Review Article on Pediatric Critical Care

Challenges in pediatric post-sepsis care in resource limited settings: a narrative review

Matthew O. Wiens[1,2,3], Niranjan Kissoon[1,4], Liisa Holsti[5]

[1]Center for International Child Health, BC Children's Hospital, Vancouver, BC, Canada; [2]Department of Anesthesia, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada; [3]Mbarara University of Science and Technology, Mbarara, Uganda; [4]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada; [5]Department of Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, BC, Canada

Contributions: (I) Conception and design: All authors; (II) Administrative support: MO Wiens, N Kissoon; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Matthew O. Wiens, PhD. Center for International Child Health, BC Children's Hospital, Vancouver, BC, Canada.
Email: mowiens@outlook.com.

Objective: The objective of this narrative review is to outline the current epidemiology and interventional research within the context of sepsis recovery, and to provide a summary of key priorities for future work in this area.

Background: Morbidity and mortality secondary to sepsis disproportionately affects children, especially those in low- and middle-income countries (LMICs), where over 85% of global cases and deaths occur. These regions are plagued by poorly resilient health systems, widespread socio-economic deprivation and unique vulnerabilities such as malnutrition. Reducing the overall burden of sepsis will require a multi-pronged strategy that addresses all three important periods along the sepsis care continuum - pre-facility, facility and post-facility. Of these aspects, post-facility issues have been largely neglected in research, practice and policy, and are thus the focus of this review.

Methods: Relevant data for this review was identified through a literature search using PubMed, through a review of the citations of select systematic reviews and from the personal repositories of articles collected by the authors. Data is presented within three sections. The first two sections on the short and long-term outcomes among sepsis survivors each outline the epidemiology as well as review relevant interventional research done. Where clear gaps exist, these are stated. The third section focuses on priorities for future research. This section highlights the importance of data (and data systems) and of innovative interventional approaches, as key areas to improve research of post-sepsis outcomes in children.

Conclusions: During the initial post-facility period, mortality is high with as many children dying during this period as during the acute period of hospitalization, mostly due to recurrent illness (including infections) which are associated with malnutrition and severe acute disease. Long-term outcomes, often labelled as post-sepsis syndrome (PSS), are characterized by a lag in developmental milestones and suboptimal quality of life (QoL). While long-term outcomes have not been well characterized in resource limited settings, they are well described in high-income countries (HICs), and likely are important contributors to long-term morbidity in resource limited settings. The paucity of interventional research to improve post-discharge outcomes (short- or long-term) is a clear gap in addressing its burden. A focus on the development of improved data systems for collecting routine data, standardized definitions and terminology and a health-systems approach in research need to be prioritized during any efforts to improve outcomes during the post-sepsis phase.

Keywords: Sepsis; post-discharge mortality; low- and middle-income country (LMIC); pediatrics; infection

Submitted Nov 14, 2020. Accepted for publication Apr 23, 2021.
doi: 10.21037/tp-20-390
View this article at: http://dx.doi.org/10.21037/tp-20-390

Introduction

Sepsis, which is life threatening organ dysfunction due to an infection, is an important cause of childhood morbidity and mortality worldwide. Sepsis can be caused by any pathogen, including bacteria, fungi, parasites and viruses including the SARS-CoV-2 virus.

Morbidity and mortality secondary to sepsis disproportionately affects children especially in low- and middle-income countries (LMICs) (1,2). Of the nearly 50 million cases and 11 million deaths secondary to sepsis in 2017, 20 million cases and nearly 3 million deaths occurred in children less than 5 years of age (1). Over 85% of cases and deaths occur in LMICs, regions which are plagued by poorly resilient health systems, widespread socio-economic deprivation and unique vulnerabilities such as malnutrition. These challenges, however, are not unique to (nor always present in) LMIC settings as systems and population vulnerabilities exist even in high-income countries (HICs) (3). In recognition of the global disparities in sepsis incidence and mortality, it is obvious that while sepsis is a syndrome due to infectious diseases, the burden and outcomes from sepsis are strongly influenced by geopolitical, economic and social undercurrents. Thus, addressing issues of sepsis calls for a broad coalition of clinicians, policy makers and civil society (4).

Acknowledging both the widespread burden and the complex nature of sepsis, the World Health Assembly and the World Health Organization declared sepsis as a global health priority through the adoption of a resolution to improve prevention, diagnosis, and management of sepsis (5). With this resolution, unanimously adopted in 2017, a renewed focus on sepsis, a disease with previously poor public recognition and understanding, has begun to take shape. This included, among many actions, establishing priorities in sepsis in infants and children. These goals must be integrated into the overarching objectives related to child health outlined in the Sustainable Development Goals (SDGs) (6). While the goals related to health (SDG #3) provide specific targets for neonatal and child survival, these goals will not be achieved without broad strategies that also address other SDG which ultimately influence health outcomes. For example, optimal health seeking, which is critical to sepsis management, is deeply influenced by poverty, education and infrastructure (SDGs #1, #4, and #9), while recovery is markedly affected by malnutrition (hunger) and access to clean water and sanitation (SDGs #2 and #6).

