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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

Subtleties and differences of managing ICU patients across South Africa, Australia and UK

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Abstract

Purpose of Review Sepsis remains one of the greatest global healthcare burdens, with an estimated greater mortality rate from sepsis in Africa. The increasing global financial, social, and political strain of the twenty-first century has created new challenges when trying to tackle this problem. We aim to compare the differences in the management of sepsis in three countries (Australia, the UK, and South Africa) that face distinctly different challenges.

Recent Findings The Surviving Sepsis Guidelines attempted to provide a good standard of care with bundles to help initiate early appropriate treatment. These bundles of care appear to improve outcomes when implemented early; however, data from Africa is lacking. There are several barriers to the implementation of guidelines, and resource-limited environments face additional challenges of staff shortages, lack of equipment and medication, and clinical pressure with increased strain capacity.

Summary Australia, the UK, and South Africa have both shared and different obstacles when addressing the burden of sepsis. Solutions for the African environment may differ from more well-resourced environments, and global cooperation and innovation will be necessary to tackle sepsis across these continents. There is an urgent need for data from the African continent to understand the burden of sepsis and to help plan and strategize potential solutions.

Keywords Sepsis · Critical care · South Africa · Australia · UK

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated immune response to infection and remains a major health problem in intensive care units (ICUs) [1]. Mortality associated with sepsis has reduced by 52.8% since 1990, as has the incidence of sepsis [2]. However, a recent analysis for the global burden of disease study revealed that while incident cases of sepsis have declined in the past 30 years, it remains a leading cause of death. In 2017, there were 48.9 million incident cases with 11 million sepsis-related deaths, accounting for approximately 19.7% of all deaths globally. Sepsis-related mortality varies according to geographical location and socio-demographic index (SDI), a ranking that describes countries based on a composite measure of income per capita, education, and fertility rates. Approximately 84.8% of all sepsis-related deaths in 2017 occurred in countries with low, low-middle, or middle SDI [2].

Three countries that are geographically and culturally diverse are South Africa, Australia, and the UK. Each country has differences in sepsis management due to variations in healthcare systems, resources, protocols, and guidelines. The

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disparity and subsequent challenges facing the three countries are represented in Table 1. The differences in population and geographical size, gross domestic product per capita, and availability of ICU capacity and staff clearly demonstrate the gap between Australia and the UK versus South Africa.

In this study, we explore the differences in the epidemiology, management, resource limitations, and outcomes of sepsis in adult ICU patients in three settings (UK, Australia, and South Africa), to highlight reasons underlying the discrepancy in sepsis management and outcomes in different locations.

Epidemiology of Sepsis

Epidemiological data is important when defining, addressing, and researching sepsis, but information regarding the burden of sepsis in resource-limited countries is limited (despite the relationship between SDI and mortality), creating a relatively skewed picture of the global perspective [3, 4]. The Intensive Care over Nations Audit identified sepsis in 18.0% of patients admitted to ICU, and 29.5% of patients during their ICU stay [4]. ICU and hospital mortality rates were 25.8% and 35.3%, respectively, and as mentioned before, varied geographically with the highest rates in Africa.

Age-standardised incidence ratio (ASIR), per 100 000 population of sepsis is shown in Fig. 1 and Table 2. South Africa has the highest ASIR compared to the UK and Australia.

The incidence of sepsis in the UK is increasing by approximately 11.5% each year [6]. Approximately 245,000 cases of sepsis were treated across the UK with similar mortality rates in each country (Wales 24%, Scotland 20%, England 20%, Northern Ireland not reported) [5••, 7]. Between April 2019 and March 2020, sepsis accounted for 30.9% of ICU admissions (53,235) with a 28.2% acute hospital mortality [8]. A 41% increase in incidence was reported between 2015 and 2017 [9] and followed the introduction of guidelines from the National Institute for Health and Care Excellence and the new international definition of sepsis in 2017 [10]. The significant increase in incidence is not only thought to be attributable to improved recognition as a result of new guidelines but can also be explained by a number of contributing factors, including an ageing population, increased immunosuppression, and antibiotic resistance [6].

