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The Relationship between Antimicrobial Stewardship and Patient Outcomes: Health Care Costs, Mortality, Complications and HCAI

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Abstract

Background and Objectives: *Inappropriate antimicrobial use has rapidly become a global concern leading to increased antimicrobial resistance. Antibiotic resistant organisms are not only becoming increasingly difficult to treat but also lead to increased treatment costs, longer duration of hospital stay and in some cases even death; over 30% of deaths have been attributed to antimicrobial resistance (AMR). In setting of ICU, AMR has been shown to be associated with increased ICU mortality, complications and cost of treatment which can be a huge burden for emerging economies. We therefore decided to conduct this before and after study to test the feasibility of a clinical protocol based ASP with respect to pattern of HCAI, acquisition of resistance and mortality.*

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 HCAI outcomes, cost, complications and mortality patterns in Pediatric ICU. Our findings revealed that there was a statistically significant reduction in health care associated infections (HCAI) from 24.2% in pre implementation (phase1) to 3.2% following implementation of ASP with statistically significant p value of 0.001, similar difference in cost of antimicrobials was also noted in both phases. Adverse drug reaction needing to stop the drug were 7% in phase 1 which statistically reduced to 1% following implementation of ASP. However we were not able to find any statistically significant change in mortality pattern between pre and post ASP implementation phases.*

Keywords: *antimicrobial stewardship (AMS), antimicrobial resistance (AMR), multi drug resistant (MDR), health care associated infections (HCAI).*

Introduction

Inappropriate antimicrobial use has rapidly become a global concern leading to increased antimicrobial resistance. Antibiotic resistant organisms are not only becoming increasingly difficult to treat but also lead to increased treatment costs, longer duration of hospital stay and in some cases even death; over 30% of deaths have been attributed to antimicrobial resistance (AMR). In setting of ICU, AMR has been shown to be associated with increased ICU mortality, length of stay (LOS), and cost of treatment(1) which can be a huge burden for emerging economies. Therefore it is amply clear that judicious use of antibiotics is an important measure to limit AMR and its subsequent complications. This concept led to the development of antimicrobial stewardship programs (ASPs) to assist in optimal selection, dosage and duration of antibiotic treatment so as to improve patient safety and outcome and decrease resistance(2). Timelines, appropriateness, duration of antibiotic uses arc the basic principles on which any ASP program rests(3). Audits, rotating antibiotic schedules, multidisciplinary approach for initiation and discontinuation, and staff education are some of the component of ASP that has been evaluated WHO estimates that at any given time 1.4 million people in developing and developed countries are affected by healthcare associated infections (HCAI)(4). The overall prevalence in the developed countries for the period between 1995-2008 was found to be between 5.1% to 11.6 %. ECDC data found a prevalence of about 7% but this proportion was up to 50 % in ICU settings; thus representing total of 25 million extra days in hospital and 13-24 million of financial burden (5).

but Health care acquired infections are a major problem leading to prolonged stay, long term disability, and increased cost of medications, increased antimicrobial resistance and even mortality. An estimated 1.4 million people in developing and developed countries at any given time are affected by HCAI(6) The overall prevalence of HCAI between 1995-2008 in developed countries was between 5.1%-11.6%, while the latest European data suggests that the proportion of infected ICU patients can be as high as 50%. In developed countries HCAI accounts for 5-15 % of hospitalized patients(7) and ICU accounts for 9-27%

HCAI surveillance in developing countries is not well developed. Diagnosis of HCAI is difficult due to lack of laboratory data, poorly maintained medical records and scarce access to lab and radiological facilities. In many settings the basic infection control measures are non existent. This is aggravated by understaffing, overcrowding, shortage of basic equipments, limited finances contributing to increased risk of HCAI. Infection rate in low and middle income group countries are 2-3 times more than developed countries. Neonatal infections were found to be 3-20 times higher in hospital born babies(8). The burden of HCAI is significantly more in ICU's where device associated infection rates are also higher(9)

