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A CLOSER LOOK AT ANTIBIOTIC RESISTANCE IN CHILDREN

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Abstract:

Antibiotic resistance is a potential threat to the public wellbeing, especially in children: According to WHO surveys, death toll associated with multidrug resistant organism is 700,000 across all ages, of which around 200,000 are infants. This soaring issue has multidimensional linkages that are specific to the pediatric age group. For example, the indiscriminate abuse and misuse of antibiotics (for nascent diagnoses and indications, or at erroneous dosing) is caused by the lack of evidence based time-tested trials in paediatrics. The dynamic nature of this age group also renders another hazard which is associated with the age-dependent modifications in the drug metabolism system (cytochrome machinery) leading to weight and dose dependent efficacy. The pediatric age group has also been inflicted by the adversities of tetracycline and fluoroquinolones, and by congenital malformations which prompt frequent hospitalization involving invasive and pharmacological interventions from the time of birth. Emerging challenges for the pediatric age are MRSA, VRSA, ESBL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae and the devastating colistin resistance. (Super-bugs). Radical measures need to be taken in order to prevent the advent of an era where a simple infection might lead to a life catastrophe.

Keywords: *multidrug resistance; antibiotics; micro-organsms; superbugs; antibiotic resistance; childhood; infections; antimicrobial stewardship*

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1. INTRODUCTION:

Currently, one of the most concerned public health issue is antimicrobial resistance (AMR) which need to dealt with iron hands on top priority by all healthcare institutions, policy makers and researchers.

For the sake of comprehension and quantification the magnitude of the threat posed by AMR, WHO estimated that globally, 700,000 deaths among all age groups occur per year due to infections caused by multidrug resistant (MDR) bacteria, of which around 200,000 are newborns [1]. In Europe, the total cases of MDR infections in pediatric patients make up to 30% of the total cases [2]. In regions of the Middle East, 90% of newborns admitted in ICU, were isolated with resistant bacteria on culture and sensitivity [3]; in various areas of South East Asia, 83% of the children with E.coli infection were found to be resistant to the first line antibiotics [4]; in Sub-Saharan Africa, 66% of neonatal sepsis and meningitis was attributed to the antibiotics resistant bacteria [5]; in a study conducted in USA, 20% of pediatric patients who were receiving colistin to treat MDR Gram negative bacteria developed resistance later [6].

The prevalence of multidrug-resistant organisms (MDROs) is on the rise and is associated with a significant morbidity and mortality. Infections caused by MDR bacteria are not only difficult to treat but is also associated with repeated and prolonged hospitalizations, prognosis, draining financial and mental and increasing morbidity and mortality [7–10]. An estimated 2.39 billion dollars estimated to have been spent to treat MDR infections in the USA alone [11, 12].

This current health problem has also threatened our future warranting dynamic and prompt response. Despite the warnings from the founder of penicillin Alexander Fleming to the scientific world still an era of antibiotic abuse in agriculture, livestock, veterinary, and human medical practices sprung up after the World War II. This abuse was a driving force for the evolution of drug resistant organisms [13, 14]. Furthermore, some studies have proved that medical malpractice has contributed to bloom MDR variants of bacteria through unnecessary, inappropriate or inadequate dosing prescriptions, which has been observed in 30% to 60% of the antibiotic therapies given to outpatients as well as to inpatients settings [15, 16].

These attitudes have not only accelerated the pre-existing phenomenon of natural selection for MDROs but also have caused the newer drugs to loss their potency as soon as they are launched into the market for example the longest period of time without resistance for vancomycin was 16 years. But this interval has dropped to only two years for penicillin, and even one year for the comparatively novel drugs e.g.daptomycin and ceftaroline [17, 18].

