ABSTRACT

Antimicrobial resistance is of global concern, and preserving the ability of many antimicrobials to kill disease-causing bacteria is likely to become more challenging over time. However, we are speeding up this process dramatically by using antibiotics too much or in the wrong way. Respecting simple key principles of optimal antibiotic prescribing together with commitment to further research in this area from the paediatric community is essential to extend the lifeline of antibiotics for the most vulnerable patients without limiting access to antibiotics for those children who require treatment.

What can we do about antimicrobial resistance?

Antimicrobial resistance (AMR) is an internationally recognised threat to health. New resistance mechanisms are emerging and spreading globally, threatening our therapeutic options for infectious diseases especially in developing countries, where second- and third-line antibiotics are unavailable or unaffordable (1,2). AMR increases the cost of health care with lengthier stays in hospitals, additional tests and the use of more expensive drugs and intensive care (1). Throughout the world, children are frequent consumers of antibiotics, and such routine use has been shown to increase the probability of AMR (3-5). The role of AMR in global childhood mortality can be illustrated in neonatal sepsis, where multidrug-resistant pathogens currently account for 30% of all global neonatal sepsis mortality according to a recent estimate in 2016 (6).

In 2017, the WHO conducted an analysis of the antibacterial development pipeline and warned of a substantial lack of new antibiotics under development to treat the increasing number of resistant infections (7). They describe a lack of treatment options especially for multidrug resistant and extensively drug resistant Gram negative pathogens, some of them causing common infections such as pneumonia or urinary tract infections. Most of the new substances in clinical development are modifications of existing classes of antibiotics with only small added value to the antibiotics currently available on the market. Additionally, most modified or innovative substances under development are for intravenous use and therefore excluded from the large sector of outpatient medicine (7).

When new antibiotics are produced, clinical trials in children are necessary for their registration and definition of optimum use. However, regulatory clinical trials investigating antibiotic efficacy are sparse, leading to delayed approval and marketing authorisation of new antibiotics for children (8). As a result, the rate of off-label prescribing in children remains high and clinicians are forced to treat their patients without proper information on dosing across age-groups or clinical safety (8,9).

One means to address the challenge of AMR is to reduce antibiotic use with the aim of limiting selection pressure for emergence of resistant bacteria. However, access to appropriate antibiotic treatment is clearly central to achieving sustainable development goals relevant to child health: infections continue to contribute substantially to child mortality and morbidity (10). At the level of the patient-clinician interaction, a limited number of key principles of optimal antibiotic prescribing need to be taken into account (**Figure 1**). In many areas of childhood antibiotic use, robust evidence to inform clinical decision-making for specific infections is currently lacking (8).

**Table 1** summarizes a number of land-mark randomized controlled trials published from 2000 onwards and addressing research questions of antibiotic use in key childhood infections from birth to 16 years of age (11-28). The literature search was done in Medline combining MeSH and free text terms for “antibiotics”, “child” and the Cochrane filter for randomized controlled trials. We selected publications published in one of four widely read medical journals (the British Medical Journal (BMJ), the Journal of the American Medical Association (JAMA), the Lancet, and the New England Journal of Medicine (NEJM)). Trials focusing specifically on yaws, trachoma, cholera, topical antibiotic applications, specific patient groups (e.g. children with cystic fibrosis, malnourished children), and preventive or prophylactic antibiotic use were not included.

Principles of optimal antibiotic treatment

Indication

Children are frequent consumers of antibiotics especially in early life, when upper respiratory tract infections including pharyngitis and otitis media are the main reasons for prescribing antibiotics (29). While antibiotic treatment for acute otitis media has been shown to reduce symptoms and signs early on during illness, this impact is small and it has also been demonstrated to be associated with more side effects, such as diarrhoea (12,24). Investigations of delayed prescribing, an alternative strategy to immediate antibiotic treatment, have identified this as an acceptable and effective strategy for mild-moderately unwell children with no data suggesting negative longer-term sequelae (30,31). Antibiotic treatment for respiratory tract infections, whether indicated or not, has also been shown to be associated with a greater risk of airways carriage and of future infections caused by resistant bacteria (4). In adults, a randomised double-blind placebo-controlled trial in volunteers investigated the direct effect of macrolides, being among the drugs of choice for the treatment of respiratory tract infections, on resistance in the oral streptococcal flora of healthy volunteers (32): Macrolide-resistance in colonizing streptococci in the oropharynx evolved rapidly and the effect of a single course of antibiotics on the oral commensal flora lasted for more than 180 days. Therefore the commensal flora could serve as a reservoir of resistance for potentially pathogenic bacteria, and is another reminder about the striking ecological side-effects of unnecessary antibiotic treatment.

