

Clinical care for severe influenza and other severe illness in resource-limited settings: the need for evidence and guidelines

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The 2009 influenza A (H1N1) pandemic highlighted the importance of quality hospital care of the severely ill, yet there is evidence that the impact of the 2009 pandemic was highest in low- and middle-income countries with fewer resources. Recent data indicate that death and suffering from seasonal influenza and severe illness in general are increased in resource-limited settings. However, there are limited clinical data and guidelines for the management of influenza and other severe illness in these settings. Life-saving supportive care through syndromic case management is used successfully in high-resource intensive care units and in global programs such as the Integrated Management of Childhood Illness (IMCI). While there are a variety of challenges to the management of the severely ill in resource-limited settings, several new international initiatives have begun to develop syndromic management strategies for these environments, including the World

Health Organization's Integrated Management of Adult and Adolescent Illness Program. These standardized clinical guidelines emphasize syndromic case management and do not require high-resource intensive care units. These efforts must be enhanced by quality clinical research to provide missing evidence and to refine recommendations, which must be carefully integrated into existing healthcare systems. Realizing a sustainable, global impact on death and suffering due to severe influenza and other severe illness necessitates an ongoing and concerted international effort to iteratively generate, implement, and evaluate best-practice management guidelines for use in resource-limited settings.

Keywords Acute respiratory distress syndrome, critical care medicine, global health, influenza, sepsis.

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Introduction

The 2009 influenza A (H1N1) pandemic highlighted the essential role of hospital care of the severely ill in the response to public health emergencies. Early reports from Mexico and Canada of intensive care units (ICUs) filled to capacity with patients with severe respiratory infections helped to calibrate the early, aggressive global public health response.^{1–3} The critical care medical community and public health reacted with unprecedented coordination to describe severe disease, to disseminate data on the epidemiology and care of pandemic patients, and to convey the impact of the outbreak on health systems.^{4–8} While the worst-case scenario of a 1918-scale pandemic was avoided, there were reports of patients with severe disease stressing critical care services in communities throughout the world.^{2,9–11} These reports show that severely ill patients can divert resources and impact the balance of care delivery even in hospitals where the overall capacity is not exceeded. This problem is particularly acute in resource-limited settings where there is decreased capacity to

manage severe illness. While building resource-intensive and highly technological ICUs is not feasible for many parts of the world, much can be done to improve care for severely ill patients in more austere environments. In this review, we discuss the inter-related issues of pandemic influenza, severe seasonal influenza, and severe illness more generally. Given the burden of severe illness in resource-limited settings, it is vital to improve capacity to care for severely ill individuals in these environments.

Impact of 2009 pandemic influenza

Estimates of 2009 H1N1 pandemic influenza morbidity and mortality differ considerably among countries.^{1,12–14} In high-resource countries, large epidemiologic studies have shown that the overall incidence of pandemic influenza requiring hospitalization was comparable to interpandemic seasons,^{15–18} but there were important demographic groups that experienced substantial increases in severe influenza disease. These groups included young adults, pregnant women, obese

persons, and indigenous persons.¹³ In low- and middle-income countries, where laboratory testing for clinical care or for public health surveillance was limited, the full impact of the 2009 pandemic has been harder to measure.^{19–21} However, modeling studies estimate that there were disproportionately increased pandemic deaths in resource-limited regions.²² Compared with the Americas, the risk of pandemic respiratory and circulatory mortality was 1.4 times higher in Southeast Asia and 2.4 times higher in Africa.²² These data underscore the importance of improving clinical management of influenza disease in resource-limited settings.

Management of severe pandemic influenza in resource-limited settings

A 2010 WHO consultation on the clinical care of pandemic influenza noted that there were limited clinical data and guidelines for the management of severe manifestations of viral infection in resource-limited settings.¹⁰ In light of the apparent paucity of data about supportive management of severe influenza-specific illness, the WHO Public Health Research Agenda for Influenza commissioned the International Respiratory and Severe Illness Center (INTERSECT) at the University of Washington to perform a systematic review on non-antiviral, supportive management of persons with severe 2009 pandemic influenza A (H1N1). A 2012 update of this review, limited to randomized controlled trials, controlled prospective cohort studies, and systematic reviews/meta-analyses found only seven pertinent studies, mostly of adults.²³ One study found benefit of convalescent plasma infusion for severe illness,²⁴ three studies found no benefit of corticosteroids for severe respiratory disease,^{25–27} and three studies had mixed results on the benefit of extracorporeal lung support for severe respiratory disease.^{28–30} No study identifying a therapeutic benefit from an intervention was applicable to healthcare delivery in resource-limited settings.

