Irrational antibiotic prescribing practice among children in critical care of tertiary hospitals

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Abstract: This study assessed the prescribing pattern of irrational use of antibiotic among children under age of 12 years in public and private sector hospitals in Pakistan. The prospective clinical evaluation of drug utilization pattern of antimicrobials from Patient Bedside File (PBF) of in-patients and Culture Sensitivity Test (CST) reports were evaluated to determine the antibiotic resistance. Two indicators recorded to assess antibiotic prescribing were; dose of prescribed antibiotic (low-dose, rational and high -dose) and Indication (valid or invalid). Antibiotics resistance for 25 selected antibiotics was determined by culture sensitivity test. This study showed that in Private Sector Hospital 77.7% neonates, 13.3% infants and 9% children admitted in ICU were receiving antibiotics, among them only 57.3% neonates, 62% infants and 59.9% children were found valid that is prescribed antibiotics for right indication. 27% neonates, 19% infants and 22.1% children were prescribed under dose of antibiotics, which may lead to antimicrobial resistance and increased cost of hospital stay. Only 29.1% neonates, 30% infants and 36.8% children were receiving rational dosing. In Public Sector Hospital, 65.6% neonates, 19.4% infants and 15% children were receiving antibiotics. Among them valid indication was found in 35.3% neonates, 35.6% infants and 39.8% in children. 33.3% neonates, 26.6% infants and 28.2% children were receiving under dose that may lead to resistance not only among those who were prescribed under dose but also such bacteria become resistant and spread to other population to increase antimicrobial resistance. The irrational prescribing of antibiotics was found very high (above 50%) in Public sector hospital (Hospital-B) for every age group whereas in Private sector hospital (Hospital-A) this practice was found near to 50%. In this study the prescribing frequency of Amikacin, Cefixime, Cefotaxime, Meropenem, Amoxicillin, Vancomycin, Azithromycin, Levofloxacin and Clarithromycin was found above 80% in both hospitals (A and B). Among these, Amoxicillin, Penicillin, Erythromycin and Cephalexin showed higher resistance i.e. 49.2%.

Keywords: Antibiotics, Neonates, Infants, Children, Culture Sensitivity Test, Tertiary Care Hospital, Patient Bedside File, Antimicrobial Therapy Failure, Antibiotic resistance

INTRODUCTION

Approximately 80% of antibiotics are used for the primary care but their inappropriate use causes health hazard that need to be addressed. In developing countries like Pakistan the overuse of antibiotics is very high and is one of the challenging tasks to overcome. Especially health of children, neonates and infants is the worldwide concern because they are highly susceptible to infections due to immature immune system and require serious monitoring. Several studies have reported that 50-85% of children receive antibiotics prescribed by physicians. Irrational use of antibiotics causes resistance and several others influential factors do exist while prescribing antibiotics for non-bacterial infections, incorrect dosage or route of administration (Warrier *et al.*, 2006; Hashemi *et al.*, 2013). Despite of considerable achievements in the development of antibiotics and anti-infectives, infectious diseases remain a significant cause of morbidity and mortality globally (Hamilton *et al.*, 2014).

In clinical and non-clinical settings, bacteria are becoming increasingly resistant to conventional antibiotics. Gram-negative bacteria increase the resistance faster than Gram-positive bacteria. There are less new and developmental antibiotics active against Gram-negative bacteria while drug development programs emerged to be inadequate to gave therapeutic cover in last 10-20 years. (Cornaglia, 2009; Tan, 2008; Baiden *et al.*, 2010; Heddini *et al.*, 2009; Vento *et al*., 2010; Wise *et al*., 2010; Boucher *et al.*, 2009; Rice, 2009; Page and Heim, 2009).

According to the World health organization (WHO) over 3 million neonatal deaths occur each year globally in early neonatal period (Hannan *et al*., 2013). Apprehensions regarding this serious threat have been increasing day by day and strategies have been developed by WHO in a collaborative work with international network for rational use of drug to improve antibiotic practice (Narayan and Mangesh, 2016).

This study mainly focused on assessing the prescribing pattern of irrational use of antibiotic among children under age of 12 years in public and private sector

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hospitals in Pakistan, who were in critical care in tertiary care hospitals.

MATERIALS AND METHODS

In this study the assessment of drug utilization pattern of antimicrobials was audited from Patient Bedside File (PBF) of in-patients and Culture Sensitivity Test (CST) reports were evaluated to determine resistance of selected List of Most commonly Prescribed Antibiotics (LMCA).