In Australia, there was a 27% increase in the incidence of sepsis from 2013–2014 to 2017–2018, though mortality rates remained unchanged. During this time, the ICD coding for sepsis changed, which may explain in part the increased incidence [11]. In addition, there were multiple sepsis awareness campaigns aiming to increase knowledge and recognition of sepsis [12, 13].

Although the age-standardised incidence of sepsis in Australia is lower compared to the UK or South Africa, the rates of hospitalisation with sepsis are 1.7 times higher in remote

Table 1 Comparison of population and resources

South Africa	Australia	UK
• Population: 60.4 million • Size: 1.22 million km^2 • GDP per capita: $6 485 • Gini index: 0.630 (118th) • Sepsis is a major burden with high but unknown mortality rates • ICU beds 3318 [63] o 2140 (private) o 1178 (public) • ICU specialists: ± 80 (2013) [76] • Sepsis management affected by limited resources and staff shortages, particularly in rural areas • The Surviving Sepsis Campaign (SSC) guidelines are used, but compliance may be suboptimal due to: o Lack of awareness o Training o Equipment • There are differences in access to antimicrobial drugs, microbiology services, and other supportive therapies	• Population: 26.4 million • Size: 7.7 million km^2 • GDP per capita: $61 224 • Gini index: 0.343 (46th) • Sepsis is a significant healthcare issue with an estimated 18,000 deaths • ICU beds 2183 (November 2021) [64] • ICU Specialists: 756 (2016) [77] • Sepsis management is influenced by the presence of well-established clinical networks, guidelines, and quality improvement • The Australian Sepsis Network (ASN) provides guidance and resources for sepsis management, including the use of personalised treatments and protocols programs annually • There are variations in the availability and funding of ICU beds, staffing models, and inter-hospital transfers	• Population: 67.7 million • Size: 242 500 km^2 • GDP per capita: $47 374 • Gini index: 0.326 (39th) • Sepsis is a major concern with around 52,000 deaths per year • ICU beds 4065 (March 2022) [65] • ICU Specialists: 642 (2019) [78] • Sepsis management is influenced by the National Institute for Health and Care Excellence (NICE) guidelines • There are differences in hospital structures, funding models, and performance indicators, which can affect sepsis management, such as early recognition and treatment of sepsis • There are variations in the adoption and implementation of sepsis management bundles and protocols across hospitals and regions

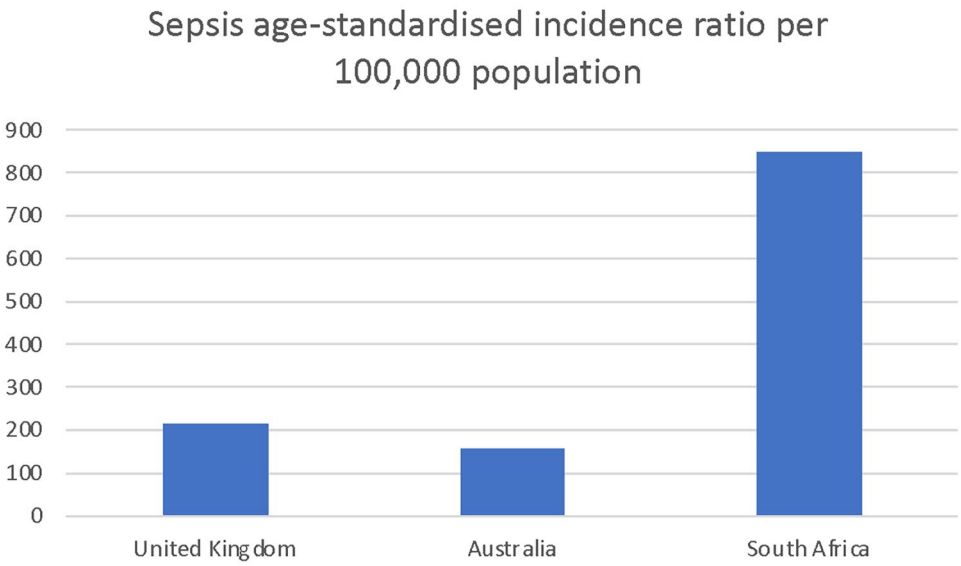

Fig. 1 Sepsis age-standardised incidence ratio per 100,000 population in the UK, Australia, and South Africa 2017 [5••]

