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

Justin R. Ortiz, Shevin T. Jacob, T. Eoin West

International Respiratory and Severe Illness Center (INTERSECT), University of Washington, Seattle, WA, USA.

Correspondence: Dr. Justin Ortiz, Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, P.O. Box 356522, 1959 NE Pacific Street, Seattle, WA 98195-6522, USA. E-mail: jrotiz@uw.edu

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.

Please cite this paper as: Ortiz et al. (2013) Clinical care for severe influenza and other severe illness in resource-limited settings: the need for evidence and guidelines. Influenza and Other Respiratory Viruses 7(Suppl. 2), 87–92.

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. 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. 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. 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. In high-resource countries, large epidemiologic studies have shown that the overall incidence of pandemic influenza requiring hospitalization was comparable to interpandemic seasons, but there were important demographic groups that experienced substantial increases in severe influenza disease. These groups included young adults, pregnant women, obese
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. 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. One study found benefit of convalescent plasma infusion for severe illness, three studies found no benefit of corticosteroids for severe respiratory disease, and three studies had mixed results on the benefit of extracorporeal lung support for severe respiratory disease. 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, influenza-attributable deaths among persons older than 65 years. 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. 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. 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. 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. Among adults worldwide, extrapolated data suggest that 15–19 million cases of sepsis and 1.15–5.5 million cases of ARDS occur annually. However, considering that about 60% of the global burden of respiratory mortality is in children <5 years of age, 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, yet there are currently little clinical data or evidence-based management guidelines to improve hospital care for patients in these settings.

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. 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.\textsuperscript{40,46} Similarly, several studies suggest that sepsis outcomes may be improved by the use of protocolized sepsis care pathways.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{51} Modifications of IMCI have also been shown to improve pneumonia outcomes when implemented in the community setting.\textsuperscript{55–57} Moreover, economic analyses have found IMCI protocolized care to be cost effective and comparable to preventative interventions such as routine childhood pneumococcal conjugate immunization.\textsuperscript{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.\textsuperscript{59} Further, some studies have shown limited or no effects of knowledge translation activities, such as clinical guideline implementation.\textsuperscript{50,61} 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.\textsuperscript{53,62,63} 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.”\textsuperscript{59} Disparities in access to critical care may partly explain some of the pandemic influenza mortality differences reported among countries.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{69–72} Alarming shortages of reliable electricity, clean water, and supplemental oxygen have been reported from hospitals in sub-Saharan Africa and Southeast Asia.\textsuperscript{73,74} Developing country health systems may be weak and hospital support from government ministries is often lacking.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. The European Society of Intensive Care Medicine also recently produced sepsis management guidelines targeted to resource-limited settings. 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.

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. 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.

Acknowledgements

We would like to thank Danielle Clark, Sherry Dodson, Terri Hough, Tim Nguyen, Kristina Rudd, Joanne Rich, and Nahoko Shindo for their assistance with this article.

Funding

Dr. Ortiz is supported by the Robert Wood Johnson Harold Amos Medical Faculty Development Program (Grant 67423). The authors have received funding from the World Health Organization for a systematic review of clinical interventions in severe pandemic influenza.

Conflict of interest

The authors report no financial competing interests.

References

1 Chowell G, Echevarria-Zuno S, Viboud C et al. Epidemiological characteristics and underlying risk factors for mortality during the autumn 2009 pandemic wave in Mexico. PLoS ONE 2012; 7:e41069.
2 Dominguez-Cherit G, Lapinsky SE, Macias AE et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 2009; 302:1880–1887.
3 Kumar A, Zarychanski R, Pinto R et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009; 302:1872–1879.
4 Mitchell MD, Mikkelsen ME, Umscheid CA et al. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. Crit Care Med 2010; 38:1398–1404.
5 Webb SA, Pettella V, Seppelt I et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009; 361:1925–1934.
6 Dwyer DE. Surveillance of illness associated with pandemic (H1N1) 2009 virus infection among adults using a global clinical site network approach: the INSIGHT FLU 002 and FLU 003 studies. Vaccine 2011; 29(Suppl 2):B56–B62.
7 Randolph AG, Vaughn F, Sullivan R et al. Critically ill children during the 2009–2010 influenza pandemic in the United States. Pediatrics 2011; 128:e1450–e1458.
8 Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. Available at http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/index.html (2009) (Accessed 6 June 2012).
9 Pandemic (H1N1) 2009, Ukraine. Available at http://www.who.int/csr/don/2009_11_01/en/index.html (2009) (Accessed 1 September 2012).
10 Clinical management of influenza and other acute respiratory illness in resource-limited settings: learning from the influenza pandemic (H1N1)2009. Available at http://www.who.int/influenza/patient_care/clinical/858-WHOGIPReport_A4_WEB_FA.pdf (2012) Accessed 6 June 2012.
11 Libster R, Bugna J, Coviello S et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010; 362:45–55.
12 Van Kerkhove MD, Mounts AW, Mall S et al. Epidemiologic and virologic assessment of the 2009 influenza A (H1N1) pandemic on selected temperate countries in the Southern Hemisphere: Argentina, Australia, Chile, New Zealand and South Africa. Influenza Other Respir Viruses 2011; 5:e487–e498.
13 Van Kerkhove MD, Vandemaele KA, Shinde V et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Medicine 2011; 8:e1001053.
14 Viboud C, Simonsen L. Global mortality of 2009 pandemic influenza A H1N1. Lancet Infect Dis 2012; 12:651–653.
Ortiz JR, Rudd KE, Clark DV, Jacob ST, West TE. Research during

Dawood FS, Iuliano AD, Reed C et al. Interim report on pandemic H1N1 influenza virus infections in sub-Saharan Africa. Bull World Health Organ 2012; 90:301–305.

