfunction were never rigidly applied, allowing marked variations in reported incidence and mortality.[12] Sepsis-3 offers a change in SOFA score ≥2 points as a more precise means of characterizing new organ dysfunction over and above the patient's baseline. While the SOFA score is not perfect, it is nevertheless well-established, has widespread familiarity within critical care, and a well-validated relationship to mortality risk.[14]

Sepsis-3 also offered a similar re-branding of septic shock. Previously, a myriad of permutations of thresholds of blood pressure and/or lactate and/or base deficit and/or fluid resuscitation volumes and/or organ dysfunction and/or use/dose of vasoactive agents resulted in a 10-fold variation in incidence and 4-fold variation in mortality.[12] Septic shock is now defined by Sepsis-3 as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone".[13] This is operationalized clinically by a vasopressor requirement to maintain a mean arterial pressure ≥65 mmHg and serum lactate >2 mmol/L despite adequate volume resuscitation.

These syndromic descriptions necessarily cover a wide range of microbiological causes and sites of infection affecting a broad spectrum of patients varying by age, gender, underlying health status, medications and co-existing acute conditions such as surgery and trauma. All

of the above factors impact to greater or lesser degrees on patient outcome. An *E coli* sepsis arising from the urinary tract carries a far lower mortality rate than an E. Coli bacteremia consequent to abdominal sepsis.[15] A previously healthy 18 year old patient with toxic shock syndrome will have different clinical, biological and outcome responses compared to a 40 year old neutropenic patient undergoing chemotherapy for leukaemia who develops a pneumonia, or an 83 year old with chronic obstructive airways disease, diabetes, chronic renal failure and fecal peritonitis from a perforated diverticulum. Yet these patients are lumped together as 'septic' into clinical trials simply by fulfilling physiologic criteria such as fluid-refractory hypotension.

Sepsis – a series of biological phenotypes with differing outcomes

It is also becoming increasingly apparent that a disparity often exists between the clinical manifestations of sepsis and underlying biological phenotypes which vary both between individuals and in the same individual over time. Sepsis triggers a dysregulated host response that includes an exaggerated but highly variable degree of systemic inflammation and, at the same time, an exaggerated but highly variable anti-inflammatory response. The GENIMS study examined 1886 patients hospitalized with community acquired pneumonia in 28 US hospitals.[16] Approximately a third developed sepsis, and a third of this more severe subset died. Elevated levels of both the proinflammatory cytokine, IL-6 and the anti-inflammatory cytokine, IL-10 measured in plasma sampled in the Emergency Department gave a 20-fold increase in risk of death at 90 days compared to low levels of both. Unbalanced (high/low) cytokine patterns had intermediate outcomes.

This disparity between eventual survivors and non-survivors extends beyond inflammation into many other pathways. Davenport et al performed a transcriptomic analysis in blood

leukocytes taken from ICU patients admitted with sepsis secondary to community-acquired pneumonia and characterized two 'endotypes'.[17] Forty-one percent had a more immunosuppressed phenotype that included features of endotoxin tolerance, T-cell exhaustion and downregulation of HLA class II. Such patients had a higher mortality compared to the remainder not showing these features (hazard ratio 2.4-2.8 in two separate cohorts). A recent follow-up paper[18] compared the two types of sepsis response signature in these pneumonia patients against a separate cohort of patients with fecal peritonitis. The transcriptomic response was largely independent of the source of infection and included signatures that reflected the immune response state and prognosis in both conditions. Similarly, Langley et al measured the plasma metabolome and proteome in patients with and without community-acquired sepsis from different causes, upon arrival in the emergency department and at 24 hours later.[19] Differences in plasma metabolites and proteins (predominantly involved in fatty acid transport and ß-oxidation, gluconeogenesis, and the Krebs' cycle) were able to discriminate between eventual survivors and non-survivors on admission. This prognostic differentiation was more pronounced 24 hours later. Of note, the metabolome/proteome were similar in survivors, regardless of severity.