In such a rapidly transforming dynamics, if radical measures are not ensued we might land in a super-bug era where just a simple infection can turn out to be fatal, and this is especially true for children, who are more vulnerable to common infections bear the antimicrobial brunt after their brith. Neonates younger than a week are more prone to suffer from this phenomenon because of the presence of MDR bacteria in their GI tract probably due to penetration from the maternal blood and contamination from the environment at the time of birth [19, 20]. According to the WHO estimates, if this practice is not checked, drug-resistant species can cause 10 million deaths each year by 2050, with an estimated annual loss of $300 billion for the healthcare system and national production [1, 7]. Thus antibiotic stewardship is the need of the hour to halt antibiotic abuse in medical practice.

For these compelling facts, we conducted a review on the current pediatric AMR, its potential threats, and strategies to overcome it.

2. The Causes of Antibiotic Resistance in Childhood

Children are usually administered more antibiotics than any other type of drug, as they are subjected to numerous infections of various organ-systems e.g. GI, respiratory, urinary and central nervous system..

2.1. Antibiotic abuse among Inpatient and Outpatient Care

The improper use of antibiotics is the leading cause of the recent antibiotic resistance emergence [21, 22]. The roots of injudicious use of antibiotic use are the lack of relevant knowledge about the causative agent and of spectrum of the antimicrobial class. These features highly influence and affect choice of drug, dose calculation, posology and duration of a treatment course. In addition, antibiotics are still commonly being prescribed for viral infections, especially in OPDs [23–25].

In 2012, for the first time, the Worldwide Antibiotic Resistance and Prescribing in European Children

(ARPEC) group sought detailed information on antibiotic use in hospitalized neonates and children from a multicenter retrospective cohort study. More than 17,000 admitted pediatric patients in 226 hospitals from 41 countries worldwide, of which 6499 inpatients received at least one antimicrobial agent They reported higher dosing rate of broad-spectrum antibiotics in certain regions, which gave the possible explanation of high incidence of ESBL-producing or carbapenem-resistant Gram-negative organisms. However, this high level of empirical broad-spectrum antibiotic administration may identified that major part of this of this practice was injudicious. Such inappropriate use was also noted by Levy et al. [26] in pediatric intensive care units (PICUs) and pediatric wards, which the authors attributed to the failure to wean off or switch to the definite regimen. In under developed and less equipped settings, the discontinuation of carbapenems was successful because of the non-availability of culture sensitive testing [27]. The ARPEC study also found a significantly high administration of amikacin in neonates admitted to Western European, Southern European, Asian and Latin American hospitals, and meropenem was being prescribed to Asian newborns at an alarming index.

A high proportion of African, Australian, Western European and Northern European children were subjected to the conventional narrow spectrum antibiotics, such as benzylpenicillin, sulfamethoxazole/trimethoprim, amoxicillin and gentamicin. whereas In Eastern and Southern Europe, Asia, North and Latin America, children were given more broad-spectrum antibiotics, mainly third-generation cephalosporins and carbapenems. Thus, it can be incurred that resource-limited settings prefer the empirical treatment with the conventional narrow-spectrum antibiotics, while developed countries opt the newer regimes of novel generation antibiotics.

In conclusion, the 2016 ARPEC study identified potential indicators of correct antimicrobial administration in pediatric populations:

- preference of broad-spectrum agents when needed
- discontinuation of empirical antibiotics according to culture sensitivity results
- rates of antibiotic use as per ward policy
- early switch from I/V to oral route
- proper documentation of the reason for prescription in the patient's medical record
- <24 h perioperative administration of antibiotics for surgical procedure prophylaxis.

2.2. Appropriate dosing for the Pediatric Age Group

The pediatric population treatments are maneuvered on the basis of their appropriate prescription, safety, posology and efficacy profiles. The age-dependent differences in their pharmacokinetics must be taken into account.

The lack of pediatric age group clinical trials of antibiotics and the subjectively assessing the body weight and converting the adult dosages into the pediatric ones is a common practice that has led to the scarcity of the evidence-based development. Thus drug toxicity and interactions are less established according to the individual needs and hence the resistance multiplies within.

