Ref: Ro J Pediatr. 2021;70(4)
DOI: 10.37897/RJP.2021.4.7

Antimicrobial resistance: A new threat in the COVID-19 era?

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ABSTRACT

During the COVID-19 pandemic antibiotic use considerably increased being partially justified by the fear of bacterial infection. Antibacterial resistance (ABR), due to increased and unjustified antibiotic use, is a major threat to the economy and global health.

In pediatric practice, antibiotics are the most common prescribed substances, both in the community and hospital setting. Unjustified use, inappropriate doses and prescription duration promote antibacterial resistance and increase mortality.

The majority of current health problems in children are viral infections, even the rates of infection are higher as in adults, fact that determines more frequent diagnostic uncertainties. More so, respiratory infections in children have a greater potential of excessive and incorrect use of antibiotics, that justifies protocol based evaluations, risk assessment and targeted treatment.

The diversity and magnitude of clinical presentation of SARS-CoV-2 infection, along with early and long-term complications and sequellae, also noticed in pediatric practice, created the premises of increased use of antibiotics, aggravating the ABR. This is a challenge for the clinician during a period when development of new antibiotics is not a priority of the pharma industry anymore.

Research of mechanisms that contribute to ABR, innovative therapies, expansion of genetics and implementation of antibiotic stewardship, together with stimulating pharma industry for developing of new substances, may have the potential of decreasing antibacterial resistance in an era of medical and economic uncertainties generated by the COVID-19 pandemic.

Keywords: COVID-19, antimicrobial resistance, antibiotics, antibiotic stewardship, SARS-CoV-2, pediatrics, multisystem inflammatory syndrome

INCREASE OF ANTIBACTERIAL RESISTANCE: A GLOBAL PHENOMENON, AGGRAVATED BY THE COVID-19 PANDEMIC

In December 2019, the World Health Organization (WHO), after being notified about an unusual outbreak of pneumonia cases in Wuhan, China, investigated and identified a novel beta-coronavirus that determined a severe acute respiratory syndrome (SARS-CoV-2) (1).

Starting of March 2020, around the globe spreading of COVID-19, determined considerable increase of antibiotics use, justified by the fear of bacterial superinfection.

The increased and unjustified, even abusive antibiotic use determines the emergence and dissemination of antimicrobial resistance (AMR), that possess a challenge for global economy and health. AMR is not an exclusive hospital or intensive care

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Article History:
Received: 13 December 2021
Accepted: 18 December 2021

patients burden, it became also a community problem, as well as of the consumers.

Current estimation of international antibiotic stewardship programs show that in 2050 AMR will be responsible for the death of 10 million people and, furthermore, will cost as much as US$ 100 trillion. It has been appreciated that the spectrum of resistance varies widely from region to region, underlining the importance of adapting interventions based on specificity of health problems and risk evaluation for certain populations and geographic areas (2).

In developed countries and with increased health budgets, AMR is a serious challenge – in the US, data from the Centers for Disease Control and Prevention (CDC) in 2019 reports 2.8 million of antibiotic resistant infections each year with over 35,000 associated deaths.

Estimation of the extension of ABR in countries with limited health budgets is poorer, which underlines the importance of implementing antibiotic stewardship programs coordinated by governmental interventions (3). Studies need to be organized and conducted at an international level to evaluate the AMR phenomenon, because pathogens do not respect borders. This issue is much more important in developing countries where data from research is scarce and conditions for spreading infectious pathogens may be optimal, especially when availability of treatment is sub-optimal (4).

More so, from the beginning of the pandemic, there are increased concerns related to supplemental and aggravating increase of AMR generated by prescriptions due to COVID-19 itself in adults and in pediatric practice, even if children have been shown to have mild outcomes (5,6).