Burden of seasonal influenza in resource-limited settings

While 2009 pandemic influenza gained attention worldwide, the burden of seasonal influenza is perhaps less widely recognized. Yet, the contribution of seasonal influenza to severe illness is substantial, especially in resource-limited settings. A variety of data support this assertion. Among children younger than 5 years of age in sub-Saharan Africa and South Asia, influenza infection and co-infections are commonly identified during hospitalizations for acute lower respiratory infections (ALRI).^{31–34} The only systematic review and meta-analysis that estimates the global burden of severe influenza disease was recently published.³⁵ The study, which analyzes only early childhood disease, reports that 99% of influenza-related cases of severe ALRI among children younger than 5 years occur

in low- and middle-income countries, and that 13% of all ALRI in this age group are associated with influenza virus infection. The study dispels the myth that influenza is only a problem in temperate regions. The authors calculated that the incidence rate of severe influenza-associated ALRI in early childhood is similar in developing countries as compared with industrialized, temperate countries (both are around 1–2 episodes per 1 000 child-years).³⁵ This pediatric study underestimates the overall burden of severe influenza, as research has demonstrated that influenza mortality among adults is considerably higher than in children.³⁶ In the United States, approximately 100 children die annually from influenza virus infection, as compared with greater than 32 000 influenza-attributable deaths among persons older than 65 years.³⁶ The burden of influenza among adults may be even higher in developing settings. Recent data from South Africa suggest that the risk of influenza mortality among the elderly in that country is greater than in the United States.³⁷ Further, countries with a high prevalence of HIV/AIDS and minimal availability of highly active antiretroviral therapy may also experience substantial risk of influenza mortality among non-elderly adults.³⁸ Thus, beyond pandemic planning and response, it is critical to optimize care of severe seasonal influenza in resource-limited settings.

Global burden of severe illness

More generally, the global burden of severe illness is poorly understood. In the United States, acute respiratory distress syndrome (ARDS) and sepsis are two of the most common severe illnesses requiring critical care.^{39,40} Among adults worldwide, extrapolated data suggest that 15–19 million cases of sepsis and 1.15–5.5 million cases of ARDS occur annually.² However, considering that about 60% of the global burden of respiratory mortality is in children <5 years of age,⁴¹ these estimates are a substantial underestimate of the total global burden of severe illness. The vast majority of severe illness occurs in low- and middle-income countries,⁴² yet there are currently little clinical data or evidence-based management guidelines to improve hospital care for patients in these settings.⁴³

Syndromic management in intensive care units

In intensive care medicine, severe illness treatment is syndromic in approach. Clinical management of two common syndromes encountered in intensive care units – ARDS and sepsis – follow standardized guidelines.^{44,45} These syndrome-focused guidelines facilitate the rapid recognition and treatment for life-threatening conditions, even before specific etiologies are identified. This approach also promotes the widespread adoption of research-proven interventions

such as low tidal volume lung protective ventilation for ARDS.^{40,46} Similarly, several studies suggest that sepsis outcomes may be improved by the use of protocolized sepsis care pathways.^{47,48} Syndromic management is therefore an important tool in improving care of severely ill patients. In resource-limited settings, where advanced diagnostic equipment may not be available, syndromic management of severely ill patients using readily available tools offers a practical and feasible strategy for care.

Syndromic management of sick children in resource-limited settings

Evidence of the benefit of syndromic management of hospitalized patients in resource-limited settings comes from the WHO Integrated Management for Childhood Illness (IMCI) program. IMCI guidelines were developed using existing clinical evidence and expert opinion to standardize healthcare provider training and care delivery in resource-limited settings.⁴⁹ The IMCI guidelines are designed to identify children in need of care by presenting signs and symptoms, and they do not require diagnostic tests that are likely unavailable in most austere settings. Studies evaluating training and implementation of IMCI guidelines have shown a substantial impact on improved management and survival related to childhood pneumonia and other common illnesses.^{50–54} For example, a cluster randomized trial in Kenya evaluating the efficacy of a multi-faceted quality improvement intervention for the management of severely ill children resulted in improved quality of clinical care when compared with a less comprehensive approach.⁵⁰ Similarly, in a pediatric outpatient and emergency unit in Malawi, directed trainings based on IMCI to improve triage and emergency care resulted in streamlined healthcare delivery and a 10% decrease in pediatric in-hospital mortality.⁵¹ Modifications of IMCI have also been shown to improve pneumonia outcomes when implemented in the community setting.^{55–57} Moreover, economic analyses have found IMCI protocolized care to be cost effective and comparable to preventive interventions such as routine childhood pneumococcal conjugate immunization.⁵⁸ It is important to highlight that clinical management guidelines may have only modest effects on important outcomes in resource-limited settings for several reasons, including an incomplete evidence base and numerous challenges to implementation.⁵⁹ Further, some studies have shown limited or no effects of knowledge translation activities, such as clinical guideline implementation.^{60,61} Nevertheless, even modest treatment effects on a high burden disease can have a massive impact when widely implemented. The IMCI experience demonstrates the potential benefits of syndromic management for persons with severe respiratory infections in resource-limited settings.