ICUs are often regarded as epicenter of infections, partly due to extremely vulnerable population, increased incidence of procedures, and use of invasive devises that breach protective barriers. Furthermore drugs prescribed in ICU disrupt the normal flora predisposing to increased risk for HCAI. Understandably ICU population has highest nosocomial infection rates of 20-30% of all ICU infections(10)(11) with impact on morbidity, and mortality.(12)(13)

We therefore decided to conduct this before and after study to test the feasibility of a clinical protocol based ASP with respect to pattern of HCAI, acquisition of resistance and mortality

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): A stewardship programme 'ASP' was implemented in PICU over a period of 6 months 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.

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. 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

Post-implementation observation (phase III): obtained 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

Preimplimentation phase: The pre-intervention phase lasted for 3 months. 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. Following observations were noted inthis phase

Adverse effects: In the pre-implementation phase 7(7%) developed adverse reactions (ADR) to various antimicrobials. These adverse effects were mostly involving renal system in form of deranged RFT requiring renal modification of current dose however in all cases these effects were reversed on conservative management.

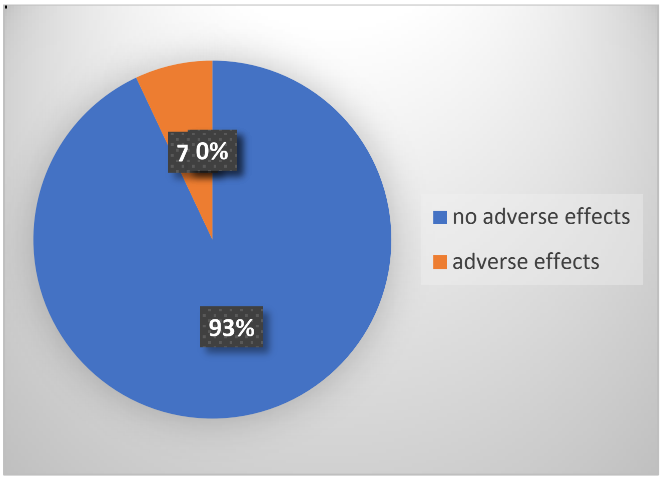

Fig.8: Number of children developing adverse effects to antimicrobials

Mortality: Of the total patient enrolled during this phase85 (85%) were shifted to a step down facility and 14 (14.1%) died

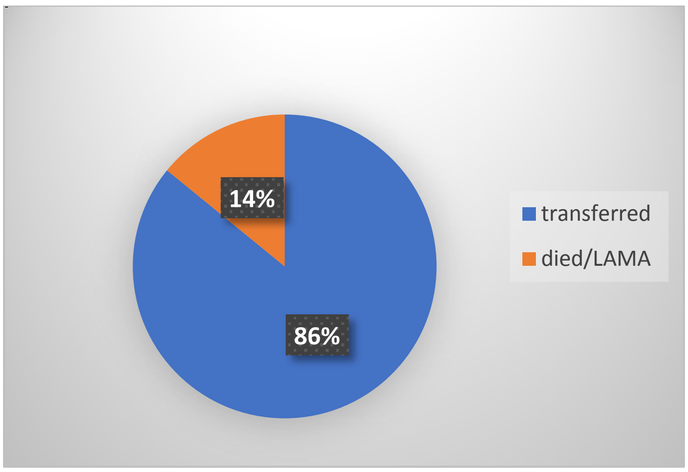

Fig. 9: Final outcome in pre-implementation phase

Postimplimentation phase: This phase lasted for 3 months. 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

Adverse effects: In post-implementation phase only 1(1%) patient developed adverse reactions (ADR) to various antimicrobials. These adverse effects were mostly involving renal system in form of deranged RFT requiring renal modification of current dose however in all cases these effects were reversed on conservative management

Mortality: Of the total patient enrolled during this phase 79(88.8%) were shifted to a step down facility and 10 (11.2%) died.