Selection of hospital

One Private and one Public Sector hospital, fulfilling the following criteria, were selected using Simple Random Sampling. Medical Superintendents of the hospitals were approached for conduction of the study and approval was obtained.

Selection Criteria for Hospitals

a. At least 100 bedded hospital
b. Functional Pediatric Intense Care Unit (PICU)with at least 05 beds
c. Functional Neonatal Intense Care Unit (NICU) with at least 05 incubators
d. Tertiary Care Set-up

Demographics of private hospital, selected for the study

Private Sector Tertiary Care Hospital, having 120 beds and functional Pediatric Intense Care Unit (PICU) with 5 beds and Neonatal Intense Care Unit (NICU) with 12 incubators and 05 baby carts.

Demographics of public hospital, selected for the study

Public Sector Tertiary Care Hospital having 1700 beds with three pediatric wards, as Pediatric Unit 1 (PU-1), Pediatric Unit 2 (PU-2) and Pediatric Unit 3 (PU-3). In PU-1, there were 18 Incubators and 03 baby carts in NICU and 10 beds in PICU. In PU-2, there were 07 Incubators and 05 baby carts in NICU and 07 beds in PICU. In PU-3, there were 12 Incubators and 02 baby carts in NICU, 09 beds in PICU.

Ethical approval

On the basis of Ethical Approval from Ethics Review Committee (ERC) (ethical number 0080315MTPHARM) of Ziauddin University, both the selected hospitals were approached and approval was obtained from concerned Medical Superintendant (MS) to review PBF and to conduct In-depth Interviews (IDIs) with concerned Physician/ Consultant regarding patients' antimicrobial therapy.

Duration of the study

The study was conducted prospectively from August 2015 to July 2016.

Pilot study

A preliminary List of Most-Commonly Prescribed Antibiotics (LMCA) among children against was developed after detailed search during August 01, 2015 to August 15, 2015 with the help of databases Embase, PubMed, Scopus, Web of Science, Google Scholar and Medline. In addition Physicians, Pharmacists, Microbiologists and Nursing staff were taken on board during the process of development of LMCA. 15 In-depth Interviews (IDIs) were also conducted. An initial pool of 45 most commonly prescribed antibiotics were short-listed and were pilot-tested for clarity in 200 prospective cases from both the selected hospitals. The preliminary LMCA was reduced to 25 most commonly prescribed antibiotics among children.

Sampling and sample size

a) Simple Random Sampling was adopted during selection of one Public and one Private Sector Tertiary Care Hospital.
b) Convenient Sampling (CS) was also adopted for recruitment of patients, fulfilling inclusion criteria.
c) 753 In-patients admitted in PICU/NICU, fulfilling inclusion criteria, were recruited from Hospital-A and 1204 from Hospital-B
d) 1706 CST reports were selected using CS method.

Patients' recruitment and consent

The Patients were recruited in the study after having attained informed parental consent and due consideration of child assent/dissent, for reviewing PBF

Inclusion criteria of patients

Patients fulfilling any three of the following criteria, were recruited for the study

(i) Age range: under 12 years
(ii) Admitted in NICU/PICU
(iii) Patients prescribed any of the antibiotics from LMCA

Exclusion criteria

All cases beyond inclusion criteria were excluded.

Instrument of analysis

The pattern of prescribing practice of antibiotic was assessed from Patients Bedside File and following three indicators were recorded during daily visit of Principal Investigator (PI).

Dose

The dose of antibiotic (s) was noted after evaluation, was categorized as Under-dose, Rational-dose or Higher-dose, after reviewing literature from Drug Index 2015.

Indication

Antibiotics were matched with the diagnosed infection and if prescribed for right indication, it was termed as "Valid" and if not for right indication, it was termed as "Invalid".

