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Antibiotic Stewardship Program (ASP) In an Out-Born Neonatal Setup In Eastern India- A Quality Improvement (QI) Initiative.

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I. Introduction:

Sepsis is among the top three leading causes of death in new-borns in India (other two are prematurity and perinatal asphyxia) [1]. This makes its prompt diagnosis and treatment very urgent. There are no quick and reliable clinical or laboratory indicators for its recognition and physicians often rely on perinatal history, clinical features and a set of screening tests; all these don't have very good predictive roles either in confirming or excluding the diagnosis of neonatal sepsis [2]. Over last many years these considerations have provided the clinicians reason and justification to use antibiotics on slight suspicion (often intuition) of sepsis in new-borns. Similar to earlier discovery that oxygen therapy is life saving in sick new-borns and later revelation that its excess use leads to many detrimental effects, the antibiotics, once considered lifesaving and mostly devoid of major side effects , have found to result in several adverse health outcomes [3]. Apart from leading to increased cost and duration of hospitalization, excessive use of antibiotics results in increased incidence of necrotising enterocolitis, candidemia, late onset sepsis and even death [4,5,6]. More importantly, emergence of multi/extensive drug resistance organisms has been acknowledged as a global health issue by WHO [5]. Evidence is also accumulating that earlier microflora in foetus provide several immunological advantages and its suppression by antibiotics during a critical period can lead to atopic diseases, inflammatory bowel disease, diabetes and obesity later in life [6].

The present QI initiative of ASP was undertaken in two neonatal units of Rani Hospital, Ranchi, Jharkhand. This is a tertiary level neonatal centre in Eastern India. Annual admission in its various neonatal ICUs is about 4000. All neonates admitted here are delivered outside and often receive primary treatment in other hospitals before arrival. Fear of sepsis is high in the minds of doctors who attend these neonates, however, the scientific basis to start antibiotics in significant number of cases is lacking, leading to excessive use of antibiotics. Once initiated on admission, there is no strict protocol about the duration of antibiotics in various clinical situations resulting in their prolong and unnecessary use. With this gap in evidence and practice the present QI initiative was planned.

II. Methodology:

The QI initiative was conducted in 3 phases:

Phase 1(last week of December 2019): A team was constituted including- the unit in charge/senior consultant as team leader, chief neonatologist/medical director as mentor and supervisor, neonatal fellow as on site monitor and the head nurse as data collector. We decided to target ASP on babies with weight 1500 grams or more for several logistic constraints. A root cause analysis (looking into various factors resulting in excessive use of antibiotics) was done by process flow chart and fish bone analysis and following key problems were identified.

1. There is no written protocol for starting antibiotics on admission
2. Once antibiotics are started there is no set guidelines for various clinical scenarios as when to stop them
3. Inadequate training of nursing staff on sepsis prevention and lack of awareness among doctors about antibiotic stewardship.

