Impact of Sepsis Management Project on Rational Use of Antibiotics in Presumed and Probable Neonatal Sepsis - A Retrospective Comparative Study

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ABSTRACT

BACKGROUND

Early diagnosis and treatment of the newborns with suspected sepsis are essential to prevent severe and life-threatening complications. In this era of multidrug resistance, it is mandatory to avoid unnecessary use of antibiotics to treat non-infected neonates.

METHODS

A retrospective comparative study was conducted in the Special Newborn Care Unit, General Hospital, Ernakulam, Kerala, for a period of six months each for pre- and post- Sepsis Management Project [SMP] implementation. Empirical antibiotics started, duration of antibiotic usage, and length of stay in presumed and probable sepsis cases admitted, were analysed and compared. During pre-sepsis management project period, manual method of blood culture technique was used. During post-sepsis management project implementation period, introduction of antibiotic guidelines, automated blood culture technique, and training on antibiotic stewardship program to clinicians, were done.

RESULTS

Average days for discharge in presumed and probable sepsis cases was reduced from 7.2 days to 5.4 days (P value < 0.05); that means reduction of 44 hours after implementation of the project. Rational usage of ampicillin and amikacin as the first line in presumed and probable sepsis cases increased from 80 % to 91 % and cefotaxime usage as first line antibiotic reduced from 18 % to 7 % after SMP implementation.

CONCLUSIONS

Rational usage of antibiotics in post-sepsis management project implementation period was due to a good adherence to the antibiotic guidelines by clinicians, introduction of automated blood culture, a good support from the microbiology lab and frequent training and awareness given to clinicians as a part of sepsis management project.

KEYWORDS

Sepsis Management Project, Rational Antibiotic Therapy, Automated Blood Culture, Neonates

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BACKGROUND

Emergence of antibiotic resistance in microorganisms has become a matter of great public health concern. Annual deaths attributable to antimicrobial resistance are estimated to be 700,000 worldwide. Future projections estimate that, by 2050, 10 million people will die worldwide each year due to increasing antimicrobial resistance. The Centers for Disease Control and Prevention have pointed out that more than half of hospital patients receive an antibiotic during their stay, and nearly a third receive a broad-spectrum antibiotic. In addition, intense antibiotic use in animal farms and for agricultural purposes strongly contributes to the emergence of antibiotic resistance. [1,2,3,4]

Bacterial sepsis is a major cause of morbidity and mortality in newborns, especially among low birth weight and preterm babies. India accounts for 30 % of the neonatal deaths globally. In India the neonatal mortality rate is 28 / 1000 live births and the incidence of neonatal sepsis is around 3.8 %.[5,6] Early diagnosis and treatment of the newborns with suspected sepsis are essential to prevent severe and life threatening complications. In this era of multidrug resistance, it is mandatory to avoid unnecessary use of antibiotics to treat non-infected infants. Blood culture is an essential tool for investigation of clinically suspected bacteraemia or septicaemia, and guidance for appropriate antimicrobial management.[7,8] Automated blood culture systems have been developed with significant improvement in reliability and time to detection of bacteria and yeasts.[9] More than 95 percent of organisms from blood cultures were detected within three days of incubation.[10] The current standard for automated blood culture testing as recommended by the College of American Pathologists (CAP) is a five-day incubation period (CAP checklist, 2014); and even for the more fastidious so-called HACEK group of organisms (e.g., *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*) and Brucella spp., incubation beyond the five days period is seldom required.[11] Empirical therapy is based on clinical diagnosis combined with evidence from literature and the educated experience of the probable pathogen causing the infection.

