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ANTIMICROBIAL STEWARDSHIP : A GUIDE TO RATIONAL ANTIBIOTIC PRESCRIPTION

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ABSTRACT

BACKGROUND AND OBJECTIVES : The concept of rational prescription of antibiotics known as *antibiotic stewardship* involves a multifaceted approach to combat the control cost and improve clinical outcome by improving antimicrobial use. Antibiotic prescribing may also be influenced by what we call as 'prescribing etiquette' which often leads to prescriber being reluctant to alter their colleague's prescription. To address this gap in knowledge and to support prescribers in their efforts to treat patient effectively, antibiotic stewardship programmes needs to be advocated. Antibiotic stewardship refers to multifaceted approach (including multiple guidelines, policies, prevalence, surveillance, reports, education and audit of practice) that healthcare organizations have adopted to optimize prescribing to improve clinical outcomes and control costs. Most of the studies on ASP are in adults and that too from developed countries. Emerging economies contribute significantly to the burden of AMR, mainly due to indiscriminate use, and poor prescribing guidelines. To add to this the higher sickness level of patients, and coexisting co- morbidities like malnutrition, pushes clinicians toward frequent empiric use of antibiotics. The clinicians have to walk a tight rope, balancing between early appropriate use and avoiding prolonged inappropriate use of antimicrobials We therefore decided to conduct this before and after study to test the feasibility of a clinical ASP with respect to rational antimicrobial use(number, dose, appropriateness and upgradation)

METHODS: This study was a prospective before and after study design which was divided into 3 phases over a span of 12 months . A pre- implementation audit (phase 1)was conducted for 1st 3 months studying various prescription practices that were being followed in ICU and general observation. Antimicrobial stewardship was implemented in phase 2 for a period of 6 months. After the implementation of ASP in PICU, a similar audit on antimicrobial prescription and usage was done in next three months (phase 3) and the results compared with the audit of pre-implementation period

RESULTS : Our study was designed to note effect of antimicrobial stewardship on rational antimicrobial use (number, dose, appropriateness and upgradation).We observed that before implementation of a formal ASP the number and duration of antibiotics were significantly higher in the pre-implementation phase as compared to post implementation phase. We observed that not only there was a significant drop in number and duration of antibiotic use but also a statistically significant reduction in the number of inappropriately prescribed treatment

KEYWORDS : antimicrobial stewardship , antimicrobial resistance , multi drug resistant

INTRODUCTION

The concept of rational prescription of antibiotics known as *antibiotic stewardship was* first given by Dr. Dale Gerding in 1980's. It involves a multifaceted approach to combat the development of resistance, control cost and improve clinical outcome by improving antimicrobial use(1). The definition states*" the use of antimicrobial in most appropriate way for the treatment or prevention of human infectious diseases having regard to diagnosis , evidence of clinical effectiveness, likely benefits, safety, costs and propensity for emerging of resistance. The most appropriate way that implies the route , dose , frequency and duration of administration have been rigorously determined"*. The primary goal of AMS is to get the desired clinical outcome with minimal side effects of antimicrobial under use including toxicity and emergence of resistance. The secondary goal is to reduce healthcare cost without compromising quality of care. s

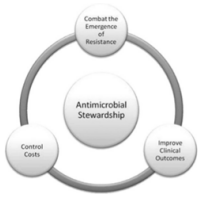


Figure 1. Goals that antimicrobial stewardship strives to achieve.

The first program to improve antimicrobial prescribing pattern was reported by Briceland and his colleagues(2). Since then many studies have cited similar approach to prescription of antibiotics using terms like optimal antimicrobial prescribing, and antimicrobial stewardship interchangeably.ASP comprises of organizational structure and action plan to implement antimicrobial stewardship in a hospital.

