Clinical Practice Guidelines

Antibiotic Stewardship in Neonatal care

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The contributors and editors have made effort to ensure that all information is according to currently accepted recommendations. However, given the rapidity with which new information emerges, the reader is urged to check for latest updates.

Executive summary

Antimicrobial resistance (AMR) is a global health threat. Inappropriate and overuse of antimicrobials is known to cause increased AMR. Neonates are a vulnerable population for infections, and neonatal sepsis is a major cause of mortality and morbidity worldwide. Therefore, antimicrobials are among the commonest drugs prescribed in neonates, more so as empirical therapy. Higher use of antimicrobial therapy is known to be associated with increased risk for necrotizing enterocolitis (NEC) and late-onset sepsis (LOS). Therefore, there is an urgent need to optimize antimicrobial use in neonatal care settings.

Antimicrobial stewardship (AMS) deals with the right use of antibiotics, in the right patient, at the right dose, for the right duration and through the right route. The broad principles of antimicrobial stewardship are the same across all age groups and settings and can be implemented in neonatal units with some adaptations. Though many neonatal units in India are practicing antimicrobial stewardship, there is a need for an evidence-based guideline to inform a context-specific standardized approach to antimicrobial stewardship (AMS).

The Guideline Development Group (GDG) on AMS short-listed 12 practice questions. Most of the questions are related to implementing the AMS in neonatal units. The basic structure of the AMS program in neonates is like that in adults. We provide a brief overview of the components and measures of the AMS program in the neonatal context in an accompanying background document (Appendix 1). The readers are requested to refer to guidelines from international and national professional organizations (CDC, WHO, IDSA, ICMR) for a detailed description (1–4).

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for grading the certainty of evidence (5). The certainty of evidence for the effect of an intervention on the outcomes of interest was graded as high, moderate, low, or very low. After grading the available studies for each outcome, recommendations were formulated based on the summary and certainty of evidence, the balance between benefits and harms, values and preferences of policymakers, healthcare providers, and parents, feasibility, and resource use, and whether costs are justifiable relative to benefits in the Indian settings.

We classified the recommendation as *strong* when there was confidence that the benefits outweigh the harms, or *weak* when the benefits probably outweigh the harms but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as *situational /context-specific* if the benefits outweigh the harms in some situations but not in others (indicated in the document as appropriate).

SUMMARY OF RECOMMENDATIONS FOR ANTIMICROBIAL STEWARDSHIP IN NEONATAL CARE

S. No.	Recommendations	Strength of Recommendations	Certainty of evidence
1.	All neonatal units including SNCUs and NICUs should have an active antimicrobial stewardship program. The program should preferably be integrated with the hospital's wider antimicrobial stewardship program.	Strong	Not graded
2.	Doctors and nurses working in SNCUs and NICUs should be trained in principles and practice of antimicrobial stewardship.	Strong	Very Low
3.	Every neonatal unit should implement a facility-specific empirical antimicrobial therapy policy. This should be based on the local antibiogram and should be periodically reviewed and updated at pre-decided intervals of not more than 12 months.	Strong	Very Low
4.	Antibiotic cycling and/or mixing may **NOT** be practiced in neonatal units.	Weak	Very Low
5.	Standard antimicrobial prescription forms (printed or electronic) mentioning the indication, dose, duration, and route of antibiotic administration should be used for prescribing antibiotics.	Strong	Not graded
6.	Regular auditing of antibiotic use (selection, indication, duration, dose and route) followed by feedback to the SNCU/NICU staff must be an integral part of the antimicrobial stewardship program.	Strong	Very Low
7.	Scheduled 'reviews' (e.g., at 48 hours, 5 days) to decide about continuation of antibiotics may be used in neonates receiving antibiotics for being at risk of sepsis due to perinatal risk factors or having culture-negative probable sepsis.	Weak	Very Low

8.	Microbiology laboratories should follow selective and cascade reporting of antibiotic susceptibility patterns. If the organism grown in culture is sensitive to a narrow spectrum first-line antibiotic, only that sensitivity pattern should be mentioned in the report.	Weak	Not graded
9.	Facilities managing neonates at risk of systemic sepsis may consider use of rapid blood culture technology, as per availability and prioritization of resources.	Weak Conditional	Very Low
10.	We suggest monotherapy in preference to combination antimicrobial therapy for treatment of culture-positive systemic sepsis.	Weak	Not graded
11.	We suggest completion of planned antibiotic course by parenteral route in preference to switching to oral antibiotics following a short course of parenteral antibiotics, in preterm and hospitalized sick term neonates.	Weak	Very Low
12.	Systemic antibiotics should **NOT** be used for prevention of sepsis in neonates with indwelling central arterial/venous catheters, invasive ventilation, total parenteral nutrition, prematurity, or non-infectious morbidities (e.g., meconium aspiration syndrome).	Strong	Very Low

Introduction

Like other age groups, antimicrobial resistance (AMR) is a serious health concern in neonates. Multidrug-resistant pathogens account for 30% of global neonatal sepsis mortality (6). The neonatal sepsis profile and AMR is also influenced by maternal antimicrobial prescription and healthcare-associated infections (6,7). Indiscriminate use of antibiotics in mothers is known to increase the risk of neonatal sepsis and emergence of MDR pathogens (7). Therefore, antimicrobial stewardship (AMS) programs for neonates should consider prenatal and intranatal exposures, apart from postnatal antibiotic exposure.

Broadly, the principles of AMS in neonates are similar to those in the other age groups. Therefore, it should be easy to integrate neonatal AMS with the hospital-wide stewardship program. However, few crucial differences in neonatal outcomes may limit the direct application of the broad program measures. For example, prematurity has large influence on the duration of hospitalization, respiratory support and intravenous lines, and the incidence of mortality. Therefore, measures like days of antimicrobial therapy, costs associated with antimicrobial use, and use of broad-spectrum or higher generation antibiotics might be more relevant measures in neonates.

Most AMS guides are not specifically framed for use in neonates (1–3,8). Recently published systematic reviews and American Academy of Pediatrics guidelines have attempted to provide neonate-specific evidence on AMS (9,10). This document aims to provide updated guidance and recommendations on antimicrobial stewardship in neonates.

Scope of the guidelines and target audience

Scope

This guideline addresses the practical aspects of implementing antimicrobial stewardship in facilities providing in-patient neonatal care. The basics of AMS have been provided in another accompanying document (Appendix 1).

Target audience

The primary audience for this guideline includes healthcare professionals (pediatricians, medical officers, nurses, and other practitioners) responsible for delivering care for neonates in health facilities at all levels, health program managers and policymakers in all settings. The information in this guideline will help develop local standard operating procedures and job aids for implementing rational use of antibiotics. Program managers and facility in-charges may also use these guidelines to set up AMS programs in special care newborn units.

Population of interest

The guidelines focus on antimicrobial stewardship in neonates admitted in hospitals of all levels in India.

METHODOLOGY

Questions relevant to clinical practice

The Guideline Development Group (GDG) short-listed 12 practice questions about AMS in neonates to be of highest priority after a survey amongst the GDG and a wider group of NNF

members. These questions deal with various aspects of AMS: prescription of antibiotics, measures to reduce overuse, and measures to implement AMS in neonatal units.

The following questions were identified to be of the highest priority:

1. Do Antimicrobial Stewardship Programs improve the listed critical or important outcomes in neonatal units?
2. Does education and training help in adoption of antimicrobial stewardship practices and improving the listed outcomes in neonates?
3. Does a facility-specific antimicrobial policy improve the listed outcomes in neonates?
4. Does antibiotic cycling/mixing strategy improve the patient outcomes in neonatal units?
5. Does the routine use of standard antimicrobial order forms improve the listed outcomes in neonates?
6. Does prospective antibiotic audit and feedback improve the listed outcomes in neonates?
7. Does a regular antibiotic review strategy (antibiotic review at 48 hours and 5 days) lead to better outcomes in neonates?
8. Does selective or cascade reporting of susceptibility tests help achieve better antibiotic stewardship practices in neonates compared to susceptibility reporting for all sensitive antibiotics?
9. Do rapid blood culture methods compared to conventional blood culture methods improve the listed outcomes in neonates?
10. Is combination antibiotic therapy superior to monotherapy in culture-positive sepsis for improving outcomes in neonates?
11. Is switching from intravenous to an oral route non-inferior to completing the antibiotic course by intravenous route, in preterm and hospitalized sick term neonates?
12. Does administering prophylactic antibiotics for specific procedures or conditions like ventilation, exchange transfusion, prematurity etc. result in improved outcomes in neonates?

Outcomes of interest

The outcomes listed below were considered for each question. Benefits and harms in critical outcomes formed the basis of the recommendations. When critical outcomes were not available, other important outcomes were considered.