areas compared to urban areas. These rates are also higher in low socio-economic areas compared to high socio-economic areas [11]. Patients living in rural and remote areas have poorer health outcomes compared to patients living in urban areas [11]. Indigenous patients are overrepresented in the rural population and are known to have poorer health outcomes compared to non-indigenous Australians [11]. Indigenous patients have a higher burden of chronic disease and are on average 15 years younger than non-indigenous patients when they are admitted to ICU [14]. A higher proportion of Indigenous patients are admitted due to sepsis compared to non-indigenous patients (11.6% vs 7.2%) [14]. This discrepancy between those in urban and remote areas, and between Indigenous and non-indigenous patients, may be explained by limited access to resources in rural and remote areas, higher burden of chronic disease, and lower socio-economic status. However, more work is needed to explain this and address the gap in healthcare outcomes in these Australian populations.

There is very little to accurately indicate the burden of sepsis in South Africa. However, it is estimated that the overall burden of sepsis in sub-Saharan Africa is high, with an estimated 16.7 million cases occurring annually [5••].

A small study from South Africa included 11 ICUs and reported the outcomes of all patients admitted over a month [15]. While sepsis was not specifically recorded, the primary reason for admission was infectious causes in 21.5% of patients. This was less than non-communicable diseases (49.6%) and trauma (29.0%). Furthermore, a single-centre study conducted amongst surgical admissions in a South African hospital complex described sepsis in 21% (1240/6020) of surgical admissions, although these were not specifically to ICU [16].

The incidence of sepsis is increasing globally, with a particularly high burden in South Africa compared to the UK and Australia. Data to explain this difference is lacking; however, the incidence of sepsis is highest in areas of lowest SDI and socio-economic status. This has downstream effects on timely access to healthcare, including early antibiotics and resuscitation, surgical availability and source control, availability of intensive care beds, long-term follow-up, and prevention of readmission through primary health care. It is important to identify the patterns of distribution of sepsis cases so that clinical resources, as well as those resources allocated to research and data collection, are allocated appropriately.

Table 2 Incidence and ICU admission rates [5••]

	UK	Australia	South Africa
Population			
Incidence sepsis cases (95% UI) 2017	245,783 (191,983–330,996)	55,251 (44,428–70,778)	433,066 (323,827–610,601)
Sepsis age-standardised incidence ratio per 100,000 population (95% UI)	216.2 (173.2–280.5)	158.8 (125.3–215)	848.0 (641.6–1,197.7)
ICU admissions	53,235 (30.9% of all general ICU admissions)	18,000 (2017)	Unknown

Management of Sepsis

The mainstay of management of patients with sepsis includes early recognition, early and appropriate administration of antimicrobials, restoration of euvolaemia and perfusion through careful intravenous fluid administration, and monitoring the response with provision of organ support as required [17]. The surviving sepsis campaign guidelines introduced the first sepsis care bundle in 2012, and the elements of this are revised regularly to represent best practice. It has been shown that adopting bundles of care can lead to reduced mortality in sepsis [18]; however, this is not the case in all settings. In addition, certain elements, such as early ICU admission, may be limited by resource availability.

The effects of initiatives introduced and adopted in the UK, Australia, and South Africa are summarised in Table 3.

There was an increase in the incidence of sepsis in both Australia and the UK from approximately 2013–2014 to 2017–2018, which may be attributed to increased awareness and recognition of sepsis through the introduction of sepsis care bundles and guidelines, and the sepsis awareness campaigns created to promote them [11–13]. Sepsis care bundle compliance has been associated with improved mortality in both countries [19•, 20, 21]. The introduction of sepsis bundles in both settings resulted in improved patient outcomes (Table 2).

There is very little data available to determine how well patients with sepsis are being managed in South Africa [22]. The national PISA trial published in 2007 attempted to assess compliance with surviving sepsis guidelines [23]. An infection control policy was only present in 77% of ICUs, with about half of the units (51%) practicing blood culture sampling. Only two-thirds of units (65%) had access to microbiologists, and only 61% had a glucose control policy. Antibiotic usage was also questionable, with 11% of patients having antibiotic therapy changed correctly after microbiology data, but only 42% of cases were adjudged to have appropriate antibiotic use. Only 26% of patients were assessed as having the correct duration of antibiotic therapy [24, 25].