Unlike many other drugs for which prescribing is kept within a specialty (anticancer, antipsychotic), antibiotics are universally prescribed by all doctors. As a result quality of antibiotic prescribing may suffer as prescriber may opt for a broader spectrum agent and longer than necessary duration of treatment. Antibiotic prescribing may also be influenced by what we call as 'prescribing etiquette' which often leads to prescriber being reluctant to alter their colleague's prescription. To address this gap in knowledge and to support prescribers in their efforts to treat patient effectively, antibiotic stewardship programmes needs to be advocated. Antibiotic stewardship refers to multifaceted approach (including multiple guidelines, policies, prevalence, surveillance, reports, education and audit of practice) that healthcare organizations have adopted to optimize prescribing to combat the emergence of resistance, improve clinical outcomes, and control costs. It advocates use of most

appropriate antibiotic indicated for the clinical condition. Over last 10 years increasing profile of healthcare associated infections (HCAIs), rising multidrug resistance, and diminishing pipeline of new antimicrobial have propelled management of HCAI into fore front. This has in turn raised the profile of ASP within healthcare institutions. Antibiotic stewardship is of great importance and relevance especially in the ICUs. Clinical decision support systems, biomarker-derived treatment algorithms, and improved knowledge regarding the different components of antimicrobial therapy represent some of the advances that have been made in stewardship. Yet, significant obstacles have prevented the full achievement of stewardship's goals, and approaches to confronting these obstacles should be appreciated. Clinicians should realize that antimicrobials are important therapeutic agents and strive to use them wisely(3) Braxton et al demonstrated that a more than 90% compliance with surgical care improvement project (SCIP) core measures significantly decreased the variability of perioperative antibiotic-ordering practices (4). Metjain et al conducted a prospective observational study to describe the use and impact of a pediatric ASP. During the 4-month study period, calls were placed to the ASP for 652 patients out of which 45% calls required an intervention by the ASP including targeting the known or suspected pathogens (20%), consultation (43%), optimize antimicrobial treatment (33%), and stop antimicrobial treatment (4%)(5). It was concluded that ASP improves the appropriateness of antimicrobial use in hospitalized children. Schulz et al in a review found that the antibiogram is neither designed nor well suited to reflect changes in hospital antimicrobial drug use and it bears an inconsistent relationship with changes in hospital antibiotic use and cannot be recommended to reliably evaluate an ASP intervention(6). Most of the studies on ASP are in adults and that too from developed countries. Emerging economies contribute significantly to the burden of AMR, mainly due to indiscriminate use, and poor prescribing guidelines. To add to this the higher sickness level of patients, and coexisting co-morbidities like malnutrition, pushes clinicians toward frequent empiric use of antibiotics. The clinicians have to walk a tight rope, balancing between early appropriate use and avoiding prolonged inappropriate use of antimicrobials We therefore decided to conduct this before and after study to test the feasibility of a clinical ASP with respect to rational antimicrobial use(number, dose, appropriateness and upgradation)

MATERIAL AND METHODS

Study design: Prospective before and after study design

Study period: 3 months-Pre-implementation audit (PHASE1)

6 months- Implementation of antimicrobial stewardship program (PHASE2)

3 months- Post-implementation audit (PHASE 3)

Observation or Pre-implementation phase (phase 1: During first 3 months of the study period, no new changes were made to the existing practice of antimicrobial prescription.An audit of the antimicrobial prescription pattern was conducted on the patients admitted to PICU during this three month period.This audit was on a structured pre-designed proforma (appendix).All patients admitted to PICU were screened daily for eligibility by the investigator and those who were on empirical antibiotics initiated in the previous 24 hours were included in the audit. Patients were monitored daily for any change in prescription of antibiotics and followed till discharge/transfer from PICU or death. Various variables like cost of antibiotics, complications, health care associated infections and outcome were noted in the pre designed performa by the investigator. The information required for this was obtained from patient records, review of nursing charts and death files and by interviewing residents, nursing staff, parents and relatives. The patients included were followed up daily till PICU discharge for any change in antimicrobial pattern and complications.