Critical

Neonatal mortality
Readmission within 30 days of discharge
Days of antibiotic therapy
Incidence of multidrug resistant (MDR) organisms
Prevalence of Resistance to Vancomycin/Carbapenems/Colistin/Polymyxin
Use of higher generation antimicrobials (Vancomycin /Carbapenems/ Colistin/Polymyxin)

Important

Duration of hospital stay
Duration of intravenous lines
Costs

Adverse drug reactions

Selection of studies

Search strategy

Using the assembled list of priority questions and critical outcomes from the scoping exercise, the guideline development group first identified recent guidelines that met AGREE criteria and addressed the questions mentioned above. In case we found current guidelines or recommendations from a prominent national or international society addressing the neonatal population, the same was adapted for context-specific situations. In case there were no guidelines or guidelines that did not address the neonatal population, we identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was out of date if the last search date was one year or more prior to the date of assessment. If any relevant review was found to be out of date, it was updated. In addition, we identified potential RCTs and cohort studies from Medline (by PubMed) and Embase (searched until December 2020 and March 2021). The reference lists of relevant articles were also searched to identify relevant studies.

Data extraction and summary tables of individual studies

A standardized form was used to extract information from relevant studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures, and results. The following quality characteristics were recorded for RCTs: allocation concealment, blinding of intervention or observers, loss to follow up, and intention to treat analysis. Where possible, the studies were stratified according to the type of intervention or exposure, study design, birth weight, and gestational age. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data and as mean differences (MD) or weighted mean differences (WMD) for continuous data where possible.

Pooled effects

Pooled effects for developing recommendations were considered wherever feasible. Pooled effects from published meta-analyses were used if they were up to date. Where pooling of results was not possible, the range of effect sizes observed in the individual studies was used in the development of recommendations.

Grading the certainty of the evidence

Certainty assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE approach was used for all the critical outcomes identified in the research question, and a GRADE profile was prepared for each quantitative outcome. Accordingly, the certainty of evidence for each outcome was rated as "high," "moderate," "low," or "very low" based on a set of criteria. The evidence provided by RCTs was considered "high-certainty" as a baseline, while non-randomized trials and observational studies provided "low-certainty" evidence. This baseline rating was then downgraded based on the risk of bias, inconsistency, imprecision, indirectness, and publication bias.

The following briefly describes how these criteria were used:

Study design

We included all kinds of study designs (Randomized controlled studies, Observational studies, before-after studies, and case-control studies). If high-quality large RCTs were available, they were preferred. Unfortunately, we did not find large RCTs addressing most questions in the neonatal population; therefore, we relied on observational data for most questions. We used the Cochrane Risk of Bias-1 (RoB-1) tool or ROBINS tool as appropriate to assess the risk of bias (11,12).

For RCTs, four criteria were used to assess limitations in the methods of the included studies; 1) *Selection bias* was assessed by analyzing how randomization and allocation concealment was done 2) *Measurement bias* can be minimized by blinding the participants and researchers to the intervention. If that is not possible, the observers measuring the outcome can be blinded. Measurement bias was less likely if the outcome was "objective." If most of the evidence was from studies where any of the above was done, the risk was low; otherwise, it was considered high 3) *Loss to follow-up:* A significant loss to follow-up can lead to bias in results; 20% loss to follow-up was chosen arbitrarily as the cut-off point. If most of the evidence was from studies where a loss to follow-up was less than 20%, the risk was low 4) *Appropriateness of analysis:* If most of the evidence was from RCTs that had analysis by intention to treat, the risk of bias was low, else it was high.

Inconsistency of the results

The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap.

Indirectness

Rating of the quality of evidence was downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e., where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons, or outcomes.

Imprecision

The degree of uncertainty around the estimate of effect was assessed. Studies with relatively few participants or events (and thus wide confidence intervals around effect estimates) were downgraded for imprecision because this was often a function of sample size and the number of events.

Publication bias

The quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention because of

selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level.

Formulation of recommendations

After grading the available studies for each outcome, recommendations were formulated based on the summary and quality of evidence, a balance between benefits and harms, values and preferences of policymakers, healthcare providers, and parents, feasibility, and resource use, and whether costs are justifiable relative to benefits in Indian settings.

Each recommendation was graded as *strong* when there was confidence that the benefits clearly outweigh the harms or *weak* when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as *situational /context-specific* if the benefits outweigh the harms in some situations but not in others (indicated in the document as appropriate).

Document review

The GDG members held several web meetings to discuss the evidence and evidence to decision framework for each question, and prepared a draft guideline document with revisions to accurately reflect the deliberations and decisions of the GDG participants. This draft guideline was then sent electronically to the GDG participants for further comments. It was then sent to peer reviewers by the editorial board. The comments and suggestions of peer reviewers were incorporated and the final draft document was submitted to the editorial board for editing process.

QUESTIONS, EVIDENCE SUMMARIES AND RECOMMENDATIONS

Practice Question 1: Do Antimicrobial Stewardship Programs improve the listed critical or important outcomes in neonatal units?

Population: Neonatal Units
Intervention: Antimicrobial stewardship program
Comparator: No formal Antimicrobial stewardship program

Summary of evidence

AMS is crucial in combating AMR. In adult units, antimicrobial stewardship programs (ASP) have been shown to reduce the antimicrobial consumption and decrease the growth of MDR organisms without increase in mortality (2). Two recent systematic reviews assessed the benefits of antimicrobial stewardship program in neonates (9,13). All studies had before and after, or time-series designs and looked at either an ASP or some of its components (Table 1).

Table 1: Summary of the evidence on Antimicrobial Stewardship Program in Neonatal Units

Author, Country; Year	Study design	Aims	Interventions	Summary of key findings
Chiu et al.; USA; 2011	Time series analysis	To evaluate the effectiveness and safety of a guideline restricting vancomycin use using various strategies of AMS program	Introduction of an electronic guideline restricting vancomycin use	• Change of vancomycin use from 6.9 to 4.5/1000 PD in hospital 1 (p=0.01) and 17 to 6.4/1000 PD in Hospital 2 (p<0.0001) • Change of infants exposed to vancomycin from 5.2 to 3.1/1000 PD (p=0.008) in hospital 1, and 10.8 to 5.5/1000 PD in hospital 2 (p=0.009)
Ting et al.; Canada; 2019	Before and after	To evaluate the effectiveness of ASP on antibiotic prescription practices	• Audit and feedback • Revision of antibiotic guideline • Education on AMS • New technology for rapid microbiological diagnosis	• Change of inappropriate meropenem antibiotic—days from 1.89 to 1.96 (RR: 1.04 (0.70–1.52)) per 1000 DOT • Change of inappropriate cefotaxime antibiotic—days from 3.56 to 1.73 (RR: 0.49 (0.33–0.71)) per 1000 DOT • Change of inappropriate vancomycin antibiotic—days from 2.70 to 1.01 (RR: 0.37 (0.22–0.60)) per 1000 DOT • No improvement of inappropriate antibiotic prescriptions in VLBW
Nzegwu et al.; USA; 2017	Time series analysis	To evaluate an ASP on prescription practices	• Development of clinical guidelines for the treatment of common infections • Audit and feedback • Education on judicious antibiotic use	• Decreased monthly antibiotic use from 270.4 to 258.8 DOT/1000 PD (p=0.7) • Decreased monthly ampicillin use from 118.6 to 103.4 DOT/1000 PD (p=0.037) • No significant change in vancomycin, cefotaxime, and gentamicin use • Decrease of LOS evaluation and prescription events per 100 NICU days (p<0.0001)

Lee et al.; USA; 2016	Time series analysis	To evaluate the effectiveness of guidelines on antimicrobial use	• Development of a local guideline • Education • Regular audits and feedback	• Change of antibiotic use from 448 to 367 DOT/1000 PD • Change of targeted broad-spectrum antibiotics from 70 to 27 DOT/1000 PD
Mc Carthy *et al. Ireland;* 2018	Before and after	To evaluate the effectiveness of local guideline + audits and electronic prescribing on antimicrobial use	• Development of local guidelines on antibiotic prescription • Education • Electronic prescribing • Audit and feedback • Multidisciplinary round	• Change of antibiotic use from 572 to 417 DOT/1000 PD (p<0.0001) • Change of prolonged antibiotic use (>36 hours) from 82 to 7.5 DOT/1000 PD (p=0.0004) • Change of protracted antibiotic use (>5 days) from 46.5 to 7 DOT/1000 PD (p=0.0009)
Cantey *et al.; USA;* 2016	Time series analysis	To inform ASP strategies determining areas where antibiotic use could be reduced safety	• Extension of ruled-out sepsis courses beyond 48 hours • Treatment duration for culture-negative pneumonia • Treatment duration for culture-negative sepsis	• Change of antibiotic use from 343.2 to 252.2 DOT/1000 PD (p<0.0001) • Change of 48 hours rule-out courses (% discontinued <48 hours) from 32% to 95% (p<0.0001) • Change of infants with culture-negative sepsis treated <5 days from 31% to 62% (p=0.04) • Change of pneumonia treatments<5 days from 36% to 72% (p<0.0001)

Abbreviations: ASP, antimicrobial stewardship program; EOS: Early-onset sepsis; DOT, days of therapy; NICU, neonatal intensive care unit; PD, patient-day.