Recommended sepsis bundles of care have not been shown to improve mortality in resource-poor settings in sub-Saharan Africa. A systematic review and meta-analysis identified three studies investigating the use of a protocol-driven sepsis strategy [26]. Two RCTs demonstrated increased mortality with 'early-goal directed therapy' [27, 28], and a third observational cohort study demonstrated improved survival after implementation of a sepsis management protocol [29]. There are currently no implemented national strategies to improve the care of patients with sepsis in South Africa.

Appropriate antimicrobial management in South Africa is affected by access to medication, unavailability of antibiotics, poor access and transportation to health facilities, and clinical strain capacity requiring patients to wait for potentially many hours before receiving attention [30]. However, simple quality improvement projects even in resource-limited environments have been shown to make a difference, such as improvement in initiation time for antibiotics [31]. The National Infection Prevention and Control Strategic Framework was published in March 2020 but remains in concept form [32].

Improvement in the management of sepsis needs to focus on access to healthcare, appropriate early implementation of antibiotics, and restoration of perfusion. The Surviving Sepsis Guidelines (SSG) aim to provide global strategies. However, controversy and dispute regarding aspects have meant that these guidelines are often adapted or modified and vary between regions and hospitals [33]. A greater challenge is the lack of research from African countries regarding compliance with sepsis management. Adherence to guidelines has been shown to improve mortality rates, ICU admission rates, and outcomes in the UK and Australia [17, 34–38]. Sepsis guideline compliance has been noted to be poor in many parts of the world including sub-Saharan Africa where mortality rates are high [17, 35, 39–46]. Increased awareness and early recognition of sepsis will help to improve compliance with management guidelines and improve outcomes for patients.

Outcomes

Sepsis is associated with increased mortality and increased risk of hospital readmission. Long-term follow-up of patients with sepsis who were enrolled in international randomised controlled trials has shown 15–23% mortality at 6 months [47], and up to 28% mortality at 12 months [48]. Long-term outcomes for survivors are also poor, with sepsis survivors having an increased risk of premature mortality and long-term physical and cognitive impairment [49, 50] compared to other patients. Prescott et. al. reported that 26.5% of severe sepsis survivors were readmitted to hospital within 30 days of discharge, while 63% were readmitted within 12 months [50]. Sepsis age-standardised mortality ratio per 100,000 population for the UK, Australia, and South Africa is shown in Fig. 2 and Table 4.

Internationally, sepsis survivors are at increased risk of long-term cognitive and functional impairment which is gaining increasing recognition as post-intensive care syndrome (PICS) [51]. Considering the increasing awareness of long-term impairments associated with sepsis and PICS, the most recent surviving sepsis guidelines recommend patients undergo assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge, and referral to a post-critical illness follow-up program if available [52•].

Table 3 Management initiatives and effect

Location	Initiative	Aims	Results
UK	Sepsis six care bundle 2006 [79]	Six actions within 1 h of diagnosis of suspected sepsis: 1. Senior review 2. Blood cultures 3. Antibiotics 4. Source control 5. Intravenous fluids 6. Monitoring	20% reduction in mortality, improved compliance since introduction of electronic prompts, reduction in ICU admissions (19 to 7%) a decrease in hospital length of stay (31, 32)
	NICE guidelines 2016 [10]	Initial management of sepsis with emphasis on early recognition and management, and introduction of early warning scores	
	Academy of Royal Colleges of Medicine 2022		
	Sepsis Trust [7]	Updated sepsis manual 6th edition	
Australia	Sepsis Kills bundle of care based on sepsis six 2011 [12]	Early recognition, aggressive fluid resuscitation, early intravenous antibiotics, ICU referral	Decrease in mortality, ICU and hospital LOS Increased proportion of patients receiving IVABs and second litre of fluid within 60 min of triage from 2009 to 2011 Mortality rate for patients treated on the ward was higher than that of patients admitted to the intensive care
	Think sepsis. Act fast. Victoria [13]		Reduced inpatient sepsis mortality by 50% (11.4 to 5.8%), reduced ICU admissions and readmissions, reduced ICU LOS by 1.2 days and reduced hospital LOS by 2.9 days Improvement in proportion of patients receiving antibiotics within 60 min (37.4% vs 58.1%) Compliance with bundle of care improved from 4.91% to 78%
	Queensland Sepsis Program – Could this be sepsis [19•]	1-h and 3-h sepsis bundles	Reduced ICU admissions, improved compliance with bundle care
	National Sepsis Program 2020 [7, 79–81]	Aim to improve recognition of sepsis, provide national sepsis guidelines and care planning for sepsis survivors	
South Africa	Surviving sepsis guidelines (international)	2007 PISA trial identified significant compliance issues with surviving sepsis guidelines due to lack of access to resources including microbiologists, lack of blood culture sampling, inappropriate antibiotic prescribing [25]	Bundles of care have not been shown to improve mortality in sub-Saharan Africa