Table 1: Most Commonly Prescribed Antibiotics (LMCA)

Abbreviation	Antibiotic	Abbreviation	Antibiotic	Abbreviation	Antibiotic
AMK	Amikacin	CPR	Cephradine	MRP	Meropenem
AMX	Amoxicillin	CLT	Clarithromycin	CIP	Oflox/Cipro
AMP	Ampicillin	CLC	Cloxacillin	OFL	Ofloxacin
AZM	Azithromycin	CAC	Co-Amoxiclave	PEN	Penicillin
CFX	Cefixime	CTX	Co-Trimaxazole	VAN	Vancomycin
CFT	Cefotaxime	ERT	Erythromycin	CPL	Cephalexin
CFZ	Ceftazidine	GTM	Gentamicin	LNZ	Linezolid
CFN	Ceftriaxone	KMY	Kanamycin		
CFR	Cefuroxime	LVF	Levofloxacin		

Table 2: Demographic Characteristic of Recruited Patients

			Age Group as per US FDA			Total
			Neonate	Infant	Child	
Hospital Name	Private Sector Tertiary Care Hospital (A)	Count	585	100	68	753
		% within Hospital Name	77.7%	13.3%	9.0%	100.0%
	Public Sector Tertiary Care Hospital (B)	Count	790	233	181	1204
		% within Hospital Name	65.6%	19.4%	15.0%	100.0%
Total		Count	1375	333	249	1957
		% within Hospital Name	70.3%	17.0%	12.7%	100.0%

Table 3: Prescribing Doses of Antibiotic

	Private Hospital (A)			Public Hospital (B)		
	Under Dose N (%)	Higher Dose N (%)	Rational Dose N (%)	Under Dose N (%)	Higher Dose N (%)	Rational Dose N (%)
Neonate	158(27.0%)	257(43.9%)	170(29.1%)	263(33.3%)	403(51.0%)	124(15.7%)
Infant	19(19.0%)	51(51.0%)	30(30.0%)	62(26.6%)	136(58.4%)	35(15.0%)
Child	15(22.1%)	28(41.2%)	25(36.8%)	52(28.7%)	100(55.2%)	29(16.0%)

Table 4: Assessment of Antibiotic Prescribing practice

	Private Hospital (A)		Public Hospital (B)	
	Valid N (%)	Invalid N (%)	Valid N (%)	Invalid N (%)
Neonate	335(57.3%)	250(42.7%)	279(35.3%)	511(64.7%)
Infant	62(62.0%)	38(38.0%)	83(35.6%)	150(64.4%)
Child	38(55.9%)	30(44.1%)	72(39.8%)	109(60.2%)

Number of participants (%)

Table 5: Frequency of resistant antibiotics among CST report of In-patients

Antibiotic	n	%	Antibiotic	n	%	Antibiotic	n	%	Antibiotic	n	%
Amikacin	48	5.6	Ceftazidine	48	5.6	Cloxacillin	360	42.2	Levofloxacin	276	32.4
Amoxicillin	420	49.2	Ceftriaxone	108	12.7	Co-Amoxiclave	276	32.4	Linezolid	36	4.2
Ampicillin	132	15.5	Cefuroxime	60	7.0	Co-Trimaxazole	288	33.8	Meropenem	168	19.7
Azithromycin	108	12.7	Cephalexin	420	49.2	Erythromycin	420	49.2	Ciprofloxacin	276	32.4
Cefixime	108	12.7	Cephradine	48	5.6	Gentamicin	276	32.4	Ofloxacin	348	40.8
Cefotaxime	84	9.8	Clarithromycin	204	23.9	Kanamycin	156	18.3	Penicillin	420	49.2
									Vancomycin	36	4.2

Table 6: Comparison of 25 Most Commonly Prescribed Antibiotics in Tertiary Care Teaching Hospitals

	Hospital-A					Hospital-B				
Age Group	Class I	Class II	Class III	Class IV	Class V	Class I	Class II	Class III	Class IV	Class V
Neonate	AMK CFX CFT MRP VAN CFN	AMX AZM CTX CFZ CFR CLT CLC ERT	AMP CPR GTM LVF PEN	LNZ CPL CAC	KMY OFL CIP	AMK AMX AZM CFX CFT CLT CTX MRP LVF	CFR CPL CAC ERT OFL VAN CIP CFN	AMP CPR PEN	CFZ KMY GTM	CLC LNZ
Infant	AMX AMK CFX CFT MRP VAN CFN	AZM CFZ CFR CPL CLT CLC CAC ERT	AMP CPR LVF PEN CTX LNZ	OFL CIP GTM	KMY	AMK AMX AZM CFX CFT CLT LVF	CFR CPL CAC ERT VAN CTX CFN MRP	AMP CPR PEN OFL CIP	CFZ KMY GTM	CLC LNZ
Child	AMK CFX CFT MRP VAN CFN	AMX CFR CPL CLT CAC ERT	CPR GTM PEN LNZ AZM CTX	KMY LVF AMP CFZ	OFL CIP CLC	AMK AMX AZM CFX CFT CLT CFN MRP	CFR ERT OFL CIP CTX AMP LVF	CPR PEN VAN CPL CAC	KMY GTM	CLC LNZ CFZ

