SPECIAL ARTICLE

Antimicrobial Stewardship in Pediatrics: An Indian Perspective

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Antimicrobial resistance has become a global menace. As the resistance patterns and numbers are progressively increasing, it has become a major cause of morbidity and mortality in hospitalized patients, especially children. Efforts are being put world-over to curb the rising resistance by various means, especially by promoting Antibiotic Stewardship Program. These are cluster of interventions targeted towards the improvement and monitoring of appropriate antimicrobial use by selecting the most optimal drug regimen, including the type of drug used, the dose, the duration of therapy and the route of administration. India has also been working consistently to control antibiotic resistance and promote implementation of antibiotic stewardship program. Although the success rates are yet not very high, due to lot of barriers, but it is important to take measures to overcome the barriers and curb the rising resistance at the earliest.

Keywords: *Antibiotics, Antimicrobial agents, Resistance*.

The horizon of therapeutic management of infectious diseases is shrinking fast. The addition of antimicrobials to the armamentarium against infectious agents is far less than the drugs being discarded because of antibiotic resistance. Antimicrobial resistance has emerged as a major health hazard over last two decades.

Centers for Disease Control (CDC) reports that more than 2 million people in USA are infected with antimicrobial-resistant organisms every year, resulting in 23000 deaths [1]; the health care cost of treating antimicrobial-resistant infections is in excess of 20 billion [2]. In the European Union, about 25000 patients die each year from infections with multidrug-resistant bacteria [1]. The situation is further worsened in developing countries due to high infectious disease burden and cost concerns.

ANTIMICROBIAL RESISTANCE: THE INDIAN SCENARIO

A study conducted by Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group has reported prevalence of 41% methicillin-resistant *Staphylococcus aureus* (MRSA) in India [3]. Multiresistant enterobacteriaceae due to the production of extended spectrum β-lactamases (ESBL) has also become rampant in India [4]. Other resistance patterns prevailing in India include multidrug-resistant extended spectrum β-lactamase producing *Klebsiella pneumoniae*, ciprofloxacin-resistant *Salmonella* enteric serovar Typhi, vancomycin-intermediate staphylococci, fluoro-quinolone-resistant *Salmonella* enteric serovar Paratyphi A, and ceftazidime-cefepime and ciprofloxacin resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanni* [4]. Prevalence of Metallo-beta-lactamase producing organisms ranges from 7-65% in India [4]. Sale of antibiotics in India is on the rise with 40-60% increase observed over last five years [5]. Studies conducted in Delhi and Vellore have shown high consumption of fluoroquinolones [4]. The rising resistance has lead to longer hospital stay, increased health care cost, increased antibiotic-related adverse effects, and overall high morbidity and mortality. Some important factors responsible for the rising antibiotic resistance in India are indiscriminate use of antibiotics, over-the-counter availability of antibiotics, laxity of regulatory bodies in approval of antibiotics, lack of public awareness about antibiotic resistance, injudicious use in veterinary practice, overburdened health infrastructure, and inequity in healthcare [6].

The resistance has also been noted for other infections like HIV, tuberculosis and malaria. As per WHO, there were about 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB) in 2013 [7]. The percentage of previously treated tuberculosis cases with MDR-TB in India is 12-30%. Of late, extensively drug-resistant tuberculosis (XDR-TB), and resistance to artemisinin-based combination therapy (ACT) for malaria is also being noticed.

EFFORTS TO CURTAIL ANTIMICROBIAL RESISTANCE

A global strategy on containment of antimicrobial resistance was introduced by the WHO in 2001 [2]. World Health Assembly in 2005 also called for rationale use of antimicrobial agents [2]. Despite this, there was

little progress on interventions for antimicrobial resistance. Causes for the slow progress were cited as: paucity of surveillance data on antimicrobial resistance; difficult to regularly update diagnostic and treatment guidelines; lack of access to rapid diagnostic facilities; lack of access to quality assured medicines at affordable prices; poor provider knowledge; insufficient training and supervision of health personnel; and perverse economic incentives. Efforts were continued to tackle these obstacles in a limited manner. Antimicrobial resistance was declared as the theme for World Health Day 2011, and a policy package released by the WHO to curtail the rising resistance of antimicrobials (***Box* 1**).