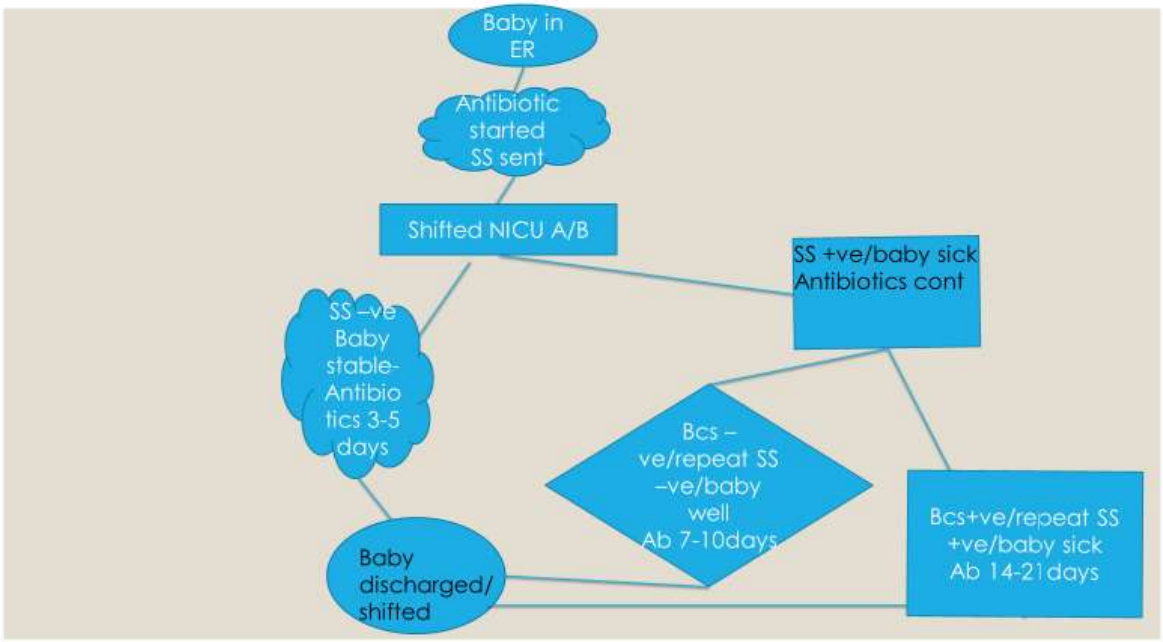


Figure 1: Process flow chart of use of antibiotics in admitted babies(Abbreviations: SS sepsis screen, Bcs blood culture, Ab antibiotics)

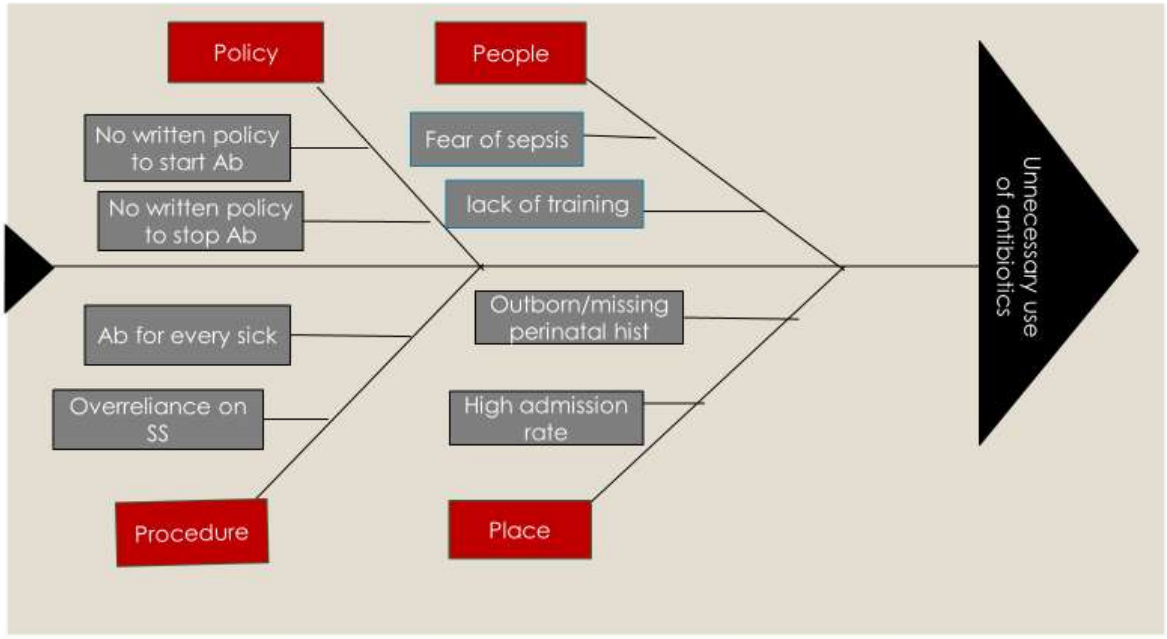


Figure 2: Fish bone analysis for use of excessive antibiotics.

Baseline data were collected for 2 months (November and December 2019) to know the existing scenario of antibiotic use in our patient population (weight 1500 grams or more) and following aims and objectives were set.

Aims and objective

1. To reduce the use of antibiotics on admission by 20% from the baseline in babies with birth weight 1500 grams or more over a period of 3 months
2. To reduce the use of antibiotics in stable, sepsis screen and blood culture negative infants by 30% from the baseline value over a period of 3 months.

3. To reduce the use of antibiotics in sick, sepsis screen positive but blood culture negative infants by 20% from the baseline value over a period of 3 months.

Since this project did not qualify as research, ethics committee's approval was not needed.

Phase 2- Plan Do Study Cycle 1(**PDSA 1**- January 2020): Two separate protocols were made after joint discussion with chief neonatologist for starting and stopping antibiotics. A separate meeting was conducted with hospital doctors to inform them about this initiative and their feedback was asked. These protocols were put on visible places in emergency room and neonatal units. After starting antibiotics the justification to continue it was discussed every day on ward rounds based on clinical condition and sepsis work up results.