Implementation of ASP (phase II):). The ASP protocol was based on the following five elements

1. Education
2. Formulary restriction and pre-authorization
3. Antibiotic 'Time Out'
4. Accountability
5. Policy

1. **Education**: We from his experiences in phase 1 of study realized that residents in PICU were more inclined towards early initiation of antimicrobials so as to prevent sepsis related complications although they knew about antimicrobial resistance, and the risks involved. The education consisted of basic orientation on the very 1st day of the PICU rotation about technique and need of hand washing, other hygienic measures during procedure and patient care, donning and doffing of universal precautions and various critical care bundles (including VAP, BSI, CLABSI etc.).The message was disseminated with help of posters, pamphlets, power point presentations, didactic lectures (in formal and informal settings), electronic communication to resident groups and mock codes. Updates on antibiotic prescribing, antibiotic resistance, and infectious disease management were provided and queries of resident were discussed and addressed. Similarly weekly classes for nursing staff were also taken on topics as described above. A checklist to follow in each patient was provided to both doctors and nurses. A de-identified case was reviewed every month with the healthcare providers to explain to them the possible changes in antibiotic therapy that could have been made in the given case. Weekly antimicrobial rounds were undertaken with microbiology team to study the pattern of resistance and decide the most effective management of HCAI. Injudicious use of antimicrobials was strongly discouraged. Posters and written instructions pertaining to general hygiene and precaution before contacting patient in isolation rooms were pasted on doors. Nurses were also encouraged to take basic hygiene classes of parents and attendants. Common clinical infectious syndromes treated in PICU (e.g., pneumonia, diarrhea, CLABSI, VAP, UTI), specific/ pathogens, specific antimicrobial agents and clinical pathway were outlined and protocolized.
2. **Formulary restriction and pre-authorization** Use of Vancomycin,Colistin, and Amphotericin were restricted. It was ensured that before initiation of these drugs the indication was reviewed with a senior consultant either in person or over phone. Only after this discussion, was authorization given for the use of the above restricted drugs. Also it was ensured that the loop was completed in a timely manner.
3. **Antibiotic administration and documentation**: The clinical diagnosis at admission and the indication for starting an antimicrobial was clearly mentioned in the file. The dose, frequency, and route of administration were verified. Appropriate cultures (blood, other body fluids when indicated) were sent prior to initiation of antimicrobial agent.A senior resident in Department of Microbiology was assigned to provide culture and sensitivity report of various body fluids at the earliest and special microbiology on call number (8151) was made available round the clock
4. **Antibiotic 'time outs':** Most of the children enrolled in study had antibiotics started empirically in PICU/emergency. Areassessment of the continuing need

and choice of antibiotics was done at 24 and 48 hours of stay when the clinical picture became clearer and more diagnostic information was available.The treating resident at that time had to ask a set of questions for each child started on empiric antibiotics

5. **Prospective audit and feedback** Prospective audit was carried out in PICU and data regarding the feasibility and barriers in implementation of ASP, antibiotic usage and resistance pattern were discussed in monthly review meetings. Feedbacks as external reviews of antibiotic therapy by an expert in antibiotic use were also obtained
6. **Implementation of policies and interventions to improve antibiotic use:**

Documenting dose, duration, and indication: Dose, duration and indication for all courses of antibiotics were specified and made readily identifiable. Making this information accessible ensured that antibiotics are modified as needed and/or discontinued in a timely manner. Evidence based facility-specific treatment recommendations (Already published - IJP protocols), national guidelines (Malaria, Typhoid, Dengue etc.) and local susceptibilities (Unit's quarterly microbial audits) and formulary options were made readily available to guide antibiotic selection and duration, particularly for common indications for antibiotic use

Post-implementation observation (phase III): After the implementation of ASP in PICU, a similar audit on antimicrobial prescription and usage was done in next three months and the results compared with the audit of pre-implementation period.

RESULT

Our study was completed in 3 phases in the Pediatric Intensive Care Unit(PICU) viz. the Pre-intervention audit phase(I), the implementation of antimicrobial stewardship program (ASP) phase(II), post implementation audit(III). The first phase consisted of general audit of the existing antimicrobial prescription practices, trends, and resistance pattern found in the PICU which were noted in a pre designed proforma. In the second phase antimicrobial stewardship program(ASP) was implemented and residents and nursing staff were familiarized with various elements of ASP. In the final or post implementation phase(III) once again an audit was conducted on a predesigned proforma as in the pre-implementation phase. The impact of antimicrobial stewardship was noted by comparing the pre-intervention and post-intervention phases in term of antibiotic usage, resistance, cost of therapy, length of stay and mortality.

