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Review

Review of sepsis in Pakistan: how far have we come?

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ABSTRACT

Pakistan is a low-middle-income country (LMIC) with a high burden of sepsis, yet there is a profound dearth of data regarding sepsis with no comprehensive review. In Pakistan, access to competent healthcare services is delayed and in places, often not available. Patients may present with sepsis after common community-acquired infections; the commonest sources of sepsis are the respiratory tract followed by the urinary tract. Gram-negative organisms are responsible for a large majority of cases of sepsis. Unfortunately, compliance with sepsis guidelines remains poor, and sepsis-related statistics do not seem to be improving significantly. Adult sepsis presents a significant burden on healthcare services, particularly in LMICs, and is a leading cause of morbidity and mortality. Many factors which affect outcomes and cost of care are amenable to prompt interventions. Consequently, there is a dire need to make concentrated efforts in implementing simple, cost-effective, and context-specific guidelines and monitoring strategies regarding the diagnosis and management of sepsis. The collection and analysis of information on sepsis in Pakistan hence remains imperative, in order to prospectively assess the effects of guideline compliance on outcomes and to formulate and refine new schemata to address emerging problems.

Introduction

Sepsis in particular poses a substantial burden on healthcare systems worldwide. Pakistan, a low-middle-income country (LMIC), struggles with the sepsis burden due to a high number of infections within its population. Since no extensive review exists on the present situation of sepsis in the country, the authors of this study aim to address this dearth in literature.

Putting Pakistan's healthcare setting into perspective, the country has a population of more than 230 million, around 63% of which belong to rural areas [1]. In 2021, 59% of the population was from the 15-64 age bracket with 40.3% of the population being less than 15 [1]. Yet, Pakistan spent only 2.95% of its Gross Domestic Product on healthcare expenditure in 2020 [1]. After the 18th constitutional amendment in 2010, health is a devolved entity, with each province responsible for its own respective health priorities and budgets. Health insurance from the private sector is rudimentary. Apart from a brief period (2020-2022) when the federal government introduced health insurance in the form of "Sehat Sahulat Card", all healthcare costs are borne by patients. Even with the expansion of public sector facilities, the largest provider of healthcare remains the private sector. The critical care network in the country is also very underdeveloped, and although existing intensive care units (ICUs) across Pakistan do have access to basic equipment, drastic inequalities in equipment distribution persist among different regions and healthcare sectors [2]. Unfortunately, extensive data for key resources for organ support interventions across Pakistan is not available. During the COVID-19 pandemic, significant efforts and resources were diverted toward strengthening ICUs through the introduction of teleconsultations for 'tele-ICUs', improved provision of oxygen, and an increase in the number of ventilators at existing healthcare facilities. Yet the fact remains that Pakistan has 1.1 physicians per 1000 people with very few opportunities for structured critical care training for physicians and nurses [1,2].

The population of Pakistan has an average life span of 66 years, which has increased compared to 59 years in 1980 [1]. Furthermore, noncommunicable diseases, such as diabetes, cardiovascular diseases, stroke, cancers, and chronic kidney diseases, are among the top causes of morbidity and mortality in Pakistan, with recent years showing a mortality rate of 60% due to noncommunicable diseases [1]. In fact, between 2009 and 2019, the country has seen a relative increase in the

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prevalence of ischemic heart disease (28.8%), diabetes (45.1%), chronic kidney disease (32.3%), cirrhosis (18.9%) and chronic obstructive pulmonary disease (10.9%) [3]. We anticipate that the rising trends in such chronic comorbidities will undoubtedly lead to an increase in susceptibility to infections and mortality.