This is true especially estimating creatinine clearance, which is extremely variable and age-dependent: for instance the glomerular filtration rate increases quickly through the first two weeks of life and then the rise becomes steady until adult rates are reached at 8–12 months of age [28]. Thus the drug clearance in the pediatric age group is highly variable.

Strategies have been developed to optimize correct pediatric dosing and combating ethical issues apart from individualized needs [29]. The application of the population PK–PD method on this population has been highly advocated and elaborated in the Guidance Documents of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [30, 31]. Physiologically based pharmacokinetic (PBPK) model, a promising method to justify drug metabolism and interactions in pediatrics considering all the natural and physical parameter [32, 33, 34].

As knowledge on pediatric physiology and biochemistry grows, by comprehension of more receptor ligand interactions and intracellular pathways drugs will be prescribed to children with greater accuracy, efficacy and safety.

2.3. Contraindicated yet sometimes the Life-Savers

It is imperative to highlight that some antibiotics have definite contraindications when it comes to pediatric age, and this narrows the range of available antimicrobial options to combat infections..

For instance, fluoroquinolones have shown to cause irreversible adverse damage on cartilage development in young animals through the inflammation and disruption of weight-bearing joints [35, 36]. The

potential time tested hazard has limited the use of fluoroquinolones in children. Apart from this fluoroquinolone has an innate predisposition to cause increased bacterial resistance. Thus risk and benefits of its use must be carefully weighed. In 2006, the American Academy of Pediatrics (AAP) recommended fluoroquinolones only in three major circumstances: (1) FDA-approved indications; (2) MDROs with no safe or effective alternative; and (3) oral fluoroquinolone sensitivity when all others are intravenous options only. They may be considered in pediatric patients with gastrointestinal infections, acute otitis media, sinusitis, lower respiratory tract infections, and pneumonia or *Mycobacterium* infections [37].

Another class is of tetracycline which was called off because of its potential to cause tooth-discoloration during the calcification process by the age of eight. [38] [39]. Another adverse effect is of photosensitivity which is less significant as compared to the permanent tooth discoloration. In older children, tetracyclines have been successfully used for respiratory infection, community-acquired *S. aureus* resistant to methicillin (*MRSA*), malaria and acne. The AAP recommends the use of tetracycline in pediatric infections when the benefits outweigh the risks of adverse events. Their indications include rickettsial infections, cholera, anthrax and they suggest prescribing doxycycline, as it has a lower risk of dental staining because of being less calcium binding [40].

2.4. Biofilms: A giant behind the curtains

Biofilms are formed as a result of with chronic subclinical infections and possess inherent antimicrobial resistance. The bacteria adhere to the damaged tissue, implants, prosthesis and indwelling catheters. Bacteria in a biofilm tend to survive being dormant and reactivate when the immune system is compromised. They warrants higher and longer duration of i/v antibiotics.

Three hypotheses have been postulated to explain the phenomenon of infectivity from the biofilms. The first hypothesis is the probability of slow or incomplete penetration of the antibiotic into the biofilm [41] ; the second hypothesis depends on the alteration of chemical milieu within the biofilm [42]; a third mechanism of antibiotic resistance is a subgroup of bacteria in a biofilm transform into a highly protected phenotypic state called “persister cells”. They often have a slow or arrested growth, and continue to survive despite severe stress. They are responsible for recurrent bacterial infections and are associated with an increased risk of AMR [43].

Since children undergo interventional procedures such central venous catheters, complex heart defect patches and ventriculoperitoneal shunts. Thus they can act as ideal breeding grounds for the bacteria converting into the biofilms limiting antibiotic penetration. Sometime the infection become so worse that the foreign body has to be removed or replaced depending on the circumstances.

They are responsible for the recurrent upper respiratory tract infections with negative growth on culture and positive on molecular testing [44, 45].