The pre-intervention phase lasted for 3 months from During this phase no changes were made to the existing antimicrobial prescription practices in PICU. The detail about empiric antibiotic prescription with respect to number, frequency, dose, route, indication etc. were noted in a pre-designed performa that was designed a priori A total of 99 children admitted to PICU during phase I received empirical antibiotics for longer than 24 hours and were enrolled in this phase. Out of the total of 99 patients evaluated, 61(61.4%) were boys and 38(38.4%) were girls with boys: girls of 1.6:1

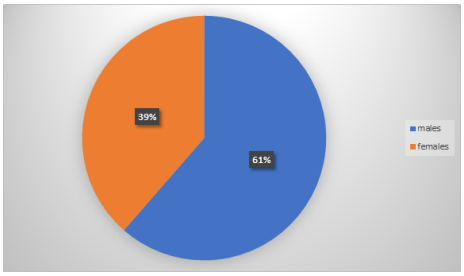


Fig 1.Gender distribution in pre-implementation phase

The mean SD (range) and median (IQR) age of children enrolled in phase I was 3 3.3 (1 month to 12 years) and 1 (3 months to 4 years) respectively. The distribution of systems involved at the time of admission is depicted in Fig.2. Respiratory illness was the commonest (n=56,56%) followed by CNS (n=24, 24.2%), sepsis(n=8, 8.1%), skin and soft tissue involvement (n=6, 6.1%) and GIT (n=4, 4%)and cardiovascular system (n=3, 3%)

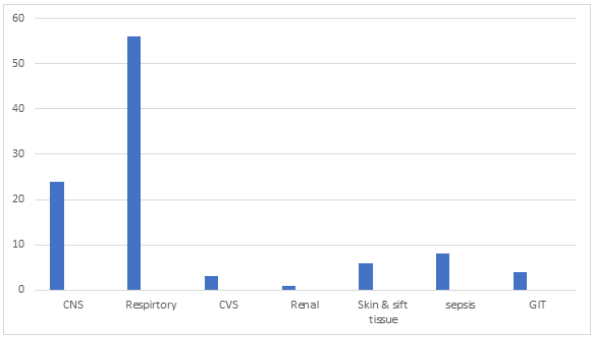


Fig 2-: Distribution of systems involved at admission

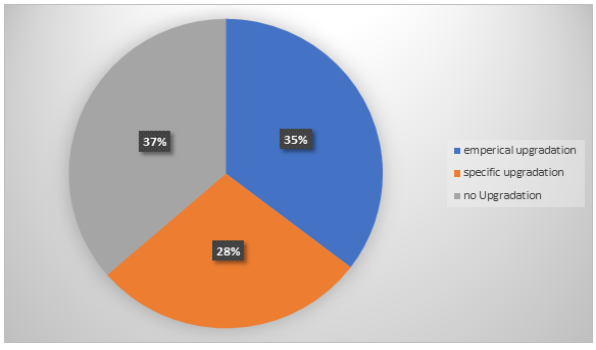


Fig 3. Upgradation of antibiotics in pre-implementation phase

The empirical antibiotics administered were assessed for various factors like dose, appropriateness, duration, frequency and routes of administration.Only in about 3(3%) dose was not calculated as per set protocol. In 16 (16%) children antibiotics were found to be prescribed inappropriately. However the duration, frequency and routes were being adhered to properly and no discrepancy was found in these variables. Twenty four(24.6%) developed HCAI during the stay in ICU and seventy five (75%) were transferred to a step down facility(wards). Formulary restricted antibiotics were started in 33(33%) patients and drugs related adverse were noted in 7(7%) patients. In 7(7%) change in antibiotics were switched from IV to oral.