Infections account for 40% of the total disease burden in Pakistan. The most prevalent infections include tuberculosis, acute respiratory infections, and diarrheal diseases [3]. The estimated HIV prevalence among the general population is estimated to be below 0.2%, however, the last official prevalence survey was conducted in 2016, hence such estimates do not represent the true current situation. Nonetheless, the number of HIV cases has been steadily increasing, since according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) "*the HIV epidemic in Pakistan is following the Asian Epidemic Modeling trend i.e. the epidemic has nearly plateaued in people who inject drugs and, moved into the sexual networks from where a gradual spill-over into the general population through bridging populations is silently taking place*" [4]. Currently, HIV is not a major factor contributing to sepsis and related morbidity and mortality in Pakistan.

Local guidelines for sepsis in Pakistan, despite poor surveillance systems and data collection, are available [5]. At our institution, The Aga Khan University Hospital, Karachi, Pakistan, which is the largest tertiary care center in the country, sepsis accounted for about 1.3% of all admissions, with sepsis-associated mortality approaching 37% [6]. However, similar recent data from other tertiary care centers is unfortunately lacking. There is a dire need to bridge this gap in literature from Pakistan to improve sepsis care and outcomes. Hence, to the best of our knowledge, this is the first review of its kind from Pakistan, which aims to bridge the gap in scientific evidence by using available literature regarding incidence, risk factors, common causative agents, management, and outcomes of adult sepsis.

Material and methods

A literature review was conducted on PubMed and Google Scholar databases to find all relevant articles published in the past 20 years in English related to "Sepsis" "SIRS" "septic shock" "bacteremia" "MODS" "multi-organ failure" and "Pakistan" from 2003-2023. This was done in order to identify as many articles as possible since literature on sepsis is already scanty in Pakistan. 550 articles were screened from which relevant information was extracted for thorough review.

Results and discussion

Incidence and mortality

In 2017, a study by Rudd et al. [7] estimated that 48.9 million incident cases of sepsis were recorded worldwide with 11.0 million sepsis-related deaths, thus representing 19.7% (18.2-21.4) of all global deaths. The highest burden of incidence and mortality due to sepsis was unsurprisingly seen in developing regions such as South Asia and Sub-Saharan Africa. It is a matter of concern that, the global burden of sepsis continues to increase with the highest burden across regions which are least equipped to deal with it. However, it is to be noted that this study by Rudd et al. [7] attempts to stratify sepsis for countries, including Pakistan, using International Classification of Diseases (ICD) codes on death records. Most major healthcare facilities in Pakistan, including government and private sector hospitals, record cause of death manually—ICD codes are used only at a few developed centers. Manually written records are difficult to retrieve in Pakistan and are often not reliable since the commonest stated cause of death on such certificates is "cardio-pulmonary arrest". Preceding and predisposing events of mortality are often not mentioned either and important information on the cause of mortality is rarely captured. Furthermore, electronic health records are available at only a few, select centers and there is no national database, thus access to mortality data (albeit unreliable) across hospitals in Pakistan is quite difficult and mortality secondary to "implicit" sepsis, as quoted by Rudd et al. [7], is rarely captured at tertiary care centers. "Explicit" sepsis leading to death may get labeled as severe sepsis, septic shock, or multiorgan failure. In Pakistan where cholera is endemic, death from diarrheal disease, both in adults and children, may be caused by hypovolemic shock rather than sepsis [3]. The same may hold true for injuries, where blood loss may lead to death rather than sepsis itself. Such extrapolation may lead to overestimation of sepsis-related mortality in a country like Pakistan, where sepsis data is scarce and unreliable.

Comparing healthcare systems, one may assume that the outcome of sepsis would be significantly worse in Pakistan, as compared to that in developed countries. A study involving 229 patients at a tertiary care hospital in Karachi showed that 43% of patients fulfilled the SIRS criteria of sepsis, out of which 35% were diagnosed with severe sepsis or septic shock. Incidence of sepsis was highest in the non-operated group (52%), followed by emergency surgery group (43%) and elective surgery group (16%). This study also highlighted that mortality within the sepsis group was nearly three times (51%) higher as compared to the non-sepsis group (17.7%) [8]. Similarly, another study conducted at the same hospital in 2006-2007 (cohort of 99 patients admitted to ICU), found that 69% of enrolled patients had sepsis and 30% had septic shock. Overall mortality due to sepsis was 36.36% [6]. In Peshawar, a smaller city in the north of Pakistan, a prospective study conducted at a tertiary care center showed that out of 450 patients admitted to the hospital, 59.6% had sepsis; 59.3% had severe sepsis or septic shock with overall mortality of 40.7% [9].