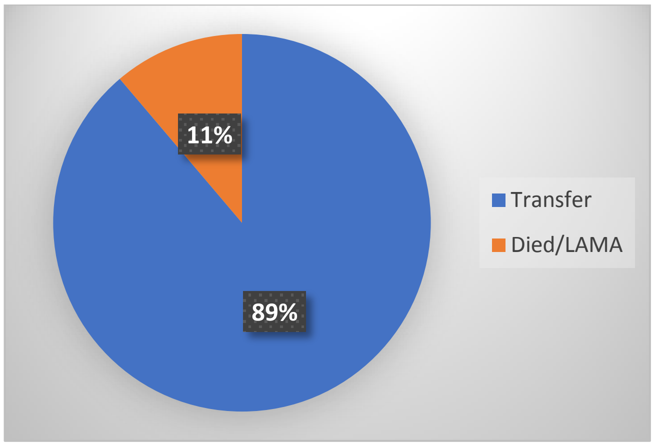

Fig.18: final treatment outcome in pre-implementation phase

Comparison between pre and post intervention phases

The pre and post intervention phases were compared with each other with respect to HCAI, cost of antibiotics , adverse effects and mortality rates

Variables			P values
	Pre (n=99)	**Post(n=89)**	
HCAI n(%)	24.2(%)	3.4(%)	0.001
Cost median (IQR)	2400	1690	0.044
Adverse effects n(%)	7 (%)	1(%)	0.01
Mortality n(%)	**14**	**10**	**0.552**

Incidence of HCAI in pre and post ASP phases:
The incidence of HCAI in pre and post implementation phases had also reduced significantly to 3.4% from 24% in pre ASP phase (p=0.001)