Summary of judgements

Balance of benefits and harm: The reviews observed that with implementation of AMS program, the units were able to reduce the use of vancomycin, broad spectrum antibiotics, higher generation antibiotics, antibiotic courses, and duration of antibiotic use without any increase in mortality rate. Though the studies did not include evaluation of the cost-effectiveness, the reduction in antibiotic use without increasing adverse effects is likely to reduce the costs. In long term, it is likely to help in reducing the AMR too.

Resources required: The units need to have a dedicated team responsible for implementation of AMS.

RECOMMENDATION

1. **All neonatal units including SNCUs and NICUs should have an active antimicrobial stewardship program.**

   The program should preferably be integrated with the hospital's wider antimicrobial stewardship program.

   Strong recommendation, Not graded

Justification: Considering the potential benefits (decreased antibiotic use and cost-saving) with no harm, we strongly recommend the universal implementation of an AMS program in neonatal settings. This recommendation aligns with those given by Center for Disease Control (CDC), World Health Organization (WHO), Indian Council of Medical Research (ICMR), American Academy of Pediatrics (AAP), and Infectious Disease Society of America (IDSA) (2,4,10,14).

Implementation considerations: This program should be context-specific and preferably integrated with the AMS program of the hospital.

***Practice Question 2*: Does education and training help in adoption of antimicrobial stewardship practices and improving the listed outcomes in neonates?**

Population: Neonatal units
Intervention: Education and training on antibiotic stewardship
Comparator: No formal education and training on antibiotic stewardship

Summary of evidence

Increasing knowledge and improving prescribing practice through education is an essential persuasive ASP intervention. The key stakeholders (especially healthcare professionals) can be educated either passively (posters, flyers, handouts, conferences etc.) or actively (face-to-face targeted sessions). The evidence for this guideline was derived from eight observational studies(15–22)(Table 2). All included studies implemented multiple strategies together rather than educational activities alone. The indirect evidence on the impact of ASP incorporating education as one of the strategies supports the intervention with benefits reported in terms of decreased antibiotic consumption, monthly antibiotic cost, length of hospital stay, and adverse drug effects without affecting neonatal mortality.

- Mortality: One observational study by Chimhini et al. (15) observed significant reduction in mortality (RR 0.66; 95% CI 0.45-0.99) after implementing the intervention compared to the baseline rate. (Very low quality of evidence)
- Adverse events (vancomycin-associated acute kidney injury): Hamdy et al. (16) reported a significant decrease in this outcome from 1.4 events per 1000 patient days to 0.1 events per 1000 patient days after implementing an ASP, including educational activities. (Very low quality of evidence)
- Length of hospital stay: One observational study reported a significant decrease in duration of stay after implementing an educational drive (part of an ASP) by one day (95% CI 0.56-1.43 days). (Very low quality of evidence)
- Antibiotic consumption: Five out of six included studies reported a significant decrease (4-28%) in the consumption of antibiotics after implementing this strategy. This outcome could not be pooled because of a lack of adjustment for time series data. Similarly, other studies reported a decrease in broad-spectrum antibiotic use but disparities in vancomycin use. (Very low quality of evidence)
- Cost: One study reported a decrease in the monthly cost of 8346$ for targeted broad-spectrum antibiotics after implementing an ASP (education being a part). However,

this study did not report the overall cost of care or total antibiotic consumption. (Very low quality of evidence)

Table 2: Summary of Findings

Education and training on antibiotic stewardship compared to no formal training in neonatal intensive care units

Outcomes	№ of participants (studies) Follow-up	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no formal training	Risk with formal training
Mortality	648 (1 observational study)	⊕◯◯◯ Very low[a,b,c,d]	RR 0.66 (0.45 to 0.99)	**207 per 1,000**	**137 per 1,000 (93 to 205)**
Vancomycin-associated AKI per 1000 patient days	2000 (1 observational study)	⊕◯◯◯ Very low[a,b,c]	IRR 0.070 (0.002 to 0.470)	**1 per 1,000**	**0 per 1,000 (0 to 1)**
Length of hospital stay	648 (1 observational study)	⊕◯◯◯ Very low[a,b,c]		**The median length of hospital stay was 3 days**	**MD 1 days lower (1.43 lower to 0.56 lower)**
Antibiotic consumption (DOT/1000 patient days)	400 (6 observational studies)	⊕⊕◯◯ Low[a,c]	Six studies, comprising 2100 and 4003 neonates in pre- and post-intervention periods, reported antibiotic consumption. The percentage decrease in antibiotic consumption ranged from 4-28%, with 5 studies showing significant decrement between pre- and post-intervention periods.		
Broad-spectrum antibiotic consumption (DOT per 1000 patient days)	8810 (1 observational study)	⊕◯◯◯ Very low[b,c,e]	% Decrease in antibiotic consumption (cefepime, meropenem, and piperacillin-tazobactam) was 61% (DOT/1000 patient days: 70 vs 27 in pre- and post-intervention periods).		
Vancomycin consumption (DOT 1000 patient days)	3179 (3 observational studies)	⊕◯◯◯ Very low[a,c,f]	Two studies showed decrease in antibiotic consumption (29%, and35%) while one study reported increase by 667% (DOT/1000 patient days: 112 vs 80; 32 vs 21; 3 vs 23 in pre- and post-intervention periods).		
Monthly cost for broad-spectrum antibiotics (Cost)	(1 observational study)	⊕◯◯◯ Very low[b,c,e]		**The mean monthly was 19389 $**	**MD 8346 $ lower (0 to 0)**

Explanations

a. Serious risk of bias due to confounding and no information on deviations from intended intervention (adherence rate not mentioned)

b. Single study (estimated effect size may not be consistent across similarly planned studies)

c. A bundle of multiple interventions was used in the studies

d. 95% CI of pooled effect size crosses the clinical decision threshold between recommending and not recommending (i.e. 0.90 <x <1.10)

e. Serious risk of bias due to confounding

f. Wide variance of point estimates across studies; intervention effects do not overlap among studies

Summary of judgements

Balance of benefits and harm: There is very-low certainty evidence that formal education and training (as a part of AMS program) helped in reduction in mortality, adverse events, hospital stay, and antimicrobial consumption. One study reported a decrease in the monthly cost of 8346$ for targeted broad-spectrum antibiotics after implementing an ASP (Table 2).

Resources required: The units need to assign teams responsible for ongoing education and training on antimicrobial stewardship.

RECOMMENDATION

2. Doctors and nurses working in SNCUs and NICUs should be trained in principles and practice of antimicrobial stewardship.

Strong recommendation, Very low certainty

Justification: Considering the potential benefits (decreased mortality, AMR, antibiotic use and cost-saving) with no harm, we strongly recommend the regular formal education and training on antimicrobial stewardship.

Implementation considerations: It is unlikely that this intervention alone will bring a significant change in the outcomes. Therefore, it should be practiced in conjunction with other interventions of the AMS bundle.

***Practice Question 3*: Does a facility-specific antimicrobial policy improve the listed outcomes in neonates?**

Population: Neonates started on empiric antibiotic therapy
Intervention: Facility-specific written antibiotic policy
Comparator: No formal facility-specific written antibiotic policy
Setting: neonatal units

Summary of evidence

Most neonates with suspected sepsis are started on empirical antibiotic therapy, because of high risk of mortality. This empirical therapy should be guided by local antibiogram. Having a written local antibiotic policy decreases the variations in prescription and helps in optimizing the use of antibiotics. Two observational studies enrolling 2705 neonates assessed the impact of implementation of facility-specific antibiotic policy on various clinical outcomes (23,24). We did a systematic review for pre-decided outcomes (Table 3).