Class-I	Antibiotics Being Prescribed in more than 80 % of Prescriptions
Class-II	Antibiotics Being Prescribed in 60-80 % of Prescriptions
Class-III	Antibiotics Being Prescribed in 40-60 % of Prescriptions
Class-IV	Antibiotics Being Prescribed in 20-40 % of Prescriptions
Class-V	Antibiotics Being Prescribed in less than 20 % of Prescriptions

Culture Sensitivity Test (CST)

The Culture Sensitivity Test (CST) report was followed from Pathology Laboratory of the hospital, and in cases where it was not ordered or patient was unable to bear the cost, the intervention by PI to perform CST was made and the concerned Physician/ Consultant were contacted to discuss the reason. After discussion, CST was requested and the Pathological Laboratory was also informed regarding Antibiotic Therapy that patient had already started.

Measuring antimicrobial resistance

1706 CST reports of recruited cases were reviewed and frequency/percentage of resistant antibiotics from LMCA among recruited cases was tabulated.

STATISTICAL ANALYSIS

Data was analyzed using SPSS version 20. Descriptive statistical tests were performed.

RESULT

In this study 1204 patients admitted in the PICU/ NICU of public sector hospital were recruited among them 65.6% were neonates, 19.4% were infants and 15% were children. In private sector hospital 753 patients were admitted in PICU/NICU, among them 77.7% were neonates, 13.3% were infants and 9.0% were children (table 2).

The under dose prescriptions of antibiotics was found 27% to neonates, 19% infants and 22.1% to the children. On the other hand, 43.9% neonates, 51% infants and 41.2% children received higher doses in the private hospital. However in public hospital 33.3% neonates, 26.6% infants and 28.7% children received under-dose while 51% neonates, 58.4% infants and 55.2% children received higher dose of prescribed antibiotics (table 3).

The percentage of irrational prescription was high in the public sector hospital as compared to the private sector. 64.7% of the invalid antibiotics prescribed to the neonates, 64.4% to the infants and 60.2% to the children admitted in PICU/NICU of public hospital and only 35.3% neonates, 35.6% infants and only 39.8% children were given antibiotics for right indication. In the private hospital irrational prescription was high in the children 44.1% as compared to the neonates 42.7% and 38% to the infants. However 57.3% neonates, 62% infants and 55.9% children were prescribed antibiotic(s) for appropriate indication (table 4).

Amoxicillin, Penicillin, Erythromycin and Cephalexin showed higher resistance i.e. 49.2% (table 5).

In this study the prescribing frequency of Amikacin, Cefixime, Cefotaxime, Meropenem, Amoxicillin, Vancomycin, Azithromycin, Levofloxacin and Clarithromycin was found above 80% in both the hospitals (table 6).

DISCUSSION

The irrational doses and invalid prescription of antibiotics in practice were comparatively higher in the public hospital than private hospital (table 3 and 4).This was may be due to overloaded and lesser interest of health care professionals. This study indicated that about 16% of the prescriptions of admitted children in ICUs in public sector tertiary care exhibited rational dose, which is an alarming situation. However, this percentage is comparatively higher (about 36.8% on average) in private hospital (table 3). The prescription of higher doses of antibiotics may give rise to Adverse Effects (AE) and increased medication cost for unnecessary administration of antibiotics. On the other hand, under dose or irrational prescriptions of antibiotics may lead to antimicrobial resistance.

Class of aminoglycoside drugs include erythromycin, Vancomycin and Amikacin were used in both sectors of hospitals above 80%. Aminoglycoside as empirical treatment for community acquired neonatal sepsis has strongly recommended by WHO. Erythromycin showed 49.2% of resistance as compared to Amikacin showed 5.6% and Vancomycin showed 4.2% resistance. An increasing trend toward erythromycin resistance was reported from Taiwan and then decreased once the use of this antibiotic was reduced. The resistance rate to erythromycin decreased from 53.1% in 1998 and 2000 to 14.6% in 2002 and 2004, and finally to 10.7% in 2006-2010 and also the amount of erythromycin-resistant *Streptococcus pyogenes* were highest among children (Sayyahfar *et al*., 2015; Huovinen 1999).