According to WHO, empirical treatment is a one timer treatment given for a presumed infection in a person, at high risk of infection.[12] In presumed and probable sepsis in newborns, antibiotics are started empirically after sending blood culture. Presumed sepsis in newborn is defined as neonate with clinical features of sepsis but rapid sepsis screen is negative**.** Probable sepsis means a neonate having clinical picture suggestive of septicaemia and presence of any one of the following criteria: Positive sepsis screen – (presence of two of the four parameters namely total leucocyte count (TLC) < 5000 / mm^3, band to total polymorphonuclear cell ratio > 0.2, absolute neutrophil count (ANC) <1500 / mm^3, C-reactive protein (CRP) >10 mg/dl and micro ESR >15 mm in the first hour) Or Radiological evidence of pneumonia. For empirical therapy in newborns, first line antibiotics are preferred, combination of Ampicillin (50 mg / Kg IV 12th hourly) and aminoglycoside (Amikacin 15 mg / Kg IV 24 hourly) may be given as first line. If there is high probability of resistant strain, combination of Cefotaxime (50 mg / Kg IV 12th hourly) and aminoglycoside (Amikacin 15 mg / Kg IV 24 hourly) may be considered.

Sepsis management project was started on 13th August 2015, at General Hospital, Ernakulam to develop a model Centre to promote rational usage of antibiotics according to culture and sensitivity, streamline the antibiotic usage and early identification and treatment of sepsis. Automated blood culture technique is used for the project,[13] primary objective of this study is to know the impact of sepsis management project on rational usage of antibiotics and duration of stay for antibiotic purpose in presumed and probable sepsis cases in neonates at Special Newborn Care Unit (SNCU), General Hospital Ernakulam.

METHODS

A retrospective comparative study was conducted in Special Newborn Care Unit [SNCU], General Hospital, Ernakulam over a period of six months each from August 14, 2014 to February 14, 2015 (pre - SMP implementation period) and August 14, 2015 to February 14, 2016 (post - implementation period SMP). Empirical antibiotics started, duration of antibiotic usage and length of stay in presumed & probable sepsis cases admitted during the period in SNCU were analysed and compared.

During pre - SMP period, manual method of blood culture technique was used. Empirical antibiotics were started after sending blood for culture and antibiotics were continued till the culture report was obtained. If no growth appeared even after 6 days in subculture, result was given as blood culture sterile on 7th day and antibiotics were stopped. During post - SMP implementation period, automated blood culture technique with a negative protocol of 5 days was used. Empirically started antibiotics after sending blood culture were continued until the culture report was received. If no signal appeared on 5th day, result was reported as sterile. Along with this, the clinical condition of the newborn babies was also taken into consideration. If the newborns were clinically better, the antibiotics were stopped, and they were discharged from the SNCU.

130 newborns during the pre - SMP implementation period and 191 neonates included during post - SMP implementation period were compared on empirical antibiotic started, length of stay in SNCU for completion of antibiotic purpose in presumed and probable sepsis.

For statistical analysis, data was entered in MS Excel and was analyzed using SPSS software version 16.0. Results on categorical variables were expressed by frequency (percentages) and continuous variables were expressed by mean (Standard Deviation). Comparison of number of days of hospital stay in pre and post SMP period was analyzed by using Paired t test. Chi square test was used to compare the antibiotic usage in pre and post SMP period. A P value less than 0.05 were considered as statistically significant.

RESULTS

The present study included a total of 321 babies with presumed / probable sepsis. Out of the 130 cases in pre - SMP period, 80 were male babies and 50 were female babies, male: female ratio being 1.6:1. During post - SMP implementation period, a total of 191 cases constituting 118 male babies and 73 female babies were included, the male female ratio being 1.62:1. In pre - SMP period, babies admitted with probable sepsis and presumed sepsis were 70 % and 28 % respectively and during post - SMP implementation period, 64 % of babies were admitted as probable sepsis and 29 % as presumed sepsis.