Multiple other biomarkers measured either in the emergency department or within 24 hours of intensive care unit admission have also shown prognostic utility. These range from simple physiological measures such as heart rate[20], point-of-care tests such as troponin[21] and lactate[22], formal laboratory tests such as thyroid function[23], coagulation markers[24] and high density lipoprotein cholesterol[25], to more esoteric tests ranging from plasma DNA,[26] autonomic dysfunction,[27] and fecal pH.[28]

Sepsis – outcomes differ by intervention according to biological phenotype

Two interesting retrospective analyses have arisen from the ARDS-NET group interrogating laboratory and clinical data taken from patients enrolled into ARDS intervention studies.[29,30] Calfee *et al* applied latent class modelling to split the patients into two 'subphenotypes'.[29] A quarter of patients had a hyperinflammatory subphenotype (characterised by higher plasma levels of inflammatory biomarkers, more acidosis, vasopressor use, and sepsis) and the remainder had a less inflammatory subphenotype where these markers were not so prevalent. The group with the hyperinflammatory subphenotype had a higher mortality, morbidity, ventilator requirement and length of stay. Notably, this subset responded positively in terms of outcome improvement (90-day mortality, ventilator-free days and organ failure-free days) to an increase in PEEP (in the ALEVOLI trial) whereas detriment was seen in the less inflamed subset. Famous *et al* confirmed a similar subphenotype picture and distribution in another of the ARDS-NET studies (the FACTT fluid management study) and found a different outcome response to fluid management.[30] The hyperinflammatory subphenotype had 90-day mortality rates of 40% with a fluid-conservative strategy versus 50% in those managed with a more liberal approach. The less inflamed subphenotype showed an opposite effect (26% mortality with fluid-conservative, 18% with fluid-liberal). They reported that a three- variable model of IL-8, bicarbonate, and tumor necrosis factor receptor-1 accurately discriminated between these subphenotypes, with sensitivity and specificity of 87% and 93%, respectively. This was superior to a model reliant only on clinical variables (bicarbonate, vasopressor use, creatinine, minute ventilation, heart rate, primary ARDS risk factor, and systolic blood pressure) which was still good at prognostication (sensitivity and specificity both 84%).

On similar lines, two further studies based on retrospective analyses of data also reveal interesting outcome differences in response to therapeutic interventions. Russell et al re-analysed the database of the VASST septic shock trial comparing vasopressin against

norepinephrine on the basis of the new Sepsis-3 septic shock criteria.[31] Only half of the enrolled patients would have fulfilled the new criteria (mean arterial pressure ≥65 mmHg and lactate >2 mmol/L after adequate volume resuscitation) and with an absolute 12% increase in 90-day mortality rate. Notably, mortality in the subset of hypotensive patients with a lactate <2 mmol/l was significantly lower in the vasopressin-treated limb, but no difference was seen in those with a lactate >2 mmol/l, in whom circulating cytokine levels were markedly higher. This implies benefit was only seen from vasopressin in the less inflamed subset of patients, who likely also had less cellular/metabolic abnormalities. On the other hand, Wong et al conducted a secondary analysis of 288 pediatric septic shock patients and divided them into two endotypes based on a 100-gene transcript signature focusing on adaptive immunity and glucocorticoid receptor signalling pathways.[33] In the endotype with increased expression of glucocorticoid receptor signalling genes, corticosteroids were independently associated with a 10-fold reduction in the risk of persisting organ failure at Day 7.

Trial design

The above studies – albeit all retrospective – suggests that patient groups differentiated by a biological signature will respond positively or negatively to standard ICU interventions such as fluid, choice of vasopressor and level of PEEP. The same principle should also be applied to trials of novel therapies or management strategies. For example, immunosuppression is increasingly recognized in critically ill patients and often present on ICU admission.[33] In a study of post-operative cardiac surgical patients, HLA-DR expression was significantly decreased in all patients on ICU admission.[34] It is rational, therefore, to avoid immunosuppressive therapies in such patients, for instance corticosteroids or antibodies directed against pro-inflammatory cytokines. Conversely, the use of immune stimulating

agents could be considered in such patients to reduce the risk of secondary infections but avoided in those patients with pre-existing excessive activation. The challenge in such trials is to find a reliable, rapidly available (ideally point-of-care) theranostic that can both indicate the suitability of a patient for entry and then to allow titration of the drug or other intervention accordingly for optimal effect. Thus, use of an immunostimulant therapy could be guided by several possible indicators, including lymphopenia,[34] monocyte HLA-DR level,[35] or other markers including *ex vivo* stimulation testing.[36] This does however create a chicken-and-egg dilemma in that the worth of a theranostic will only be realized once the trial is concluded so a leap of faith is necessary that the purported biomarker will appropriately guide the intervention and is not simply an epiphenomenon.