Choice of antibiotic drug

In many children with suspected or proven bacterial infection, initial or even on-going management is empiric. In some cases, such as bloodstream or urinary tract infections, this will be followed by adjustment once microbiology culture results become available. To choose the optimal empiric antibiotic or combination, one should consider the following factors: likelihood of pathogens and their source (based on information from rapid tests like e.g. Gram stain), the likelihood of possible drug resistance (known carrier of resistant pathogens, recent exposure to antibiotics or exposure to healthcare facilities, local resistance patterns) and host factors that may change one’s choice of antibiotic class (e.g. immunocompromised, renal impairment, allergy, pregnancy). Importantly, antibiotic choices are based on in vitro information related to the causative pathogen or microbial epidemiology of the target infection (33). The relationship between empiric treatment that is concordant to the identified pathogen and its antibiogram and good clinical outcomes is not fully understood, although adult data suggest that concordance may be important in severe systemic bacterial infections (34). Based on this, current guidelines on first-line therapies may explicitly aim to maximize treatment concordance, recommending very broad-spectrum options for empiric therapy, but do not take into account the potential negative effects of overuse of these agents (35).

A recent cluster-randomized, crossover trial investigated different recommended empiric treatment strategies for moderately severe community-acquired pneumonia (CAP) in adults, consisting of either beta-lactam therapy alone, combination therapy with a beta-lactam plus a macrolide or monotherapy with a fluoroquinolone for empirical treatment. The authors showed that a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam-macrolide combinations or fluoroquinolone monotherapy with regard to 90-day mortality in CAP (36). Unfortunately, pragmatic (and therefore widely generalizable) randomised controlled trials of this nature to investigate effectiveness of antibiotic treatment strategies in children are largely lacking, or are limited to specific conditions in the lower and middle income country setting (37).

Delivery (dose, route and duration)

Some factors of AMR are bacteria specific, but one factor of major importance in the emergence of resistance is suboptimal dosing (38). Low daily beta-lactam doses and a longer duration of treatment with a beta-lactam antibiotic are associated with an increased risk of pharyngeal carriage of penicillin-resistant Streptococcus pneumoniae (39). This has been replicated in a randomized controlled trial, in which short-course, high-dose therapy of amoxicillin reduced a child’s risk of posttreatment carriage of pneumococci non-susceptible to penicillin and to trimethoprim-sulfamethoxazole compared with standard therapy (40). Again, however, the relationship between dose and resistance selection is not straightforward, exemplified by the UK, which despite traditionally low-dosing strategies for oral beta-lactams does not have a particularly high prevalence of pneumococcal penicillin non-susceptibility compared with its European neighbours (41). A randomised controlled trial investigating the impact of lower and higher dose amoxicillin treatment on clinical and microbiological outcomes is currently enrolling children discharged from hospital with a diagnosis of CAP in the UK and Ireland (https://www.capitstudy.org.uk).

Severity of infection may necessitate intravenous treatment during the early empiric stages when children are unable to tolerate or reliably absorb oral antibiotic treatment or when inclusion of agents that can only be given intravenously is deemed necessary. Antibiotic regimens should be converted from intravenous to oral administration as soon as is feasible and clinically indicated. This intervention leads to shorter length of hospital stay for the patient with e.g. reduced probability of catheter-related or nosocomial infections and costs (42). However, the frequent start of parenteral empiric treatment combined with uncertainty about when to convert to oral therapy without harming the patient may lead to unnecessary prolongation of intravenous therapy. Again, robust evidence supporting rapid oral step-down therapy is lacking for many indications and recommendations are often based on observational data (43). To bypass this, Mertz et al. suggested a medical checklist with bedside criteria for switching from IV to oral antibiotics in adult patients on general medical wards, including defervescence for > 24 hours, clinical improvement and immunocompetence. They were able to show that this simple method could shorten the duration of IV therapy without any negative influence on the outcome of treatment (42).