Reducing the overall burden of sepsis will require a multi-pronged strategy that addresses all three important periods along the sepsis continuum—pre-facility, facility and post-facility. Pre-facility aspects are largely community focused, with prevention, early recognition and effective referral being the primary areas of focus. Facility-focused aspects of sepsis include triage, clinical management and discharge. Post-facility aspects of sepsis include the immediate convalescent period as well as the management of longer-term sequelae. Of these aspects of sepsis care, post-facility issues have been largely neglected in research, practice and policy (7). The reasons for this are complex, but a lack of recognition of the burden of post-discharge morbidity and mortality is likely to play an outsized role.

The post-facility sequelae of sepsis can be divided into both short- and long-term. During the initial post-facility period, mortality is high with as many children dying during this period as during the acute period of hospitalization mostly due to recurrent illness (including infections) which are associated with malnutrition and severe acute disease (7,8). Long-term outcomes, increasingly labelled as post-sepsis syndrome (PSS) (9), often characterized by a lag in developmental milestones and suboptimal quality of life (QoL) are not well characterized in LMICs, but have been well described in HICs (10,11).

This aims of this narrative review are to outline the challenges among survivors of acute sepsis in LMIC settings, review the current research, outline research gaps and propose recommendations for the research priorities.

Literature search

In this narrative review, the authors relied of three sources of evidence from which to identify relevant articles to include. First, the authors performed a literature search using PubMed. MeSH terms including “developing country”, “sepsis”, “pediatrics”, “child health”, “child development”, “developmental disabilities”, “follow-up

studies", "patient discharge", "continuity of care" and "quality of life" as well as keywords including "post-sepsis syndrome", post-discharge mortality", post-discharge morbidity" and "post-discharge readmission". This was not a systematic search as there was no formal methodology for reviewing abstracts, choosing full-texts or the extraction of specific, predefined data.

The second source of evidence used were references identified through the citations of included studies and systematic reviews. Finally, the authors used their own repositories of articles which were relevant for this review.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tp-20-390).

Section 1: short-term outcomes among sepsis survivors

Sub-section 1: epidemiology

Data on post-discharge mortality is scant in many LMICs, though it has been increasing significantly over the last several years (7,8,12-17).

Studies of post-discharge mortality are generally not specific to sepsis, in part due to the difficulties in applying sepsis criteria in LMIC settings, and the strong focus on specific disease states, such as malaria, pneumonia, diarrhea and malnutrition, within child-health research. However, most of these populations would likely consist of children either with sepsis, or at high risk of developing sepsis. Indeed, nearly 90% of children met the international consensus conference sepsis criteria in a study from Uganda which included children under 5 years of age who were admitted with a suspected infection (18). The most recent systematic review on pediatric post-discharge mortality included several disease populations, including pneumonia, malaria/anemia, diarrhea, malnutrition and also general admissions or admissions due to any suspected infectious disease. Despite the significant heterogeneity in these populations, and differences in their study designs, there is consistency within several aspects of their results. While the rates of post-discharge mortality vary significantly, these rates are often similar to rates of in-hospital mortality (7). In this systematic review, studies demonstrated that illness severity is tied to the persistence of vulnerability following hospital discharge. Indeed, the risk factors for post-discharge mortality are often related to illness severity, hypoxemia, anemia, abnormal coma score, and recent prior admission. HIV is the key co-morbidity associated with post-discharge risk, though it remains a risk factor of relatively low prevalence. Malnutrition (as reflected in anthropometry measures), is the most important risk factor for post-discharge mortality for two main reasons. First, because of its strong independent association with mortality after discharge, and second because it is a highly prevalent co-morbidity, thus affecting a substantial number of children living in settings where post-discharge mortality is common. A growing body of literature on the complex interactions between malnutrition, immunity and infection is beginning to emerge (19,20). It is well established that environmental enteric dysfunction, a disorder of chronic intestinal inflammation, is common among children in LMIC settings. Environmental enteric dysfunction leads to a vicious cycle when persistent exposure to poor hygiene environments leads to immune paralysis, recurrent infection and continued intestinal inflammation. Additional work on the intestinal microbiota of malnourished and well-nourished children has suggested an important link between its establishment during gestation and early infancy and outcomes later in childhood (19,21).

The link between sepsis and post-discharge mortality was also clearly demonstrated in a recent study of children admitted with severe acute malnutrition, most of whom had an admission diagnosis of either pneumonia or diarrhea (22). In this nested case-control study from Kenya, a sepsis-like immunopathogenic profile, at the time of discharge, was noted to be common among children who died early during the post discharge period (cases), compared to those who survived without requiring readmission for at least 1 year following discharge (controls).