References

1. Eddy DM. Practice Policies: Where Do They Come From? JAMA 1990; 263:1265-75
2. Sackett DL Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312: 71–72.
3. Eddy DM. Evidence-Based Medicine: a unified approach. Health Matters 2005; 24: 9-17
4. Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250–1256
5. Dellinger RP, Levy MM, Carlet JM et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36:296–327
6. Dellinger RP, Levy MM, Rhodes A et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39:165–228

7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017; 43:304-377.
8. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014; 370:1583–93.
9. Lamontagne F, Meade MO, Hébert PC, Asfar P, Lauzier F, Seely AJE, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive Care Med 2016; 42:542–50.
10. Perner A, Singer M. Fixed minimum fluid volume for resuscitation: Con. Intensive Care Med. 2016 (ePub) DOI 10.1007/s00134-016-4581-3
11. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. Crit Care. 2014; 18:503.
12. Shankar-Hari M, Phillips GS, Levy ML et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315:775–787
13. Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315:801–810
14. Raith EP, Udy AA, Bailey M, McGloughlin S, Macisaac C, Bellomo R, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 2017; 317:290–300
15. Jauréguy F, Carbonnelle E, Bonacorsi S et al. Host and bacterial determinants of initial severity and outcome of Escherichia coli sepsis. Clin Microbiol Infect. 2007; 13:854-62
16. Kellum JA, Kong L, Fink MP et al. Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 2007;167:1655–63.

17. Davenport EE, Burnham KL, Radhakrishnan J, Slowther A-M, Humburg P, Hutton P, et al. Genomic landscape of the individual host response andoutcomes in sepsis: a prospective cohort study. Lancet Respir Dis. 2016; 4: 259-271
18. Burnham KL, Davenport EE, Radhakrishnan J et al. Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. Am J Respir Crit Care Med. 2016 (ePub 10.1164/rccm.201608–1685OC)
19. Langley RJ, Tsalik EL, Velkinburgh JCV, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. Sci Transl Med 2013; 5:195ra95.
20. Beesley SJ, Wilson EL, Lanspa MJ, Grissom CK, Shahul S, Talmor D, et al. Relative bradycardia in patients with septic shock requiring vasopressor therapy. Crit Care Med 2017; 45:225–33.
21. de Groot B, Verdoorn RC, Lameijer J, van der Velden J. High-sensitivity cardiac troponin T is an independent predictor of inhospital mortality in emergency department patients with suspected infection: a prospective observational derivation study. Emerg Med J. 2014; 31:882–8.
22. Houwink API, Rijkenberg S, Bosman RJ, van der Voort PHJ. The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. Crit Care 2016; 20:56.
23. Wang F, Pan W, Wang H, Wang S, Pan S, Ge J. Relationship between thyroid function and ICU mortality: a prospective observation study. Crit Care. 2012; 16:R11.
24. McClintock D, Zhuo H, Wickersham N, Matthay MA, Ware LB. Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury. Crit Care 2008; 12:R41.

25. Cirstea M, Walley KR, Russell JA, Brunham LR, Genga KR, Boyd JH. Decreased high-density lipoprotein cholesterol level is an early prognostic marker for organ dysfunction and death in patients with suspected sepsis. J Crit Care. 2017; 38:289–94.
26. Kung C-T, Hsiao S-Y, Tsai T-C, et al. Plasma nuclear and mitochondrial DNA levels as predictors of outcome in severe sepsis patients in the emergency room. J Transl Med. 2012; 10:130.
27. Schmidt H, Müller-Werdan U, Hoffmann T, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. Crit Care Med. 2005; 33:1994–2002.
28. Osuka A, Shimizu K, Ogura H, et al. Prognostic impact of fecal pH in critically ill patients. Crit Care. 2012;16:R119.
29. Calfee CS, Delucchi K, Parsons PE et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med. 2014; 2:611–20.
30. Famous KR, Delucchi K, Ware LB, et al. Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy. Am J Respir Crit Care Med. 2017; 195:331–8.
31. Russell JA, Lee T, Singer J, Boyd JH, Walley KR, Vasopressin and Septic Shock Trial (VASST) Group. The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience. Crit Care Med. 2017 Mar 22.
32. Wong HR, Atkinson SJ, Cvijanovich NZ et al. Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids. Crit Care Med. 2016; 44:e1000–3.
33. Lukaszewicz AC, Grienay M, Resche-Rigon M et al. Monocytic HLA-DR expression in intensive care patients: Interest for prognosis and secondary infection prediction. Crit Care Med 2009; 37: 2746-2752

34. Oczenski W, Krenn H, Jilch R et al. HLA-DR as a marker for increased risk for systemic inflammation and septic complications after cardiac surgery. Intensive Care Med 2003; 29:1253–1257.
35. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. Shock. 2014; 42:383–91.
36. Meisel C, Schefold JC, Pschowski R, et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. Am J Respir Crit Care Med 2009; 180: 640–48.
37. Bermejo-Martin JF, Andaluz-Ojeda D et al. Defining immunological dysfunction in sepsis: A requisite tool for precision medicine. J Infect. 2016; 72:525–36.