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EDITORIAL

Empirical antibiotic treatment for children suffering from dysentery, cholera, pneumonia, sepsis or severe acute malnutrition

In this special supplement of Paediatrics and International Child Health, there are five reports on systematic reviews of literature, focusing on empirical antibiotic treatment for children suffering from dysentery [1], cholera [2], pneumonia [3], sepsis [4] or severe acute malnutrition [5]. These conditions are estimated to cause about a third of the 5–6 million deaths annually of children under 5 years of age [6]. Appropriate antimicrobial treatment would significantly reduce their mortality, but the choice of antibiotic is often not straightforward. Besides the specific infection and epidemiology of the aetiological agents and their resistance to antibiotics, this choice is affected by formulation, pharmacokinetics, cost and the availability of suitable medicines as well as many other issues that affect national and international health-care policies and practices.

The reviews were originally solicited by the World Health Organization (WHO) that has the mandate to support its member states through the provision of normative guidance on health promotion. There are two main tools to implement this normative support for the reduction of mortality from childhood infectious diseases: the WHO model list of essential medicines (EML) and technical guidelines about health promotion or case management of sick children. The WHO EML compiles medications considered to be most effective and safe to meet the key needs in a health system and it is frequently used by countries to help develop their own national lists of essential medicines. Technical guidelines, on the other hand, give guidance to health practitioners on the role and use of medicines in specific situations.

The EML and the WHO technical guidelines are regularly updated by a rigorous, transparent and evidence-based process. These updates are motivated by the discovery of new medicines, other scientific innovations, changes in medical supply and cost and changing microbial epidemiology and emerging bacterial resistance to antimicrobial agents. The five reviews published in this supplement served to inform the WHO expert committees who formulated the latest edition of the EML, published in June 2017 [7]. A systematic review of evidence on the safety, efficacy and feasibility of various antibiotic treatment options for selected bacterial infections in children was especially relevant for this update as both scientists and regulatory authorities published some new concerns about the safety of two drugs that the WHO was recommending for dysentery or cholera treatment: fluoroquinolones and azithromycin (if used in combination with antimalarial drugs) [8,9].

In the first paper, Williams and Berkley review data on the treatment of dysentery, i.e. bloody diarrhoea assumed to be caused by Shigella species. At the beginning of this millennium, more than 100 million episodes of dysentery were estimated to occur annually in children under 5 years of age [10], and there is no evidence to show that the incidence would have fallen much since then. The review focuses on papers published after 2005 when the most recent technical WHO guideline was published [11]. The authors conclude that there are few new data to warrant a change in the WHO recommendation to treat children with dysentery primarily with ciprofloxacin and secondarily with pivmecillinam or ceftiaxone. As an alternative, the authors suggest azithromycin and cefixime as orally administered second-line drugs, although with certain caveats.

A second paper by Williams and Berkley focuses on the empirical management of children with cholera, a condition that affects approximately 3 million individuals each year [12]. The latest WHO recommendation in 2005 is a three-day course of tetracycline for children with severe dehydration and no antibiotics for children with less dehydration [13]. The authors conclude that there is no reason to question the key role of fluid resuscitation. Regarding antimicrobial therapy, however, there is new evidence that single-dose azithromycin would be equally or more active, but logistically easier and with a more favourable safety profile than the recommended three-day tetracycline.

In their third paper, Williams and Berkley review recent publications on the empirical management of children with severe acute malnutrition (SAM), a condition that is estimated to affect some 20 million children annually and is associated with high mortality, often from infectious causes. The most recent WHO recommendation for this condition was in 2013 [14] and it suggests empirical oral amoxicillin for children with SAM and no complications, and parenteral benzylpenicillin and gentamicin for those with complications. In their review, William and Berkley find little new evidence to warrant a change in this policy. When technical guidelines are next updated, some fine-tuning might be undertaken to harmonise the recommended dosages of amoxicillin for various diseases.

The fourth paper in the series by Mathur and his collaborators focuses on the management of children with community-acquired pneumonia which is estimated to account for approximately 15% of all deaths of under-5 children. In 2014, WHO recommended a five-day course of oral amoxicillin for uncomplicated pneumonia and intravenous ampicillin

or penicillin combined with gentamicin for severe conditions [15]. As for SAM, the systematic review did not reveal new data to justify a change in the recommended empirical therapy. However, the authors note significant gaps in knowledge of the actual patterns of antibiotic use and of the relative efficacy of alternative medicine in various contexts.

In the fifth review, Fuchs and others appraise the recent scientific literature on the optimal management of neonates and infants with sepsis or possible serious bacterial infection in low- and middle-income countries. They identified five adequately designed and powered studies that compared antibiotic treatment in a low-risk community and were published after the most recent WHO guidelines (2013) [16]. Again, the review did not bring forward reasons to change the current advice to use parenteral gentamicin and penicillin as a primary combination for hospital-based patients and intramuscular gentamicin and oral amoxicillin when referral is not possible.

The five reviews and the underlying original scientific papers were reviewed by two expert WHO committees, one that focused especially on technical guidelines for paediatric infectious conditions and another that was in charge of compiling the WHO 2017 update on EML. In January 2018, the EML was presented at the 142nd session of the WHO Executive Board (EB). As a series of WHO EB recommendations, the EML will guide national and international policies on the use of antibiotics for the next years. Through this policy-level influence, these five reviews will thus have a significant impact on paediatric public health, especially in low- and middle-income countries. Publication in Paediatrics and International Child Health will reinforce this positive effect by reaching a wider group of scientists and practitioners who make the final choices of antibiotic therapy for individual sick children.

One common theme in all five reviews and subsequent expert committee discussions is a major concern about the threat of an increased prevalence of antimicrobial resistance (AMR). This is often related to the prescription of antibiotics for conditions that do not actually have a bacterial origin or to the selection of ineffective or unnecessarily broad-spectrum antibiotic, when the clinician is unsure of the aetiology or antimicrobial sensitivity of a potential pathogen. To ensure the judicious use of antibiotics and the future availability of effective drugs for the management of important paediatric infections, the scientific community will need to develop reliable, inexpensive and easy-to-use point-of-care tests to detect microbiological aetiology and antibiotic sensitivities of common childhood infections. I certainly hope that many readers of Paediatrics and International Child Health will take up this development challenge!

Disclaimer

The opinions expressed in this paper are the author's own and do not necessarily reflect the policy of the WHO.

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