One key observation in studies of post-discharge mortality is that most post-discharge deaths do not occur during a subsequent hospital readmission, but rather at home, or occasionally in transit while seeking care (7). Low levels of maternal education (level of schooling achieved) is associated with a higher probability of death outside of a health facility (23). Care seeking during a recurrent illness is hampered by financial constraints as well as the complex pathways to care due to poor continuity of care between communities and health facilities. Mothers of vulnerable children are often tasked with navigating diverse challenges at many different levels during the care-seeking process, including at the individual, household and facility level (24). Therefore, efforts to address out-of-hospital deaths must work to equip caregivers, who are generally mothers, to properly navigate the health system. At the same time the

Table 1 Randomized controlled trials of pharmacologic interventions during the post-discharge period

Study	Country/countries	Population	Intervention	Outcome	Effectiveness demonstrated	Outcome rate/observed reduction
(26)	Kenya	1,778 malnourished children discharged following infection	Daily co-trimoxazole ×6 months	Mortality	No	Approx. 15% at 1 year in both groups
(27)	Uganda/Malawi	3,986 children with severe anemia discharged from hospital	Multi-nutrient intervention with or without co-trimoxazole ×3 months	Mortality	No	Approx. 8% at 6 months in all groups
(28)	Kenya	1,400 children <5 discharged from hospital	Azithromycin ×5 days	Mortality or readmission	Ongoing	NA
(29)	Malawi	1,414 discharged and severe malarial anemia	Intermittent preventative therapy with artemether lumefantrine ×2 months	Mortality or readmission	Yes, but limited to first 3 months	Adjusted protective efficacy: 31% (95% CI: 5–50)
(30,31)	Kenya/Uganda	1,049 discharged and severe malarial anemia	Intermittent preventative therapy with dihydroartemisinin-piperaquine ×10 weeks	Mortality or readmission	Yes, but limited to first 3 months	HR: 0.65 (95% CI: 0.54–0.78)

health system must become more responsive to the needs of families with which it interacts.

While post-discharge mortality among children with sepsis is observed most acutely in LMIC settings, issues of persistent vulnerability are observed in both high- and low-income country settings. In the United States, for example, even among children with no known comorbidities, approximately 15% are readmitted within the first 6 months following an episode of severe sepsis, though death is uncommon (25). Such observations point to both the generalizability of this vulnerability as well the potential preventability of mortality.

Sub-section 2: interventional research

No studies have evaluated interventions to improve post-discharge outcomes among children specifically diagnosed with sepsis, though several randomized controlled trials have enrolled children where a significant proportion would have been septic. These trials have primarily focused on pharmacologic agents (generally antibiotics/antimalarials) to improve post-discharge outcomes, though only those therapies focused on post-discharge malaria prevention have shown any promise (*Table 1*).

Studies attempting to address health system and social vulnerability challenges as a means to improve post-discharge outcomes are few despite recognition of their importance and association with improved post-discharge outcomes (23,24,32). A small proof of concept study evaluated a discharge kit, which was comprised of (I) education, (II) simple health incentives (soap, mosquito net, health pamphlets) and a post-discharge follow-up referral. This study demonstrated a statistically significant, three-fold increase in post-discharge health seeking and a doubling of post-discharge readmissions, likely secondary to improved health seeking, and also showed a non-significant 30% reduction in mortality. In addition, this same research group developed risk-stratification models to apply this intervention to high-risk children in a future study (33,34).

Section 2: long-term outcomes among sepsis survivors

Sub-section 1: epidemiology

Much of the research reporting the effects of sepsis on infants and children worldwide has focused on preventing mortality. However, recognition of the true burden of sepsis can only be understood and ameliorated when post-sepsis morbidity is accurately documented and rehabilitation is provided as needed (35). In adults, PSS is now recognized as a cluster of multisystem, physical, immunological, cognitive, adaptive and psychological changes that persist, for some, even 10 years post-hospitalization (9). Indeed, as many as 50% of adults who survive sepsis report persisting negative impacts on cognition and function, as well as psychological

deficits and worsening medical conditions, all of which can last months to years following initial recovery (36).

While the reporting of PSS is becoming more frequent in adults, research reporting long-term health and QoL outcomes following sepsis in infants and children is beginning to grow from well-resourced countries. For example, in HICs, research describing long-term neurodevelopmental outcomes in preterm infants who experience early or late on-set sepsis while in the neonatal intensive care unit (NICU) is substantive enough that systematic reviews have been possible (37,38). Very low birth weight infants who have either early or late-on-set, culture proven sepsis from a variety of pathogenic sources are at higher risk for poor post-NICU physical growth, and for cognitive, motor (including cerebral palsy), visual and auditory impairments up to school age (37,38). Even though this reporting includes two systematic reviews, more recent long-term follow-up data on neonatal neurodevelopmental outcomes following sepsis is lacking.

However, research on long-term outcomes in LMIC settings, where neonatal sepsis prevalence is the highest, is very sparce. To the best of our knowledge, only two studies have reported specifically on neurodevelopmental outcomes in infants who suffered from sepsis in the neonatal period in LMICs. In a small rural Kenyan sample of term born infants, compared to controls, those who had sepsis had poorer gross motor/eye-hand coordination difficulties at 2 years of age (39). In Turkey, in another small cohort of very low birthweight infants assessed at 4–6 years of age, those who had had sepsis were more likely to have low cognitive scores and a higher prevalence of hyperactivity (40).

Unlike systematic long-term multidisciplinary follow-up of neonatal patients in HICs, long-term follow-up of pediatric sepsis survivors is not yet routine even in HICs. Nevertheless, what is known indicates a high and long-lasting burden of adverse outcomes. For example, in HICs, children admitted to the pediatric intensive care unit (PICU) for sepsis and assessed 3–6 months post-discharge showed lower IQ (albeit scores were within the normal range) and verbal recall than healthy control children; teachers also reported greater deterioration in academic and classroom performance (41). In a study evaluating post-sepsis effects in children approximately 1 year post-illness, researchers found that 42% of children had moderate or severe permanent sequelae including psychosocial, motor, or sensory changes (42). More recently, in addition to adverse neurodevelopmental outcomes, changes in QoL scores of survivors of pediatric sepsis have been reported (43). In the short-term, 3 months post septic shock, greater illness severity was associated with poorer health-related QoL (HQoL) scores with these poorer outcomes affecting over 1/3 of children; these changes persisted for at least one year post discharge (10,11).

