Unexplained Benefits of Antibiotics in Childhood: Empiricism in Need of Enlightenment

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(See the major article by Gilliams et al on pages 585–92.)

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Infections remain relentless causes of morbidity and mortality, particularly in the developing world. Pneumonia, diarrhea, and malaria kill 3.5 million, 2.5 million, and 655,000 people annually, respectively, and disproportionately injure children less than 5 years of age [1]. Any reduction in this burden to children should be welcomed.

In this issue of *The Journal of Infectious Diseases*, Gilliams et al [2] report that by adding azithromycin to chloroquine to treat childhood malaria, the incidences of subsequent respiratory and gastrointestinal infections are lowered, and times to next pulmonary and diarrheal illness are prolonged. For every 7 children treated with chloroquine-azithromycin for malaria, 1 case of respiratory-tract infection and 1 case of gastrointestinal-tract infection were apparently averted. This work extends prior efforts in Ethiopia, demonstrating that mass azithromycin treatment for trachoma reduced all-cause and infectious childhood mortality [3] and that azithromycin was associated with reduced mortality in a cluster-randomized trial for trachoma control [4]. The data of Gilliams et al also complement those of Trehan et al, who demonstrated a 40% reduction in mortality in Malawian children by adding amoxicillin or cefdinir to ready-to-use therapeutic food regimens for the outpatient treatment of acute severe malnutrition [5].

Why might the addition of azithromycin to chloroquine reduce gut and respiratory infections? It is possible that the illnesses averted in the azithromycin antibiotic group were, in reality, unusual presentations of malaria [6, 7]. However, these children had no smear evidence of malaria when they had these gut and lung infections, making this explanation less likely. Alternatively, the azithromycin could have fortuitously inhibited growth of a specific pathogen acquired by a susceptible child before or during the course of the antibiotic treatment, thereby prohibiting pathogen population expansion or preventing colonization. The nonplasmoidal, nonchlamydial target(s) of azithromycin in this cohort might have been *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhi*, nontyphoidal salmonella, other gram-negative bacilli, group B streptococcus, and even mycobacteria, based on studies of childhood sepsis in Africa [8–13].

Another potential explanation for the success of azithromycin is that it altered the host’s commensal microbial population such that a yet to be encountered pulmonary or intestinal pathogen did not take hold. Finally, azithromycin might have had a nonspecific antiinflammatory effect that ameliorated the manifestations of illnesses that resemble lower-respiratory-tract infections or gastroenteritis [14].

There are precedents for antibiotics conferring unintended benefits. For example, 4 decades ago, Steigman et al, at Mount Sinai Hospital in New York, reported the complete absence of early-onset group B *Streptococcus* (GBS) infections in their newborns, which they associated with universal use of intramuscular penicillin to prevent ophthalmia neonatorum [15]. They stated “...we believe there is an urgent need to encourage appropriate, carefully designed prospective alternate case studies in order to determine whether a serendipitous observation can or cannot prevent deaths due to early-onset invasive GBS disease...”

Intrapartum antibiotic prophylaxis of women, prompted by controlled studies and guided by diagnostic microbiology [16], is now established as an intervention to reduce the morbidity and mortality of early-onset GBS infections [17]. Sometimes the benefit of antibiotics is demonstrated before the etiology of a disease is
known. Enterotoxigenic E. coli were identified as the cause of traveler’s diarrhea in 1975 [18], but over a decade earlier, Kean et al demonstrated that antibiotics prevented or ameliorated this entity [19]. These authors cautioned “…it requires no great medical sagacity to predict that if such drugs are administered without adequate precautions … toxic symptoms will occur.” They were prescient: current guidelines do not recommend antibiotics for the prevention of traveler’s diarrhea because of the adverse effects of these drugs, and concern about selecting resistant bacteria [20]. Moreover, and most pertinent to the work of Gilliams et al, there is an effective alternate strategy to prophylaxis for traveler’s diarrhea that involves halting incipient episodes by early syndrome recognition and treatment with antibiotics.

Azithromycin has a good safety profile, but no drug is harmless. Like other macrolides, azithromycin might be associated with sudden cardiac death [21], and has a low rate of hepatic, gastrointestinal [22], and ototoxic side effects [23]. The resistance of nasopharyngeal isolates of S. pneumoniae increases after mass azithromycin distribution for trachoma [24], and susceptibility increases after macrolide pressure is released [25]. Nonetheless, despite our ignorance as to the reason for their effectiveness, children in low-income settings at risk for life-threatening infections do seem to benefit from short courses of antibiotics.

It is likely that antibiotics used inappropriately have, to this point in history, saved more lives than they have cost. This gilded therapeutic era is probably saved more lives than they have cost. This gilded therapeutic era is probably in its twilight, but the current side-effect “price” of potentially helpful antibiotics (eg, azithromycin and β-lactams) is low, and their “value” (ie, aversion of death or of potentially serious gastrointestinal or pulmonary infections) is high. The low numbers needed to treat or to avert cases of pneumonia and of diarrhea, as calculated by Gilliams et al, reflect the high frequency of such illnesses and the continued susceptibility to antibiotics of their putative causative agents. These antimicrobial “market conditions” are unlikely to persist, and we cannot continue to rely on microbiologically unenlightened empiricism. It is now time to learn why and how fortuitously timed azithromycin and β-lactam antibiotics prevent deaths, acute lower-respiratory tract infections, and gastrointestinal illnesses in children in Malawi and elsewhere. Specifically, it is crucial to determine what etiologic agents are being inhibited by antibiotics, and what illnesses are unlikely to respond [13]. Diagnostic, treatment, and preventive strategies should then be built on such knowledge, as was done for neonatal GBS infection and traveler’s diarrhea. If expanded use of antibacterial agents is adopted to prevent severe childhood infections without knowing their exact targets, side effects and resistance might soon thwart the advantages they confer on recipient populations.

Notes

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