

Acute Respiratory Infection: Boston University's Collaborative Research Work in the Last Decade

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In the last decade, Boston University, in collaboration with the Child and Adolescent Health Division of the World Health Organization (WHO), has conducted a number of multi-center clinical trials aimed at reducing the childhood mortality associated with acute respiratory infections (ARI). These studies have addressed questions of program relevance and challenges faced by implementing WHO case management guidelines. The spectrum of research studies has extended from endorsing WHO guidelines for using antibiotics in all children with fast breathing to evaluation of ARI guidelines for management of severe pneumonia. Research priorities have included assessing the capacity of community health workers to provide appropriate early treatment to children with pneumonia and to manage both pneumonia and malaria in countries with a dual burden of these childhood illnesses. These contributions are likely to have a long lasting impact on reducing the mortality and morbidity associated with childhood pneumonia.

Key Words: Pneumonia, ARI case management, Antimicrobial agents.

Childhood pneumonia has been recognized as a global public health problem for many years. Parallels drawn between pneumonia and 'the Cinderella of Communicable Diseases'(1) and 'the Forgotten Killer of Children,'(2) have been successful in bringing this problem to the center stage and promoting the advocacy for pneumonia as a public health priority in developing areas. The global Acute Respiratory Infection (ARI) Control Program was initiated by the World Health Organization (WHO) in late 1980s to urgently respond to the alarming under-five pneumonia mortality, which accounts for 19 percent of all under five deaths - more than any other illness(2). ARI control programs were soon initiated across the globe. Case classification and clinical management guidelines including choice of antimicrobial agents promoted by the WHO ARI Control Program were simple, based on available evidence and primarily focused on delivery of services through primary care and community health workers.

As the ARI control program was implemented, realities on the ground posed significant barriers to reaching the most vulnerable children. These challenges included training health workers to recognize the signs of severe pneumonia such as counting respiratory rate and identifying chest indrawing. Challenges faced in implementing the new clinical guidelines pertained to choice of antibiotics, management of wheezing and symptoms requiring referral. More research and stronger evidence were needed to justify continuation or modification of the WHO's Global ARI Control Program guidelines.

The Center for Global Health and Development at Boston University (BU) recognized the need for program-relevant research assessing the effectiveness of global guidelines for diagnosing and treating ARI. A specific 'ARI Portfolio' was developed at BU to focus on operations research and to respond to some of the key questions and concerns regarding pneumonia case management guidelines. In

collaboration with the Child and Adolescent Health Division of the WHO, BU has conducted a set of clinical trials designed to improve ARI case management at different levels of severity and reduce pneumonia-associated childhood mortality and inappropriate use of antimicrobials (*Table 1*).

ORAL ANTIBIOTICS FOR SEVERE PNEUMONIA

Unavailability of injectable antibiotics within health facilities, lack of trained staff to administer injections, and other resource constraints often made management of severe pneumonia with injectable antibiotics difficult or even impossible. Additionally, the risk of needle-borne infections, non-compliance by the patient/family, and family and administrative costs emerged as possible barriers to using injectable penicillin for treatment of severe pneumonia as per WHO guidelines. This led BU, IndiaCLEN, and other global partners to form the Amoxicillin Penicillin Pneumonia International Study (APPIS) group to address the question “*Can we replace injections with oral therapy for severe pneumonia?*” This multi-country, randomized, equivalency trial conducted in Columbia, Ghana, India, Mexico, Pakistan, South Africa, Vietnam and Zambia enrolled 1,702 children at 9 study sites to evaluate the efficacy of oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3-59 months. The results showed a treatment failure of 19% and 22% in both the groups at 48 hours and 5 days, respectively. Thus, the study findings concluded that injectable penicillin and oral amoxicillin are clinically equivalent for severe pneumonia treatment in controlled settings. In addition, the study also noted important potential benefits of oral treatment vis-à-vis injectables, like reduced risk of needle-borne diseases, need for hospitalization, and referral costs(3).