Long-term data specific to childhood neurodevelopmental and HQoL outcomes in LMICs is lacking. The only study to report post-discharge data is found in a global study of outcomes 28 days following pediatric sepsis, 45% of children were reported to have mild-severe disability; 1 in 5 children had a new functional disability (44). However, this study reported functional outcomes by combining HICs and LMICs together and 28 days after infection is too short to qualify as "long-term" to fully examine lasting sequelae.

Taken together, the data which is available indicate that infants and children who survive sepsis are at very high risk for developing permanent impairments that impact their function and QoL. Yet, the full societal burden remains largely unknown because we do not have systematic, long-term, detailed developmental information on most pediatric survivors of sepsis. What is available is from small regions within select HICs, is short-term and/or is often missing key aspects of development (e.g., motor, school, QoL outcomes). Furthermore, we know little about how sepsis specifically impacts neurodevelopment and QoL in infants and children in LMICs where health systems differ substantially, access to high quality health care and education is challenging and poverty adds to poor developmental outcomes.

Sub-section 2: interventional studies

The first step to effective post-sepsis developmental and educational intervention is timely and accurate identification of post-sepsis developmental morbidity. A relatively clearer picture of the long-term impact of neonatal sepsis in HICs is possible largely because of the availability of multidisciplinary follow up programs, and national and international neonatal networks (e.g., Canadian Neonatal Network, National Child Health and Human Development Neonatal Research Network) which have been established and have been data sharing for over 20 years. More health care providers are recognizing the importance of providing in-hospital access to rehabilitation services and long-term follow-up to survivors of pediatric intensive care, generally (45). As these programs and new networks emerge, it will be important that they include sepsis as its own diagnostic category for pediatric PICU survivors.

Moreover, to the best of our knowledge, no research is

available describing the efficacy of providing in-hospital or post-hospital rehabilitation to infants and children diagnosed specifically with sepsis, though these priority areas have been outlined and implied in the World Health Assembly sepsis resolution (5,46). Thus, how best to provide rehabilitation services to neonates and children with sepsis requires immediate attention (WHO Global Disability Action Plan 2014–2021). Indeed, according to the United Nations Convention on the Rights of People with Disabilities (CRPD), access to timely, well-resourced rehabilitation care is considered a basic human entitlement (47), and it is a global health priority (48). In a recent survey, a majority of physicians working in HIC PICUs reported a lack of guidelines for providing PICU-based rehabilitation; nevertheless, even without evidence supporting efficacy, the majority already consulted rehabilitation professionals regularly for individual cases (45).

Integrated, systems-based approaches to understanding the broader, global human resource needs for access to best practice post-sepsis rehabilitation are needed. For example, developing international system standards for classifying these resources has begun so that global monitoring and development can take place (49). Next, providing stronger evidence related to efficacy of rehabilitation post-sepsis is required. In a systematic review, researchers found that for post-hospital rehabilitation across all age groups and conditions, there remains limited empirical studies and limited engagement of researchers from LMICs reporting outcomes of rehabilitation community-based services, which are purported to be the best way to provide such care (50).

In addition, developing, implementing, scaling up and evaluating evidence-based programs for early, low-cost screening of neurodevelopmental status and HQoL at hospital discharge and referral to follow-up are needed (51). While rehabilitation centers may be more common in HICs and effective preventative programs do exists for some populations, such as preterm infants (52), establishing multisite, community run clinics in LMICs show promise for monitoring development in high risk infants and children (53). Moreover, community-based child care centers may offer opportunities for access to rehabilitation services for children post-sepsis (54).

Section 3: priorities for future research

Sub-section 1: sepsis recognition and data systems

The definition of sepsis is widely accepted among experts: Sepsis is the life-threatening organ dysfunction caused by a dysregulated host response to infection. However, how to best operationalize this definition has been much more challenging, especially in resource limited settings where sepsis occurs frequently (55). The 2005 pediatric consensus criteria for sepsis are the most recent and broadly accepted criteria for pediatric sepsis, though these are not easily operationalized in many settings where septic children present as they call for clinical data rarely available in these settings. This has severely hampered efforts to address sepsis in a systematic way. In an effort to address the World Health Assembly sepsis resolution, which has specifically included a focus on improved detection and diagnosis, renewed efforts to build more flexible and inclusive sepsis criteria have been initiated (56). However, despite the resolve to develop criteria applicable to LMICs, the data which would be ideal to their development has not matured in the same way as in high income settings. As a result, these criteria, when they are developed, will still have limited validity compared to those developed for use HIC settings.