Another critical element in the safe use of antibiotics lies in restricting their administration to the minimum duration required for efficacy. The idea that stopping antibiotic treatment early encourages antibiotic resistance is no longer supported by evidence, while taking antibiotics for longer is known to increase the risk of resistance (44). However, few data are available to inform clinicians on optimal duration of therapy in children. McMullan et al. systematically reviewed the evidence for minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections, comparing shorter courses with traditionally longer durations. In many infections, especially when clinical improvement is rapid, emerging data suggest that traditional long durations of intravenous antibiotics might be unnecessary (43).

“Individualizing” delivery: Personalised antibiotic therapy

The optimal dose, route and duration of antibiotic treatment are influenced by diverse host and disease factors. Rigid recommendations for antibiotic therapy based on poor evidence largely ignore this fact. Stratified recommendations, such as those for the management of acute otitis media and pharyngitis published by the National Institute for Health and Care Excellence, are one step towards a more adapted approach to antibiotic use (45,46). As used in these guidelines, clinical „biomarkers“ such as severity of symptoms or symptom improvement might be best to guide initiation and stopping or antibiotics (44). In the hospital setting, laboratory biomarkers may offer some relevant information for clinical-decision making. Looking at neonatal sepsis, a recent randomised controlled trial from Stocker et al. assessed whether procalcitonin-guided decision making for suspected early-onset sepsis could safely reduce the duration of antibiotic treatment. Almost 10% of term and late-preterm neonates in high-income countries are suspected for early-onset sepsis and treated with antibiotics during their first days of life while the prevalence of culture-proven early-onset sepsis in these countries is 0.1% or less (47). Results of the trial indicate that procalcitonin-guided decision leads to a reduced duration of antibiotic therapy and length of hospital stay. The rate of observed re-infection stayed low and no study-related mortality was observed (47). The SATT-trial (Simplified Antibiotic Therapy Trial) recently carried out a three-arm, randomised equivalence trial in young infants with clinical severe infection and no possibility for hospital admission in low and middle income countries. Two simplified antibiotic regimens requiring fewer injections (combination of intramuscular gentamicin and oral amoxicillin or benzylpenicillin and gentamicin administered intramuscularly followed by oral amoxicillin) were shown to be equivalent to a reference treatment (benzylpenicillin and gentamicin, administered intramuscularly during whole treatment) (48). This clinical trial could prove important in helping to improve access to care and newborn survival in children deprived of the option of hospital referral.

So what can we do about antimicrobial resistance? (Or: How do we get ourselves out of this?)

**Figure 1. Key principles of optimal antibiotic prescribing**

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| * Core elements of in- and outpatient antibiotic stewardship include commitment, stewardship program interventions, tracking and reporting, education and expertise. |
| * Be critical of how we use antibiotics in day to day practice, and be curious about how we should use antibiotics in day to day practice. |
| * Evaluate and re-evaluate indication, dose, route and duration during antibiotic treatment. Be aware of your patient’s clinical response to treatment instead of rigid courses of antibiotic treatment. |
| * Before changing an established therapy due to laboratory results on antimicrobial resistance patterns, first review clinical outcome of your patient. |
| * Be committed to high quality research investigating both efficacy and safety of antibiotic use. We’re in need for better research to develop a robust evidence base to inform practice and policy. |

To combat the global threat of AMR, simple steps to optimize the use of antibiotics are needed. The approach outlined includes a basic message, and should be used during routine care of all children receiving antibiotics. However, many evidence gaps remain, and commitment to further research in this area from the paediatric community is essential. If we determine and start to use the right drug at the right time at the right dose for the right duration, we might be able to considerably extend the lifeline of antibiotics for the most vulnerable neonatal and paediatric patients without limiting access to antibiotics for those children who require treatment.

*Abbreviations*: Antimicrobial resistance (AMR); Acute otitis media (AOM); Community-acquired Pneumonia (CAP); High-income country (HIC); Intravenous (IV); Low or middle-income country (LMIC); World Health Organisation (WHO); United Kingdom (UK); United States (US); Urinary tract infection (UTI)

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