Due to millions of cases globally, the COVID-19 pandemic had a devastating impact on the society as a whole, and the long term repercussions on AMR have been considered as an aggravating concern for the healthcare system (7,8,9). This was partially due to the elevated antibiotic use in patients infected with SARS-CoV-2, considered to be prone to bacterial co-infection, despite the viral nature of the syndrome (10,11,12). The reports on that were more accentuated at the beginning of pandemic.

It has been shown that, despite frequent antibiotic prescription to patients with COVID-19, the prevalence of bacterial co-infection or secondary infection in hospitalized patients is low (3.5% and 14.3% respectively) (11). This allowed a potential increase of selective pressure for developing AMR, especially in high risk patients in a strained healthcare system with scarce surveillance capacity. This could finally lead to a long lasting, aggravating phenomenon of an already increased AMR with limited intervention capacity (13,14).

ORIGINS OF AMR IN PEDIATRIC PRACTICE AND CHALLENGES FOR THE CLINICIANS

In pediatric practice, antibiotics are the most common prescribed substances both in the community and hospital setting. Unjustified use, inappropriate doses and prescription duration promote antibacterial resistance and increase mortality.

Tackling antibiotic resistance during the COVID-19 pandemic is a new challenge for the pediatrician, especially in an era when multi-drug resistant bacteria will soon overwhelm this medical area (15).

The majority of current health problems in children are viral infections, even the rates of infection are higher as in adults, fact that determines more frequent diagnostic uncertainties. More so, respiratory infections in children have a greater potential of excessive and incorrect use of antibiotics, fact that justifies protocol based evaluations, risk assessment and targeted treatment. Uncertainty may lead to more antibiotic prescribed, even in mild cases of COVID-19 in children, as well as it has been shown in complications like multisystem inflammatory syndrome in children (MIS-C) (16). Prescription of antibiotics was high, mostly in severely affected children and sometimes because of poorly understood pathophysiological underlined mechanisms.

As the majority of children undergo other viral infections during the SARS-CoV-2 waves, the use of antibiotics have to be rationally evaluated.

Antibiotic resistance in pediatric infections is a subject of concern for all clinicians and is a part of the global emerging threat that leaves us in front of the questions that are directed to the origins of the phenomenon.

The causes of increasing AMR in general are determined by several main mechanisms (17): abuse of antibiotics (there is a direct relationship between the consume and the dissemination of resistant bacteria, the lack of prescription regulations and easy access); the inappropriate prescription (frequent incorrect or unnecessary therapies even in intensive care units, sub inhibitory or under therapeutic concentrations may determine increase of AMR through genetic alteration); extensive use in agriculture (growth factors, transfer of resistant bacteria, alteration of microbiome).

The origins of AMR in pediatrics in contrast support more arguments than the previous ones and may be regarded as a sensitive tool in order to predict the near future as it is an emerging threat that needs immediate action (18).

According to WHO data, infections caused by multi-drug resistant (MDR) bacteria produce more than 700,000 deaths across all ages, with one third in newborns (19). Interestingly, even if Sir Alexander Fleming already warned the scientific and medical community regarding antibiotic overuse in 1945, an era of abuses in agriculture, veterinary and human medical practices started after World War II and determined the driving force in bacterial resistance. Furthermore, inappropriate use, medical malpractice contributed to selection of MDR bacteria that constitutes the overwhelming actual burden of AMR (20).

The main driving mechanisms of the pediatric phenomenon are: antibiotic misuse and overuse in hospitalized children and outpatient care, that is reflected by the lack of de-escalation or discontinuation of antibiotics according to culture results, even in intensive care units; use of older antibiotics vs. newer ones, depending on available hospital, ward or country resources, posology and dosing in pediatric population, which is characterized by variability in pharmacokinetics in children, lack of clinical trials that drives extrapolation of pharmacodynamics and pharmacokinetics based on adult studies, the necessity of a ”developmental pharmacology” that adapts pediatric needs and, last but not least, intervention of regulatory organisms as the Food and Drug Administration, European Medicines Agency (21,22,23), lack of options when choosing antibiotics that are contraindicated in children, modern predisposing conditions: biofilms (bacterial adaptation mechanisms that lead to AMR) and chronic diseases (24).