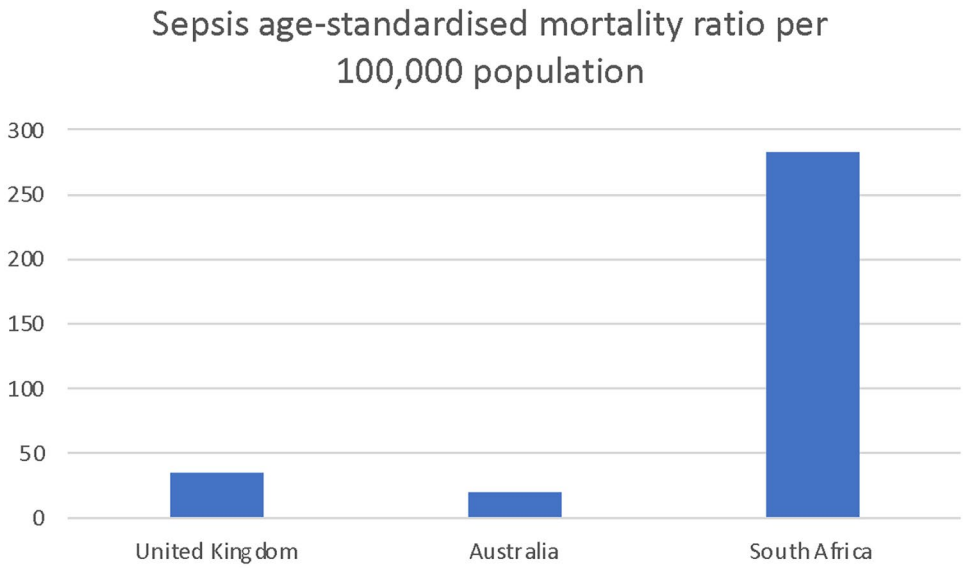

Fig. 2 Age-standardised mortality ratio per 100,00 population in the UK, Australia, and South Africa in 2017 [5••]

In the UK, higher mortality is associated with increased organ dysfunction on admission to ICU, with 64.5% mortality if 4 or more organ dysfunction is present compared to 7.1% if no organ dysfunction is present. In comparison with non-sepsis ICU admissions, there is an increased rate of readmission to ICU (19–32%), most commonly due to unresolved or recurrent infection. Approximately 40% of admissions with sepsis will experience long-term sequelae which can take up to 18 months to recover. Post-sepsis syndrome symptoms can either be physical, cognitive, and psychological [7, 8]. Approximately 30% of survivors of all ICU admissions die in the subsequent year, most commonly from underlying chronic illnesses.

In the UK, ICU follow-up clinics are recommended for every patient admitted to ICU for more than 3 days, approximately 2 months after discharge. The access to follow-up clinics has increased over recent years, with approximately 74% of trusts now having outpatient clinics in 2021 in comparison to 27% in 2013. These are predominantly nurse lead with limited access to psychological support, occupational therapy, and physiotherapy. Involvement of primary care during the recovery phase of critical illness [53]. Currently, there is no standardised pathway for follow-up, this has been highlighted as needing to be addressed to improve equity of access to services across the UK. In addition, the importance of early engagement with primary care in the recovery phase of critical illness with their involvement in long-term management to reduce mortality from chronic illness, address polypharmacy, and reduce unplanned hospital readmission is felt to be key to improve long-term outcomes. Despite increased access to follow-up clinics, there is limited data on outcomes and no data is routinely collected [54].