Table 3: Summary of Findings

Facility-specific written antibiotic policy implementation compared to No written policy for empiric antibiotic therapy in neonates

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No policy	Risk difference with facility-specific written antibiotic policy implementation
Mortality	2705 (2 observational studies)	⊕◯◯◯ Very low[a]	**RR 0.69** (0.48 to 0.99)	51 per 1,000	**16 fewer per 1,000** (27 fewer to 1 fewer)
Duration of Hospital stay	2452 (1 observational study)	⊕◯◯◯ Very low[a,b]	-	MD **0.4 lower** (1.03 lower to 0.23 higher)	
Antimicrobial resistance rates to higher antibiotics	535 (1 observational study)	⊕◯◯◯ Very low[a]	**RR 0.71** (0.45 to 1.14)	506 per 1,000	**147 fewer per 1,000** (278 fewer to 71 more)
Antimicrobial resistance rates to higher antibiotics – Vancomycin	201 (1 observational study)	⊕◯◯◯ Very low[a,d]	**RR 0.92** (0.66 to 1.27)	441 per 1,000	**35 fewer per 1,000** (150 fewer to 119 more)
Antimicrobial resistance rates to higher antibiotics - Carbapenem (Meropenem/Imipenem)	334 (1 observational study)	⊕◯◯◯ Very low[d]	**RR 0.57** (0.44 to 0.74)	546 per 1,000	**235 fewer per 1,000** (306 fewer to 142 fewer)
Proportion on neonates having IV line	2452 (1 observational study)	⊕◯◯◯ Very low[a,b]	**RR 1.27** (0.95 to 1.71)	60 per 1,000	**16 more per 1,000** (3 fewer to 43 more)
Percentage of babies on higher antibiotics	4904 (1 observational study)	⊕◯◯◯ Very low[a,c]	**RR 3.28** (0.14 to 77.97)	25 per 1,000	**56 more per 1,000** (21 fewer to 1,898 more)
Percentage of babies on higher antibiotics - Meropenem/Imipenem	2452 (1 observational study)	⊕◯◯◯ Very low[a,b,c]	**RR 0.92** (0.65 to 1.31)	49 per 1,000	**4 fewer per 1,000** (17 fewer to 15 more)

Explanations

a. Wide 95% CI

b. there is a significant difference in the before and after population in several VLBW neonates which can directly impact the outcome

c. There may be a lot of subjectivity in starting antibiotics.

d. Multiple other interventions were also carried out, therefore difficult to attribute it to the intervention alone.

Summary of judgements

Balance of benefits and harm: There is very low certainty evidence that the use of written antibiotic policy reduces mortality (2 studies; RR-0.69; 95% CI 0.48-0.99); and AMR to carbapenems (1 study; RR 0.57, 95 % CI- 0.44 to 0.74) (Table 3).

Resources required: There are minimal costs associated with the intervention. In fact, there may be a cost saving if the local antibiotic policy is drafted considering the antibiograms, adverse effects and cost of antibiotics.

RECOMMENDATION

3. Every neonatal unit should implement a facility-specific empirical antimicrobial therapy policy. This should be based on the local antibiogram and, should be periodically reviewed and updated at pre-decided intervals of not more than 12 months.

Strong recommendation, Very-low certainty evidence

Justification: Due to possible benefits on mortality and AMR with minimal costs and adverse effects, we recommend that each unit should develop and implement a facility-specific empiric antibiotic policy based upon local microorganism profile and antibiogram. IDSA, AAP, and ICR also suggest using facility-specific written antimicrobial policy in all healthcare settings (2,4,10).

Implementation considerations: It is unlikely that this intervention alone will bring a significant change in the outcomes. Therefore, it should be practiced in conjunction with other interventions of the AMS bundle.

***Practice Question 4*: Does antibiotic cycling/mixing strategy improve patient outcomes in neonatal units?**

Antibiotic cycling/ rotation strategy: A specified antibiotic is used as a preferred option for empirical initiation of antibiotics during a scheduled period. After that period, another antibiotic, usually from a different class of antibiotics, becomes the preferred option of empirical therapy for all patients needing anti-bacterial treatment.

Antibiotic mixing strategy: The first-line antibiotic is alternated in consecutive patients according to a pre-established protocol.

Patient or population: Neonates
Setting: Neonatal units
Intervention: Antibiotic cycling or mixing
Comparison: no cycling or mixing

Summary of evidence

Evidence for the use of antibiotic cycling and mixing was obtained from the meta-analysis published in 2020 (25). The meta-analysis included 12 studies, all of which were in adults and from developed countries. The only neonatal study addressing this question partly was from the USA published in 2002 (26). However, the study did not assess the critical outcomes of mortality, rates of hospital-acquired infections, and duration of hospital stay. It only assessed colonization rates with resistant bacilli.

Summary of judgements

Balance of benefits and harm: Pooled analysis (in adults) showed very low -quality evidence of a reduction in the risk of mortality during the hospital stay OR 0.89 (95% CI: 0.82-0.97), healthcare associated infections OR 0.89 (95% CI: 0.82-0.98), and incidence of infections with multidrug resistant organisms OR 0.81 (95% CI: 0.74-0.88)(25). Only one neonatal study assessed this strategy. They found that there are higher colorization rates with resistant bacilli in cycling phase (10.7 vs 7.7%)(26). A modelling study showed that combination antimicrobial therapy significantly outperforms the strategies of antibiotic mixing, and cycling for empirical antibiotic therapy (26a).

Resources required: The strategy of antibiotic mixing and cycling may increase the cost of care based on the cost of antibiotics used. Also, it requires a dedicated team who ensures timely change in policy and tracks the AMR pattern. Close monitoring and periodic evaluation on infection rates and changing resistance patterns must be performed by units deciding to use antibiotic mixing or cycling strategies, to know the risks and benefits on the neonates.

RECOMMENDATION

4. Antibiotic cycling and/or mixing may NOT be practiced in neonatal units.

Weak recommendation, Very low-quality evidence

Justification: The group believes that there is not enough evidence from neonatal studies supporting the use of antibiotic mixing or cycling. The data from adult studies is quite old, and a recent modelling study found combination empirical antibiotic therapy is better than antibiotic mixing and cycling.

***Practice Question 5*: Does the routine use of standard antimicrobial order forms improve the listed outcomes in neonates?**

Patient or population: Neonates
Setting: Neonatal units
Intervention: Standard antimicrobial prescription form
Comparison: No Standard antimicrobial prescription form

Summary of evidence

Evidence for the use of standard antimicrobial order forms compared to no forms is derived from an observational study in an adult medical unit of the USA published in 1984 (27). Echols et al. observed that after introducing the antibiotic order form, there was a significant decline in the number of antibiotic treatment courses and the percentage of patients receiving any antibiotic (27). None of the neonatal studies evaluated this question, and there were no studies from low- and middle-income countries.

Summary of judgements

Balance of benefits and harm: The possible benefits of standard antimicrobial forms include more uniformity in antibiotic prescriptions, decrease in dosing errors, and timely review of antibiotic decisions.

Resources required: The costs of organizing the standard forms are minimal. Standardized prescriptions may actually lead to cost savings by rational use of antibiotics.

RECOMMENDATION

5. Standard antimicrobial prescription forms (printed or electronic) mentioning the indication, dose, duration, and route of antibiotic administration should be used for prescribing antibiotics.

Strong recommendation, Not graded

Justification: Standardized antimicrobial forms mentioning indication, dose, duration, and route are likely to make the practice of antibiotic prescription more uniform, decrease prescription and dosing errors, and help in timely review of decisions on antibiotic continuation/ change. Standardized prescription forms may potentially decrease both overtreatment and inadequate treatment. Although no studies have evaluated these charts, considering the potential benefits and minimal costs, the guideline panel made this recommendation.

Implementation considerations: Implementing standard antimicrobial forms needs good coordination between doctors and nurses, training sessions, ongoing evaluation, audit, and feedback.

***Practice Question 6*: Does prospective antibiotic audit and feedback improve the listed outcomes in neonates?**

Prospective audit and feedback involves a review of antimicrobial therapy by an expert in antibiotic use, accompanied by suggestions to optimize use, at some point after the antibiotics have been prescribed. This feedback can be during routine ward rounds, patient handover meetings, or during scheduled antibiotic rounds. Feedback should be constructive and based on real data.

Patient or population: Neonates on antimicrobials
Setting: Neonatal units
Intervention: Prospective antibiotic audit and feedback
Comparison: No active intervention

Summary of evidence

Evidence for the use of prospective audit and feedback compared to standard treatment (no audit or feedback) is derived from two neonatal studies evaluating the critical outcomes of mortality, culture-proven sepsis, necrotizing enterocolitis, duration of hospital stay, and readmissions to the hospital (28,29). Two more studies provided data on days of antibiotic therapy (21,30). Of these, three studies were conducted in high-income countries (21,28,29) and one in a middle-income country (30). Pooled analysis (table 4) showed low-quality evidence of no reduction in mortality, culture-proven sepsis, duration of hospital stays, and readmission after discharge using prospective audit and feedback. There is very low-quality evidence that the use of prospective audit and feedback decreases rates of clinical sepsis with OR of 0.55 (95% CI: 0.48, 0.62) and days on antibiotic therapy with111 fewer days per 1,000 patient days (95% CI: 138 fewer to 80 fewer).