Similarly chronic conditions, such as cystic fibrosis (CF), are associated with significant morbidity and mortality due to recurrent acute and chronic infections leading to frequent and hospitalizations and increasing the chance of MDR. Also because opportunistic organisms jump in to create havoc for the host [46].

3. Emerging Challenges

The WHO has recently published a list of bacteria for which new antimicrobials are desparately needed [47]. This has seethed from the progressive exhaustion of the research and development of pipeline of new antibiotics. The urgently needed antibiotics for the pediatric population include oral preparations for community-acquired infections with high morbidity, like drug resistant *ESBL-producing Enterobacteriaeceae*, *Neisseria gonorrhoeae*, and *Salmonella typhi*.

3.1 Multidrug Resistant Staphylococcus Aureus (MRSA)

Although *MRSA* infections are less common in children few resistant strains were noted in infections in adults and children who had no prior predisposing risk or hospital contact [48].

Trimethoprim-sulfamethoxazole and clindamycin are often used in the treatment of Community Acquired *MRSA*: resistance to trimethoprim/sulfamethoxazole is relatively uncommon, though clindamycin resistance has emerged in the last decade [49]. To help limit *MRSA* spread, the application of mupirocin ointment into anterior nares has been put in practicectogether with chlorhexidine baths: since these practiced was established, resistance to mupirocin and chlorhexidine have emerged [50].

Vancomycin has long been considered as a last resort for *MRSA* infections since the isolation of vancomycin-intermediate susceptible *Staphylococcus aureus* from a surgical wound of a Japanese child [51].

Of the other available options daptomycin is of no use in treating lung infections as it binds surfactant with its subsequent degradation [52]. Ceftaroline though overlooked has a good efficacy on *MRSA*, with both on or off label indications [53],

3.2 ESBL-Producing Enterobacteriaceae (ESBL-Ent) and Carbapenem-Resistant Enterobacteriaceae (CRE)

In the U.S.A., there has been a rapid increase in the cases of *ESBL-Ent* infections in children [54]. International studies have revealed that an increase in *ESBL-Ent* colonization is related toyounger gestational age, low birth weight, antibiotic use and prolonged invasive mechanical ventilation [55]. Outside the neonatal age, the risk factors are same as that of the adult population [56, 57]. Available antimicrobial alternatives for *ESBL-Ent* include piperacillin-tazobactam, ceftazidime-avibactam, cefepime, fluoroquinolones, aminoglycosides, tigecycline, fosfomycin and carbapenems, but their use remains limited and controversial because of the safety profiles unclear dosage guidelines. However it is also preferable to de-escalate carbapenem dosing after empirical therapy..

Resistance to carbapenems is attributed to the production of carbapenemases. According to 2013 CDC report addressed this occurrence to be around 50% mortality rate in hospitalized patients with bloodstream *CRE* infection [16]. A significant increase in *CRE* frequency in some pediatric populations was noted, especially for the *Enterobacter* species, from 0% in 2000 to 4.5% in 2012, especially in ICU settings [58]. Therapeutic options for *CRE* are few, and pediatric options are further limited: the use of tigecycline is carefully weighed for people <18 years of age due to its safety profile; colistin and other polymyxins have optimal dosing issues for the pediatric population; oral fosfomycin may be used for *CRE* bladder infection, though dosing guidelines are available only for older children and adolescents [59]. Moreover, *ESBL-Ent* and carbepenemase-producing bacteria are often carriers of other plasmid-transmitted genes that confer resistance also to aminoglycosides, sulfonamides and fluoroquinolones, which characterizes these bacteria as true MDROs [60].

