Title:

Antimicrobial stewardship in children: where to from here?

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Conflicts of interest

We have no conflicts of interest to declare.

Abstract and Key Words

Abstract

Antimicrobial resistance is an ever-developing global threat and children are becoming increasingly affected. In addition to established antimicrobial stewardship measures, it is important to recognise the need for a paediatric focus to manage the physiological and pathological differences unique to children.

Most studies on paediatric antimicrobial stewardship are drawn from resource-rich, hospital settings. They support interventions including antimicrobial stewardship programmes, bundled groups of interventions, guidelines, and education initiatives. These must be tailored

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to specific institutions, populations and resources as translating interventions between these may not be effective.

There are knowledge gaps in paediatric antimicrobial stewardship which pose challenges to designing both interventions and research in this area. These include quantifying antimicrobial consumption, defining antimicrobial stewardship outcomes and understanding the development of antimicrobial resistance. Finding answers to fill these gaps needs urgent attention.

There is also a need to think outside the box to improve antimicrobial stewardship in children. Potential opportunities include intravenous antibiotics at home via hospital-in-the-home programmes, earlier switching to oral antibiotics, repurposing old antibiotics, and re-evaluating children labelled as having antibiotic allergy. Using all of the possibilities available gives us the best chance of staying ahead of the relentless march of antimicrobial resistance in children.

Keywords

Infectious Diseases, Pharmacology, International Child Health

Abbreviations

AMR: Antimicrobial Resistance

AMS: Antimicrobial Stewardship

ASI: Antibiotic Spectrum Index

ASID: Australasian Society of Infectious Diseases

C. Difficile: Clostridium Difficile

CDC: Centers for Disease Control and Prevention

DDD: Defined Daily Dose

DOT: Days of Therapy

EMR: Electronic Medical Records

HAI: Hospital Acquired Infections

IDSA: Infectious Disease Society of America

IV: Intravenous

LMIC: Low- and Middle-income countries

MDR: Multidrug-resistant

NICU: Neonatal Intensive Care Unit

WHO: World Health Organisation

Introduction

‘Stewardship is leaving a system better than you found it.’ -- Michael Barber.

With the enormity and urgency of a worldwide pandemic, it would be easy for antimicrobial resistance (AMR) to be treated as less of a priority, but it remains a long-term critical global health crisis.(1) Children are increasingly affected, particularly those in neonatal intensive care units (NICUs) and healthcare settings in low and middle income countries (LMIC).(2, 3) There has been increased antibiotic prescribing since the start of the COVID-19 pandemic, through attempting to reduce or manage secondary bacterial infections.(4) Increased antibiotic use risks the development of more resistant bacteria through selective pressure. With this growing threat to our ability to treat infections, it is crucial that we optimise the systems within which we practice, with multi-faceted approaches to decrease infection spread through infection control and decrease resistance acquisition through stewardship of antibiotics.

Antimicrobial stewardship (AMS) has been defined as ‘coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration.’(5) The basic model of effective AMS is similar between adult medicine and paediatrics, requiring an AMS programme with governance, education, antimicrobial policies and audit and feedback. However, as anyone who has tasted clindamycin suspension or managed a febrile 5-day-old child will attest to, children are not just little adults and seldom follow the rules.

What makes children special?

The spectrum of physiological and pathological differences, the increased diagnostic uncertainty and fewer available medications in paediatrics promote unique challenges to AMS and highlight why there is a need for a paediatric focus when devising AMS strategies. In many cases, paediatric antibiotic dosing has been extrapolated from studies of adult patients. Pharmacokinetics and pharmacodynamics in children are not the same as in adults (different renal capacity, liver function and volume to weight ratio, for example), and they change dramatically from the neonatal period to adolescence. Not accounting for these risks subtherapeutic regimens further contributing to AMR, or supratherapeutic regimens causing adverse events and toxicity.

Children have the highest use of antibiotics of any age group outside of the elderly, with 50% of Australian children receiving antibiotics by their first birthday.(6) They receive antibiotics during a critical period in their growth and development, with the long-term effects, particularly on the microbiome, as yet unknown. Neonatal intensive care units (NICUs) represent an increasing burden of AMR. While AMR is currently relatively low for older children in resource-rich countries, AMR is rising in all age groups, especially in LMIC.(3)

What should we do in children?