Post implementation phase

This phase lasted for 3 months from. The details about empiric antibiotic prescription with respect to number, frequency, dose, route, indication etc. were noted in a pre-designed proforma similar to the first phase. A total of 89 children admitted to PICU during phase III received empirical antibiotics for longer than 24 hours and were enrolled in the phase. Out of the total of 89 patients evaluated 50(56.2%) were boys an 39(43.8%) were girls with boys:girls of 1.2:1.

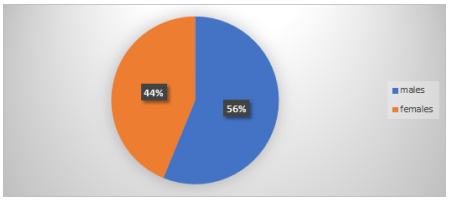


Fig 10. Gender distribution in pre-implementation phase

The mean SD (range) and median (IQR) age of children enrolled in phase III was 4 3.3 (1 month to 12 years) and 3 (1.3 to 6.5) years respectively. The distribution of systems involved at time of admission is depicted in Fig.11; tropical illnesses/sepsis was commonest (n=32, 36%) followed by respiratory(n=28, 31.5%), CNS(n=21, 23.6%), GI (n=9, 10%), skin and soft tissue involvement (n=5, 5.6%) and cardiovascular system (n=2, 2.2%)

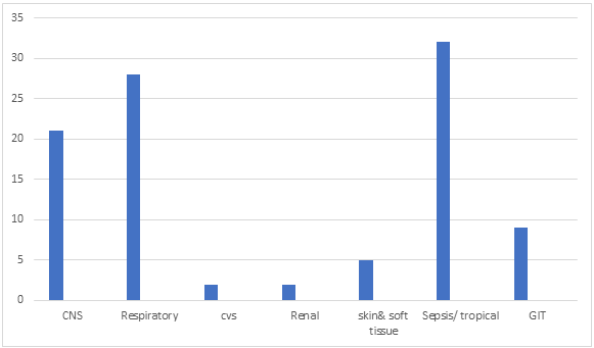


Fig .11-: Distribution of systems involved at admission in post-implementation phase

Out of 89 children started on empirical antibiotics 28(31.5%) required empirical upgradation for various reasons like clinical/radiological worsening, persistent fever etc. and in 31(35%), antibiotics were upgraded in response to specific culture reports. In remaining 29(32%) no change in antibiotics regimes were made

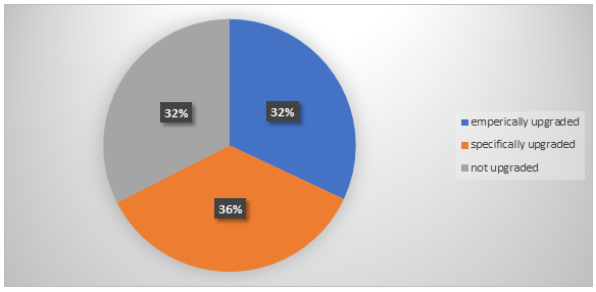


Fig.12. Upgradation of antibiotics in post-implementation phase

The empirical antibiotics administered were assessed for various factors like dose, appropriateness, duration, frequency and routes of administration. Only in 1(1%) patient the dose was not calculated as per set protocol and in 1(1%) the antibiotics were found to be prescribed inappropriately. However the duration, frequency and routes were being adhered to properly and no discrepancy in these variables was found. Three (24.6%) developed HCAI during the stay in ICU and 86 (96.6%) were transferred to a stepdown facility(wards). Formulary restricted antibiotics were started in 11(12.5%) patients and drug related adverse events were noted in only 1(1.13%) patient. In 2(2.2%) change in antimicrobials from IV to oral was made.

Comparison between pre and post intervention phases

The pre and post intervention phases were compared with each other with respect to days of antibiotic therapy, incidence of HCAI , proportion of resistant organism, cost of antibiotics, length of ICU stay and mortality. The comparative data is presented in table.