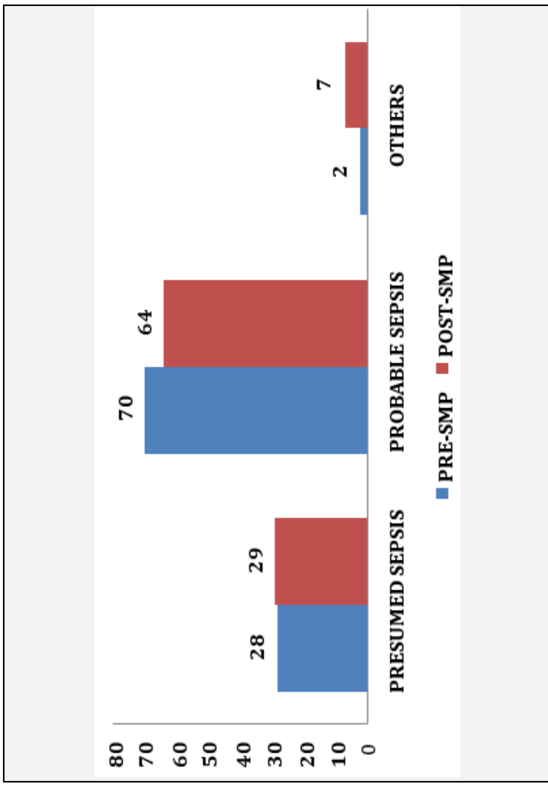

Figure 1. Diagnosis in Percentages in the Pre SMP & Post SMP Periods

The birth weight of babies included in the study during pre - SMP period and post - SMP period were comparable. There was no significant difference ($p = 0.347$) between mean birth weight of babies during pre - SMP period (2.91 Kg) and post - SMP period (3.03 Kg).

In the pre - SMP period, out of the 130 babies diagnosed with presumed & probable sepsis, 65 babies (50 %) were given antibiotics for 7 days, 27 babies (21 %) for 6 days and 12 babies (9 %) for 5. In the post - SMP period, out of the 191 babies diagnosed with presumed & probable sepsis, 10 babies (5 %) were given antibiotics for 7 days, 66 babies (35 %) for 6 days and 98 babies (51 %) for 5 days (Table 1).

During the pre - SMP period 42 (32 %) babies with presumed or probable sepsis got discharged on or before 6 days. However, 178 (93 %) babies with presumed or probable sepsis got discharged on or before 6 days during post - SMP implementation period. This difference in early discharge was found to be statistically significant ($p < 0.001$).

Average length of stay in presumed and probable sepsis cases were 7.2 days and 5.4 days in pre - SMP and post - SMP implementation period respectively at SNCU. Average time to get discharged in presumed or probable sepsis cases was significantly reduced by 44 hours after the implementation of SMP ($p<0.001$).

Duration in Days	5	6	7
Pre - SMP	9 %	21 %	50 %
Post – SMP	51 %	35 %	5 %

Table 1. Duration of Antibiotic Usage

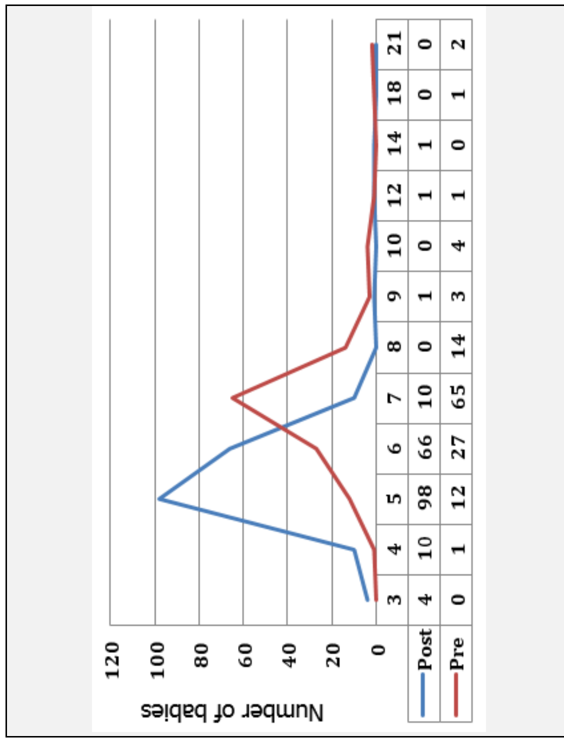

Figure 2. Comparison of Number of Days of Hospital Stay in Pre- and Post- SMP Period