Table 4: Summary of Findings

Prospective antibiotic audit and feedback compared to no active intervention in neonatal units

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with audit	Risk with Prospective audit and feedback
Mortality	15120 (2 observational studies)	⊕⊕◯◯ Low[a]	**OR 1.10** (0.96 to 1.26)	**64 per 1,000** (56 to 73)	**OR 1.10** (0.96 to 1.26)
Culture proven sepsis	15120 (2 observational studies)	⊕⊕◯◯ Low	**OR 1.04** (0.80 to 1.34)	**16 per 1,000** (13 to 21)	**OR 1.04** (0.80 to 1.34)
Clinical sepsis	15120 (2 observational studies)	⊕◯◯◯ Very low[b]	**OR 0.55** (0.48 to 0.62)	**59 per 1,000** (52 to 67)	**OR 0.55** (0.48 to 0.62)
Days of antibiotic therapy per 1,000 patient days	4000 (2 observational studies)	⊕◯◯◯ Very low[c]	**OR 0.63** (0.56 to 0.72)	**358 per 1,000** (331 to 389)	**OR 0.63** (0.56 to 0.72)

Prospective antibiotic audit and feedback compared to no active intervention in neonatal units

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with audit	Risk with Prospective audit and feedback
Readmission rates	13540 (1 observational study)	⊕◯◯◯ Very low[d]	**OR 0.92** (0.67 to 1.27)	**11 per 1,000** (8 to 15)	**OR 0.92** (0.67 to 1.27)
Length of hospital stay	15,120 (2 observational studies)	⊕⊕◯◯ Low	MD **0.03 lower** (0.41 lower to 0.34 higher)	**8618**	MD **0.03 lower** (0.41 lower to 0.34 higher)

Explanations
a. ROBINS-I tool was used for assessment ; b. I2 statistic of 94% ; c. I2 statistic of 90% ; d. A wide confidence interval of 0.67 to 1.27

Summary of judgements

Balance of benefits and harm

The benefits of prospective audit and feedback namely reduction in clinical sepsis rates and days on antibiotic therapy occur with no increase in harms. Hence, health care providers, policymakers, and parents in both high-income and low-and middle-income countries are likely to give a high value to the use of prospective audit and feedback.

Resources required: The use of prospective audits and feedback can result in cost savings due to shorter courses of antibiotics. The implementation of this strategy requires the availability of a team including pharmacist, microbiologist, pharmacologist, and clinician.

RECOMMENDATION

6. Regular auditing of antibiotic use (selection, indication, duration, dose and route) followed by feedback to the SNCU/NICU staff must be an integral part of the antimicrobial stewardship program.

Strong recommendation, Very low certainty evidence

Justification: Prospective audit and feedback reduces antibiotic therapy duration and episodes of clinical sepsis without increasing mortality. Several international organizations (CDC, IDSA, WHI, AAP) recommend it to be an integral part of the AMS program (2–4,10).

Implementation Considerations: The implementation needs multi-departmental collaboration. In the published studies, the team providing prospective audit and feedback comprised a pharmacist, a microbiologist, and a pharmacologist working with the clinician and the administration. Innovative strategies can be used to involve microbiology and pharmacology departments to overcome the challenges in resource-limited settings.

***Practice Question 7*: Does a regular antibiotic review strategy (antibiotic review at 48 hours and 5 days) lead to better outcomes in neonates?**

Antibiotic review is one of the prescriber-led feedback strategies for antimicrobial stewardship. It includes review of the ongoing requirement and choice of antibiotics at a time point (usually 48 hours and 5 days) when the clinical course and additional diagnostic information are available. This review can include decision on continuation of antibiotic therapy, its appropriateness, de-escalation, and duration of therapy (CDC 2014).

Patient or population: Neonates on antibiotic therapy
Setting: Neonatal intensive care units
Intervention: antibiotic review
Comparison: no such strategy

Summary of evidence

The evidence (table 5) for this question was derived from 13 observational studies (16,18–20,22,31–36). Most of the included studies implemented multiple strategies together rather than antibiotic review alone. Additionally, most studies had a mechanism for review reminder in the form of a modified prescription order, automatic 48-hour stop orders or faculty-driven reviews in rounds.

Mortality: Four observational studies, comprising 18352 participants, reported this outcome. There was no significant difference (OR 1.10; 95% CI 0.96-1.24) in mortality between the intervention and control groups. (Very low quality of evidence)
Treatment failure: Though defined differently by various studies, none of the three studies reported any increase in treatment failures or readmission rate between the two groups. (Very low quality of evidence)
Adverse events (vancomycin-associated acute kidney injury): Hamdy et al. (16) reported a significant decrease in this outcome from 1.4 events per 1000 patient days to 0.1 events per 1000 patient days after implementation of an ASP including antibiotic timeout strategy(16). (Very low quality of evidence)
Length of hospital stay: As reported by three studies, there was a significant increase in duration of stay after the implementation of antibiotic review strategy (part of an ASP) by 1.97 days, however the 95% CI (0.1-3.8 days) reflects the uncertainty of evidence and clinical insignificance. (Very low quality of evidence)
Antibiotic consumption: Six out of eight included studies reported a significant decrease (4-76%) in the consumption of antibiotics after implementation of this strategy. This outcome could not be pooled because of lack of adjustment for time series data. Similarly, other studies reported decrease in broad-spectrum antibiotic use and vancomycin use. (Very low quality of evidence)
Multi-drug resistant (MDR) organism isolation: Two studies reported a significant decrease in MDR organism isolation rate (colonization) before and after implementation of an ASP (with antibiotic timeout component), but 95% CI (RR 0.71; 0.53 to 0.96) shows the uncertainty of this estimate. Another study reported significant decrease in MRSA nasal colonization growth rate after the intervention (OR 0.33, 95% CI 0.15 to 0.72). (Very low quality of evidence)

Cost: One study reported decrease in the monthly cost for targeted broad-spectrum antibiotics after the implementation of an ASP by 8346$. However, the overall cost of care or total antibiotic consumption was not reported in this study. (Very low quality of evidence)

Table 5: Summary of Findings

Antibiotic review compared to no such strategy for antibiotic therapy in neonates					
Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with no such strategy	**Risk with antibiotic review**
Mortality	18352 (4 observational studies)	⊕◯◯◯ Very low[a,b,c]	**OR 1.10** (0.96 to 1.24)	55 per 1,000	**60 per 1,000** (53 to 67)
Treatment failure	1452 (1 observational study)	⊕◯◯◯ Very low[c,d,e]	**RR 0.55** (0.22 to 1.39)	30 per 1,000	**16 per 1,000** (7 to 41)
Readmission within 30 days	13540 (1 observational study)	⊕◯◯◯ Very low[b,c,e,f]	**RR 0.92** (0.67 to 1.27)	12 per 1,000	**11 per 1,000** (8 to 15)
Vancomycin-associated acute kidney injury	2000 (1 observational study)	⊕◯◯◯ Very low[b,e,g]	**IRR 0.070** (0.002 to 0.470)	1 per 1,000	**0 per 1,000** (0 to 1)
Antibiotic consumption (Days of therapy per 1000 patient days) (DOT/1000 patient days)	400 (8 observational studies)	⊕◯◯◯ Very low[a,b]	Eight studies (11915 and 10689 neonates in pre- and post-intervention periods). The % decrease in antibiotic consumption ranged from 4-76%, with 6 studies showing significant decrement between pre- and post-intervention periods.		
Broad-spectrum antibiotic consumption (Days of therapy per 1000 patient days)	8810 (1 observational study)	⊕◯◯◯ Very low[b,e,f]	The % decrease in antibiotic consumption was 61% (DOT/1000 patient days: 70 vs 27 in pre- and post-intervention periods).		
Multi-drug resistant organism growth rate (colonization) (MDR)	16042 (2 observational studies)	⊕◯◯◯ Very low[b,f,j]	**RR 0.71** (0.53 to 0.96)	14 per 1,000	**10 per 1,000** (7 to 14)

Antibiotic review compared to no such strategy for antibiotic therapy in neonates					
Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no such strategy	Risk with antibiotic review
Monthly cost for targeted broad-spectrum antibiotics (Cost)	(1 observational study)	⊕◯◯◯ Very low[a,b,c]		Mean monthly cost for targeted broad-spectrum antibiotics was $**19389**	MD **8346 $ lower** (0 to 0)

Explanations

a. Serious risk of bias due to confounding, deviations from intended intervention (adherence rate not mentioned in most studies) and no information on missing data.
b. A bundle of multiple interventions was used in the studies, therefore the estimated effect size is reflective of the bundle, rather than a single intervention.
c. The 95% CI crosses the clinical decision threshold between recommending and not recommending intervention (crossing null).
d. Serious risk of bias due to confounding and no information on missing data.
e. Single study (estimated effect size may not be consistent across similarly planned studies)
f. Serious risk of bias due to confounding
g. Serious risk of bias due to confounding and deviations from intended intervention (adherence rate 50%)
h. Considerable heterogeneity (I-squared >70%) and wide variance of point estimates across studies
i. The 95% CI crosses the clinical decision threshold between recommending and not recommending intervention (<0.1 SD or Z score).
j. 95% CI of pooled effect size crosses the clinical decision threshold between recommending and not recommending (i.e. 0.90 <x <1.10)

Summary of judgements

Balance of benefits and harms

The above studies report benefits in terms of antibiotic consumption, monthly cost, multidrug resistant microbial growth and adverse drug effects, without any increased harms in terms of mortality, treatment failure or readmission rates.