3.3 Colistin Resistance

In mid-1990s, the rapid rise of MDR Gram-negative cases forced the clinicians to reconsider and reuse the abandoned antibiotics, such as fosfomycin and, more interestingly, colistin. After being introduced, colistin was quickly replaced by newer, safer parenteral antibiotics because of its nephro and neurotoxicity. As this drug was reintroduced in clinical pediatrics as salvage therapy for stubborn MDR Gram-negative infections, patterns of resistance were for the first time described and reported. It was mediated through mcr-1 gene via plasmid transfer. [61-64].In short, colistin activity needs to be preserved, as it is one of the very last few drugs effective against carbapenem-resistant Gram-negative organisms.

4. Future Concerns and Recommendations

4.1 Combating the Emergence of AMR

A first step needed for controlling of AMR is the implementation of an antimicrobial stewardship strategy in both in-patient and out-patient settings. Antimicrobial stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen including dosing, duration of therapy and route of administration" [65]. Thus, the measures that must be undertaken to combat the emergence of AMR and reverse the phenomenon should include:

- An Institutionalized team of experts should be formed comprising of infectious disease specialists, clinical pharmacologists, microbiologists and pediatricians to framework guidelines, provide advice on antimicrobial use and share evidence base knowledge.
- Regular auditing and reviewing of the institutional supply of antimicrobial prescriptions and preparations;
- Pharmacodynamics/pharmacokinetic-guided dosing, considering physiological variations and developmental differences of the individual child.
- Use of flowcharts and mobile software for calculating the correct dosages [66].

4.2 Quick and Accuarte Diagnosis

Empirical treatments although lifesaving can seed the antibiotic resistance ultimately: 50% of antibiotics are administered before the establishment of a working diagnosis and hence least is known about the culprit organism [13]. A rapid diagnosis is therefore essential to ensue the definite treatment protocol for the infectious disease. Accurate antimicrobial susceptibility testing (AST) is in practice in developed countries to minimize the incidence of AMR. Moreover, in most advanced diagnostic centers, molecular testing such as nucleic acid amplification, integrating mass-spectrometry and biosensor-based AST and third generation technologies of whole

genome sequences (WGS) are available and are able to quickly identify pathogens and test for drugs' susceptibility genes [67]. Moreover the determination of the best antimicrobial dose based on individualized pharmacokinetic parameters is essential to establish the minimum inhibitory concentrations, avoiding AMR emergence and limiting its spread. This is particularly useful for the pediatric population where timing of intervention and correct dosing based on the antimicrobial spectrum is considered.

4.3 Novel Antibiotics for Children: Hype vs Hope

There are some novel antibiotics developed and approved for pediatric use in the clinical settings directed against MDR pathogens, such as ceftaroline [68, 69] and ceftazidime/avibactam [70]. Other new antibiotics are showing promising results in the pediatric age group, such as ceftolozane/tazobactam [71], tedizolid [72] or dalbavancin [73], but more clinical trials are needed to confirm their efficacy.

Specific pharmacokinetics studies ought to be undertaken to establish the age specific best dosage regime. This will allow us to conserve the new potent ammunition of drugs for a rainy day. Furthermore, the whole scientific community should collaborate with pharmaceutical enterprises to engage and boost the R&D of pharmacological drugs by including children in trials.

5. CONCLUSIONS:

Antibiotic resistance is a global health threat, summoning the advent of a post-antibiotic era where children will succumb to a simple, previously treatable infection.

Specific pediatric issues, such as injudicious and unwanted antibiotic prescriptions for less likely diagnoses, the limited available options from the R&D, the lack of trials on children, and the diversity of the individual parameters remain the key culprits in this regard.

This modern world problem warrants new panel of solutions. These may include the formation of disease specialist teams for evaluating the antibiotic prescriptions in wards, the use of an integrated software that is equipped to consider multiple variables suggest a specific drug and dosage, the implementation of quick accurate antimicrobial susceptibility tests and molecular testing to direct an empirical therapy, encouraging the use of new antibiotics and including children in both old and new drugs clinical trials for evidence-based practices.

Conflicts of Interest:

The authors declare no conflict of interest in the production of this work.

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