From available literature, it is evident that sepsis-related mortality is higher in Pakistan in comparison to developed countries with better healthcare facilities. For example, a study conducted in Australia and New Zealand, reported sepsis-related mortality of 18.4% in 2012, while also showing a marked decrease in sepsis-related mortality rates over a span of 12 years [10]. Subsequently, while mortality rates of sepsis patients in high-income countries (HICs) have improved in recent decades, there is little evidence to support a similar trend in LMICs, indicating an urgent need to quantify trends in disease progression in order to tackle this healthcare burden.

Looking at regional data, studies from Pakistan seem to share similar sepsis numbers with other parts of Asia, where sepsis-related mortality is also prevalent, and compliance to sepsis bundles is poor—the latter also being true for most healthcare centers in Pakistan. Almost mirroring the statistics obtained from Pakistan, a study including 16 Asian countries, reported a hospital mortality of 44.5% due to sepsis and septic shock [11]. Hence, along with other Asian LMICs, sepsis continues to be an important cause of morbidity and mortality, with indicators worsening over time possibly secondary to increasing population, poverty, poor healthcare services, and rising resistance to antibiotics.

Factors associated with sepsis and sepsis-related mortality

Development and outcomes of adult sepsis seem to be contingent upon non-modifiable factors, such as age, gender, and comorbid conditions. They are related to several modifiable factors as well, such as length of hospital stay, site of injury, and type of surgery. However, there is an absence of widespread sepsis data with more sophisticated stratification, such as hospital department of presentation, type of procedure, etc. in developing countries. To this effect, in a study at a tertiary care center in Karachi, univariate analysis showed that age, APACHE II score, type of admission, diabetes mellitus, ischemic heart disease, chronic kidney disease, and general surgery were significant independent predictors of sepsis. On multivariate regression, female gender and non-operative admission were also found to be significant predictors of sepsis [8]. These conclusions are difficult to ratify in the context of Pakistan, because of the non-availability of any robust similar studies.

Increasing age has been implicated as a factor associated with increased incidence of sepsis and sepsis-related mortality. This associa-

tion was seen by a study conducted in Pakistan's capital city Islamabad, where 55.2% of sepsis patients were from 71-100 years of age, while 29.6% of patients were between 56-70 years and only 15.2% were less than 55 years of age. Furthermore, more than half of expired patients were found to be over 70 years of age [12]. A retrospective observational study in another metropolitan city, Karachi, found age (per year increase) to be a significant factor influencing sepsis (odds ratio [OR] = 1.037) [8]. In contrast, in a study conducted in Peshawar, although the median age of sepsis patients was 58 years, the patient's age was not found to be a significant outcome predictor [9]. Therefore, it seems that although sepsis may mostly affect those who are above 50 years of age and may have a worsening prognosis with increasing age, more studies are required from Pakistan to show this association to be significant. Internationally, sepsis is a leading cause of prolonged hospitalization of the elderly, and it has been postulated that this is likely due to elderly patients having a higher incidence of comorbidities such as obesity, diabetes, and dementia [13]. Nonetheless, most international sepsis studies have shown age to be correlated to sepsis-related mortality regardless of the region. Even in HICs like Europe, the incidence of sepsis has been shown to increase sharply in octogenarians [14].