Protocol for starting IV antibiotics in Emergency for babies equal or more than 1500 grams

1. Baby is more than 24 hours old and was admitted outside
2. Significant maternal risk factors: Leaking PV>24 hours, maternal fever 100.4 F or more, foul smelling liquor, other features of chorioamnitis like maternal TLC >14000, recent maternal UTI, unclean vaginal delivery
3. Baby has features suggestive of sepsis if:

Does not look well as told by caregiver
Lethargic, poorly feeding
Respiratory distress, de-saturation (no congenital heart disease)
Vomiting/abdominal distention
Seizure without h/o perinatal asphyxia
Sclerema
Bleeding
Renal failure
Poor perfusion/shock

Protocol to continue IV antibiotics in NICU A&B (if started on admission) for babies equal and more than 1500 grams

1. Clinical features suggestive of sepsis
2. Positive blood culture
3. Lab suggestive of sepsis: At least 2 of them (in case of High CRP/PCT single criterion may suffice).

TlC less than 4000
I/T >20%
ANC <1800
CRP>10
PCT: First 12 hours after birth=>0.8 ng/ml
12-24 hours after birth =>8 ng/ml
48 hours after birth =>2 ng/ml

Protocol to stop IV antibiotics (total antibiotics days) in NICU A&B in babies equal or more than 1500 grams

1. Not meeting the criteria to start antibiotic (if started in Emergency)
2. Baby is clinically stable, sepsis screen is negative twice (24 hours apart) and 48 hours blood culture showing no growth: 2-3 days of antibiotics
3. In sick babies with sepsis screen positive but blood culture negative: 5-7 days of antibiotics if clinical response observed and 2 screen negative 24 hours apart
4. In sick babies with sepsis screen positive but blood culture negative who did not respond to first line antibiotics and second line antibiotics introduced: 7-10 days
5. In blood culture positive with otherwise stable course and 2 screen negative 24 hours apart: 10 days(this can be 7 days in CONS)
6. In blood culture positive sick babies/MDR bacteria: 14 days
7. All proven meningitis: 21 days
8. Fungal sepsis: 3-4 weeks (repeat culture 1 week after starting antifungal and continue treatment for another 2 weeks if repeat culture negative).

Phase 3- PDSA 2:(February and March2020): Weekly teachings and video sessions were conducted for nursing staffs. Also, written hands outs were put on prominent places in NICU. Following areas were covered in these sessions-

1. Adherence to strict hand hygiene
2. Asepsis precaution during blood sampling
3. Minimum 1 ml blood for blood culture
4. Good housekeeping
5. Encouraging mother's milk and kangaroo mother care for babies who are qualified for these.

Statistical analysis: Following data were collected and reviewed weekly:

1. Numbers of babies started on antibiotics on admission
2. Total antibiotic days in screen and culture negative babies who have stable clinical course
3. Total antibiotic days in screen positive sick babies whose blood culture is negative
4. Total antibiotic days in culture positive babies

The mean antibiotic days with confidence intervals and mean differences with p value of above parameters from the baseline were calculated using IBM SPSS.

III. Results:

Before Study: The baseline data showed that total 82 babies with birth weight =>1500 grams were admitted in 2 months (November and December 2019) and all (100%) received antibiotics.

Out of these, 41.5 %(34/82) had both sepsis screen and blood culture negative, 36.5 %(30/82) had sepsis screen positive but blood culture negative, 22 %(18/82) had blood culture positive result irrespective of their screen reports; the mean antibiotic days in these groups was 5.0, 9.6 and 12.9, respectively.

Table 1: Before study -mean antibiotic days (total 82)

Percentage (%).	SEPSIS SCREEN.	BLOOD CULTURE.	MEAN ANTIBIOTIC DAYS (95 % CI)
41.5(34/82).	Negative	Negative.	5.0(4.03-5.97)
36.5(30/82).	Positive	Negative.	9.6(8.14-11.13)
22(18/82)	Neg/pos.	Positive	12.9(10.33-15.56)

After Study: After the ASP was implemented (Jan-March2020) total 140 new-borns with weight 1500 grams or more were admitted in our unit. Out of these 82.15 % (115/140) received antibiotics. Compared to before ASP the difference of (17.85%) was significant , this slightly fell short of our initial target of 20% reduction from the baseline.