In Australia, 40% of sepsis survivors will represent to hospital within 30 days, while 75% will represent within 365 days [49] and 14.2% are readmitted to ICU [55]. A recurrence of sepsis is expected in approximately 25% of total survivors [49]. Although Australians in rural and

Table 4 Outcomes of sepsis [5••]

	UK	Aus	SA
Sepsis age-standardised mortality ratio per 100,000 population (95% UI)	34.8 (29.8–40.6)	19.9 (17.2–23.1)	283.3 (238.3–334.8)
Sepsis deaths	47,860 (40,515–56,244)	8702 (7457–10,197)	134,680 (110,363–162,718)
Recurrent episodes	Rate of readmission to ICU 19–32%	Rate of readmission to ICU 14.2% Rate of representation to hospital within 30 days 40%, within 365 days 75% Recurrent sepsis expected in 25% Outcomes poorer in rural and remote areas and Indigenous patients	Unavailable

remote areas are known to have poorer health outcomes and less access to health services [11], it has been shown that patients admitted to regional and rural ICUs have lower mortality rates after ICU admission [56]. Patients in rural and remote areas of Australia are more likely to live in areas of socio-economic disadvantage, to undergo transfer to a hospital with a higher level of care, and more likely to have an ICU readmission during subsequent hospital admissions [56]. The adjusted risk of death and 12-month mortality is higher for indigenous than non-indigenous Australians who are admitted to an ICU [14]. Further work is required to address this gap in healthcare and outcomes in Australia, where only 2% of ICUs have an ICU follow-up clinic [57]. Long-term outcome data, particularly as it relates to patient-centred outcomes, is thus lacking.

There is no up to date published data on outcomes of patients with sepsis in ICUs in South Africa. Evidence from sub-Saharan Africa is limited and a recent meta-analysis examined 15 studies with 2800 participants. The pooled in-hospital mortality for Sepsis-2 defined sepsis and severe sepsis was 19% (95% CI 12–29%) and 39% (95% CI 30–47%) [58•]. HIV remains a significant problem with most of these patients being infected. Mycobacterium tuberculosis was the most common cause of bloodstream infection. Outcomes beyond 30 days were not available. Mortality in this region remains high with estimated mortality rates of 19% and 39% for sepsis and severe sepsis, respectively [58•]. These estimates will obviously vary between countries but can be as high as 64.4% and 82.1% for sepsis and severe sepsis, as was found in two ICUs in Rwanda [59].

Sepsis mortality rates vary between geographical locations and are worse in disadvantaged socio-economic areas. As mortality rates improve, more work is required to address long-term sequelae of sepsis to optimise quality of life in sepsis survivors and to prevent readmission and limit the burden on health care systems.

Discussion

Sepsis remains a common and significant problem, with widespread morbidity and mortality across the globe, but is particularly high in Africa with an estimated mortality of 30–47% [58•]. Early initiation of appropriate management is important in dealing with this worldwide problem. Bundles of care have been shown to be effective in resource-rich settings, together with initiatives to raise awareness and early recognition of sepsis. These have not yet been shown to be beneficial in Africa, although data in this region is limited. Adoption of guidelines and dissemination of protocols may be easier in regions that are better resourced, staffed, and where clinical strain capacity is less [30, 60, 61].

Healthcare System and Resources

South Africa has a well-developed two-tier system of private and public healthcare systems. However, the public healthcare system serves 84% of the population with only 50% of the total national health expenditure [62]. Healthcare resources can be limited in some areas, leading to challenges in providing consistent and high-level critical care. Access to advanced equipment and specialised treatments is restricted in certain regions. The prevalence of certain diseases, such as HIV/AIDS and tuberculosis, might influence the case mix and treatment strategies in ICU, with a much larger population of immunosuppressed ICU patients [15].

