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EDITORIAL COMMENTARY

Treating Sick Young Infants With Only Fast Breathing With Oral Amoxicillin in Resource-Limited Settings: Taking the High Road?

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(See the Major Article by Tikmani et al on pages 184–9.)

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Pneumonia is one of the leading causes of childhood deaths, including among neonates [1]. Clinical diagnosis and treatment of pneumonia still remain a challenge in children, especially in neonates and young infants up to 2 months of age. The World Health Organization (WHO) includes fast breathing (defined as ≥60 breaths per minute) in young infants up to 59 days of age as a sign of pneumonia and recommends treatment with antibiotics [2]. In neonates, fast breathing could also be due to transient tachypnea of the newborn, prematurity, birth asphyxia, or congenital heart disease along with infections. A small proportion of healthy young infants breathe faster than 60 breaths per minute [3]. We know that not all respiratory infections are bacterial in origin requiring antibiotics. However, it is extremely difficult to clinically differentiate between bacterial and other causes of pneumonia. Some have argued that fast breathing alone should not be categorized as pneumonia and not be treated with antibiotics at all [4], especially in neonates [5]. But unless we can get a good rapid diagnostic point-of-care test for pneumonia, this debate will continue.

In 2015 the WHO published a guideline for managing possible serious bacterial infection (PSBI) with simplified antibiotic regimens in young infants up to 59 days of age when referral is not feasible to reduce young infant mortality rates [6]. This guideline is intended for use in resource-limited settings. The guideline reported results of a systematic review analyzing whether a simpler antibiotic regimen delivered in ambulatory settings was as effective as a combination of injectable penicillin and gentamicin for at least 7 days (standard of care) among neonates (0–28 days old) and young infants (0–59 days old) presenting with fast breathing as the only sign of PSBI. The review identified a single open-label randomized trial, the African Neonatal Sepsis Trial (AFRINEST), which was conducted across Africa in the Democratic Republic of Congo, Kenya, and Nigeria [7]. AFRINEST enrolled 2196 infants randomized to either oral amoxicillin or injectable penicillin plus gentamicin, and demonstrated equivalence of feasibility and safety of the 2 regimens on the basis of outcomes of treatment failure at day 8, relapse, mortality within 2 weeks, and adherence. Evaluating existing evidence utilizing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [8], the WHO guideline development group made 2 strong recommendations for children with fast breathing as the only sign of illness. First, young infants up to 6 days of age with fast breathing as the only sign of illness should be referred to hospital, and if referral was not feasible, they should be treated with oral amoxicillin for 7 days. Second, young infants 7–59 days of age with fast breathing as the only sign of illness do not need referral and should be treated with oral amoxicillin for 7 days by a trained health worker on an outpatient basis. Moving from an injectable to an oral regimen marked a paradigm shift for managing isolated tachypnea in sick young infants, to ensure that all babies in resource-limited settings will have access to treatment.

At the time of development of this WHO guideline, no evidence was identified from other parts of the world. That is why the results of the study by Tikmani et al, published in this issue of *Clinical Infectious Diseases*, strengthen the evidence in 4 ways. First, this first of its kind double-blind randomized controlled equivalence trial in young infants was conducted in a low-income

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setting of Pakistan. Second, the investigators have gone a step ahead by adding an untreated control group, thus for the first time proving need and efficacy of antibiotics for the treatment of fast breathing alone in young infants in low-resource settings, laying to rest some of the criticism of AFRINEST [5]. Third, a careful analysis of the outcomes with no mortality and low rates of treatment failure and relapse with oral amoxicillin use is consistent with WHO recommendations. Finally, the outcome assessors were blinded to the treatment assignment, thus eliminating differential bias that may have led to overestimation of treatment failure and providing robustness and coherence to the results of the systematic review reported in the WHO guideline document [6].

The investigators report that the trial was stopped early on the advice of the data and safety monitoring board (DSMB) after enrollment of one-third of the study sample size. There has been some criticism of stopping trials early [9], and some might think that this trial was stopped prematurely. DSMBs play a critical role in the conduct of clinical trials by evaluating the perils and benefits of an intervention and augment the safety of trial participants [10]. Deaths in a placebo group are something that is very hard to ignore, especially when there are none in the oral antibiotic group.

Use of oral amoxicillin for isolated fast breathing for treatment of pneumonia in young infants in low-resource settings has limitations. While outpatient oral amoxicillin is affordable, is universally accessible, and has better medication compliance, it may not be as safe among premature infants or those with very low birth weight, in whom respiratory distress may be caused by conditions other than infections. Prematurity rates are disproportionately higher in low-resource settings [11], and lead to substantial neonatal morbidity and mortality. Tikmani et al's study excluded babies born before 37 weeks or with weight <1800 grams, whereas AFRINEST had excluded young infants with weight <1500 grams [2]. The WHO guideline is also not applicable to infants weighing <1500 grams for whom referral and injectable antibiotic therapy are mandatory [6]. Effectiveness and safety of oral amoxicillin is also conditional on reliable detection of cyanosis and hypoxia, which are signs of critical illness. Healthcare workers need to be trained for detection of cyanosis until availability and use of pulse oximetry can be ensured in these settings.

WHO, along with other stakeholders, has worked with governments and local bodies in several countries in Africa and South Asia to establish public-sector early implementation sites for the new WHO guideline to manage PSBI where referral is not feasible [12]. There is a commitment to continue to monitor new evidence to support or modify these recommendations even as they are implemented. It is essential to learn lessons from these implementation research sites to address limitations and barriers to the potential scale-up of this guideline in low-resource settings, where most neonatal deaths are occurring. The overall objective is to increase access to effective treatment for all those sick young infants who need it.

Notes

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