In the United States of America, CDC guidelines on management of multidrug- resistant organisms in health care settings were released in 2006 [1]. In 2009, "Get smart for health care campaign" was launched for improving the use of antimicrobials [1]. Further in 2013, the need to improve antimicrobial use was highlighted as one of the key strategies to address the problem [1]. CDC in 2014 recommended that all acute care hospitals should implement antimicrobial stewardship program (ASP) to curtail the menace of antimicrobial resistance [1].

ANTIMICROBIAL STEWARDSHIP PROGRAM

Antimicrobial stewardship program (ASP) was formally defined in 2007 by the Infectious Diseases Society of America as "a cluster of interventions targeted towards the improvement and monitoring of appropriate antimicrobial use by selecting the most optimal drug regimen including the type of drug used, the dose, the duration of therapy and the route of administration" [8].

Nathwani and Sneddon [9] have described a 30% rule on antimicrobial prescription which states that 30% of all hospitalized inpatients at any given time receive antimicrobials; over 30% of antibiotics are prescribed inappropriately in the community; up to 30% of surgical prophylaxis is inappropriate; and 30% of hospital pharmacy costs are due to antimicrobial use. Looking at these figures, it is essential that all hospitals should build up and implement ASP.

Box 1 WHO POLICY PACKAGE TO COMBAT ANTIMICROBIAL RESISTANCE

- Commit to a comprehensive, financed national plan with accountability and civil society engagement
- Strengthen surveillance and laboratory capacity
- Ensure uninterrupted access to essential medicines of assured quality
- Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care· Enhance infection prevention and control
- Foster innovations and research and development for new tools.

NEED OF ASP FOR PEDIATRIC AGE GROUP

Consumption of antibiotics is very high in pediatric population. More than 60% of child patients receive at least one antibiotic during their hospitalization; and more than 90% children receive antimicrobials if they are undergoing surgery, having central venous catheter, having prolonged ventilation, or are in the hospital for >14 days [10]. Repeated antimicrobial use is most common in children being treated for cancers, those having undergone transplants, and those with immunosuppressive conditions like cystic fibrosis. Increased or repeated use of antibiotics is often associated with adverse drug events, especially due to dosing errors. Antimicrobial-associated diarrhea caused by *C. difficile* infection has increased over the last few years [11]. Neonates are especially vulnerable since they receive broad spectrum antimicrobials much more frequently than older children. Moreover, they are more prone to early upgradation of antimicrobials due to high risk of morbidity and mortality. Neonates also have maximum risk of antimicrobial associated severe adverse effects, including necrotizing enterocolitis, invasive candidiasis, increased hospital stay, and bacterial resistance. The risk of necrotizing enterocolitis (NEC) increases by 4% with each added day of hospitalization after 5 days [12]. Invasive candidiasis in neonates on broad spectrum antimicrobials has shown an increase from 2.4% to 20.4% [12].

With the recognition of the various challenges noted with antibiotic use in pediatric and neonatal population, Pediatric Infectious Disease Society (PIDS) in 2010 formed the Pediatric Committee of Antimicrobial Stewardship with the mission of advancing pediatric antimicrobial stewardship in various clinical settings, promoting research, and developing antimicrobial stewardship educational programs [13]. The American Academy of Pediatrics also recommends implementation of ASP [13].

Standard guidelines on what to do and what not to do have been developed by the WHO [14] to minimize selection of resistant organisms, and maximize better outcomes. These are reproduced in ***Box* 2** and **3**.

Antimicrobial stewardship program should be developed so as to get the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on resistance and other ecological adverse events. The main goals include:

BOX 2 WHAT NEEDS TO BE DONE?

- Appropriate empirical antimicrobial therapy, with right dose, for right duration and at right time.
  - Delayed therapy or modifying the initial antimicrobial therapy does not improve the outcome.
  - Multidrug-resistance organism predisposes for inappropriate therapy.
- Early and accurate identification of the pathogen and susceptibility.
- Combination or monotherapy chosen on the basis of the pathogen identified.
- De-escalation of initial broad spectrum therapy after definitive diagnosis (generally based on microbiology reports).

Improve patient outcome: improve infection cure rate, reduce surgical infection rate, reduce mortality and morbidity;

Improve patient safety: reduce antimicrobial consumption without increasing mortality or infection related readmissions; reduce *C. difficile* colonization or infection by controlling the use of higher antimicrobial;

Reduce resistance: restrict relevant agents; and

Reduce health care costs.