Archer B, Cohen C, Naidoo D et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis 2012; 12:687–695.

Ortiz JR, Rudd KE, Clark DV, Jacob ST, West TE. Research during public health crises: a systematic review of severe pandemic influenza management. Crit Care Med. (In press).

Hung IF, To KK, Lee CK et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011; 52:447–456.

Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 2011; 183:1200–1206.

Linko R, Pelttia V, Ruokonen E et al. Corticosteroid therapy in intensive care unit patients with PCR-confirmed influenza A(H1N1) infection in Finland. Acta Anaesthesiol Scand 2011; 55:971–979.

Martin-Loeches I, Lisboa T, Rhodes A et al. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)2009 influenza A infection. Intensive Care Med 2011; 37:272–283.

Breed KH, Henzler D, White CW et al. Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. Can J Anaethes 2010; 57:240–247.

Noah MA, Peek GJ, Finney SJ et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011; 306:1659–1668.

Roch A, Lepaul-Ercole R, Grisoli D et al. Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. Intensive Care Med 2010; 36:1899–1905.

Rudan I, Boschi-Pinto C, Bieglov Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008; 86:408–416.

Berkeley JA, Munywoki P, Ngama M et al. Viral etiology of severe pneumonia among Kenyan infants and children. JAMA 2010; 303:2051–2057.

Brooks WA, Goswami D, Rahman M et al. Influenza is a major contributor to childhood pneumonia in a tropical developing country. Pediatr Infect Dis J 2010; 29:216–221.
53 Marsh DR, Gilroy KE, Van de Weerd R, Wansi E, Qazi S. Community case management of pneumonia: at a tipping point? Bull World Health Organ 2008; 86:381–389.
54 Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis 2003; 3:547–556.
55 Addo-Yobo E, Anh DD, El-Sayed HF et al. Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: the MASS study. Trop Med Int Health 2011; 16:995–1006.
56 Ashraf H, Mahmud R, Alam NH et al. Randomized controlled trial of day care versus hospital care of severe pneumonia in Bangladesh. Pediatrics 2010; 126:e807–e815.
57 Yeboah-Antwi K, Pilingana P, Macleod WB et al. Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. PLoS Medicine 2010; 7:e1000340.
58 Niessen LW, ten Hove A, Hilderink H et al. Comparative impact assessment of child pneumonia interventions. Bull World Health Organ 2009; 87:472–480.
59 Maitland K, Kiguli S, Opoka RO et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011; 364:2483–2495.
60 Bhutta ZA, Soofi S, Cousens S et al. Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. Lancet 2011; 377:403–412.
61 Carlo WA, Goudar SS, Jehan I et al. Newborn-care training and perinatal mortality in developing countries. N Engl J Med 2010; 362:614–623.
62 Murthy S, Wunsch H. Clinical review: international comparisons in critical care – lessons learned. Crit Care 2012; 16:218.
63 Burkle FM Jr, Argent AC, Kissoon N. The reality of pediatric emergency mass critical care in the developing world. Pediatr Crit Care Med 2011; 12:5169–5179.
64 Kissoon N. Pandemic H1N1 2009: are we comparing apples with oranges? Pediatr Crit Care Med 2012; 13:364–365.
65 Kissoon N. H1N1 in Japanese children – more data but even more questions. Pediatr Crit Care Med 2012; 13:611–612.
66 Jacob ST, Moore CC, Banura P et al. Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population. PLoS ONE 2009; 4:e7782.
67 Baker T. Critical care in low-income countries. Trop Med Int Health 2009; 14:143–148.
68 Jacob ST, Banura P, Baeten JM et al. The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study. Crit Care Med 2012; 40:2050–2058.
69 Baelani I, Jochberger S, Laimer T et al. Availability of critical care resources to treat patients with severe sepsis or septic shock in Africa: a self-reported, continent-wide survey of anaesthesia providers. Crit Care 2011; 15:R10.
70 Dunser MW, Baelani I, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. Crit Care Med 2006; 34:1234–1242.
71 Westcott M, Martiniuk AL, Fowler RA, Adhikari NK, Dalipanda T. Critical care resources in the Solomon Islands: a cross-sectional survey. BMC Int Health Hum Rights 2012; 12:1.
72 Kwizera A, Dunser M, Nakibuuka J. National intensive care unit bed capacity and ICU patient characteristics in a low income country. BMC Res Notes 2012; 5:475.
73 Belle J, Cohen H, Shindo N et al. Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries. J Infect Dev Ctries 2010; 4:419–424.
74 Hsia RY, Mbembati NA, Macfarlane S, Kruk ME. Access to emergency and surgical care in sub-Saharan Africa: the infrastructure gap. Health Policy Plan 2012; 27:234–244.
75 Riviello ED, Letchford S, Achieng L, Newton MW. Critical care in resource-poor settings: lessons learned and future directions. Crit Care Med 2011; 39:860–867.
76 Clinical management of adult patients with complications of pandemic influenza A (H1N1) 2009: Emergency guidelines for the management of patients with severe respiratory distress and shock in district hospitals in limited- resource settings. Available at http://www.who.int/csr/resources/publications/swineflu/mai_h1n1.pdf (2010) (Accessed 13 June 2012).
77 World Health Organization. IMAI District Clinician Manual: Hospital Care for Adolescents and Adults. Guidelines for the Management of Illnesses with Limited Resources. Geneva: World Health Organization, 2012.
78 Dunser MW, Festic E, Dondorp A et al. Recommendations for sepsis management in resource-limited settings. Intensive Care Med 2012; 38:557–574.
79 Child survival call to action. Available at http://www.apromise-renewed.org/A_Call_to_Action.html (2012) (Accessed 6 January 2013).