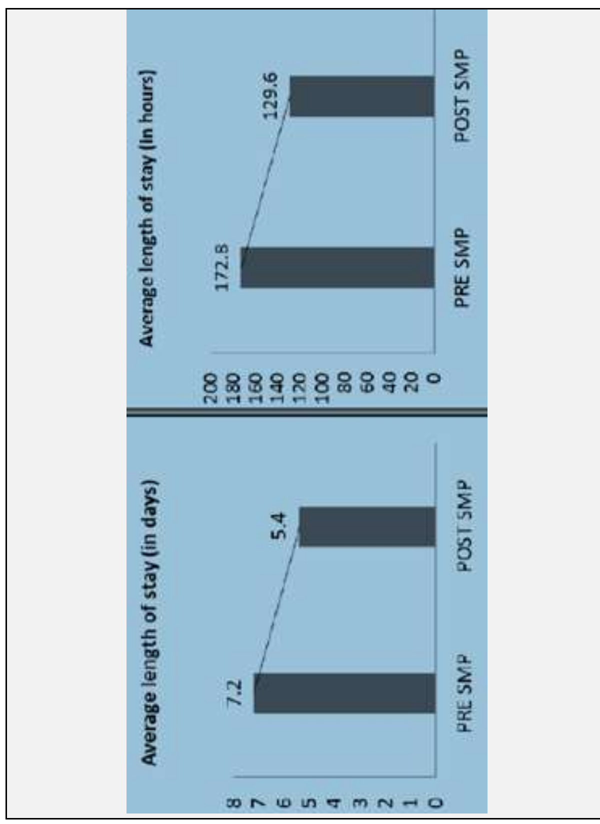

Figure 3. Average Length of Hospital Stay

	Mean	SD	95 % CI	P Value
Pre SMP	7.2	2.4	1.341-2.228	0.001*
Post SMP	5.4	1.2		

Table 2. Average Length of Stay in Pre SMP And Post SMP Period

Average length of stay in presumed and probable sepsis cases were 7.2 days and 5.4 days in pre SMP and post SMP implementation period respectively at SNCU. Average time to get discharged in presumed or probable sepsis cases was significantly reduced by 44 hours after the implementation of SMP ($p < 0.001$).

Rational usage of antibiotics was noticed to be significantly different before and after implementation of SMP. Usage of Ampicillin and Amikacin as first line in presumed and probable sepsis cases was increased from 80 % to 91 % and usage of Cefotaxime as first line antibiotic is reduced from 18 % to 7 % during post - SMP implementation period ($p = 0.018$).