PREDICTORS OF TREATMENT FAILURE ON ORAL AMOXICILLIN

The findings from a subgroup analysis of 857 children who received amoxicillin for severe pneumonia in the APPIS study demonstrated the ability to predict treatment failure with pulse oximetry data after 12 hours of observation. The results suggested that the degree of hypoxia

increases risk of treatment failure of severe pneumonia. In the absence of a pulse oximeter to measure blood oxygen saturation, information gathered (vitals, clinical and danger signs) after 24 hours is equally valuable for improving prediction of treatment failure(4).

FAILURE OF STANDARD ANTIMICROBIAL THERAPY IN CHILDREN WITH HIV AND PNEUMONIA

A sub-analysis of the APPIS study findings mentioned above, was undertaken in 2006 to determine whether children aged 3-59 months with mild or non-symptomatic human immunodeficiency virus (HIV) infection and WHO-defined severe pneumonia have a higher failure rate than do HIV-uninfected children, when treated with the standard WHO treatment of parenteral penicillin or oral amoxicillin. Two study sites with high HIV prevalence in Durban, South Africa and Ndola, Zambia were included. Primary outcome measures were clinical treatment failure at day 2 and day 14. The results of this study suggested that HIV-infected children with severe pneumonia fail WHO-standard treatment with parenteral penicillin or amoxicillin at day 2 and day 14 more often than do HIV-uninfected children, especially young infants. Standard case management of ARI using WHO treatment guidelines was thus determined to be inadequate in areas of high HIV prevalence. These findings demonstrated the urgent need to reappraise empiric antimicrobial therapy for severe pneumonia associated with HIV-1(5).

AMBULATORY CARE FOR SEVERE PNEUMONIA

In addition to difficulties related to referral and transport, hospitalization of children with severe pneumonia is problematic in low resource settings due to the lack of essential supplies such as needles and syringes in the health facility, and the risk of nosocomial infections. In many situations, referral to a health facility is not possible due to socio-economic and cultural barriers. These critical barriers make a strong case for ambulatory care for children with severe pneumonia. The “New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia (NO-SHOTS) Study” was conducted in 7 study sites in Pakistan by BU faculty

TABLE 1 ARI PROGRAMMATIC CHALLENGES AND EVIDENCE FROM BOSTON UNIVERSITY COLLABORATIVE RESEARCH

Challenges/ Questions	Study (Ref)	Sites	Conclusions
Can oral therapy be a replacement for injectable antibiotics in treating severe pneumonia?	(3)	Columbia, Ghana, India, Mexico, Pakistan, South Africa, Vietnam, Zambia	-Injectable penicillin and oral amoxicillin are equivalent for severe pneumonia treatment in controlled settings -Potential benefits of oral treatment : reduces risk of needle born infections, need for hospitalization, referral and costs
Can children with severe pneumonia be managed with ambulatory care?	(6)	7 study sites in Pakistan	Home treatment with high-dose oral amoxicillin is equivalent to parenteral ampicillin for severe pneumonia without underlying complications
Do we continue with chloramphenicol as the first line treatment for very severe pneumonia?	(7)	Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia	Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for community acquired pneumonia
What are the predictors of treatment failure on oral amoxicillin?	(4)	India, Vietnam, South Africa, Zambia, Pakistan, Columbia, Mexico	- Degree of hypoxaemia increases risk of treatment failure of severe pneumonia. - Use of pulse oximeter improves detection of children with severe pneumonia at risk
What is the treatment failure rate of amoxicillin in children with non severe pneumonia?	A multi-center observational study of clinical outcome following amoxicillin treatment of non-severe pneumonia in children 2-59 months of age (NARIMA Study)	South Africa, Vietnam	Low treatment failure rates for non severe pneumonia thereby endorsing IMCI treatment guidelines
Do children aged 3-59 months with mild or asymptomatic HIV infection and severe pneumonia have a higher treatment failure than non HIV children when treated with the standard WHO treatment?	(5)	South Africa, Zambia	Higher treatment failure rates seen with children aged 3-59 months with mild or asymptomatic HIV infection and severe pneumonia
Does enhanced community management of severe pneumonia among children 2 – 59 months of age by CHW's improve the proportion of clinical treatment failures compared with the current standard of care consisting of referral to a health facility?	Cluster randomized trial of community case management of severe pneumonia with oral amoxicillin in children 2-59 mo	Pakistan	Study in progress
Is home-based treatment of severe pneumonia both effective and safe in settings different than existed in Pakistan with the NO-SHOTS study?	Safe outpatient treatment of severe pneumonia in children with oral amoxicillin in four countries	Vietnam, Bangladesh, Ghana and Egypt	Data under analysis
Can CHW's effectively treat and manage malaria and pneumonia in children under 5 in Zambia?	Integrated management of malaria and pneumonia study	Zambia	Data under analysis