In the 2-year retrospective study in Karachi, comorbid conditions like diabetes mellitus, ischemic heart disease, and chronic kidney disease were positively associated with sepsis [8]. Supporting this, an Islamabad study found a large proportion of patients (60%) to have sepsis-related mortality in those who had DM, HTN, and/or IHD [12]. However, in Peshawar, comorbid conditions were found to minimally contribute to poor sepsis outcomes (OR = 1.007 [0.0985-1.030]) [9]. Nonetheless, the conclusions from the former studies are in line with those noted around the world—comorbidities are regularly noted as predictors of sepsis in medical literature, and the number of comorbidities has been shown to enhance the risk of sepsis.

Studies on the correlation of sepsis outcomes with gender show conflicting results. A study conducted in Karachi in a surgical ICU reported higher sepsis-related mortality in females [8]. Yet, a study from Peshawar did not reflect any association between mortality and female gender (OR = 1.070 [0.655-1.749]) [9]. Interestingly, another sepsis study looking at medical ICU patients from Karachi (54% males, 46% female with similar age distribution) reported a 70% greater mortality in men, which was related to higher interleukin-6 levels [15]. While the influence of gender-related outcomes in sepsis remains unclear, the global age-standardized sepsis incidence in 2017 was found to be higher among females [7]. Although studies from Pakistan failed to accurately determine the effect gender has on sepsis and sepsis-related outcomes, most clinical studies conducted globally have also been unable to show a consistent difference in sepsis outcomes attributable to gender.

Etiology and source of sepsis infection

Sepsis may develop after a nosocomial infection, or in a place like Pakistan, where access to competent healthcare is often delayed or not available, patients may present with sepsis after common community-acquired infections. The commonest source of sepsis in most studies in Pakistan is the respiratory tract. Ullah et al. [9] found that the most common cause of severe sepsis in their cohort was pulmonary infections (42.2%), followed by urinary tract infections (18.7%). Similarly, in 2013 Siddiqui et al. [6] concluded that the commonest site of infection leading to sepsis was also the respiratory tract (48%). Another study has shown that the most common infection documented in sepsis-related deaths was pneumonia [12]. Apart from this, soft tissue infections, abdominal infections, and those arising from indwelling catheters were also noted as leading causes of sepsis [9,12]. Yet interestingly a recent study conducted by Raza et al. [16] in a population of 653 septic shock patients admitted to a quaternary care hospital in Karachi, found that the most common source of infection in septic shock patients was unspecified (43.6%) followed by respiratory origin (24.7%). This does not differ significantly from what has already been previously noted in sepsis studies around the world, where respiratory origins of sepsis are still the leading source, followed by genitourinary and abdominal sources [17].

Looking at the etiology, gram-negative organisms are more commonly identified as a cause of sepsis in Pakistan. The recent septic shock study by Raza et al. [16] found that most patients had negative cultures (58.7%), but among those with positive cultures, gram-negative organisms were most commonly isolated (19.6%). In another study from Karachi, out of a cohort of 99 patients, 49 were culture-positive, showing a higher frequency of gram-negative (59%) compared to gram-positive organisms (28%) [8]. Concurring with this, Ullah et al. [9] found that *Escherichia coli* (*E. coli)* was the most commonly observed causative agent, followed by *Candida albicans, Acinetobacter baumannii* (*A. baumannii)* and *Methicillin-Resistant Staphylococcus Aureus*. They also concluded that having a positive blood culture was more likely to be associated with mortality (OR = 1.964 [1.101-3.503]). Moreover, they found that having a positive urine culture (19.3% of which were *E. coli)* had lower odds of mortality compared to negative urine cultures (OR = 0.351 [0.188-0.656]). This is in contrast with another study at a public sector hospital in Pakistan, which showed an association of a positive *E. coli* culture with higher mortality. The latter study found *E. coli* to be the most commonly isolated organism in sepsis, with 44.5% positive urine cultures [18]. This increase in mortality may reflect delay in diagnosis of infection and/or failure to implement appropriate antibiotic and fluid therapy at the onset of urosepsis.