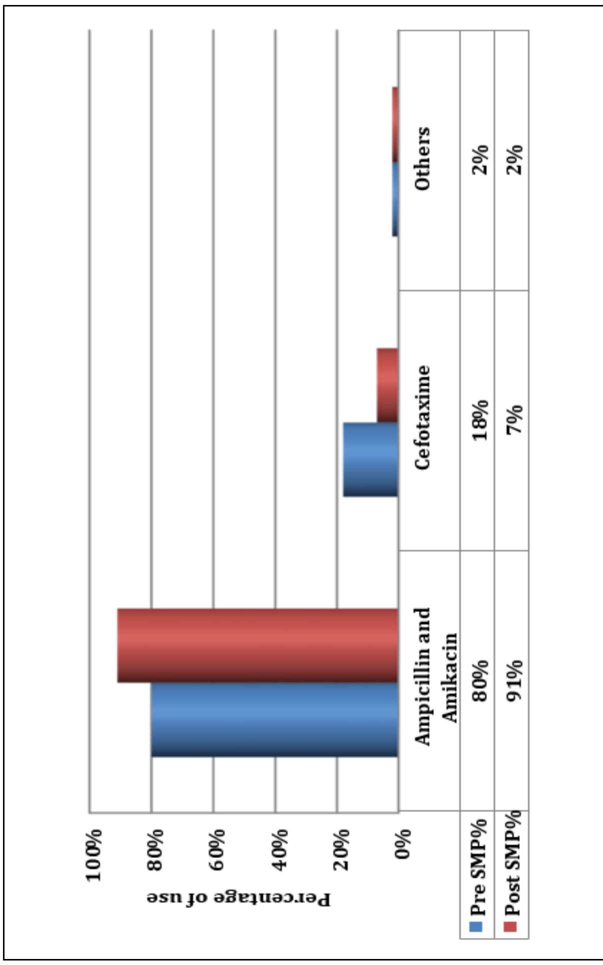

Figure 4. Comparison of Antibiotic Usage during Pre- and Post-SMP Implementation

	Ampicillin & Amikacin	Cefotaxime	Others	P Value
Pre - SMP	80 %	18 %	2 %	0.018*
Post - SMP	91 %	7 %	2 %	

Table 3. Comparison of Antibiotic Usage during Pre- and Post-SMP

DISCUSSION

Out of the 130 cases in pre SMP period and 191 cases in post SMP implementation period, male female ratio is 1.6:1 and 1.62:1 respectively. In this study male babies outnumbered the female babies, in presumed & probable cases during pre - SMP and post - SMP implementation period. This is comparable with studies conducted in India and abroad. The reason for male preponderance is unknown, but this could be due to sex-dependent factors. The synthesis of gamma globulins is probably regulated by X–linked immunoregulatory genes and as males are having one X chromosome, they are more prone for neonatal septicaemia than females.[14,15,16]

During pre - SMP period, antibiotics were given for 7 days for 50 % of babies, 6 days for 21 % and 5 days for 9 % babies respectively. In post - SMP period with automated blood culture with a five days negative protocol, antibiotics were given for 7 days for 5 % babies, 6 days for 35 % babies and 5 days for 51 % babies in presumed & probable sepsis cases. Majority of babies got discharged on 5th day (51 %) during post implementation period of SMP. Average duration of stay in SNCU for antibiotic purpose was reduced from 7.2 days to 5.4 days during post - SMP period. Thus, average time to discharge in presumed and probable sepsis cases has reduced by 44 hours due to the introduction of automated blood culture. Babies who got discharged from SNCU in presumed and probable sepsis cases on or before 6 days in pre - SMP and post - SMP implementation period were 32 % and 93 % respectively. After implementation of sepsis management project majority of babies (93 %) with presumed and probable sepsis got discharged on or before 6 days. Probably the most important moment for changing antibiotic therapy is when the results of blood culture specimens from patients with signs and symptoms of sepsis become available. Blood culture specimen analysis was considerably improved by the introduction of automated blood culture system.[17]

During pre SMP period, Ampicillin and Amikacin were used as first line in 80 % cases and Cefotaxime used as first line in 18 % and in post SMP implementation period Ampicillin and Amikacin used as first line in 91 % cases and Cefotaxime as first line in 7 % cases. Usage of Ampicillin and Amikacin as first line antibiotics in presumed and probable sepsis cases is increased (80 % to 91 %) and Cefotaxime usage as first line antibiotic is reduced from 18 % to 7 % during post - SMP implementation period.