An extremely high level of resistance 49.2% was noted against penicillin and median resistance to Ampicillin was observed that was 15.5%. Ampicillin is semi-synthetic penicillin with an additional amino acid synthesized onto the penicillin molecule (S.K Sharma *et al.,* 2015). Both the antibiotics were used 40-60% in both hospitals.

Class of Cephalosporins in the study contribute to over 80% of prescribed antibiotics in pediatrics in both hospitals (table 6) and are recommended as first-line antibiotics in various community-acquired infections (Ramesh *et at.,* 2012; Sriram *et al.,* 2008). Cefixime belongs to the 3rd generation of cephalosporins and showed 12.7% of resistance as compared to the cephalexin that belongs to the 1st generation of cephalosporins has showed 49.2% of resistance (table 5 and 6).

Amoxicillin was also observed resistance 49.2% and was prescribed to the both hospitals. Above 80% was prescribed to the infants and 60-80% were prescribed to the neonates and child in the hospital A whereas in the hospital B amoxicillin prescribed above 80% to the children (table 5 and 6).

Meropenem belongs to the subgroup of Carbapenems and showed emergence of resistance (19.7%) and being prescribed in both sectors of hospitals among children was more than 80%.

In Pakistan more than 58.7million persons are living below the poverty line that means they earn less than 1.25$ per day. In this circumstance, additional cost of avoidable medicine is a supplementary economic burden on health care system of Pakistani population (Arshad *et al*., 2015).

Globally about nine million children less than five years of age die every year, with pneumonia, diarrhea and with other common prevalent diseases. Many of these disease conditions could be treated with safe and effective antibiotics. On the other hand, irrational use of these available antibiotics has led to adverse drug reactions and drug resistance to the usual pathogens and infections by unusual usage. Thus, it is need of time to promote the appropriate and safe drugs utilization especially in children (Yewale, 2012).

CONCLUSION

The study concludes that irrational prescribing practice was found in both the settings, but in public sector hospital the situation is more distressing (table 4). This practice needs to be addressed by drastic steps to minimize antimicrobial resistance. The initiation of bacteriological culture test at the start or as early as possible before the antibiotic use may help in streamlining the therapy from empirical to targeted therapy. Appropriateness of indication for prescribing antibiotic was also not satisfactory. About 63% children admitted in public hospital ICUs received antibiotics for no indication and/or for wrong indication and in private hospital the percentage was comparatively lesser that was 40% (table 5).

There is a need of organized management with trained microbiologist, clinical pharmacist and infection control nurse and hospital administrator for antibiotic management and prevention of resistance. They can potentially optimize harmful prescribing errors for best outcomes, minimizing detrimental adverse effects and occurrence of resistance (Princess *et al.,* 2015). These errors in therapy can be well addressed by the proper implementation of antimicrobial stewardship programs at least in tertiary care settings. The primary goal of antimicrobial stewardship is to make sure the appropriate and rational prescription of antibiotic is crucial to prevent emergence of resistant strains. In this concern, vigilant microbiologic monitoring, Standard laboratory, clinical pharmacist and adequate with well trained staff are mandatory for infection control (Lodha *et al.,* 2001). In addition, antimicrobial stewardship has efficient strategies to balance the favorable clinical outcomes and antimicrobial resistance (Bilal bin *et al.,* 2015). In the Asia-pacific region, limited human and fiscal resources, together with the lack of information technology, are regarded as the main barrier to effective antimicrobial stewardship program (Apisarnthanarak *et al.,* 2015). The factors contributing to antimicrobial resistance are complex and diverse and range from unregulated use of antibiotics in the community and hospital settings, poor infection control policies, and the unavailability of culture facilities or point of care tests. The stewardship programs recommended by the developed countries require personnel, resources and time, which are currently completely lacking in the Pakistani healthcare system.

REFERENCES

Apisarnthanarak A, Lapcharoen P, Vanichkul P and Srisaeng-Ngoen T (2015). Design and analysis of a pharmacist-enhanced antimicrobial stewardship program in Thailand. *American J. of Infection Control*, **43**: 956-959.

Arshad R, Khurshid S, Masood J, Farhan N and Maham T (2015). A study of unnecessary use of Antibiotics at a Tertiary care hospital: Urgent need to implement antimicrobial stewardship programs. *J. of Young Pharm.,* **7**(4): 311-318.