Australia generally benefits from a well-developed healthcare system with a higher number of ICU beds per capita and resources compared to South Africa and even the UK [63–65]. The management of ICU patients in Australia often follows evidence-based guidelines and protocols, with a focus on multidisciplinary care and patient safety. The country's vast geographical and remote areas may present challenges in terms of access to specialised care for critically ill patients. Telemedicine and emergency medical services are well established and may help to improve prompt delivery of treatment, but this will remain a challenge in such a large country [66].

The National Health Service (NHS) in the UK provides comprehensive healthcare services with well-established critical care services. However, like many healthcare systems, the NHS may face capacity challenges, especially during peak demand periods, as demonstrated during the COVID-19 pandemic [67]. There are challenges facing the NHS in terms of staffing, and despite the smaller geographical size when compared to Australia, the relatively dense urban areas, with smaller remote regions, and an ageing population [68].

Staffing shortages are probably more common in an African context, potentially leading to challenges in providing continuous care and expertise. The World Health Organisation identified 83 countries in Latin America, Africa, and Asia where minimum healthcare worker-to-population ratios were not met [69]. Inadequate staffing, together with insufficient knowledge regarding early identification of sepsis and early initiation of management also contribute to potentially worse outcomes [70]. Both the UK and Australia tend to have well-developed and standardised training programs, which can contribute to differences in practices.

Clinical capacity and strain in resource-poor areas influence the ability to deliver effective management of patients. This is seen in several areas, including access to surgery, medication, appropriate monitoring equipment, laboratory tests, and human resources. Access to surgery is limited in many regions. By 2035, it is estimated that over 70% of the world's population will be living in countries below the

recommended surgical rate [71]. The clinical demands make research challenging. More affluent healthcare systems can place more emphasis on medical research and innovation, which can lead to better auditing, clinical governance, and the adoption of new technologies and treatment strategies in ICUs. This is clearly seen in the national UK ICNARQ and ANZICS CORE database systems. South Africa is yet to develop and implement a national critical care database.

Cultural and Ethical Considerations

While all three countries are multi-cultural, both cultural and socio-economic factors can influence medical decision-making. Family involvement in healthcare decisions might be more prominent in certain regions, and cultural sensitivity is vital when treating patients with different backgrounds. Healthcare providers must be aware of various cultural and religious beliefs that could impact patient care and decision-making, particularly with regard to life-support measures, use of blood products, end-of-life care, and organ donation.

Cultural and behavioural barriers to implementing and following guidelines exist [72, 73]. These barriers can be challenging to overcome, particularly tackling scepticism, lack of motivation, and aligning incentives with behaviour. Cultural aversion to adopting the use of guidelines needs to be addressed at levels of leadership, education, training, staff engagement [74], and team models [75].

Tackling Sepsis in the Next Decade

Significant differences exist in sepsis management across the globe. Australia, the UK, and South Africa require different strategies to address these challenges, particularly in the areas of access to healthcare, education and training, and national sepsis programs. Restructuring of acute public healthcare delivery with implementation of early sepsis treatment bundles may provide some solutions, but the underlying poverty and national health issues in low SDI countries remain an enormous barrier. Global, collaborative research from Africa and South Africa is required to identify areas where easy gains can be made, and implementation of a national database system would facilitate this objective. It is essential to note that these differences are not exhaustive and may be subject to change over time. The management of ICU patients with sepsis requires a holistic and patient-centred approach that considers local contexts and resources. Collaboration, education, and ongoing quality improvement efforts can contribute to reducing the burden of sepsis and improving patient outcomes. As sepsis mortality improves, we must look to long-term outcomes and focus on longitudinal care to address morbidity in survivors.

Conclusion

Sepsis remains a global healthcare problem, but mortality rates are highest in Africa and low-socio-demographic countries. Early and appropriate implementation of interventions such as antibiotics, intravenous fluid management, and organ support through bundles of care appears to improve outcomes in well-resourced countries. This may not necessarily be the same in comparatively poorly resourced countries such as the South African public healthcare system. New and innovative solutions need to be studied to enable similar improvements without staffing and resource expenses. Cultural and behavioural barriers need to be tackled and included in future sepsis programs. Improvement in the global care of sepsis patients requires more information from poorly resourced countries through collaborative international research. Sepsis patients who survive ICU appear to have long-term outcomes that are being recognised but require greater understanding.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

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- • Of importance
- •• Of major importance

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