

Sepsis – past, present and future

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Singer M. Sepsis – past, present and future. *Journal of Nepalese Society of Critical Care Medicine*. 2023 Jul;1(2):1-3.

Submitted : 25 June 2023
Accepted : 30 June 2023
Published Online : 9 July 2023
Conflict of Interest : None
Source of Support : None

Understanding, identification and management of sepsis has evolved considerably over the last few decades. It continues to do so, though at a faster trajectory as new technologies and diagnostics are developed. Outcomes have also improved in line with earlier recognition and better overall care. Over the course of my professional career in critical care spanning almost four decades, I have witnessed considerable change that has been generally positive. However, multiple challenges remain. While I am confident that many will be solved, some may become more taxing.

THEN

In the 1980s, sepsis was considered to be a systemic inflammatory response to infection.¹ The patient suffered from ‘severe sepsis’ when sepsis was associated with ill-defined organ dysfunction, and ‘septic shock’ was a variably described state with numerous cut-off values of blood pressure and/or lactate. Patient management was quite different. Patients were routinely volume-overloaded and grossly so. These Michelin men and women were unrecognizable from their usual selves. I recall querying the logic of this approach. Oxygen would have further to travel through oedematous tissues to reach the cells, excess pressure would be applied on cells and drainage tubes (such as the ureters and bile ducts) impairing their functionality, and it would be far more onerous and destructive to ventilate wet sponge-like waterlogged lungs. It was not uncommon to have multiple chest drains placed for recurrent pneumothoraces. I was however wrongly reassured that increased capillary leak was a normal part of the host response to sepsis and that this excess fluid was purely ‘cosmetic’ would all go away once the patient recovered.

We have thankfully learnt to be more frugal with fluid loading and to encourage deresuscitation with normalisation of fluid balance once the patient has stabilised. We also over-fed, over-sedated, and over-treated with antibiotics. However, we have learnt to be more circumspect – lower tidal volumes, less sedation, fewer calories, shorter courses of antibiotics. Less was definitely more and the patients benefitted from this.

We deployed strategies such as early goal-directed therapy² and tight glycaemic control³ as we were promised by the Surviving Sepsis Campaign (SSC) that these were vital to save lives and that we would be remiss in our duty to patients if we did not deploy them.^{4,5} Subsequent multicentre studies could not however confirm their utility. The SSC also exhorted us to give antibiotics immediately as every hour’s delay would cost lives.⁶ While unnecessary delay should certainly be avoided, this haste is not justified for cases of lower severity and diagnostic uncertainty.⁷

Monitoring, diagnostics, imaging and organ support devices have become increasingly sophisticated. Point-of-care technology has dramatically shortened the time to obtain useful bedside information, as has the internet. Dr Google, PubMed, Medscape and their other colleagues have become vital companions offering instant gratification yet not always providing accurate guidance. Ventilators are more patient-friendly, and these are complemented by enhanced non-invasive and extracorporeal respiratory support devices. Pulse oximeters are now ubiquitous, echocardiography and bronchoscopy are routinely accessible at the bedside, and we no longer need the surgeon to perform most tracheostomies.

We also became increasingly aware that critical care should not have walls. Sick patients should be promptly identified and actively treated before they are admitted to critical care. Outreach teams were created to support staff on general wards. Early Warning Scores such as NEWS⁸ were implemented to identify deteriorating patients in the emergency department and the ward as well as in the community, and to indicate the required response time and expertise of the responding clinician. Patients were mobilised earlier and a much greater emphasis was placed on rehabilitation and psychological support for survivors.

Epidemiology has considerably improved, partly due to the advent of electronic data collection and the tightening of criteria. Scoring systems such as APACHE⁹ and SOFA¹⁰ have enabled better characterisation of disease severity and mortality risk. Such scores have also facilitated comparisons between hospital systems and temporal changes. The Sepsis-3 definitions characterised sepsis as a life-threatening dysregulated host response to an infection, placing more emphasis on the role of the host rather than the triggering pathogen in determining illness severity and outcomes.¹¹ Sepsis-3 also provided clear criteria for characterizing new organ dysfunction (using a change in SOFA score ≥ 2 points) and septic shock.