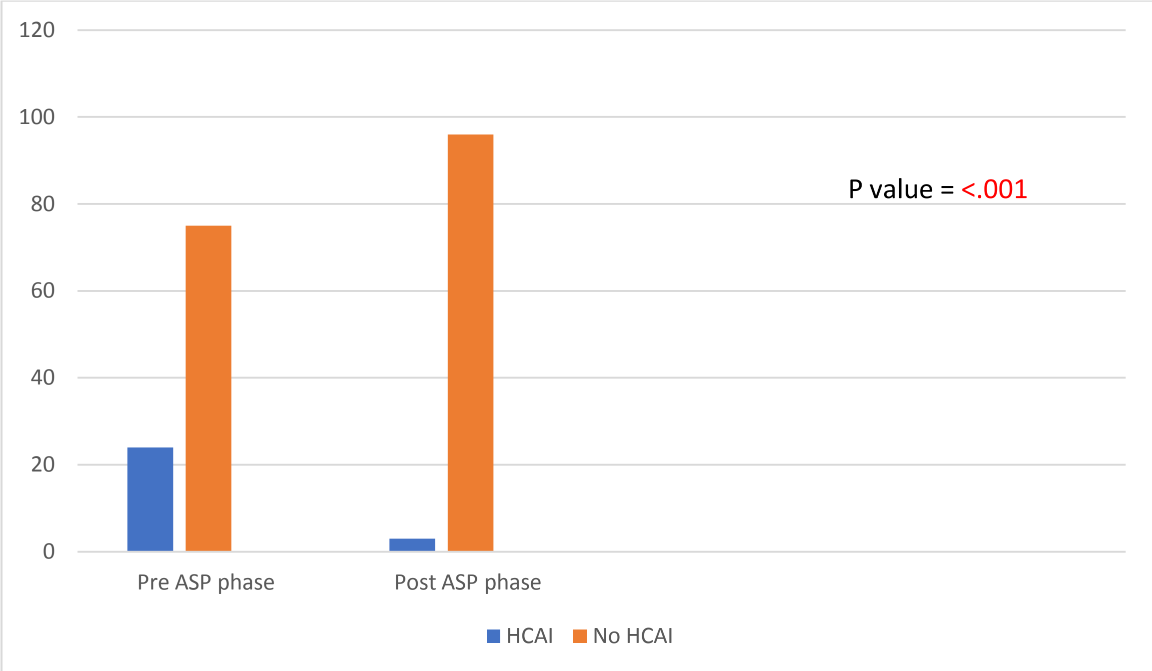

Fig.21: Incidence of HCAI in pre and post ASP phases

Cost of antibiotics
Patient in pre-implementation phase had a median expenditure of Rs2400, Rs 2300, Rs 4930 in total, empirical and specific therapy respectively. During the post ASP phase the median expenditure came down significantly to Rs1690, Rs1224, Rs 1589 for total, empiric and specific therapy respectively. This difference in cost between both phases was statistically significant (P= 0.044, 0.013, 0.019).

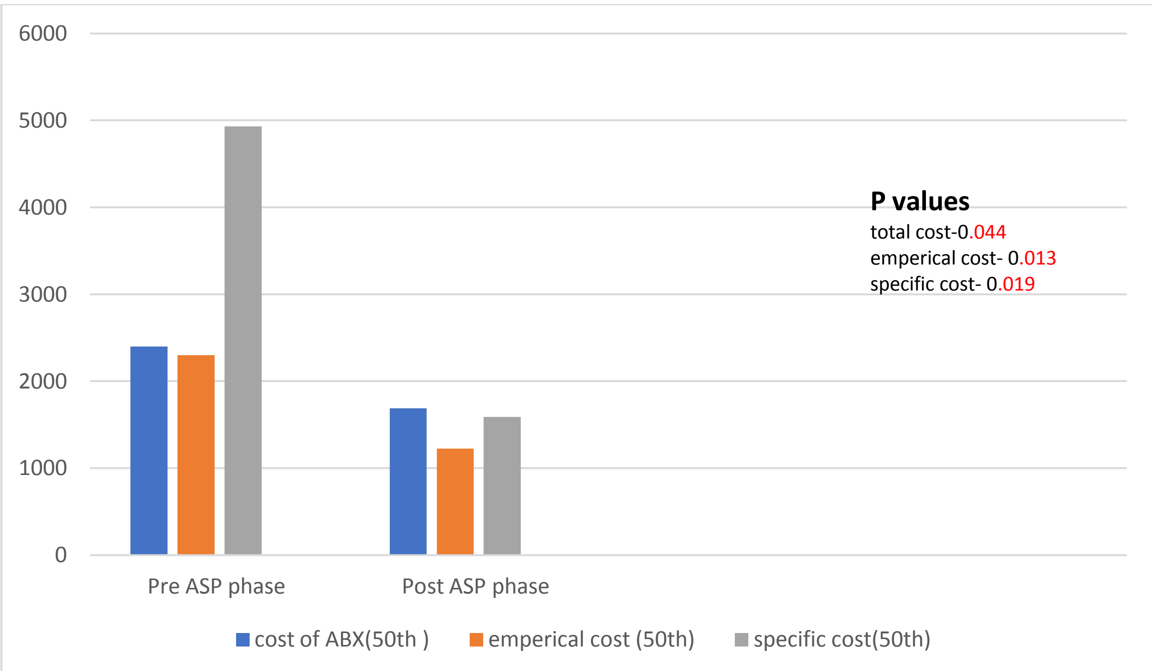

Fig.22: Cost comparison in pre and post ASP cohorts

Adverse effects in pre and post ASP cohorts: The frequency of adverse effect in both phases was significantly different (7% vs 1% : p= 0.001) almost all adverse effect in pre-implementation phase was related to deranged RFT and dose modification.