Similar to scientific evidence in Pakistan, international literature has also reflected our findings. A study conducted at a center in Colombia showed poor outcomes in sepsis patients where *E. coli* was exclusively isolated in blood culture, as opposed to those where *E. coli* was isolated in urine culture with or without bacteremia [19]. Furthermore, a sepsis study conducted in India reports that the predominant infection site leading to sepsis is the respiratory tract and the most frequently isolated organisms were Gram-negatives. *A. baumannii* was the most commonly isolated organism; this is reflective of predominantly hospitalized patients who may have developed sepsis after prolonged ICU stay [20].

Several other etiologies can also present as sepsis but may be treated differently. Regarding viral etiologies in Pakistan, there have been high cases of dengue, Crimean-Congo fever, hepatitis, measles, and polio over the last decade [21]. Given the recently catastrophic flooding in the country last year, cases of water-borne diseases, such as dengue and leptospirosis, have consequently risen even further. Although respiratory and cerebral spinal fluid BioFire has recently become available in Pakistan, extensive data for viral diagnostics are not widely available. Pakistan also has a high burden of malaria- luckily identification of complicated malaria is not difficult because of the widespread availability of point-of-care testing. However, this has consequently led to a widespread, unchecked empiric use of artemisinin-based regimens for febrile illnesses in the country. Furthermore, the true burden of fungal infections remains unknown in the country, with an estimated (1.78%) affected by a serious fungal infection according to a recent study [22].

Susceptibility of sepsis-causing organisms

Dealing with sepsis and antimicrobial resistance (AMR) has been called "two sides of the same coin". In view of this, we used data from the Pakistan AMR Network (PARN) to evaluate how antibiotic susceptibility varied in different tertiary healthcare hospitals in different cities of Pakistan over the past several years. PARN is a national organization that aims to provide central information regarding AMR in the country, create awareness, and share protocols with respect to AMR and infection control.

Our effort was hampered by the fact that such data is not available consistently over the years for each hospital featured and where available, it is not always stratified with reference to individual antibiotics. To adjust for this, inpatient data from at least one hospital from three major cities (Karachi, Lahore, and Islamabad) was used for the purpose

Table 1
Susceptibility data of *Acinetobacter* species and *Escherichia Coli* from 2015-2022 across different hospitals in Pakistan.

Acinetobacter species – Percentage sensitivities						
City	Hospital (year)	%Ampicillin (# of isolates)	%Ceftriaxone (# of isolates)	%Amikacin (# of isolates)	%Meropenem (# of isolates)	%Ciprofloxacin (# of isolates)
Islamabad	SIH (2015)	-	5 (-)	16 (-)	8 (-)	8 (-)
Lahore	SKMCH (2020)	-	13 (123)	56 (123)	48 (123)	45 (123)
	LGH (2022)	18 (2927)	8 (2927)	49 (2927)	41 (2927)	23 (2927)
Karachi	AKUH (2020)	-	-	28 (489)	14 (461)	15 (467)
	JPMC (2020)	-	-	48 (63)	-	70 (63)
Escherichia Coli – Percentage sensitivities						
City	Hospital (year)	%Ampicillin (# of isolates)	%Ceftriaxone (# of isolates)	%Amikacin (# of isolates)	%Meropenem (# of isolates)	%Ciprofloxacin (# of isolates)
Islamabad	SIH (2015)	3 (-)	17 (-)	92 (-)	93 (-)	21 (-)
Lahore	SKMCH (2020)	1 (1856)	15 (1856)	95 (1856)	79 (1856)	20 (1856)
	LGH (2022)	6 (2537)	20 (2537)	74 (2537)	61 (2537)	22 (2537)
Karachi	AKUH (2020)	6 (2017)	20 (2021)	96 (2021)	82 (1301)	25(2024)
	JPMC (2020)	-	78 (121)	16 (121)	-	74 (121)

AKUH, Aga Khan University Hospital; LGH, Lahore General Hospital; JPMC, Jinnah Postgraduate Medical Centre; SIH, Shifa International Hospital; SKMCH, Shaukat Khanum Memorial Cancer Hospital; #, number; -, not available.