in collaboration with WHO and the Pakistan Institute of Medical Sciences, Children's Hospital. Of the 2,037 children aged 3-59 months with severe pneumonia included in this study, the hospitalized group received parenteral ampicillin followed by oral amoxicillin and the home-based group received oral amoxicillin. This study concluded that home treatment with high-dose oral amoxicillin is equivalent to parenteral ampicillin for severe pneumonia without underlying complications(6).

However, since enrollment for the NO-SHOTS study occurred in the outpatient departments of tertiary care facilities in Pakistan, generalizability of the findings across varied geographic areas and health care settings was limited. To address this gap, BU researchers recently completed a study to determine if home-based treatment of severe pneumonia is both effective and safe beyond the results that were obtained by the NO-SHOTS team in Pakistan. This study was conducted in 4 geographically diverse countries (Bangladesh, Egypt, Ghana and Vietnam). Results are pending. Likewise, the IndiaCLEN Multicentre Trial of Home versus Hospital Oral Amoxicillin for Management of Severe Pneumonia in Children (ISPOT study) was also commissioned at 4 study sites in India. So far 540 children have been recruited and 505 children have completed the study. The study is in progress and 3 more study sites have been added.

COMMUNITY CASE MANAGEMENT OF SEVERE PNEUMONIA WITH ORAL AMOXICILLIN

In order to take the NO-SHOTS study one step further and prove the effectiveness of community based treatment, the Community Management of Severe Pneumonia with Oral Therapy (COMSPOT) group is currently conducting a cluster-randomized, controlled trial that aims to reduce infant and child severe pneumonia mortality by utilizing services of lady health workers (LHWs) in two sites in Pakistan to identify and treat severe pneumonia in the community versus referral to a local health facility. The study hypothesizes that community-based treatment will have a substantial positive impact on the many children with severe pneumonia who cannot reach referral facilities due to transportation difficulties.

REVISITING WHO GUIDELINES FOR THE CHOICE OF ANTIBIOTICS FOR SEVERE PNEUMONIA

WHO ARI Management Guidelines recommend chloramphenicol as the first line antibiotic for treatment of very severe pneumonia. Chloramphenicol has several limitations as a bacteriostatic antibiotic, including increased resistance of bacteria, particularly *H. influenzae* and *S. aureus*, and risk of bone marrow toxicity in malnourished children. These limitations led to questions about whether to continue with chloramphenicol as the first-line treatment for very severe pneumonia. The Severe Pneumonia Evaluation Antimicrobial Research (SPEAR) Study, a collaboration between Boston University, WHO and Johns Hopkins University, conducted an open label randomized controlled trial with 958 children from tertiary care hospitals in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia. The study results showed more treatment failures with chloramphenicol at day 5 as well as by days 10 and 21. Isolation of *S. pneumoniae* was associated with increased risk of treatment failure in the chloroamphenicol group at day 21, thus concluding that injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for community-acquired pneumonia(7).