Challenges to caring for the severely ill in resource-limited settings

Global disparities in access to care for severe illness are substantial.^{43,62,63} WHO reported in 2009 that poor clinical outcomes of pandemic influenza were associated with delays in seeking health care, limited access to supportive care, and “rapidly progressive overwhelming lung disease which is very difficult to treat.”⁹ Disparities in access to critical care may partly explain some of the pandemic influenza mortality differences reported among countries.^{64,65} For example, during the early phase of the H1N1 pandemic, reported ICU mortality in middle-income Mexico was twice that of high-income Canada.^{2,3,14} Access to typical health technologies used to manage critically ill patients such as pulse oximetry, invasive hemodynamic monitoring, blood gas analyzers, and mechanical ventilation may be limited or absent in resource-limited settings.^{66,67} Hospital care is often delivered by nurses and non-specialist doctors who may have limited time, resources, training, and access to information to manage severely ill patients,^{67,68} particularly during a public health emergency like the 2009 influenza pandemic. From the few surveys of ICU resources in resource-limited settings, data suggest that many hospitals are ill equipped to dedicate sufficient personnel and supplies required by patients with severe illness.^{69–72} Alarming shortages of reliable electricity, clean water, and supplemental oxygen have been reported from hospitals in sub-Saharan Africa and Southeast Asia.^{73,74} Developing country health systems may be weak and hospital support from government ministries is often lacking.⁶⁷ Thus, strategies to improve care delivery in low- and middle-income countries must address challenges of improving access to care, training and retention of healthcare providers, supply chain management, and strengthening healthcare systems.⁴² Any new healthcare intervention designed to improve management of severe influenza disease must be integrated into the current health system structure and strengthen healthcare delivery overall if it is to be successfully adopted and remain sustainable.

Guidelines for care of the severely ill in resource-limited settings

Despite the absence of sophisticated equipment and abundant resources, including ICUs, it is likely that many lives in resource-limited settings can be saved by promoting the basic tenets of severe illness management.^{42,67,75} Examples include simple triage systems to rapidly identify ill patients, protocolized supplemental oxygen therapy managed by non-physician staff, infection source control, and early antimicrobial therapy for sepsis based on local antimicrobial

susceptibility testing, prompt fluid resuscitation for septic shock, and standardized infection control measures such as hand cleaning. Several recent global initiatives have developed guidelines for the syndromic management of severe influenza and other severe illness in resource-limited settings. During the H1N1 influenza pandemic, the WHO assembled a group of experts to generate a document addressing management of severe respiratory distress and shock in resource-limited settings.⁷⁶ More recently, similar advice was produced by the WHO for the clinical management of novel coronavirus from outbreaks in 2012 in the Middle East (publication pending). The WHO Integrated Management of Adult and Adolescent Illness (IMAI) program, a sister initiative to IMCI, created a comprehensive manual for the care of hospitalized patients by clinicians in district hospitals that includes sections on severe illness management.⁷⁷ The European Society of Intensive Care Medicine also recently produced sepsis management guidelines targeted to resource-limited settings.⁷⁸ These largely expert opinion-based documents fill major gaps in management guidelines but require quality clinical research to provide missing evidence and refine best-practice recommendations. A reminder of the importance of evidence generated by studies in at-risk populations was provided by the unexpectedly harmful effect of fluid boluses for Kenyan children with severe infection in the FEAST (fluid expansion as supportive therapy) trial.⁵⁹

Conclusion

Severe illness, influenza-related and otherwise, causes a profound burden of disease in resource-limited settings. Quality clinical management is an essential element in mitigating this burden. In support of this, a recent call to action by UNICEF, and several governmental and non-governmental organizations, focuses global attention on treatment of preventable childhood deaths, including respiratory infections.⁷⁹ Syndromic management approaches to the care of severe illness seem practical and feasible. However, there are few data to guide the optimal management of severely ill patients in these resource-limited settings. While several recent initiatives now provide long awaited guidance for clinicians in resource-limited settings, a sustainable, global impact on outcomes due to severe influenza and other severe illness will require an ongoing and concerted international effort to implement, evaluate, and refine these guidelines.

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Conflict of interest

The authors report no financial competing interests.

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