Resources required: Since this strategy usually involves self-driven efforts by prescribers, this would not impose much costs on the health facilities. Instead, limited evidence suggests this can lead to moderate savings in decreased antibiotic consumption and their costs.

RECOMMENDATION

7. Scheduled 'reviews' (e.g., at 48 hours, 5 days) to decide about continuation of antibiotics may be used in neonates receiving antibiotics for being at risk of sepsis due to perinatal risk factors or having culture-negative probable sepsis.

Weak recommendation, Very low certainty evidence

Justification: This strategy led to decreased antibiotic consumption, costs, and adverse drug events without causing an undue increase in harm (mortality, treatment failures, or readmission rates). However, the evidence is indirect (mainly from adults) and is not from low- and middle-income countries. Therefore, guideline panel gives weak recommendation in favour of intervention.

Implementation Consideration: The intervention can be implemented at no or minimal costs to the health facilities, irrespective of the level of neonatal care. The intervention is likely to be acceptable to key stakeholders, including healthcare professionals and policymakers, given the impact on antimicrobial resistance and cost-effectiveness.

***Practice Question 8*: Does selective or cascade reporting of antibiotic susceptibility tests help achieve better antibiotic stewardship practices in neonates compared to susceptibility reporting for all sensitive antibiotics?**

Selective or cascade reporting is one of the restrictive strategies of antimicrobial stewardship that various international organizations have recommended. It refers to reporting antibiotic susceptibility tests (AST) to broad-spectrum antibiotics only after the organism is found resistant to narrower-spectrum antibiotics. However, the unrevealed susceptibility reports to other antibiotics can be retrieved from the microbiology laboratory on request.

Patient or population: Neonates on antibiotic therapy
Setting: Neonatal units
Intervention: Selective or cascade reporting of antimicrobial susceptibility
Comparison: Universal susceptibility reporting

Summary of evidence

The currently available evidence, though limited, supports this strategy in the adult population (37). There are no studies on neonates. A recent review (Tebano 2020) described studies on selective AST reporting in adults (inpatients and outpatients)(37). The studies reported improvement in antibiotic use, reducing unnecessary and inappropriate prescribing, but without any firm conclusion on the impact on antimicrobial resistance. Though most of the studies in the review were not powered enough to detect undesirable outcomes, none of them reported increased unintended consequences (mortality, readmission rate, length of stay, etc).

The current recommendations of various professional bodies are summarized in table 6.

Table 6: Summary of recommendations on selective reporting of antibiotic susceptibility tests

Organization	Recommendation	Category
Infectious Diseases Society of America (2016)(2)	We suggest selective and cascade reporting of antibiotics over-reporting of all tested antibiotics.	Weak recommendation, low-quality evidence
WHO Practical Toolkit, (2019)(38)	Where possible, microbiologists support the ASP team by reporting on MDR organisms and selectively reporting susceptibility data to the facility management and prescribers.	Not graded
British Society for Antimicrobial Chemotherapy (2018)(14)	"Selective reporting of microbiology results" has been mentioned as a short timescale, low-level intervention.	Not graded
Indian Council of Medical Research (2018)(4)	• Undertake selective antimicrobial susceptibility testing, especially those that are listed in the formulary • Selective reporting of only relevant/first-line drugs alone	Not graded

Summary of judgements

Balance of benefits and harm : The adult studies reported improvement in antibiotic use, reducing unnecessary and inappropriate prescribing, but without any firm conclusion on the impact on antimicrobial resistance. Though most of the studies in the review were not powered enough to detect undesirable outcomes, none of them reported increased unintended consequences (mortality, readmission rate, length of stay, etc). The clinicians of the facility must be aware of the selective reporting process and interact with the laboratory if the organisms reported are resistant or the antibiotic reported sensitive cannot be used.

Resources Required: Evidence from the adult population suggests no or minimal costs for implementing the intervention (37). Since this intervention involves a policy change, its implementation will likely be inexpensive, but no studies have assessed the workload on physicians. It requires 24x7 support from microbiology laboratory. Few studies have reported no additional laboratory workload apart from more calls from the clinical team for comprehensive susceptibility reports.

RECOMMENDATION

8. Microbiology laboratories should follow selective and cascade reporting of antibiotic susceptibility patterns. If the organism grown in culture is sensitive to a narrow spectrum first-line antibiotic, only that sensitivity pattern should be mentioned in the report.

Weak recommendation, Not graded

Justification: Based on the above reported benefits, various international and national organizations (IDSA, WHO, BSAC, ICMR) recommend the implementation of selective or cascade reporting for antibiotic susceptibility tests by the microbiology laboratory.

Implementation Consideration: There could be various barriers to the implementation of selective reporting: lack of resources (logistics and human resources), communication between physicians and laboratory, and resistance among physicians due to loss of autonomy, lack of awareness etc.

***Practice Question* 9: Do rapid blood culture methods compared to conventional blood culture methods improve the listed outcomes in neonates?**

The conventional blood culture methods take 36-72 hours for organism identification and are laborious. Until a culture sensitivity report is available, the neonates receive empirical therapy. Recent rapid blood culture methods are semi-automated and give results within 18-24 hours and therefore may help to give targeted antimicrobials and reduce the duration of empirical therapy in those whose cultures are negative. The timely escalation or de-escalation of sensitive antimicrobials may improve patient outcomes.

Population: Neonates suspected to have sepsis
Intervention: Rapid blood culture methods
Comparison: Conventional blood culture
Setting: Neonatal Units

Summary of evidence

In adults, the use of rapid blood culture methods has been associated with shorter time to initiation of appropriate antibiotic therapy, and shorter time to escalation/de-escalation of antibiotic therapy (Moderate quality evidence, consistently seen in all studies)(2,39,40). However, the effects on mortality, length of stay, and hospital costs were inconsistent across studies (low-quality evidence)(2,39). Also, the optimal implementation of rapid culture methods requires increased laboratory resources and additional costs.

Summary of judgements

Balance of benefits and harm : None of the desired clinical or microbiological outcomes have been studied in neonates.

Resources Required: The implementation will require additional laboratory resources (equipment, culture bottles), therefore, warrants additional costs and training of human resources.

RECOMMENDATION

9. Facilities managing neonates at risk of systemic sepsis may consider use of rapid blood culture technology, as per availability and prioritization of resources.

Weak Conditional, Very-low certainty evidence

Justification: There is no direct evidence of the benefit or harm of the intervention in neonates. However, considering the existing adult data and recommendations, the use of rapid blood culture methods in resource adequate settings might be considered. IDSA also suggests rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens combined with active ASP support and interpretation (2).

Implementation Consideration: The implementation of rapid culture methods shall require additional laboratory resources (equipment, culture bottles), therefore, warrants additional costs and training of human resources.

***Practice question 10*: Is combination antibiotic therapy superior to monotherapy in culture-positive sepsis for improving outcomes in neonates?**

Monotherapy means starting single sensitive antibiotic for treatment of culture-proven sepsis. Combination therapy refers to using a sensitive antibiotic in combination with another class of synergistic antibiotic aimed to improve the efficacy with concomitant decrease in risk for antimicrobial resistance.

Population: Neonates with culture-positive sepsis
Intervention: Combination therapy
Comparison: Monotherapy
Setting: Neonatal Units

Summary of evidence

We could not find out any head-to-head trial in neonatal population comparing combination therapy to monotherapy. Most of the available literature is from adults. Therefore, the recommendations are extrapolated from indirect evidence. A recently published systematic review (6 case control studies and 2 RCTs) comparing the effect of combination (colistin-based/ polymyxin B-based/ minocycline-based/ carbapenem-based/ tigecycline-based and various other combinations) therapy with monotherapy in adults with multidrug-resistant gram-negative organisms did not find any significant difference in mortality(41). However, when the analysis was limited to case-control studies, the combination therapy reduced mortality (RR 0.83, CI 0.73-0.93, P=0.002) (41). Another meta-analysis studying the effect of beta lactamases with combined therapy of beta lactamase with aminoglycoside did not reveal any advantage of combination therapy (42). A third metanalysis comparing the effect of polymyxin monotherapy with polymyxin based combination therapy (with tigecycline, carbapenem, aminoglycosides and gentamycin) in Carbapenem resistant Klebsiella showed decrease in mortality (10 studies, 481 patients and OR of 2.04 (95% CI: 1.35 to 3.08, P = 0.0007) as well as ventilator associated pneumonia with combination therapy (43).

Table 7 summarizes the information about combination therapy in various guidelines.