In order to achieve better criteria for sepsis, while also at the same time advancing the objectives of the World Health Assembly resolution to improve the prevention, diagnosis and management of sepsis, more coordinated and higher quality data systems must be developed. This is crucial to not only to facilitate the essential research required, but more importantly for the maturation of data systems that can monitor and evaluate the very programs designed to improve pediatric sepsis outcomes. The adoption of digital health technology in LMICs is accelerating at an unprecedented rate, providing wide ranging opportunities to leverage growing technological advances with health (57). However, for such advances to translate into improved sepsis care, both in hospital and following discharge, these must be part of a coordinated and systematic approach. The recently launched Pediatric Sepsis CoLaboratory represents an effort to leverage the growing technological advances to improve data generation, data sharing and quality improvement (58). Through coordinated efforts to develop standardized terminologies for terms, outcome definitions and operating procedures, the Pediatric Sepsis CoLaboratory is well positioned word towards facilitating a more coordinated approach to sepsis research and care. Similar efforts in data standardization and sharing through research networks in high income settings have led to dramatic improvements in research and practice in many areas of pediatric care, including sepsis (59,60). Such efforts

in LMICs, as they mature, will be critical in the validation of short- and long-term outcomes relevant to sepsis, as well as the sepsis criteria themselves.

An important limitation of any data-dependent initiative is that oftentimes the highest quality data, as well as the highest proportion of data, come from sources that are disproportionately advantaged through funding, human resources, infrastructure or geography. It is therefore important to recognize that the data may not fully represent the population of interest. Efforts should always include an attempt to identify data gaps as well how these gaps may have influenced the conclusions. Despite these limitations, however, the accumulation of high quality and well-defined data remains imperative to advancing sepsis care, especially in LMIC settings, which have often been insufficient for the development of context specific policies and guidelines.

Sub-section 2: progress through innovation

Health system challenges

Most improvement in sepsis outcomes globally have been achieved through better supportive care and quality improvement initiatives, though these have been concentrated in developed countries (61,62). Similar system focused efforts, though designed for LMIC contexts, which additionally address vulnerabilities related to poverty and education as well as geographical factors that frequently affect health seeking ability, are likely to play an important role in improving post-discharge outcomes. Indeed, any novel intervention, whether a new pharmacologic therapy, a health worker or patient focused behavioral change intervention, or a community-based support program, must eventually be embedded into a complex system which must deliver care to patients with wide ranging individual medical vulnerabilities, such as HIV, malnutrition or anemia. Furthermore, since post-discharge outcomes focus on the post-hospital period, these interventions are naturally community focused, at least in part, and thus are further affected by social and economic determinants of health such as poor nutrition and housing and low education. Given these challenges, it is of utmost importance that research initiatives, regardless of the design or the type of intervention, establish appropriate stakeholder partnerships early. A diverse research team, inclusive of representatives from the community, potential implementing partners, local ministries of health, and other relevant organizations or individuals, is essential to the design of research programs with potential for eventual scaling. Later phases of implementation must ensure that health systems within which they are implemented capture key metrics to facilitate both the integration and monitoring of new interventional approaches for post-discharge care.

Therapeutic interventions

Improving outcomes following hospital discharge must be established as a key priority in sepsis research. Most of the interventional work to date has focused on therapeutic interventions, generally antibiotics or antimalarials. Other therapeutic options have not yet been explored, though other developments in sepsis research may hold potential promise to improve post-discharge outcomes. The use of synbiotics (pre-pro-biotics) for example, have shown a potential effect in sepsis prevention and could be evaluated in the post-discharge context (63). Also, deficiencies in micronutrients, such as zinc, selenium, vitamin D and others have been associated with sepsis, and may therefore play a role in post-sepsis recovery where recurrent illness occurs frequently (64-67). Future studies should further explore whether these deficiencies, and supplementation, affect post-discharge outcomes. To date, the only study evaluating a micronutrient intervention to improve post-discharge outcomes in an LMIC setting was the aforementioned study of a multimineral multivitamin alongside iron among children with severe anemia, though this did not result in any effect on post-discharge outcomes (27). Recently acute kidney injury as well as elevated levels of autoantibodies (which are themselves associated with kidney injury) have been found to be associated with pediatric post discharge mortality among children with severe malaria (68,69). This and related work may lead to new therapeutic targets that may further improve post-discharge outcomes (70,71).

Health system interventions

A notable gap in the interventional research to date are health system interventions. The discharge process is a key period of vulnerability during facility care, and has been advocated as a critical area for innovation, research, practice and even legislation in HIC settings (72). A similar emphasis is only beginning to emerge in LMIC settings, though a robust and standardized approach, with opportunities for task shifting, have the potential to substantially improve care and patient satisfaction. The fact that most post-discharge deaths do not occur in a facility suggest that appropriate health seeking and access to care, at both the individual and health system levels, are important barriers during the post-discharge period. Therefore, efforts to

improve the transition from hospital to home, and to also better understand and reduce barriers to subsequent care, are urgently required. Addressing issues of malnutrition, and its community-based management, following discharge is also an area of considerable importance given the high underlying prevalence of acute malnutrition among children with sepsis, and its important association with post-discharge mortality (73,74). While the individual RCT is considered the gold standard for evaluating many interventions, there are limitations to RCTs that may make them unsuitable for evaluating complex interventions, especially ones focused in improving care delivery (75). For these, alternative designs may be preferable. These may include quasi-experimental time series designs, or the development of adaptive designs based on a quality improvement model of care.