Assessing the success

Successfull implementation of antimicrobial stewardship program (ASP) can be assessed based on antimicrobial consumption in terms of daily dose, cost and days of treatment, antimicrobial adverse events, resistance patterns, intervention and monitoring. Clinical outcome measurements are assessed based on cure versus failure, (both clinically, and microbiologic), superinfection, and reinfection [1].

IMPLEMENTING ANTIMICROBIAL STEWARDSHIP

The first step is to have a policy on optimal antimicrobial use to ensure documentation of doses, duration, and indications for antibiotics; and developing facility specific treatment recommendations in the health facility [1]. Other interventions for antimicrobial stewardship include the following:

- Designing and executing policies on antimicrobial "time out" which means there should be a reassessment of the need and choice of the antibiotics started empirically at the time of admission. This is usually done after 48 hours once more clinical and laboratory data is available.

BOX 3 WHAT SHOULD NOT BE DONE?

- Treat non-infectious or nonbacterial syndrome
- Treat colonization or contamination
- Treat longer than necessary
- Fail to make adjustment in a timely manner
- Prescribe antibiotic with spectrum of activity not indicated

- Adhering to the dictum of "Prior authorization" that requires the availability of an antibiotic expert who can review and decide the need of antibiotics before the therapy is initiated.
- *Prospective audit and feedback*: This involves an external review by an antibiotic expert regarding antibiotic therapy in very sick patients where broad spectrum antibiotics are given. An audit is done by a team separate from the treating team.
- Regular changes from intravenous to oral treatment so that patients need less intravenous access.
- Dose adjustments in cases with organ dysfunction and dose optimization like those with therapeutic drug monitoring, higher doses for achieving CNS penetration, doses for highly resistant bacteria.
- Automatic alerts to avoid unnecessary duplication of drugs which have overlapping spectra.
- Time sensitive automatic stop orders for certain prescriptions like antibiotics given for surgical prophylaxis.

Capacity building and sensitization of all the stake-holders is an integral pre-requisite of this program. The multidisciplinary team members comprise of an infectious disease physician, clinical pharmacist, microbiologist, infection preventionist, hospital epidemiologist, infor-mation system specialist, quality improvement staff, laboratory staff and nurses.

The eight key steps for implementing an ASP have been outlined and explained in an earlier publication [9].

SUCCESS STORIES

At present, antimicrobial stewardship programs are being implemented in various pediatric clinical fields including neonatology, community-acquired pneumonia, inpatients, and longterm-care patients. Majority of current programs have started after 2007. Though there are lots of barriers in implementation of stewardship policies as discussed previously, lately hospitals have started producing data with a successful outcome. Newland, *et al.* [15] reported that 38% and 36% of Freestanding Children's Hospitals in US have an ASP in

place in 2014; or in the process of implementation, respectively.

In a major study done in pediatric population with community-acquired pneumonia [16], a significant change was noted in the pattern of antibiotic prescription after the release of stewardship guidelines. The use of ampicillin increased from 2% to 44% whereas prescriptions of ceftriaxone decreased from 56% to 28%. The change was followed for one year and was found to remain constant. In another study by Bizarro, *et al*. [12], conducted in NICU setting, a significant decrease in the incidence of central line associated blood stream infection (from 8.4 to 1.28 per 1000 central lines) was noted after an educational intervention as a part of antibiotic stewardship program.

CURRENT STATUS IN INDIA

With the available data, the situation is not too promising. The first global survey conducted by Howard, *et al.* [17] reported 53% coverage in Asia. According to another survey conducted on antimicrobial programs in India by Sureshkumar, *et al.* [18], more than 50% hospitals in India do not have an ASP. The common barriers reported include: lack of funding and human resource, lack of information technology, higher priorities, lack of awareness of administration, and prescriber opposition [7].

The first major step towards curtailing the rising antibiotic resistance was taken in 2009 with the launch of Global Antibiotic Resistance Partnership [19]. It was started to create a platform for developing actionable policy proposals on antibiotic resistance in low- and middle-income countries. India, Kenya, South Africa and Vietnam in 2011, in a multidisciplinary approach, made multiple recommendations so as to implement it at a priority stage and second-tier stage. *Priority stage recommendations* included surveillance on antibiotic resistance and use, increasing use of diagnostic tests, strengthening infection control committee, in-service training for physicians, continuing education for pharmacist, distributing Standard Treatment Guidelines (STGs) to the hospital staff, and regulate veterinary use. The *second tier recommendations* were to regulate over the counter sale, prioritize funding for research, issue guidelines and checklists, and study impact of seasonal influenza vaccine on pregnant females.