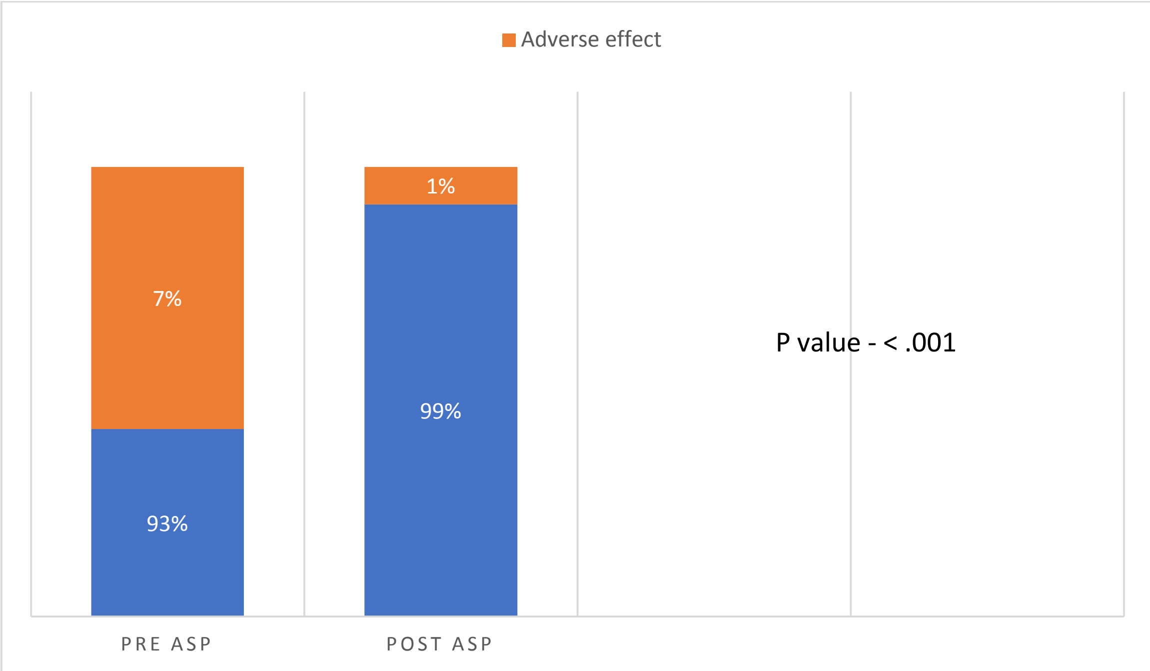

Fig. 25 : Adverse effects in pre and post ASP cohorts

Mortality: The mortality rates in pre and post implementation cohorts were similar [14 %vs. 11.2%; P=0.663