of this review. Furthermore, all data was taken from 2015-2022 to compare the most recent data available. The data for two gram-negative rods, Acinetobacter species, and *E. coli*, is shown in Table 1. Only two have been chosen for purposes of brevity as they were found to be implicated most often in sepsis patients in Pakistan. The antimicrobials have been chosen to represent a class each (amikacin [AMK]; aminoglycosides, ampicillin [AMP]; penicillin, ceftriaxone [CRO]; cephalosporins, meropenem [MEM]; carbapenems, ciprofloxacin [CIP]; quinolone).

A. baumannii is a common nosocomial organism, mostly acquired by patients with prolonged hospitalization or ICU stay. It was the second most common microbial isolate from a sepsis cohort in a study from Peshawar [9]. Frequency of isolation may just be reflective of local prevalence in the healthcare facility rather than the propensity of the organism to cause infection leading to sepsis. It may also relate to length of hospitalization and ease of colonization because of less robust infection prevention and control practices. Undoubtedly, AMR in sepsis patients is a cause of concern worldwide, shared by both HICs and LMICs. For example, a study in Indonesia demonstrated that over 50% of bacterial isolates were resistant to the six most frequently used antibiotics (levofloxacin, ceftazidime, ciprofloxacin, cefotaxime, ceftriaxone, and erythromycin) [23]. This corresponds to the high levels of resistance we have noted to ceftriaxone in Pakistan (Table 1).

In 2019, Kenyan researchers showed *A. baumannii* displayed high susceptibility to amikacin (77%) and poor susceptibility to ciprofloxacin (69-76%) and meropenem, a situation similar to that in Pakistan [24]. Tewari et al. [25] also described the increasing incidence of MDR *A. baumannii* across the world, with a 53.3% sensitivity to carbapenems in their study. This study, and several more from India and Vietnam, have shown *A. baumannii* to be susceptible to tigecycline [26]. Currently, limited data from Pakistan shows similar results.

While *A. baumannii* susceptibility pattern may be reflective of antibiotic use in healthcare facilities, the susceptibility pattern of *E. coli* may be more reflective of antibiotic burden in the environment. Release of pharmaceutical waste in the environment and the use of antibiotics in animal feed may all be contributory. An exhaustive literature review across many countries concluded that American strains had the lowest resistance to ciprofloxacin (0.008%), as compared to Southeast Asian strains (43%) [27]. With unrestricted over-the-counter availability of antibiotics and over 160 brands of ciprofloxacin available in the market in Pakistan, a large majority of gram-negative organisms are now resistant to the agent. Most *E. coli* strains remain susceptible to amikacin.

It is important to note that this review of antimicrobial susceptibility data is by no means exhaustive; the aim is to underscore the challenge that AMR poses, especially in our part of the world, and emphasize how it will determine empiric and definitive use of antibiotics in sepsis and septic shock in the future.

Sepsis guidelines

In the context of Pakistan's healthcare setting, Hashmi et al. [5] have outlined sepsis management recommendations, stratifying them according to the facilities available in different types of hospitals, which they divided into three categories: basic, intermediate, and tertiary. They enlisted fluid resuscitation, vasopressors, maintaining oxygen saturation ≥90% oxygen, non-invasive ventilation or mechanical ventilation with lung protective strategies, and prompt administration of antibiotics as essential interventions. Along with this, they indicated a need to keep upper blood glucose ≤180 mg/dl, daily use of pharmacoprophylaxis against venous thromboembolism, use of stress ulcer prophylaxis, and the need to undertake other complication-specific measures. These guidelines are revised, and an updated version is expected soon.