In this group 22.14% (31/140) had both sepsis screen and blood culture negative, 38.57% (54/140) had sepsis screen positive but blood culture negative and 22.14% (31/140) had blood culture positive irrespective of their sepsis screen report; the mean antibiotic days in these 3 sub-groups were 2.68, 7.24, and 11.06, respectively. In stable babies with sepsis screen and blood culture negative results the mean antibiotic days were reduced by 46.4% from the baseline; this was highly significant($p<0.0001$) and far exceeded our set target. Also, in babies who were sick with sepsis screen positive but blood culture negative, mean antibiotic days were reduced by 24.5% from the baseline, this reduction was again highly significant($p<0.001$). The mean antibiotic days in blood culture positive cases were reduced by 14.2% from the baseline which was not a significant reduction($p=0.123$), however, this was not included in our aims and objectives.

Table 2: After study- mean antibiotic days (total 140)

Percentage (%).	Sepsis screen.	Blood culture.	Mean antibiotic days (95 % CI)
22.14(31/140).	Negative	negative	2.68(2.04-3.31)
38.57(54/140).	Positive	negative	7.24(6.56-7.91)
22.14(31/170).	Pos/neg.	positive	11.06(9.93-12.18)

Figure 3

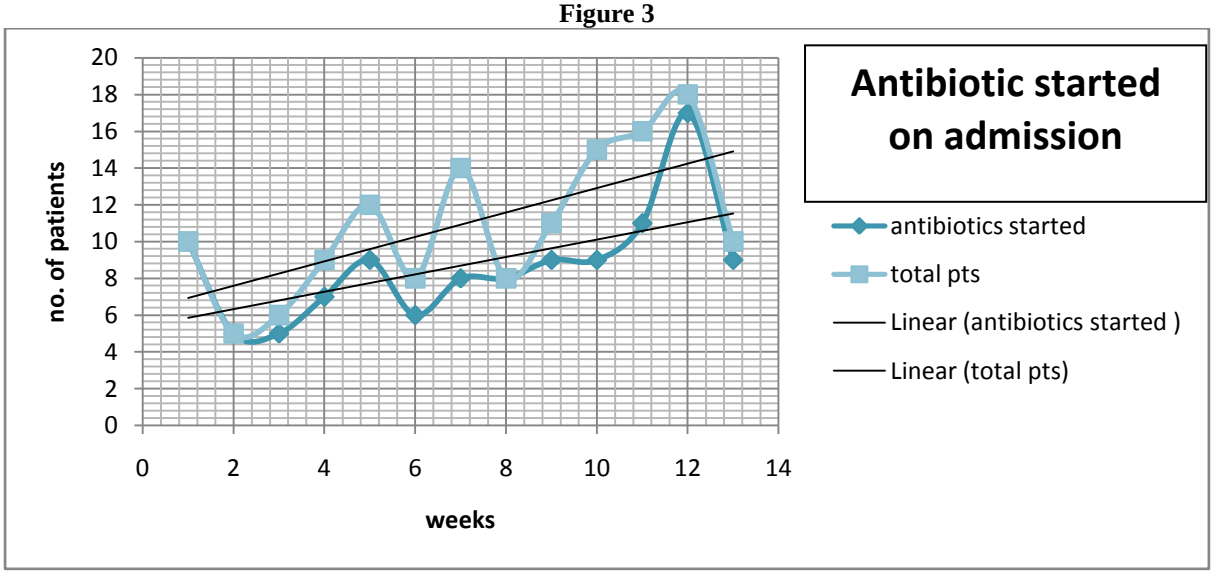
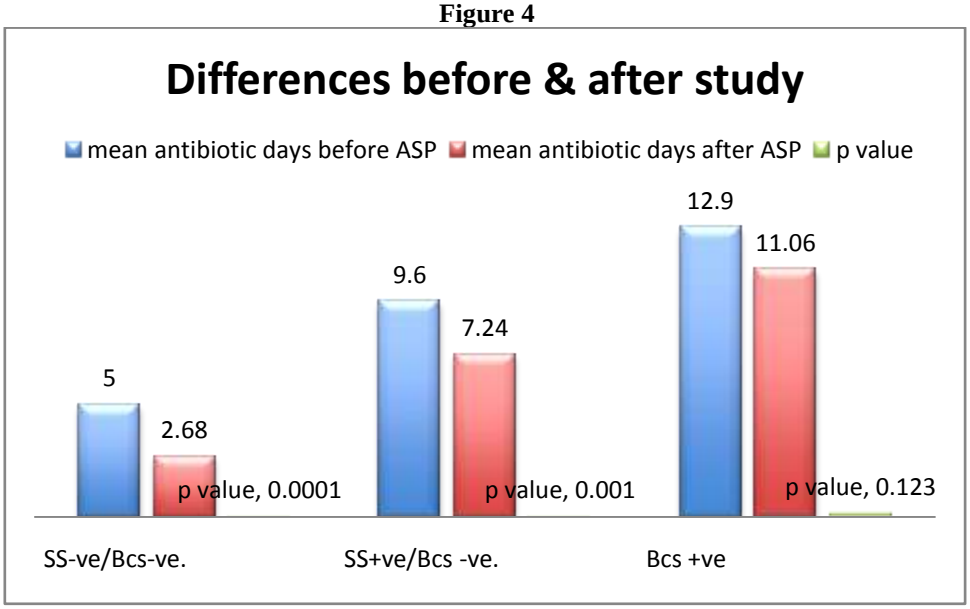