Baiden F, Owusu-Agyei S, Webster J and Chandramohan D (2010). The needfor new antibiotics. *Lancet*, **375**: 637-638.

Bilal bin Y, Rozina A and Junaid M *et al*. (2015). A study of unnecessary use of Antibiotics are a tertiary care hospital: Urgent need to implement antimicrobial stewardship programs. *J. of Young Pharmacists,* **7**(4): 311-318.

Boucher HW, Talbot GH, Bradley JS, *et al.* (2009). Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin. Infect Dis*., **48**: 1-12.

Cornaglia G. (2009). Fighting infections due to multidrug-resistant Gram-positive pathogens. *Clin Microbiol Infect.,* **15**: 209-211.

Hannan A, Qamar Muhammad U, Usman M, Ahmad K, Waheed I and Rauf K(2013). Multidrug resistant microorganisms causing neonatal septicemia: In a tertiary care hospital Lahore, Pakistan. African *Journal of Microbiology Res*., 7(19):1896-1902.

Hashemi S, Nasrollah A and Rajabi M (2013). Irrational antibiotic prescribing: a local issue or global concern? *EXCLI J.,* **12**: 384-395.

Heddini A, Cars O, Qiang S and Tomson G (2009). Antibiotic resistance in China a major future challenge. *Lancet*, **373**: 30.

Huovinen P (1999). Antibiotic usage and the incidence of resistance. *Clinical Microbiology and Infection*. **4**(5): 4S12-4s16.

Lodha R, Chandra U, Natchu M, Nanda M and Kabra SK (2001). Nosocomial infections in Pediatric intensive care units: *Indian J. of Pediatrics.,* **68**: 1063-1069.

Narayan Deshmukh S and Mangesh Mahajan M (2016). A study of prescription pattern of antibiotics in paediatric In-patients at a tertiary care hospital in central India. *IJPR*., **6**(8): 286-290.

Page MG and Heim J (2009). Prospects for the next anti-pseudomonas drug. *Curr. Opin. Pharmacol.,* **9**: 558-565.

Princess Cole C, James Peter B and Kargbo Alusine T (2015). An evaluation of the prescribing patterns for under-five patients at a Tertiary Paediatric Hospital in Sierra Leone. *J. Basic Clin. Pharm*., **6**(4):109-114.

Rajabi M (2015). An evaluation of the prescribing patterns for under-five patients at a Tertiary Paediatric Hospital in Sierra Leone. *J. Basic Clin. Pharm*., **6**(4): 109-114.

Ramesh L, Samgeeta S and Hussainy SR (2012). Analysis of antimicrobial prescriptions in pediatrc patients in a teaching hospital. *Asian J. Pharm. Clin. Res*., **5**: 124-128.

Rice LB (2009). The clinical consequences of antimicrobial resistance. *Curr. Opin. Microbiol.,* **12**: 476-481.

Sayyahfar S, Fahimzad A, Naddaf A and Tavassoli S (2015). Antibiotic Susceptibility Evaluation of Group A Streptococcus Isolated from Children with Pharyngitis: A Study from Iran. *Infect Chemother*. **47**(4): 225-230.

Sharma S.K, Singh L and Singh S (2013).Comparative study between Penicillin and Ampicillin. *Sch.J.App.Med.Sci*.1(4): 291-294.

Sriram S, Mathew L and Manjula AS *et al*. (2008). Assessment of antibiotic use in pediatric patients at a tertiary care teaching hospital. *IJOPP*; **1**: 30-6.

Tan TT (2008).Future threat of Gram-negative resistance in Singapore.*Ann Acad Med Singapore*, **37**: 884-890.

Vento S and Cainelli F (2010). The need for new antibiotics. *Lancet,* **375**: 637.

Warrier I, Du W, Natarajan G, Salari V and Aranda J (2006). Patterns of drug utilization in a neonatal intensive care unit. *J. Clin. Pharmacol*., **46**(4): 449-455.

Wise R and Piddock L (2010). The need for new antibiotics. *Lancet*, **375**: 638.

World Health Organization Global Strategy for Containment of Antimicrobial Resistance (2015). Available at: http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf. Accessed 27 August 2015.

Yewale Vijay N and Dharmapalan D (2012).Promoting Appropriate Use of Drugs in Children. International Journal of Pediatrics.

Zaidi AK, Huskins WC and Thaver D *et al* (2005). Hospital-acquired neonatal infections in developing countries. *Lancet*., **365**: 1175–1188