Regrettably, in developing countries like Pakistan, compliance with such guidelines remain poor, and sepsis-related statistics do not seem to be improving significantly. A multi-national survey across Asia found low compliance rates to resuscitation (7.6%) and management bundles (3.5%) [11]. There are many reasons for this and in a 2018 paper evaluating obstacles to sepsis management in LMICs, the authors highlighted many factors, some of which are applicable to Pakistan. The fact that the sepsis burden is simply much higher here and the healthcare resources limited, that sepsis guidelines are invariably drawn from HICs and are not always generalizable to all LMICs, that target populations (with their age and comorbid distributions), pathogens and AMR status vary greatly across different regions and that resource-poor settings rarely have a culture of documentation and research which would provide the scaffolding for setting-specific and cost-effective guidelines to be drawn up. It follows that sepsis bundles are more likely to be followed in HICs and in institutions with academic affiliations.

Moving forward

Like most LMICs, Pakistan faces the challenge of poor primary healthcare infrastructure and scarce secondary and tertiary care facilities, affecting both timely diagnosis of sepsis and appropriate management ultimately affecting sepsis survival. All tertiary care hospitals have microbiology labs on site, with the basic capacity of performing cultures in addition to other routine tests. Furthermore, high-quality tests are available at private facilities (a few of which are College of American

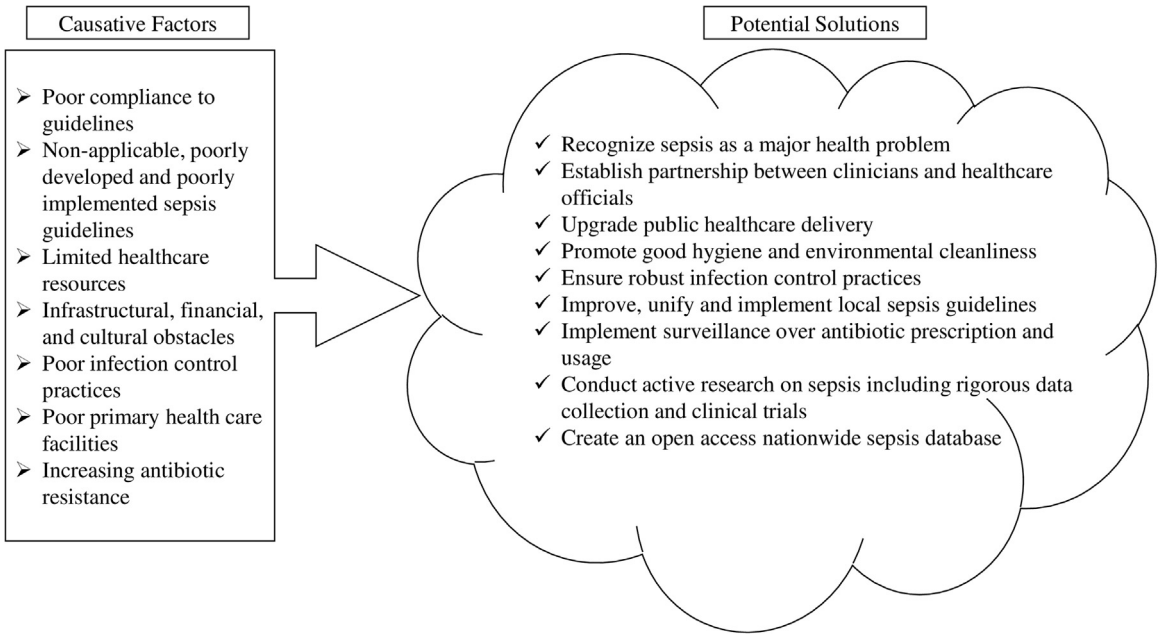

Figure 1. Causative factors and potential solutions for sepsis disease burden in Pakistan.

Pathologists accredited). However, once again these are presumably not optimally utilized because of cost.

Figure 1 (created by the authors of this study) summarizes common causative factors and potential solutions for the sepsis disease burden in Pakistan. Ullah et al. [9] remarked that the higher mortality rates in Pakistan due to sepsis can in part be attributed to the fact that the quality of primary care here is patchy and early recognition of the severity of illness is often missed. The delay in seeking medical attention is due to a motley of infrastructural, financial, and cultural obstacles that require a direct redressal of wealth inequalities and upgradation of public healthcare delivery. The latter would include stealthily staffed primary healthcare centers with strong referral systems to expedite management.