Economic evaluation and advocacy

In all areas of intervention development, the eventual transition from research to practice necessitates a compelling economic evaluation. Such evaluations are required by policy makers to prioritize competing priorities within limited health budgets. The tremendous burden of post-discharge mortality in the pediatric population is best quantified using disability adjusted life years, which combine both years of life lost due to premature mortality as well as years of life lost due to disability. To date, these metrics have not been applied to any post-discharge mortality research that we are aware of.

Scientific and economic justification, however, is insufficient to create substantial changes to improve post-discharge outcomes. The important role of strong advocacy cannot be overestimated. Those working towards improving sepsis outcomes, both in the immediate post-acute period as well as over the months and years following a sepsis event must incorporate key knowledge translation and advocacy components into their work plans. Building early linkages with key stakeholders, including ministries of health, professional associations, patient advocacy groups, potential implementing partners (government and non-government), is critical to the eventual successful uptake of new knowledge onto both policy and practice. Such partnerships generally go beyond a mere unidirectional knowledge translation but rather benefit through bi-directional knowledge transfer. The science of delivery is closely linked to this as it supports a culture of continuous learning and adaptation of both programs and the implementing organizations.

Conclusions

Outcomes among survivors of sepsis is increasingly recognized as a key metric in sepsis care. Evidence suggests that readmission and mortality during the early post-discharge period, as well persistent limitations in neurodevelopment and QoL during the late post-discharge period, are key barriers to achieving the World Health Assembly sepsis resolution targets. While a robust recovery from sepsis remains a challenge globally, the burden of impact is concentrated in resource limited settings where most pediatric sepsis cases occur, and where health systems and communities are least equipped to provide care during the vulnerable post-discharge period. Interventional research must focus not only on the development of effective interventions, but on effective means of integrating these interventions into complex and often poorly functional health systems. Despite the critical need for new and innovative approaches to improving post-discharge care, general improvements to the delivery of care, including during discharge and during routine post-discharge follow-up, should be a primary focus for health providers and policy makers as they seek to improve sepsis care in their settings.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Jan Hau Lee, Vijay Srinivasan, and Debbie Long) for the series "Pediatric Critical Care" published in *Translational Pediatrics*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-390

Peer Review File: Available at http://dx.doi.org/10.21037/tp-20-390

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-390). The series "Pediatric Critical Care" was commissioned by the editorial office without

any funding or sponsorship. Dr. LH reports grants from Canadian Institutes of Health Research Canada Research Chair, during the conduct of the study. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.
2. Tan B, Wong JJ, Sultana R, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. JAMA Pediatr 2019;173:352-62.
3. Chang CD. Social determinants of health and health disparities among immigrants and their children. Curr Probl Pediatr Adolesc Health Care 2019;49:23-30.
4. Dugani S, Laxminarayan R, Kissoon N. The quadruple burden of sepsis. CMAJ 2017;189:E1128-9.
5. Reinhart K, Daniels R, Kissoon N, et al. Recognizing sepsis as a global health priority - a WHO resolution. N Engl J Med 2017;377:414-7.
6. Transforming our world: the 2030 Agenda for Sustainable Development. 2015. Available online: https://sdgs.un.org/2030agenda
7. Nemetchek B, English L, Kissoon N, et al. Paediatric postdischarge mortality in developing countries: a systematic review. BMJ Open 2018;8:e023445.
8. Wiens MO, Pawluk S, Kissoon N, et al. Pediatric post-discharge mortality in resource poor countries: a systematic review. PLoS One 2013;8:e66698.
9. Huang CY, Daniels R, Lembo A, et al. Life after sepsis: an international survey of survivors to understand the post-sepsis syndrome. Int J Qual Health Care 2019;31:191-8.
10. Zimmerman JJ, Banks R, Berg RA, et al. Trajectory of mortality and health-related quality of life morbidity following community-acquired pediatric septic shock. Crit Care Med 2020;48:329-37.
11. Zimmerman JJ, Banks R, Berg RA, et al. Critical illness factors associated with long-term mortality and health-related quality of life morbidity following community-acquired pediatric septic shock. Crit Care Med 2020;48:319-28.
12. Childhood Acute Illness and Nutrition Network. Childhood Acute Illness and Nutrition (CHAIN) Network: a protocol for a multi-site prospective cohort study to identify modifiable risk factors for mortality among acutely ill children in Africa and Asia. BMJ Open 2019;9:e028454.
13. Chami N, Hau DK, Masoza TS, et al. Very severe anemia and one year mortality outcome after hospitalization in Tanzanian children: a prospective cohort study. PLoS One 2019;14:e0214563.
14. Hau DK, Chami N, Duncan A, et al. Post-hospital mortality in children aged 2-12 years in Tanzania: a prospective cohort study. PLoS One 2018;13:e0202334.
15. Madrid L, Casellas A, Sacoor C, et al. Postdischarge mortality prediction in Sub-Saharan Africa. Pediatrics 2019;143:e20180606.
16. Ngari MM, Obiero C, Mwangome MK, et al. Mortality during and following hospital admission among school-aged children: a cohort study. Wellcome Open Res 2021;5:234.
17. Talbert A, Ngari M, Bauni E, et al. Mortality after inpatient treatment for diarrhea in children: a cohort study. BMC Med 2019;17:20.
18. Wiens MO, Larson CP, Kumbakumba E, et al. Application of sepsis definitions to pediatric patients admitted with suspected infections in Uganda. Pediatr Crit Care Med 2016;17:400-5.
19. Gwela A, Mupere E, Berkley JA, et al. Undernutrition, host immunity and vulnerability to infection among young children. Pediatr Infect Dis J 2019;38:e175-7.
20. Owino V, Ahmed T, Freemark M, et al. Environmental enteric dysfunction and growth failure/stunting in global child health. Pediatrics 2016;138:e20160641.
21. Subramanian S, Huq S, Yatsunenko T, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 2014;510:417-21.
22. Njunge JM, Gwela A, Kibinge NK, et al. Biomarkers of post-discharge mortality among children with complicated