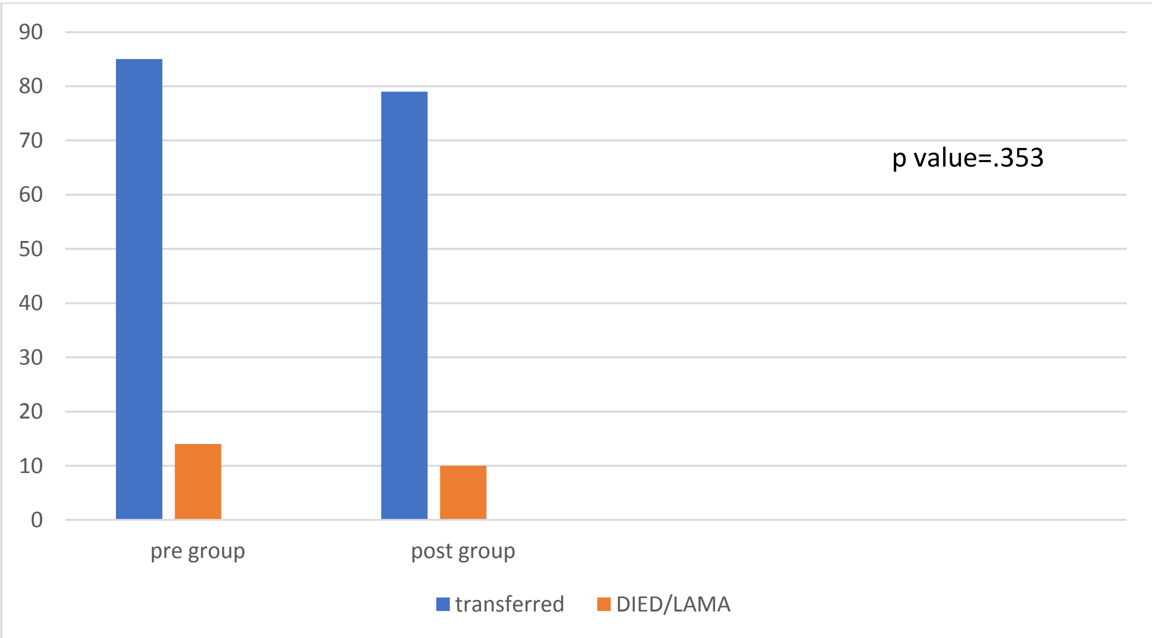

Fig.26: Mortality pattern in pre and post ASP cohorts

Discussion

Our study was designed to improve the current stewardship practices being followed in the Pediatric Intensive Care Unit through implementation of an Antimicrobial Stewardship Program (ASP) and to assess the difference in cost of antibiotics, difference in HCAI rates , adverse effects and mortality rates in a before and after study design.

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[14]. In a study on patients admitted in ICU, Kollef et al. found significantly reduced mortality in those patient who received appropriate antibiotics compared to those who did not receive appropriate antibiotics (18% vs 42% ; p=0.001)[15]. Similar results were described by Apisarnthanarak et al where they showed increased mortality due to inadequate antimicrobial therapy in NICU[16]. This emphasizes the point that appropriateness of antibiotics has a significant impact on final outcomes and this can be ensured by good antimicrobial stewardship programs. Multiple drugs used in children exposes them to higher risk of adverse drug reactions. We observed a reduction in adverse effects from (7% to 1%) between pre and post ASP possibly due to reduction in multiple classes of antibiotics being prescribed, and more rational preparation and dosing.

We also found a significant decrease in cost of antibiotics between pre and post ASP implementation phases. Similar findings were reported by Timbrook TT et. al who showed significantly decreased antibiotic expenditure after ASP[17]. Jenkins TC et. al also suggested similar cost differences between pre and post ASP phases of their study[18]. Kaki et al describes a similar cost reduction from 38% to 11% after implementation of antimicrobial stewardship[19], probably related to more rational and judicious use of antibiotics during implementation phase. contradictory to our study Kaki R et. al states no change in health care associated infection rates in their study[19]

We observed a significant reduction in HCAI rates between pre and post implementation phases (24 % to 4% ; P=0.001) similar to results shown by Nowak et.al[20], wherein a significant reduction in ventilator-associated pneumonia rates(p=0.001) was noted after implementation of ASP[21]. Residents and nurses were familiarized with hand hygiene technique and donning and doffing of universal precautions, and compliance to it was strictly ensured. Residents and nursing staff were taught about various critical care bundles in ICU through group discussion and PPT. Commonly used procedure techniques were demonstrated to them by role play and video presentations and dialogue. The implementation of antimicrobial stewardship did not have significant effect on certain variables like length of PICU stay and mortality patterns between both groups.

In our study we found no significant difference in morality between pre ASP and post ASP phases (14 % vs 11 %; P=0.663).Similar results were described by Taggart et al where no significant change in mortality pattern was noted between pre-ASP and post ASP groups[22]. In contrast to our study Raymond DP et. al describes significant reduction in mortality rates (p=0.001) after implement of ASP[23]. Most of the studies on changing of mortality pattern in hospitals after antimicrobial stewardship are done on much more stable cohort and those who stay in hospital for a longer time (wards etc)

Conclusions

Implementation of an Antimicrobial Stewardship Program (ASP) in our PICU reduced the incidence of HCAI and cost of antibiotics. However it did not make a difference to the mortality

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