Some of the most effective interventions to reduce antibiotic use and AMR globally are larger than the remit of AMS in children. These include immunisation programmes, infection

control measures and regulation of antibiotic use in agriculture. Nonetheless, everyone has responsibility for this issue, so what can we do? Different solutions must be offered for different settings, whether it is in a resource-rich or resource-poor environment, in hospitalised patients, intensive care units or community practice. Different AMS interventions for children have been studied in these settings (figure 1). These range from larger interventions such as international guidelines or AMS programmes to smaller projects such as education-based initiatives or local antibiotic restrictions. Most of the research has been in hospital-based, resource-rich environments with fewer studies in the community or developing countries.

What we know works

Clinical guidelines

Clinical guidelines in AMS are designed to help practitioners prescribe antibiotics appropriately. These guidelines may be international (World Health Organisation (WHO): AWaRe), multinational (Australian and New Zealand Paediatric Infectious Diseases group: IV-Oral Switch) or national (Infectious Diseases Society of America (IDSA): AMS). (5, 7, 8) While there is limited evidence on the impact of international guidelines on paediatric AMS, there are several successful studies of national and local guidelines. Zhang *et al* found a reduction of 11-42% in total antibiotic use in 5 tertiary-children's hospitals in China following the introduction of national guidelines, although gains were mitigated by a gradual increase in spectrum of antibiotics used.(9) Chiu *et al* introduced a local vancomycin use guideline in 2 NICUs which resulted in over 40% reduction ($p<0.01$) in infants exposed to vancomycin without increase in mortality.(10) Development of guidelines is an opportunity for everyone, even with limited resources, to impact local prescribers.

AMS programmes and bundles

AMS programmes are large hospital-based strategies designed to ensure that antibiotics are prescribed appropriately to improve outcomes and reduce costs. These depend on partnership between the hospital's clinical leadership and experts in AMS, including infectious diseases physicians, microbiologists, and pharmacists. In a retrospective study, Hersh *et al* showed a 11% reduction in antibiotic use in children's hospitals with AMS programmes compared to 8% in control hospitals ($p=0.04$).(11) The study coincided with publication of the IDSA AMS guidelines, likely accounting for the fall that also occurred although to a lesser degree in antibiotic use in control hospitals.(5)

These are resource-intense initiatives which may not be feasible in developing countries. An alternative approach is through AMS bundles consisting of a small number of evidence-based practices that are implemented concurrently. Murni *et al* showed a decrease of 14% in hospital-acquired infections (HAI), 22% in inappropriate antibiotic use and 2% in mortality in a children's teaching hospital in Indonesia following the introduction of an AMS bundle consisting of a hand-hygiene campaign and WHO guidelines on antibiotic prescribing.(12)

Audit and feedback

All effective programmes rely on audit (checking the practice) and feedback (relaying the results back to the practitioner) to maintain clinical standards. For antibiotic prescribing, this is easier in settings that have personnel resources to do this, particularly with access to electronic medical records (EMR). Newland *et al* documented a 7% monthly decline in DOT for all antibiotic use ($p=0.45$) and 17% for targeted antibiotics ($p<0.001$) in a hospital undergoing audit and feedback compared to 5 control hospitals.(13)

Educational interventions

Simple educational interventions, such as informing prescribers of existing guidelines or emerging issues can reap large rewards. A one-day seminar on upper respiratory tract infections in accordance with Centers for Disease Control and Prevention (CDC) guidelines for community-based physicians in Israel reduced antibiotic prescription rates by 5% for otitis media and increased the odds ratio of appropriate antibiotic treatment by 1.8 ($p<0.01$). (14, 15) Given the high use of antibiotics in the community, where there is less AMS oversight, this could be a high yield intervention.

Antibiotic restriction and approval

Restriction programmes that require approval for selected antibiotics reduce both use of antimicrobials and costs. An example of a novel approach was by Agwu *et al* in who introduced an online rapid approval/refusal system with dispensing through text messaging to a tertiary-paediatric hospital in Baltimore. They found a 12% reduction in restricted antibiotic dispensing with over USD300,000 projected savings on medications annually.(16)

What don't we know?