The National Policy for Containment of Antimicrobial Resistance [20] has created a task force to review the current situation regarding manufacture, use and misuse of antibiotics in the country; to recommend the design for creation of a national surveillance system for antibiotic resistance; to initiate studies documenting prescriptions patterns and establish a monitoring system for the same; to enforce and enhance regulatory provisions for use of antibiotics in human and veterinary and industrial use; to recommend specific intervention measures such as rational use of antibiotics and antibiotic policies in hospitals; and to review the diagnostic methods pertaining to antimicrobial resistance monitoring.

Chennai Declaration

A joint meeting of Medical Societies in India was held in 2012 at the 2nd Annual Conference of the Clinical Infectious Disease Society (CIDSCON) in Chennai to develop a road map to tackle the challenge of antimicrobial resistance [21]. Chennai Declaration was a major step towards antibiotic stewardship policy in India. The aim was to initiate efforts to formulate a policy to control the rising trend of antimicrobial resistance with following objectives:

- To regulate over-the-counter sale of antibiotics;
- In-hospital antibiotic usage monitoring;
- Audit and feedback;
- Initiate measures to step up microbiology laboratory facilities; and
- National antimicrobial resistance surveillance system.

The measurable goals of the Policy are reproduced in ***Box* 4.**

Efforts by Indian Council of Medical Research and Indian Academy of Pediatrics

In 2012, Indian Council of Medical Research (ICMR) started a program on antibiotic stewardship, prevention of

BOX 4 GOALS OF THE CHENNAI DECLARATION [21]

First year

- Formulation of a national policy to combat antimicrobial resistance
- efforts to implement major components of the policy
- 60% compliance rates to major recommendations by stakeholders

Second year

- Compliance rate 70%
- efforts to implement minor components of policy
- India achieving the status of a country with a functioning antibiotic policy despite limitations

Next five years

- >90% compliance to major components of the policy
- India achieving the status of a country with a functioning antibiotic policy comparable to countries with high quality infection control and antibiotic policy compliance rates

infection and control [22]. This program brings together from the disciplines of clinical pharmacology, microbiology, infectious disease, nursing, intensive care, hospital infection control and surgical specialties; and is delivered through a training workshop involving participation of 20 centers. The workshop is aimed to train the participants with skills and understanding required for infection prevention and control practice; knowledge and skills required for development and implementation of antimicrobial policy guidelines for rational use of antibiotics to curb antibiotic resistance; and ability to plan and conduct research projects in antibiotic policy, infection prevention and control practice. Indian Academy of Pediatrics joined hands with ICMR in 2014 to discuss and deliberate over the magnitude of the problem, reasons and possible solutions to tackle the antimicrobial resistance among children in India. The meeting culminated in formulating a 4-point plan (***Box* 5**) [6].

Factors such as inequity of health care in India, irrational prescription of antibiotics, the understaffed hospitals where it becomes difficult to arrange a separate team for running antibiotic stewardship programs, non-allopathic doctors prescribing allopathic medicines, lack of funds specially in government sector hospitals, poor understanding of the clinicians regarding importance of antibiotic stewardship, problems of over the counter available antibiotics are the common barriers in Indian setting. It is essential to find solutions to the above problems so as to get successful implementation of the ASP.

CONCLUSION

Antimicrobial resistance is a major threat to human life in the coming decades. It is essential to take some urgent steps to curtail this rising resistance. The ASP is one of the key strategies to prevent the emergence of antimicrobial resistance but the success of this program needs joint efforts at the level of community, patient, and the healthcare provider.

BOX 5 IAP-ICMR 4-POINT PLAN TO TACKLE ANTIMICROBIAL RESISTANCE

1. Developing and disseminating National Antibiotic Guidelines for Children 2014 – The IAP-ICMR document
2. Educating doctors – both pediatricians and other doctors – as well as public on rational antibiotic use
3. Developing infection control guidelines for small hospitals and nursing homes, training the owners of such establishments and ensuring compliance by the members
4. Collecting and collating data on antimicrobial resistance from the clinicians

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