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 apparently averted. This work extends this burden to children should be welcomed.

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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 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.

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**References**