There are significant knowledge gaps in several areas of AMS in children and these hamper our ability to develop the best interventions. Some of these are due to the difficulties in transferring measures from adult medicine, including both measures of antibiotic consumption, and outcome measures of AMS effectiveness. Antibiotic use in adults is quantified using defined daily dose (DDD), which is not transferable to paediatrics due to weight-based dosing and different dosing regimens at different ages. A more useful measure, particularly in hospitalised children is days of therapy (DOT). However, unless a hospital has EMR, this is very labour-intensive and the majority of healthcare settings, particularly those in LMIC, do not have the resources to do this routinely or comprehensively. The right outcome measure is also problematic in children. In adults, outcomes of AMS effectiveness include mortality from invasive AMR infections and rates of *Clostridium difficile* infection. Children have more robust immune systems and fewer co-morbidities than hospitalised adults, so the risk of death is low. Additionally, healthy, antibiotic-naïve young children are commonly colonised with *C. difficile*, so this is not a useful marker of AMS.

Understanding the development of AMR remains challenging for paediatric and adult medicine alike. Most studies on AMR in children are focused on high risk groups such as neonates and hospitalised children in specific settings, and the findings are difficult to generalise across settings in different intensity or resource environments. There are few studies of community AMR or development/acquisition of AMR in children. Studies on

antibiotic prescribing across regions could be overlaid against future paediatric AMR studies, which may help us understand how prescribing affects resistance.

What else could we be doing?

In times of crisis, one adage is to do more of the same but better, and this applies to tackling AMR through AMS. However, given the challenges in paediatrics, it is worth thinking outside the box to improve AMS. Some ways to think about potential interventions include replace, relocate, reduce, repurpose, and relabel antibiotics. In addition to replacing some of our dogma about antibiotics, there are many opportunities to replace intravenous (IV) antibiotics with oral, and clinical decision scores can support these.(17)

Relocating children out of hospital benefits their well-being and reduces the risk of HAI, either by stopping antibiotics, switching to orals or administering IV treatment at home. The CHOICE trial showed non-inferiority of IV ceftriaxone at home versus IV flucloxacillin in hospital for children with moderate/severe cellulitis directly from the emergency department, with associated significantly improved quality of life and reduced costs. Because of the association between use of third generation cephalosporins and development of extended-spectrum beta-lactamase (ESBL) production in bacteria that has been found in some intensive care settings, the authors assessed the effect of this short-term ceftriaxone use in previously healthy children on their colonising bacteria. Despite the use of a broader spectrum agent there was no difference between cohorts in colonisation rates with multidrug-resistant pathogens at 1 week or 3 month follow up.(18) Reducing the duration and spectrum of antibiotics requires better measures of antibiotic use and appropriateness. A novel metric called the antibiotic spectrum index (ASI), compares the relative breadth of antibiotic use, and is used in conjunction with DOT.(19) It is potentially a powerful tool to measure both quantity and quality of prescribing.

Repurposing older antibiotics in a different context is now being considered in children such as using fosfomycin for multidrug-resistant urinary tract infections, and even antibiotics previously considered to have side effects that were too toxic, such as colistin.(20) Finally, children who are labelled as having an allergy to an antibiotic, most commonly penicillin, are denied our simplest, narrowest spectrum antibiotics. These children are therefore frequently prescribed broader antibiotics, putting them at increased risk of developing resistant organisms and increased healthcare need.(21) Relabelling them as not having an allergy involves working with allergists to increase access to allergy clinics and safety testing.

Where to from here?

The best AMS interventions are ones that fit your institution and resources. We should practise the evidenced-based aspects of AMS, and tailor them to our respective settings. AMS should ideally be implemented at a systemic level, targeting resources through national programmes to improve processes from the top down. However, every clinician working in child health has personal responsibility to optimise the care they provide, regardless of resources, ranging from running an all-encompassing AMS program, to educating juniors and nursing staff, to introducing simple guidelines. Finally, we should continue to empower

prescribers and engage with consumers to make more appropriate decisions with antibiotics to continue the fight against AMR.

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	Resource-rich	Resource-poor	Hospitalized	Intensive care	Community/ outpatient/ GP
International consensus guidelines		+			
National policy/guidelines	+++	++	+++		+
Local AMS program bundle	+++	++	+++	+++	+
Local guidelines	+++	+	+++	+	+
Antimicrobial restriction	+++	++	+++	+	
Behavioural approaches	+		+		
Education	+	+	+		+
Audit and feedback	++	+	++	+	
Microbiology reporting	+		+		
Clinical decision rules		+	+		+
Diagnostic tools		++	+		
Other...	++				

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