Table 7: Summary of guidelines on combination therapy

Guideline	Comment on combination therapy
ICMR (2018)(4)	Available data suggest insufficient evidence to support combination therapy. In many cases they are redundant and unnecessary.
CIDRAP ASP (2019)(44)	No mention about combination therapy
CDC (2015, 2019)(3)	Optimal combination therapy is necessary for difficult to treat organisms like Pseudomonas aeruginosa, Acinetobacter sp. and multi-drug resistant Enterobacteriaceae which have more than one mechanism of developing drug resistance. Combination therapy should be provided as per local susceptibility data.
IDSA (2016)(2)	Due to scarcity of available evidence does not give any recommendation for combination therapy.
WHO (2019)(38)	Discourages unnecessary combinations (like combining antibiotics of overlapping spectrum, antibiotics interacting with other medications or antibiotics which are clinically not effective for a particular pathogen)

Summary of judgements

Balance of benefits and harm : The studies showing beneficial effects were observational in nature and at high risk of bias. Metanalysis of RCTs alone failed to show similar results. Furthermore, the effect was shown against a particular organism after using given combination, therefore it cannot be generalized.

Resources Required: Fixed dose combinations are often more costly as compared to monotherapy.

RECOMMENDATION

10. We suggest monotherapy in preference to combination antimicrobial therapy for treatment of culture-positive systemic sepsis.

Weak *recommendation, Not graded*

Justification: As of now, treating with single sensitive agent in culture positive sepsis has become standard of care. All guidelines recommend against routine use of combination therapy in culture-proven sepsis (Table 7). These recommendations are mainly due to concern of increased antimicrobial resistance and costs associated with non-judicious combination therapy. The evidence favoring combination therapy is from observational studies which are done in critically ill patients and are at high risk of bias. Also, the results are not consistent across studies, therefore downgrading the overall certainty. Therefore, wherever possible monotherapy (based on culture report) should be preferred. In critically sick neonates with proven sepsis with highly virulent multidrug resistant organisms (e.g., multi-drug resistant Enterobacteriaceae), a combination therapy might be used on case-to-case basis after discussion with microbiologist, infectious disease specialist and clinical pharmacologist. The choice of antibiotic combination should be based upon local susceptibility data.

***Practice Question 11*: Is switching from intravenous to an oral route non-inferior to completing the antibiotic course by intravenous route in hospitalized preterm or term sick neonates?**

Population: Neonates with suspect/culture-positive sepsis
Intervention: Switching to oral therapy after certain interval
Comparison: Continuing parenteral therapy for entire course
Setting: Neonatal Units

Summary of evidence

In pharmacokinetic studies, the oral absorption and bioavailability of various antibiotics (Penicillin, Ampicillin, Amoxicillin, Flucloxacillin, chloramphenicol, and linezolid) has been studied (45). It was found that oral antibiotics generally reach their maximum concentration later and have lower bioavailability than parenteral administration. However, adequate serum levels for bacterial killing are reached in most cases. The C_{max} achieved in neonates was like adults without any increased adverse effects. This pharmacokinetic data paved the way for efficacy and safety trials in this population.

There are no randomized controlled trials from hospital settings or preterm neonates. The only evidence we have is in term infants from community-based trials. Three large community-based trials compared various antibiotic regimens in young infants (0-60 days)(46–48). They included a significant proportion of term neonates with one or more signs of severe infection. All three showed that switching to broad-spectrum oral antibiotics after a short course of parenteral therapy (2 days in these trials) is non-inferior to continuing parenteral antibiotics for the total duration. Meta-analysis of these three trials showed that the odds ratio for treatment failure (OR:0.95; 95% CI: 0.79 to 1.16) and mortality (OR:1.11; 95% CI: 0.72 to 1.72) are similar in both groups (45).

One retrospective study compared the effect of a short course of IV therapy (< 4 days) followed by oral treatment with total IV therapy in children (0-60 days, neonates-48) with acute pyelonephritis. They also found that oral switch therapy has a similar efficacy and safety profile as IV therapy(49).

Summary of judgements

Balance of benefits and harm : Switching to oral antibiotics is an attractive proposition potentially offering shortening of hospital stay, reducing costs and risks associated with hospitalization. The potential harms are possibility of treatment failure, relapses, mortality and sequelae due to partial treatment. These concerns are higher in the preterm and sick neonates, and in infections due to more virulent organisms. In the absence of any evidence from hospital settings and in preterm neonates, it is not possible to be sure of the safety of switching to oral route in preterm and hospitalized sick term neonates.

RECOMMENDATION

11. We suggest completion of planned antibiotic course by parenteral route in preference to switching to oral antibiotics following a short course of parenteral antibiotics, in preterm and hospitalized sick term neonates.

Weak *recommendation, Very-low certainty evidence*

Justification: There are no studies evaluating oral versus parenteral antibiotics in preterm or sick term neonates. Even the studies mentioned above did not provide separate data for the neonatal population. Therefore, we are not sure about the safety of oral switch therapy in preterm and sick term neonates. Moreover, there are conerns that partially treated sepsis may lead to longterm complications. Therefore in absence of evidence, clinicians will prefer choosing a time-tested route (parenteral). Hence, we suggest completion of planned antibiotic course by parenteral route only.

***Practice Question 12*: Does administering prophylactic antibiotics for specific procedures or conditions like ventilation, exchange transfusion, prematurity etc. result in improved outcomes in neonates ?**

Population: Neonates with ventilation, exchange transfusion, prematurity
Intervention: Prophylactic antibiotics
Comparison: No prophylactic antibiotics
Setting: Neonatal Units

Summary of evidence

We found seven Cochrane reviews related to antibiotic prophylaxis in the neonatal population published in literature from 2000 to 2018. We updated the literature search until October 2021 for all these reviews but did not find any additional relevant studies for inclusion. We performed additional two systematic reviews for "low-risk preterm neonates" and "Transient Tachypnea of Newborn (TTNB)." Therefore, the evidence is based on nine reviews for different indications.

- *Antibiotic prophylaxis for neonates with a central venous catheter (CVC)* (50): Three RCTs (Cooke 1997; Harms 1995; Spafford 1994), comprising 271 neonates, were included in this review. The intervention comprised of daily administration of prophylactic antibiotics to neonates with CVCs (peripherally inserted central catheters or small-diameter silicone catheters), compared to no prophylaxis. The intervention had no effect on mortality (RR 0.68; 95% CI 0.31, 1.51), decreased the rate of proven bacterial sepsis (RR 0.38; 95% CI 0.18, 0.82) and the rate of suspected or proven bacterial septicemia (typical RR 0.40; 95% CI 0.20, 0.78). No resistant organisms colonizing infants were identified in any of the studies. (Very low certainty evidence)

- *Antibiotic prophylaxis at the time of CVC removal* (51): Only one RCT (Hemels 2011), comprising 88 neonates, was included in this review. The intervention was two doses of

cefazolin at CVC removal, compared to no antibiotics in the control group. The intervention did not affect mortality (not estimatable, no event in either group) or the rate of late-onset sepsis (RR 0.09; 95% CI 0.01 to 1.60). (Very low certainty evidence)

- *Antibiotic prophylaxis for neonates born through meconium-stained liquor* (MSL)(52): Four RCTs, comprising 695 neonates, were included in this review, of which, three studies (Basu 2007; Lin 2005; Shankar 1995) evaluated neonates with MAS while one (Goel 2015) assessed asymptomatic neonates born through meconium stained liquor (MSL) . The intervention was administration of prophylactic antibiotics for 3-7 days after birth, compared to no antibiotics. The intervention did not affect mortality (RR 1.69; 95% CI 0.23 to 12.53 in neonates with MAS and, RR 1.07; 95% CI 0.22 to 5.18 in asymptomatic MSL-born neonates) or the rate of sepsis in neonates with MAS (RR 1.54, 95% CI 0.27 to 8.96 or asymptomatic MSL-born neonates (RR 0.76, 95% CI 0.25 to 2.34). (low certainty evidence)

- *Vancomycin prophylaxis for preterm neonates on IV fluids* (53): Five RCTs (Baier 1998; Cooke 1997; Kacica 1994; Moller 1993; and Spafford 1994), comprising 371 preterm neonates, were included in this review. The intervention was continuous vancomycin infusion in three studies and intermittent daily doses in two studies, compared to no prophylaxis in the control group. The intervention was continued till the duration of intravenous (parenteral nutrition) therapy or a maximum of four weeks in most studies. The intervention had no effect on mortality (RR 0.79; 95% CI 0.40 to 1.58) (Low certainty), decreased the rate of sepsis (RR 0.11; 95% CI 0.05 to 0.24) and the rate of CONS sepsis (RR 0.33; 95% CI 0.19 to 0.59) (very low certainty of evidence).