Multiple novel interventions were also trialled on the basis of encouraging albeit poorly designed animal studies. Yet apart from a short-lived dalliance with activated Protein C,¹² none of these 'magic bullet' therapies have been licensed due to a repeated and depressing failure to conclusively demonstrate any impact on patient outcomes.

NOW

We are maturing as a specialty but still have much to learn. We increasingly recognize iatrogenic harm and take appropriate steps to reduce this. However, many other established management dogma remain. For instance, do we need to routinely use thromboprophylaxis and proton pump inhibitors in most patients? How quickly should we commence renal replacement therapy? The utility of our current strategies needs to be challenged, limiting use to those patients who will benefit.

Knowledge of the pathophysiology underlying sepsis has also markedly improved. For example, we increasingly appreciate the role of mitochondrial dysfunction as a mechanism underlying organ dysfunction and can make a reasoned argument that it is in part protective, saving the organs from irreparable damage through excessive oxidative stress.¹³ Many other physiological and biochemical changes may also be adaptive and not necessarily deleterious. We also recognize that while the septic patient is inflamed they are usually immunosuppressed to varying degrees,¹⁴ and that this immunoparesis may be present even at the time of ICU admission. However, little of this knowledge has translated as yet to the bedside in terms of directed treatments to either prevent deterioration and/or enhance recovery and long-term survivorship. We do better appreciate the impact of critical illness on long-term outcomes¹⁵ – physical, psychological and cognitive – but have still to implement integrated systems to enhance rehabilitation and recovery post-ICU/hospital discharge.

There is now general recognition that sepsis is a syndrome rather than a specific condition and that septic patients fall into subsets (variably called subphenotypes or endotypes) with different biological signatures.¹⁶ These signatures can be identified clinically but also from various 'omic investigations: transcriptomic, proteomic, metabolomic etc. Responses to specific treatments will likely depend upon the particular subset into which the patient falls, albeit acknowledging that the signatures will change through the course of the patient's illness and treatment modified accordingly. However, these different signatures have yet to be integrated into a whole descriptor of the body's biological status. A developing field is that of theranostics – using biomarkers (single or combination panels) to identify patient subsets with potential treatable traits and to titrate therapies to optimal effect. Such studies are now being implemented. While success is not guaranteed, the likelihood of finding successful treatments for specific patients should be far greater than the current 'one-size-fits-all' approach.

FUTURE

The future is both rosy and challenging. We will have the ability to identify pathogens rapidly (within minutes to a few hours), to determine targeted antibiotic regimens, and to predict sepsis in advance of it manifesting clinically. We will be able to identify specific pathways that can be activated or suppressed to reduce mortality and morbidity, shorten length of stay and enhance long-term survivorship. Imaging and monitoring capabilities will improve. Wireless technologies such as wearables and implanted chips will detect physiological and biochemical derangements in advance of obvious clinical deterioration and this can be undertaken outside the physical critical care unit or even remotely. We will be able to monitor antibiotic concentrations in real time and assess the performance and adequacy of perfusion in individual organ beds, Machine learning will offer accurate diagnostic support and will also assist in optimising individualised patient management.

All of the above will come at a cost. While technology will become faster and cheaper it will still be expensive and will place a huge burden on all healthcare systems, especially in low and middle income countries. There will be an imperative to confirm outcome benefits and cost effectiveness, and generalisability/applicability to different locations around the world. There will also be a challenge in having enough appropriately trained staff to manage the technology. Automation will obviously assist but this should not replace patient-facing clinicians who should remain front and centre for decision-making, communications with patient and family, dealing with the ethical and moral conundrums that will continue to arise, and providing that crucial human touch of sympathy and compassion.

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