Ambulatory Management of Chest-Indrawing Pneumonia

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(See the Major Article by Agweyu et al on pages 1216–24.)

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In 2010, after reviewing the evidence about management of chest-indrawing pneumonia, the World Health Organization (WHO) recommended that national programs adopt oral amoxicillin for outpatient pneumonia treatment [1, 2]. Shortly thereafter, when this same evidence was reviewed by Kenyan clinicians, policy makers, and academics, they declined to adopt this policy for Kenya, citing concerns that previous evidence showing equivalence of oral amoxicillin to injectable penicillin did not include enough high-mortality settings such as sub-Saharan Africa. To address this, Agweyu et al conducted a pragmatic trial in Kenya showing that oral amoxicillin is equivalent to injectable penicillin for treatment of chest-indrawing pneumonia in children [3]. The results of this study, published in this issue of *Clinical Infectious Diseases*, demonstrate that even in Kenya, among a cohort of children (N = 527) with a high degree of comorbidities, overall mortality is low (0.8%) in those with WHO-defined chest-indrawing pneumonia who receive treatment. This study reinforces previous trials showing the equivalence of these 2 regimens [4, 5] and has important policy implications for settings where pneumonia is still a leading cause of childhood death. These results should facilitate policy change in Kenya (and other African countries), allowing human immunodeficiency virus (HIV)-uninfected children with chest-indrawing pneumonia to be treated as outpatients with oral amoxicillin.

Although progress has been made [6], pneumonia continues to be a major killer of children aged <5 years despite effective interventions such as vaccines against measles, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b; exclusive breastfeeding; and appropriate case management. Unfortunately, coverage of these interventions remains poor in many low-resource settings, particularly for exclusive breastfeeding and pneumonia treatment [7]. Thus, to achieve further reductions in childhood pneumonia mortality and morbidity, we urgently need new strategies that move effective treatment into the community to reach more patients.

To understand why studies like this are so important, it is helpful to remind ourselves how the current WHO recommendations for treatment of chest-indrawing pneumonia with oral amoxicillin came about and why they are critical in the continued fight to reduce child mortality. In early 1980s, to address high childhood pneumonia mortality [8], the WHO program for control of acute respiratory infections (ARIs) first recommended standard case management for pneumonia in children aged 2–59 months, which included oral cotrimoxazole for treatment of fast-breathing pneumonia on an outpatient basis and referral for injectable therapy for children with lower chest-indrawing and danger signs [9, 10]. In the late 1990s, these guidelines were simplified and incorporated into the now-ubiquitous Integrated Management of Childhood Illness algorithm [11]. While these guidelines were highly influential, by 1991 data from Pakistan on children with ARIs showed that 62% of *S. pneumoniae* strains had decreased susceptibility to cotrimoxazole, of which 31% were fully resistant [12]. Still, observational clinical outcome data from Pakistan showed that >90% of children with fast-breathing pneumonia responded to oral cotrimoxazole [13]. Nonetheless, owing to the lack of controlled trials, it was unclear whether the recommendations

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were both safe and effective for care and treatment of pneumonia.

To address this evidence gap, a randomized placebo-controlled trial was conducted in Pakistan comparing oral cotrimoxazole with oral amoxicillin for treatment of fast-breathing and chest-indrawing pneumonia, which showed that clinical treatment failure rates were equivalent for fast-breathing pneumonia, but amoxicillin was superior to cotrimoxazole in treating chest-indrawing (82% vs 67% cure rate, respectively) [14]. This led to the Amoxicillin Penicillin Pneumonia International Study (APPIS) multicenter trial in Colombia, Ghana, India, Mexico, Pakistan, South Africa, Vietnam, and Zambia comparing oral amoxicillin to injectable penicillin for treatment of chest-indrawing pneumonia, which showed that both regimens were equivalent for clinical treatment outcomes [4]. The pneumonia intravenous oral antibiotic treatment multicenter trial in England compared oral amoxicillin with intravenous penicillin in children hospitalized with severe pneumonia and found treatment outcomes to be equivalent [15]. This study was unique in that it was conducted in a highly industrialized setting and enrolled only radiologically confirmed cases.

These carefully conducted studies generated the evidence base demonstrating that oral amoxicillin was both superior to cotrimoxazole and equivalent to injectable penicillin for treatment of chest-indrawing pneumonia. Proposed as justification for changing WHO policy to move case management to an outpatient setting, these studies were considered insufficient because they were all done in a hospital setting. To address this shortfall, the new outpatient short course home oral therapy for severe pneumonia (NO-SHOTS) multicenter trial compared oral amoxicillin treatment at home on an outpatient basis to injectable ampicillin in the hospital and reported equivalence in treatment outcomes and similar safety profiles [5]. This trial was further supported by safety data from an observational multicenter study in Bangladesh, Egypt, Ghana, and Vietnam showing low treatment failure rates across communities and geographic regions [16].

In 2012, after considering this new evidence utilizing the Grades of Recommendation, Assessment, Development and Evaluation Working Group process, the WHO guidelines development panel strongly recommended that oral amoxicillin be used to treat chest-indrawing pneumonia (without danger signs) as outpatient treatment in low-HIV settings, whereas in high-HIV settings, such children should be referred for hospitalization and injectable therapy [2]. This recommendation should bring access to treatment for more children with pneumonia in low- and middle-income countries and reduce hospitalizations, but more evidence is needed to determine whether outpatient care is as effective as hospital-based care across diverse settings.

This is why Agweyu et al's study is so important, as it shows that oral therapy is as effective and safe as injectable therapy even in a high-mortality setting [3]. Restricting this approach to children with chest-indrawing pneumonia, in the absence of danger signs, identifies the subset of children with lower mortality, as was seen here as well as in APPIS and NO-SHOTS. Although this includes cases of viral infection and bronchospastic disease, there are also certainly some bacterial pneumonia or mixed viral–bacterial infections [17] for which antibiotics are appropriate. Early initiation of oral antibiotics in the community has recently been shown to be superior to more delayed referral for hospital treatment with injectable antibiotics, thus supporting the role of antibiotic treatment in this population [18].

Recently, critics have restated old concerns that antibiotic trials such as these cannot truly determine equivalence in the treatment of bacterial pneumonia due to the unavoidable inclusion of patients with viral infection, which creates a bias toward the null that can make 2 treatments appear equivalent, even if one is superior (Pollyanna phenomenon) [19, 20]. We previously addressed this criticism in part [21]. Although it is true that Agweyu's study cannot be used as evidence that oral therapy is as effective as injectable therapy for treatment of pure bacterial pneumonia, this is not the issue. Agweyu et al's study, and the other chest-indrawing pneumonia equivalence studies, show it is safe and no less effective to treat this relatively low-mortality subset of childhood pneumonias at home on an outpatient basis as in the hospital. Ambulatory treatment of pneumonia with oral antibiotic allows earlier treatment initiation, lower costs to the healthcare system and patients, reduced iatrogenic complications associated with hospitalization, and lowered burden on family members from prolonged hospitalization, at the risk of overtreatment of nonbacterial pneumonias with antibiotics. Until there are sufficient tools to diagnose bacterial pneumonia in low-resource facilities or in the community, this approach will reach more children, including those with mild bacterial pneumonia or cases of viral pneumonia at risk of bacterial secondary infection. Although there may be considerations about the most robust methodologies for this type of research, these data provide an appropriate and pragmatic way forward for management of childhood pneumonia.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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