severe acute malnutrition. Sci Rep 2019;9:5981.
23. English L, Kumbakumba E, Larson CP, et al. Pediatric out-of-hospital deaths following hospital discharge: a mixed-methods study. Afr Health Sci 2016;16:883-91.
24. Zakayo SM, Njeru RW, Sanga G, et al. Vulnerability and agency across treatment-seeking journeys for acutely ill children: how family members navigate complex healthcare before, during and after hospitalisation in a rural Kenyan setting. Int J Equity Health 2020;19:136.
25. Czaja AS, Zimmerman JJ, Nathens AB. Readmission and late mortality after pediatric severe sepsis. Pediatrics 2009;123:849-57.
26. Berkley JA, Ngari M, Thitiri J, et al. Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial. Lancet Glob Health 2016;4:e464-73.
27. Maitland K, Olupot-Olupot P, Kiguli S, et al. Co-trimoxazole or multivitamin multimineral supplement for post-discharge outcomes after severe anaemia in African children: a randomised controlled trial. Lancet Glob Health 2019;7:e1435-47.
28. Pavlinac PB, Singa BO, John-Stewart GC, et al. Azithromycin to prevent post-discharge morbidity and mortality in Kenyan children: a protocol for a randomised, double-blind, placebo-controlled trial (the Toto Bora trial). BMJ Open 2017;7:e019170.
29. Phiri K, Esan M, van Hensbroek MB, et al. Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. Lancet Infect Dis 2012;12:191-200.
30. Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention with monthly dihydroartemisinin-piperaquine for the post-discharge management of severe anaemia in children aged less than 5 years in Uganda and Kenya: study protocol for a multi-centre, two-arm, randomised, placebo-controlled, superiority trial. Trials 2018;19:610.
31. Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention in the postdischarge management of severe anemia. N Engl J Med 2020;383:2242-54.
32. Nemetchek B, Khowaja A, Kavuma A, et al. Exploring healthcare providers' perspectives of the paediatric discharge process in Uganda: a qualitative exploratory study. BMJ Open 2019;9:e029526.
33. Wiens MO, Kissoon N, Kabakyenga J. Smart hospital discharges to address a neglected epidemic in sepsis in low- and middle-income countries. JAMA Pediatr 2018;172:213-4.
34. Wiens MO, Kumbakumba E, Larson CP, et al. Scheduled follow-up referrals and simple prevention kits including counseling to improve post-discharge outcomes among children in Uganda: a proof-of-concept study. Glob Health Sci Pract 2016;4:422-34.
35. Peters C, Kissoon N. Surviving sepsis in children: our job is only half done. Pediatr Crit Care Med 2019;20:568-9.
36. Mostel Z, Perl A, Marck M, et al. Post-sepsis syndrome - an evolving entity that afflicts survivors of sepsis. Mol Med 2019;26:6.
37. Alshaikh B, Yusuf K, Sauve R. Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: systematic review and meta-analysis. J Perinatol 2013;33:558-64.
38. Bakhuizen SE, de Haan TR, Teune MJ, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. Acta Paediatr 2014;103:1211-8.
39. Gordon AL, English M, Tumaini Dzombo J, et al. Neurological and developmental outcome of neonatal jaundice and sepsis in rural Kenya. Trop Med Int Health 2005;10:1114-20.
40. Kavas N, Arısoy AE, Bayhan A, et al. Neonatal sepsis and simple minor neurological dysfunction. Pediatr Int 2017;59:564-9.
41. Als LC, Nadel S, Cooper M, et al. Neuropsychologic function three to six months following admission to the PICU with meningoencephalitis, sepsis, and other disorders: a prospective study of school-aged children. Crit Care Med 2013;41:1094-103.
42. Clark LJ, Glennie L, Audrey S, et al. The health, social and educational needs of children who have survived meningitis and septicaemia: the parents' perspective. BMC Public Health 2013;13:954.
43. Syngal P, Giuliano JS Jr. Health-related quality of life after pediatric severe sepsis. Healthcare (Basel) 2018;6:113.
44. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191:1147-57.
45. Treble-Barna A, Beers SR, Houtrow AJ, et al. PICU-based rehabilitation and outcomes assessment: a survey of pediatric critical care physicians. Pediatr Crit Care Med 2019;20:e274-82.
46. Kissoon N, Reinhart K, Daniels R, et al. Sepsis in children:

global implications of the world health assembly resolution on sepsis. Pediatr Crit Care Med 2017;18:e625-7.
47. Skempes D, Bickenbach J. Strengthening rehabilitation for people with disabilities: a human rights approach as the essential next step to accelerating global progress. Am J Phys Med Rehabil 2015;94:823-8.
48. Heinemann AW, Feuerstein M, Frontera WR, et al. Rehabilitation is a global health priority. Arch Phys Med Rehabil 2020;101:728-9.
49. Jesus TS, Landry MD, Dussault G, et al. Classifying and measuring human resources for health and rehabilitation: concept design of a practices- and competency-based international classification. Phys Ther 2019;99:396-405.
50. Cleaver S, Nixon S. A scoping review of 10 years of published literature on community-based rehabilitation. Disabil Rehabil 2014;36:1385-94.
51. Sharma R, Gaffey MF, Alderman H, et al. Prioritizing research for integrated implementation of early childhood development and maternal, newborn, child and adolescent health and nutrition platforms. J Glob Health 2017;7:011002.
52. Spittle AJ, Anderson PJ, Lee KJ, et al. Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years. Pediatrics 2010;126:e171-8.
53. Ngabireyimana E, Mutaganzwa C, Kirk CM, et al. A retrospective review of the Pediatric Development Clinic implementation: a model to improve medical, nutritional and developmental outcomes of at-risk under-five children in rural Rwanda. Matern Health Neonatol Perinatol 2017;3:13.
54. Gelli A, Margolies A, Santacroce M, et al. Improving child nutrition and development through community-based childcare centres in Malawi - The NEEP-IE study: study protocol for a randomised controlled trial. Trials 2017;18:284.
55. Wiens MO, Kumbakumba E, Kissoon N, et al. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. Clin Epidemiol 2012;4:319-25.
56. Menon K, Schlapbach LJ, Akech S, et al. Pediatric sepsis definition-a systematic review protocol by the pediatric sepsis definition taskforce. Crit Care Explor 2020;2:e0123.
57. Olu O, Muneene D, Bataringaya JE, et al. How can digital health technologies contribute to sustainable attainment of universal health coverage in Africa? A perspective. Front Public Health 2019;7:341.
58. The Pediatric Sepsis CoLaboratory. Available online: https://www.bcchr.ca/pediatric-sepsis-data-colab
59. The Canadian Neonatal Network. Available online: http://www.canadianneonatalnetwork.org/
60. Neonatal Research Network. Available online: https://neonatal.rti.org/
61. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. Lancet 2010;376:1339-46.
62. Riviello ED, Sugira V, Twagirumugabe T. Sepsis research and the poorest of the poor. Lancet Infect Dis 2015;15:501-3.
63. Panigrahi P, Parida S, Nanda NC, et al. A randomized synbiotic trial to prevent sepsis among infants in rural India. Nature 2017;548:407-12.
64. Cariolou M, Cupp MA, Evangelou E, et al. Importance of vitamin D in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and meta-analysis. BMJ Open 2019;9:e027666.
65. Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev 2016;12:CD005436.
66. Li S, Tang T, Guo P, et al. A meta-analysis of randomized controlled trials: Efficacy of selenium treatment for sepsis. Medicine (Baltimore) 2019;98:e14733.
67. Saleh NY, Abo El Fotoh WMM. Low serum zinc level: The relationship with severe pneumonia and survival in critically ill children. Int J Clin Pract 2018;72:e13211.
68. Conroy AL, Opoka RO, Bangirana P, et al. Acute kidney injury is associated with impaired cognition and chronic kidney disease in a prospective cohort of children with severe malaria. BMC Med 2019;17:98.
69. Mourão LC, Cardoso-Oliveira GP, Braga ÉM. Autoantibodies and malaria: where we stand? Insights into pathogenesis and protection. Front Cell Infect Microbiol 2020;10:262.
70. Rivera-Correa J, Conroy AL, Opoka RO, et al. Autoantibody levels are associated with acute kidney injury, anemia and post-discharge morbidity and mortality in Ugandan children with severe malaria. Sci Rep 2019;9:14940.
71. Rivera-Correa J, Rodriguez A. Autoimmune anemia in Malaria. Trends Parasitol 2020;36:91-7.
72. Berry JG, Blaine K, Rogers J, et al. A framework of pediatric hospital discharge care informed by legislation, research, and practice. JAMA Pediatr 2014;168:955-62; quiz 965-6.
73. Alvarez Morán JL, Alé GBF, Charle P, et al. The effectiveness of treatment for Severe Acute Malnutrition

(SAM) delivered by community health workers compared to a traditional facility based model. BMC Health Serv Res 2018;18:207.
74. López-Ejeda N, Charle-Cuellar P, F GBA, et al. Bringing severe acute malnutrition treatment close to households through community health workers can lead to early admissions and improved discharge outcomes. PLoS One 2020;15:e0227939.
75. Minary L, Trompette J, Kivits J, et al. Which design to evaluate complex interventions? Toward a methodological framework through a systematic review. BMC Med Res Methodol 2019;19:92.

Cite this article as: Wiens MO, Kissoon N, Holsti L. Challenges in pediatric post-sepsis care in resource limited settings: a narrative review. Transl Pediatr 2021;10(10):2666-2677. doi: 10.21037/tp-20-390