TREATMENT FOR NON-SEVERE PNEUMONIA

WHO recommends use of antibiotics for children recognized to have pneumonia based on clinical finding of fast breathing irrespective of whether pneumonia is of bacterial or non-bacterial etiology. Although ARI control programs aim to treat all pneumonia cases, children with wheeze and those with non-bacterial infections may present with fast breathing without a need for antibiotics. Prescribing antibiotics to these children may increase the community prevalence of antimicrobial resistance. When WHO established these treatment guidelines for simple pneumonia, antimicrobial resistance was not common among the major lower respiratory tract bacterial pathogens, was not geographically widespread, and was not rapidly increasing in prevalence throughout the world. However the epidemiological and pharmacological context has changed, making it necessary to reduce

inappropriate antibiotic use, and sharpen the specificity of the Integrated Management of Childhood Illness (IMCI) guidelines. In order to assess the rationale of administering antibiotics to these children, a prospective observational study was conducted to determine the failure rate of oral amoxicillin in non-severe pneumonia at two sites: University of Natal Medical School, Durban, Republic of South Africa, and Pediatric Hospital #1, Ho Chi Minh City, Republic of Vietnam.

The results of this study (under publication personal communication) showed very low treatment failure rates from amoxicillin when used for non-severe pneumonia, thereby endorsing WHO guidelines of using antibiotics in all children with fast breathing. Non-severe pneumonia appeared to be adequately treated with the standard amoxicillin therapy. The failure rate at 48 hours was 2.6%, which was considerably lower than the 12% failure rate. The beneficial role of amoxicillin in treating all children with non-severe pneumonia, whether due to bacterial or non-bacterial etiology, cannot be established with a high degree of certainty in the absence of microbiological confirmation of blood culture or lung aspirates. Nevertheless, the high rate of positive radiological findings suggests that bacterial infection remains a frequent cause of non-severe pneumonia. The very low failure rate with amoxicillin further suggests that it retains significant efficacy for the treatment of this condition in these areas.

MANAGEMENT OF MALARIA AND PNEUMONIA AT THE COMMUNITY LEVEL IN ZAMBIA

Pneumonia and malaria are the two leading causes of morbidity and mortality among under five children in Zambia. In rural areas, most sick children, including those with malaria and pneumonia, are seen by community health workers (CHW) because primary care facilities are not readily accessible. Zambia is now deploying artemether-lumefantrine (AL) at the community level for the treatment of malaria, but there are concerns about over-usage of this expensive drug. For pneumonia, under the current policy, CHWs refer children to the nearest health facility, which may be located some distance

away, leading to many children having delayed treatment or no treatment at all.

BU has recently completed a cluster-randomized controlled study assessing the effectiveness and feasibility of having CHWs manage malaria with the aid of malaria rapid diagnostic tests (RDTs) and pneumonia based on WHO case management guidelines. In the intervention arm, CHWs conducted RDTs for malaria on children, treated those with confirmed parasitemia with AL, and treated non-severe pneumonia with amoxicillin. In the control arm, CHWs treated children for malaria based on presence of fever and referred pneumonia cases to the nearest health facility. All CHWs were trained to refer children with signs of severe malaria or pneumonia to the nearest health facility. Preliminary results show that for pneumonia, 66.8% (176/285) in the intervention group received early and appropriate treatment compared to 11.3% (18/160) in the control group (RR 5.5; 95% CI 3.5 – 8.6)(8). The capacity of CHWs to use RDTs, AL and amoxicillin to manage malaria and pneumonia at the community level is very encouraging. This model has the potential to reduce over usage of AL and provide early and appropriate treatment to children with pneumonia.

CONCLUSION

Boston University in collaboration with its global partners including the Child and Adolescent Health Division of the WHO has conducted several studies that have resulted in the modification of national and international pneumonia treatment guidelines including a revision to the ARI component of the WHO IMCI guidelines. These contributions are likely to have a long lasting impact on reducing the mortality and morbidity associated with childhood pneumonia.

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