There is also an obvious need to recognize sepsis as a major health problem at a national level and for professional advocacy regarding its management. Governments, provincial and federal, must ensure that community causes of infection are reduced; and that there is promotion of good hygiene and environmental cleanliness. Also essential is ensuring that there are robust infection control practices in all healthcare centers, which is unfortunately not the case. It has also been shown via a survey that there are considerable gaps in the knowledge of doctors and nurses when it comes to healthcare-associated infections [28]. Needless to say, this can often lead to critical lapses in sepsis identification and management.

Increasingly, the need for sepsis-related education is being recognized. Sepsis and septic shock are almost invariably part of undergraduate curricula. At our hospital, undergraduate medical students are required to rotate through pediatric and adult intensive care and high-dependency units as part of their training, ensuring that they observe and learn the management of sepsis. Additionally, sepsis care guidelines were published by the Medical Microbiology and Infectious Diseases Society of Pakistan [5]. In 2014, the Pakistan Society of Critical Care Medicine, formed a multidisciplinary committee of physicians managing critically ill patients in teaching and non-teaching hospitals of Karachi at government and private healthcare setups. The thirteen-member committee consisted of eight anesthesiologists, three pulmonary and critical care physicians, one full-time intensivist, and one pediatric intensivist—all heading the ICUs in their respective hospitals. The guidelines they formulated have been widely disseminated to use for sepsis care across Pakistan. However, work remains to be done, since a recent survey found that only 37.9% of physicians in Pakistan had adequate theoretical knowledge of sepsis [29]. Yet, they noted that more recently graduated trainees showed significantly better knowledge, which is encouraging.

The challenge for Pakistan is compounded by poor diagnostics and AMR. In 2018 the Pakistan Global Antibiotic Resistance Partnership launched a report that highlighted several troubling findings that rooted the AMR seen in Pakistan: an unnecessarily large number of registered products, misleading advertisements, polypharmacy, non-qualified practitioners (“quacks”) availability of over-the-counter drugs without prescription, an occasional bias toward costly broad-spectrum antibiotics, lack of surveillance systems, and widespread use of antibiotics in poultry, animals, and agriculture [30]. We have already shown that AMR is increasing in Pakistan, and the aforementioned are important reasons contributing to this concerning rise. To address these, there must be a partnership between clinicians, veterinarians, public health officials, researchers, and policymakers.

For such partnerships to be fruitful, there must be attempts to develop a rigorous culture of data collection, including clinical trials regarding sepsis incidence, etiology, mortality, predictors, and management. Although we attempted to extract whatever sepsis data was available, we were unable to do a robust sepsis data analysis due to the lack of existing literature from Pakistan. We propose that there be a central, standardized, meticulously updated, and open-access database for the collection of sepsis patients’ and AMR data. It is only when this is available that data-driven interventions that are innovative and suited to a low-resource setting can be designed and implemented.

Conclusion

Adult sepsis is a burden on all healthcare setups, particularly in LMICs such as Pakistan, leading to morbidity and mortality in all age groups. Many of the factors which affect morbidity, mortality, and cost of care are amenable to interventions. There is a dire need for a concerted effort to implement simple, cost-effective, and context-specific guidelines regarding the diagnosis and management of sepsis in Pakistan. We believe this can be best done when sepsis-related data in Pakistan is rigorously collected and analyzed, and that data is continuously used to assess the effects of guideline compliance on outcomes and to formulate and refine new strategies to address emerging problems.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

HAR and BJ take responsibility for data integrity and accuracy of the provided data. HAR, BJ, and APH contributed to study concept and design. MMK and MHA contributed to the creation of the table and figure. All authors participated in the write-up of the final manuscript.

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