CONCLUSIONS

After the implementation of SMP, average duration of stay for babies in SNCU in presumed and probable sepsis cases is 5.4 days. Majority of babies (93 %) with presumed and probable sepsis got discharged on or before 6 days. Ampicillin and amikacin are used as first line antibiotics in presumed and probable sepsis cases in majority (91 %) and cefotaxime used as first line antibiotic is reduced (18 % to 7 %) during post SMP implementation period. Guidelines are the highest standards of scientific evidence and adherence to guidelines assures most appropriate scientific and evidence-based healthcare to mankind. Rational usage of antibiotics in post SMP implementation period were due to a good adherence to the antibiotic guidelines by clinicians, introduction of automated blood culture, a good support from the microbiology lab and frequent training and awareness given to clinicians as part of sepsis management project.

Sepsis management project helps in the early diagnosis and management of sepsis, rational usage of antibiotics, thereby preventing the development of antibiotic resistance and streamline the antibiotic usage in SNCU. The spread of antimicrobial resistance (AMR) is an urgent, global threat, raising the possibility of a world without effective antibiotics. Among the initiatives being planned to prevent or at least control such a crisis, special attention is required for newborn babies (neonates), since their immune system is not yet fully developed, and therefore they are particularly vulnerable to infection. Treatments are delivered often without knowledge of optimal dosing, efficacy of the drugs, off-label use, inappropriate choices to the given pathogens and resistance patterns involved, and inadequate formulations. The overall outcomes are: a waste of resources (and costs), poor clinical outcomes and steep community costs in the form of the generation and spread of more resistant bacteria. In 2015, among the 5.9 million deaths in children under the age of 5 years, 45 % died in the neonatal period. This portion exceeds 50 % in several regions.[18] In 2012, an estimated 6.9 million [uncertainty range (5.5 – 8.3 million)] possible serious bacterial infections (SBI) occurred in neonates in South Asia, Sub-Saharan Africa, and Latin America.[19] The burden of neonatal sepsis is huge in the country. Hospital-based studies suggest an incidence of 30 per 1000 live births, whereas community-based studies indicate an incidence of 2.7–17 % of all live births.[20,21]

Estimates have revealed that antimicrobial resistance (AMR) killed 700,000 people worldwide per year and is predicted to target 10 Million for 2050.[22] Globally over 63,000 tonnes of antibiotics were used in livestock in 2010, with 3 % of consumption occurring in India.[23]The role of antibiotic policies is to guide physicians to prescribe all-appropriate antibiotics, avoid unjustified prescription, reduce the emergence of antibiotic-resistant bacteria, support high-quality clinical practice and minimize unnecessary expenses.[24,25,26] Successful implementation of an antibiotic policy is as important as development of the policy itself. However, studies have shown that adherence to policy recommendations has been suboptimal averaging 40 %.[27] Appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance. Given the association between antimicrobial use and the selection of resistant pathogens, the frequency of inappropriate antimicrobial use is often used as a surrogate marker for the avoidable impact on antimicrobial resistance.[28,29] The combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria.[30]

Addressing antibiotic resistance will need both local and global efforts, and multidisciplinary and multifaceted intervention. Private-public partnership for antibiotic stewardship programme, prevention of infections by vaccines and hygiene practices especially hand hygiene, access to antibiotics for all who need them, with conservation through prioritization of medical use by limiting use for growth promotion in animals and plants, conservation through prescription-tailored to diagnosis like developing quick and accurate diagnostic tools that allow distinction between viral and bacterial infections and providing the resistance pattern of the bacterium, conservation through controlled access by instituting antibiotic stewardship programs, will be the key elements in the fight to preserve the unique and vulnerable resource of antibiotics.

What is Already Known?

Rational antibiotic therapy in an institution needs sustainable behavioural change, good adherence to antibiotic guidelines by clinicians and a well-equipped microbiology lab.

What This Study Adds?

Rational antibiotic therapy in an institution is achieved by good adherence to the antibiotic guidelines by clinicians, introduction of automated blood culture, good support from the microbiology lab and frequent training and awareness of clinicians for a sustainable behavior change as a part of infection prevention control program.

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