FUTURE DIRECTIONS: ANTIBIOTIC STEWARDSHIP AND STEPPING BACK FROM THE EDGE

Antibiotic stewardship (AS) is represented by a coordinated set of strategies meant to measure and to improve prescription of antibiotics by clinicians and the use by the patients. The aim converges to improving of patient care and prognosis through optimal therapies, reducing collateral effects through decrease of antibiotic resistance and lowering the costs of antimicrobial therapies. It is a concept introduced by the Infectious Diseases Society of America in 2007 (25).

The core elements of hospital antibiotic stewardship programs have to be centered on the following elements: leadership commitment (dedicating necessary human, financial and technology resources), accountability (appointing a single leader responsible for programmed outcomes), drug expertise (accounting a single pharmacist leader responsible for improving antibiotic use), action (implementing at least one recommended action such as systemic evaluation after 48 hours of initial treatment), tracking (monitoring antibiotic resistance and prescribing patterns), reporting (regular reporting for informations about antibiotic use and resistance to the medical staff), education (medical staff education regarding AMR and optimal prescribing).

All major medical regulation organizations implement the principles of antibiotic stewardship in order to responsibly use and prescribing by the clinicians, having as aim the patient health.

In pediatric practice, AS has to be centered by the differences in common infectious conditions, drug-specific considerations and the registrations of treatment recommendations that depend on the place where it applies for (outpatient/inpatient, personnel, infrastructure), the used approaches in effectiveness evaluation and the level of knowledge (26).

THE FUTURE OF AMR, ARTIFICIAL INTELLIGENCE AND THE HUMAN MIND

An interesting proposal of a revolutionary field, artificial intelligence (AI), is extremely useful in many human activities, including medicine, and it refers to adapting the needs for fighting against AMR in pediatrics.

Considering pediatric infectious disease, AI could play a role in enriching AS effectiveness (27). This could mean that integrating the intelligence of a machine in the human thinking it would be possible to predict and evaluate infectious disease and even make appropriate antibiotic prescriptions.

Based on modern research, it would be possible to predict AMR, to have collaborative efforts together with the pharma industry, to discover new molecules, to enhance diagnostic procedures, to reduce costs. Most of the proposed solutions are not intended to replace personal medical judging and expertise, but to provide a useful tool in the battle with AMR.

Limitations of AI have to be taken in consideration when thinking of lack of large amount of pediatric data and randomized controlled trials, data protection and security.

If thinking of relevance to global health research, al-driven interventions that aim to fight AMR may be summarized as four categories: diagnosis, patient morbidity and mortality risk assessment, disease outbreak prediction and surveillance, health policy and planning (28). If these directions may be accomplished, and ethical, practical and regulatory considerations will be clarified, the global health community may benefit in fighting the overwhelming pandemic of multi-drug resistant bacteria.

CONCLUSIONS

The diversity and magnitude of clinical presentation of SARS-CoV-2 infection, along with early and long-term complications and sequelae, also noticed in pediatric practice, created the premises of increased use of antibiotics during the COVID-19 pandemic aggravating the AMR.

Diagnosis uncertainty, associated comorbidities, the polymorphism of clinical presentation in MIS-C, limited antibiotic stewardship incentives in low and middle income countries, poor surveillance of antibiotic prescription along with decreased interest of pharma industry for developing new molecules needed in the fight against AMR are the challenging issues for the clinician during the COVID-19 pandemic.

Rethinking new strategies of stimulating pharma industry for investing in research for new molecules, international collaborative relationships through medical and scientific societies and governments and, last but not least, responsibility and clear judgement in decision making regarding antibiotic use may brighten up the perspective of fighting against AMR, amid actual and also future pandemics.

Conflict of interest: none declared
Financial support: none declared

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