Variables			P values
	Pre (n=99)	Post(n=89)	
Upgradation of antibiotics n(%)	35(%)	31.5(%)	0.643
Inappropriate Dose n(%)	3(%)	(1%)	0.693
Appropriateness n(%)	16(%)	(1%)	0.001
No. of antibiotics n(%)	3.00	2.00	0.001

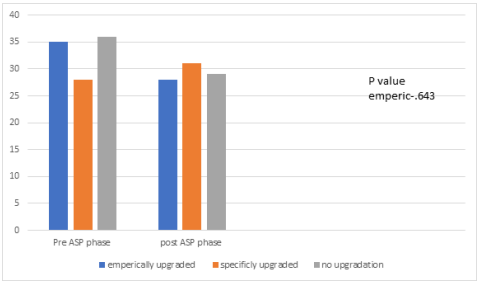


Fig.19: comparison of upgradation pattern of antibiotics in pre and post-ASP phases

2. comparison of dose and appropriateness of antibiotics between pre and post ASP phases

The proportion of inappropriate antibiotic use of 16% in pre-intervention phase was reduced significantly to 1% in post ASP phase (p=0.001). Similarly the frequency of inappropriate dose in post intervention phase was also reduced significantly (3% to 1 %; P=0.001

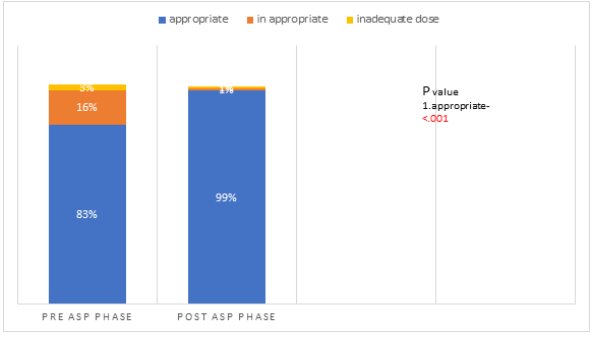


Fig.20 :Comparison of Dose and Appropriateness of antibiotic between pre and post ASP phases.

DISCUSSION

Our study was designed to improve the current antimicrobial prescription practices being followed in the Pediatric Intensive Care Unit through implementation of an Antimicrobial Stewardship Program(ASP) and to assess the difference in days of antibiotic therapy, duration, cost and rational upgradation of antimicrobials in a before and after study design.

We observed that before implementation of a formal ASP the number and duration of antibiotics were significantly higher in the pre-implementation phase as compared to post implementation phase. Our findings were comparable with findings of Hersh AL et al who in their study comparing differences in average antibiotic use in various pediatric hospitals from 2004-2012, found substantial decline in average antibiotic use from 11% in pre-stewardship phase to around 8 % in post antimicrobial stewardship phase (p=0.04)(7). Similarly Hou D et al, demonstrated a significant reduction in antimicrobial prescriptions after implementation of short period of antimicrobial stewardship program (P=0.01)(8). In another study by Lee KR et al. done in a tertiary children's hospital a similar significant decline in antibiotic use was observed after implementation of antimicrobial stewardship program(9). Cairns KA et al in their study found that there was a 17 % reduction in broad spectrum antimicrobial use after implementation of ASP over a period of 30 months. Morrill et.al in their 6 point assessment on antimicrobial stewardship, noted median length of stay was 1 day shorter between the two phase(10)

Our observations along with the published literature clearly have shown that a formal ASP acts as a check that not only decreases the consumption of inappropriate antibiotics but also shortens therapy. Also we noted that higher proportion of patient was being treated by single antibiotic instead of multiple antibiotics as used earlier before implementation of ASP. Thus overall it results in an effective antimicrobial policy.

We observed that not only there was a significant drop in number and duration of antibiotic use but also a statistically significant reduction in the number of inappropriately prescribed treatment (decreased from 16 % to 1 %) between the pre and post intervention phases. Agwu et al reported a similar decrease of 32% in inappropriate antimicrobial prescription pattern after antimicrobial stewardship implementation(11)

CONCLUSION :

In our study we found out that there was significant reduction in duration and number of antimicrobials between pre and post implementation phases, there was also decrease in consumption of antibiotics .

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