Table 3: Comparison between before and after study results for mean antibiotic days

Groups.	Before study (CI).	After study (CI)	Difference	Significance ('p' value)
SS-ve/Bcs-ve.	5.0(4.03-5.97).	2.68(2.04-3.31).	46.5%	0.0001
SS+ve/Bcs -ve.	9.6(8.14-11.13).	7.24(6.56-7.91).	24.5%	0.001
Bcs +ve	12.9(10.33-15.56).	11.06(9.93-12.18).	14.2%	0.123

Figure 4



IV. Discussion:

This is perhaps the first QI initiative for antibiotic stewardship in an out-born neonatal unit of a private hospital in Eastern India. This was rather a challenging task in a hospital only recently accredited for post graduate teaching and having high admission rate. Perinatal services are not well developed in most of the centres in the region, babies are referred here with incomplete antenatal history and circumstances of birth

events are not well known. We treaded carefully limiting our QI initiative in only two NICUs (of total 8 levels of NICUs); also, we targeted our ASP on infants with weight 1500 grams or more. The idea to select weight over gestation was based on the premise that our region has high rate of growth retarded new-borns and the detail maternal record is not often available.

We showed 17.85% reduction in antibiotic use in admitted babies (25/140). This was a significant difference from the base line value where 100% (82/82) babies received antibiotics after admission. This fell slightly short of our target of 20% reduction from the baseline.

In babies who had a stable clinical course with both sepsis screen and blood culture negative the mean duration of antibiotics was reduced from 5 to 2.68 days- a 46.4% reduction (far exceeding the target of 30%) which is highly significant($p<0.0001$). Also, those admitted new-borns who had a sick clinical course with sepsis screen positive but blood culture negative results, the mean antibiotic days were reduced from 9.6 to 7.24- a 24.5% reduction (exceeding the target of 20%), again a highly significant difference($p<0.001$).

Blood culture positive babies, though not included in aims and objective, showed a modest reduction in mean antibiotic days from 12.9 to 11.06- 14.2% reduction, which was not significant($p=0.123$).

None of our patients had any adverse effect due to early stoppage of antibiotics. The impact of this ASP could be observed in other babies also who are admitted in our NICUs.

Similar to our results, Behera et al reduced antibiotics use in admitted new-borns from a base line value of 94% to 77%($p<0.001$) in their NICU. This QI initiative was done in a government teaching hospital in Odessa, India. They developed guidelines to start antibiotics based on various clinical and laboratory criteria stratifying the risk factors for sepsis [9].

Damera et al in their special care neonatal unit in Nalgonda, Telangana, India, did QI initiative for ASP and significantly reduced antibiotic uses in admitted patients- from 22.2% to 4.9%($p<.0001$). They also showed significant reduction in total antibiotic days- from 1179 to 196 days/1000 patient days($p<.0001$). Also, the cost analysis showed significant saving in INR [10].

Limitations: We targeted this QI initiatives in babies with birth weight 1500 grams or more, this significantly limits the scope of ASP as the most vulnerable group for all the neonatal morbidities and mortality are the infants with very low birth weight-VLBW (<1500 gram). However, undocumented benefit is to be seen in our NICU where even VLBW babies are receiving antibiotics for lesser duration than before. Also, we did not calculate total antibiotic days/1000 admitted patients for the sake of simplicity limiting the comparison of this QI initiative with other studies.

Team: Dr Khalid M Saifullah(MD, MRCP-Paediatrics)- Senior consultant & unit in charge NICU A&B, planned, designed and wrote this QI initiative, Dr Rajesh Kumar(DM-neonatology)- Chief neonatologist & medical director, did supervision and mentoring, Dr Prateek Sinha(DNB, fellow Neonatology), registrar NICU A&B did statistical analysis and Sister Shobha- In-charge nurse NICU A&B, collected and entered the data in software.

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Conflict of interest: None

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