- *Antibiotic prophylaxis for low-risk preterm neonates* (54): Two RCTs (Tagare 2010; Ruoss 2021), comprising 195 preterm neonates, were included in this review. The intervention was the administration of prophylactic antibiotics for 2 or 5 days after birth, compared to no antibiotics. The intervention did not affect mortality (RR 0.84; 95% CI 0.30 to 2.34) or the rate of culture-positive sepsis (RR 0.36; 95% CI 0.04 to 3.74). (Very low certainty evidence)

- *Antibiotic prophylaxis for transient tachypnea of the newborn* (TTNB)(55): There was only one eligible study (Dehdashtian 2018), comprising 130 newborns with TTNB, which evaluated the use of prophylactic ampicillin and gentamicin (until blood culture was reported sterile), compared to no antibiotics. Three newborns had CONS positive culture in intervention group while two newborns (but not treated) in control group (RR 0.66, 95% CI 0.11 to 4.06). Mortality was not reported, but the duration of hospital stay was significantly lower in the control group. (Very low certainty evidence)

- *Antibiotic prophylaxis for indwelling umbilical arterial catheter* (UAC)(56): Two quasi-randomized trials (Bard 1973; Cowett 1977), comprising 212 neonates, were included in this review. The intervention was daily administration of prophylactic antibiotics till the neonate required UAC, compared to no antibiotics. The review authors decided not to pool results due to the poor quality. We preferred to pool the results as the study characteristics were similar in these two trials. The intervention did not affect mortality (RR 1.31; 95% CI 0.62 to 2.75) or the rate of peripherally drawn blood culture positive neonates (RR 0.14; 95% CI 0.02 to 1.13). (Very low certainty evidence)

- *Antibiotic prophylaxis for procedural umbilical venous catheter* (UVC)(57): One quasi-randomized trial (Pulido 1985), comprising 29 neonates, was included in this review. Prophylactic antibiotics were given for 3 days after UVC insertion (for exchange transfusion

for jaundice or polycythemia). The intervention did not affect the risk of sepsis (no events in either group) or culture positivity (5/15 vs 5/14, all considered contaminants). (Very low certainty evidence)

- *Antibiotic prophylaxis for ventilated neonates* (56): One of the studies included in the Cochrane review (Lyon 1998) evaluated the effect of erythromycin on chronic lung disease rather than infection, hence was excluded for this review. One RCT (Harris 1976), comprising 54 neonates, was included in this review. There were 28% post-randomization exclusions, severely affecting the conclusions. The intervention did not reduce mortality (not estimatable, numbers not reported) but decreased the risk of systemic infections (RR 0.35; 95% CI 0.13 to 0.96). (Very low certainty evidence)

Summary of judgements

Balance of benefits and harm : With our current understanding of the multi-dimensional and life-long individual as well as societal adverse effects created by the use of antibiotics, prophylactic antibiotics have virtually no role in today's world. The trivial benefits seen in decades old studies with weak methodology stand no where in front of the proven harms. On the other hand, rigorous implementation of infection control practices is proven to decrease the rates of infections.

RECOMMENDATION

12. Systemic antibiotics should NOT be used for prevention of sepsis in neonates with indwelling central arterial/venous catheters, invasive ventilation, total parenteral nutrition, prematurity, or non-infectious morbidities (e.g., meconium aspiration syndrome).

Strong recommendation, Very low certainty evidence

Justification: It is worth noting that the positive impact of prophylactic antibiotics on sepsis reported for few indications (CVC, preterm neonates on parenteral nutrition, ventilation) was found in old trials conducted more than 20 years ago. Since then, our understanding and implementation of infection prevention and control has progressed substantially. Therefore, the relevance of these findings is debatable in the present era. Moreover, prophylactic antibiotics can increase the risk of late-onset sepsis with MDR and NEC. Therefore, we recommend against the routine use of prophylactic antibiotics in above clinical scenarios. Rather we suggest rigorous implementation of asepsis routines, aseptic non touch techniques, and hand hygiene to decrease nosocomial sepsis.

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Appendix 1 : Antimicrobial Stewardship in Neonates

What is Antimicrobial Stewardship?

As per a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS), antimicrobial stewardship is defined as "*A set of coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents, by promoting the selection of optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration to reduce or avoid their use*" (1,2). In simple terms antimicrobial stewardship (AMS) is the use of "the right antibiotic, for the right indication (right diagnosis), on the right patient, at the right time, with the right dose and route, causing the least harm to the patient and population" (3).

What do we need Antibiotic Stewardship Program?

Antimicrobial resistance (AMR) is a global health and development threat. It requires urgent multisectoral action to achieve the Sustainable Development Goals (SDGs). World Health Organization (WHO) has declared that AMR is one of the top 10 global public health threats facing humanity.

Global status

For common bacterial infections, including urinary tract infection (UTI), diarrhea, sepsis, very high antibiotic-resistant rates are reported. For example, the ciprofloxacin resistance rate varied from 8.4-92.9% for *Escherichia coli* and from 4.1-79.4% for *Klebsiella pneumoniae* in countries reporting to the Global Antimicrobial Resistance and Use Surveillance System (GLASS) (4,5). As of Apr 30, 2021, 109 countries or territories are enrolled in GLASS, comprising 107 in the GLASS-AMR module. India is also a part of this global network.

To maintain uniformity, the SDG monitoring framework included a new AMR indicator in 2019. This indicator monitors the frequency of bloodstream infections due to two specific drug-resistant pathogens: methicillin-resistant *Staphylococcus aureus (MRSA);* and *E. coli* resistant to third-generation cephalosporins. In 2019, 25 countries provided data to GLASS on bloodstream infections due to MRSA, and 49 countries provided data on bloodstream infections due to *E.coli*. In this database, the median rate of MRSA was 12.11% (6.4–26.4), and that for *E. coli* resistant to third-generation cephalosporins was 36% (15.2–63.0). Such high rates are problematic as there is no new drug in the pipeline in the near future.

According to the CDC report**,** more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result**.**

Economic Impact: Global

As per World Bank Report 2017, each year, 700,000 people die of AMR. Without action, the death toll could rise even higher, to as many as 10 million deaths annually by 2050, and cause a 3.8 percent reduction in the annual gross domestic product (GDP). Low-income countries would lose more with the loss exceeding 5% of GDP in 2050. The global increases in healthcare costs may range from US$300 billion to more than US$1 trillion per year by 2050.

AMR Status in India

Like other LMIC's, In India, the problem of AMR is many folds compared to high-income countries. Regional studies report high AMR among pathogens such as *Salmonella*, *Shigella*, *Pseudomonas, E.coli, Klebsiella*, and *Acinetobacter.* As per recent GLASS data, the meropenem resistance of Acinetobacter is about 35% (30-37%) (5). Though there are no formal estimates on the economic burden in India, it is likely to be many folds compared to high-income countries. Studies have shown that there is a significant relationship between MDR and mortality. Infections with MDR are associated with 2-3 times higher mortality (6).

AMR in Neonates

In 2016, the first estimate of neonatal deaths attributable to AMR was published (7). As per this report, MDR pathogens account for 30% of all global neonatal sepsis mortality. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) are responsible for an increasing number of outbreaks of healthcare-associated infection in NICUs and are associated with substantial morbidity and mortality. The rising prevalence of MDR Acinetobacter spp, even from a community setting, highlights the emergence of a dangerous situation (8). Moreover, MDR sepsis was found to be associated with higher mortality. The neonatal sepsis profile and AMR is also linked to maternal sepsis profile and healthcare-associated infections. Indiscriminate use of antibiotics in mothers is known to cause increased LONS in neonates and the emergence of MDR pathogens. Therefore interventions should also be directed to optimize both antenatal (to mother) and postnatal antimicrobial stewardship.

Antibiotics are frequently used both in inpatient and outpatient settings, with a significant proportion of antibiotic use considered unnecessary. In multiple studies, the misuse and overuse of antimicrobialswas associated with increased AMR risk, more severe disease, prolonged hospitalization, increased mortality, and increased healthcare costs (9).

How is antimicrobial stewardship in neonates different?

There are certain peculiar issues in the neonates that require due consideration before extrapolating strategies from pediatric and adult population.

a) ***Challenges in Diagnostic Stewardship:*** The signs and symptoms of neonatal sepsis are non-specific and closely mimic non-infectious etiologies like hypoglycemia, hypothermia, apnea of prematurity, polycythemia, and congenital heart disease. Many of these may not be diagnosed by clinical examination alone, more so at extremes of gestations. To add to the difficulty, the point of care tests like C-reactive protein, Procalcitonin, and complete blood counts physiologically vary widely in first few days of life and cannot be relied upon for the diagnosis of early onset sepsis. Due to low blood volume and other sampling issues, the blood culture yield in neonatal sepsis is can be low and it takes at least 24-48 hours to report. Therefore, empirical antimicrobial therapy based on signs and symptoms or even risk factors is a rule rather than exception in neonatology.

b) ***Challenges in Management:*** There are no evidence-based guidelines on the duration, and choice of antimicrobial use in neonates. In culture-negative sepsis (75-80% of all suspect sepsis), there is no consensus on the duration of therapy. Even for culture-proven sepsis and meningitis, the recommendations of administering antibiotics for 14 and 21 days respectively are not evidence-based. The neonatal dosages for antimicrobials are derived from older opulation. As the renal functions (Glomerular Filtration Rate and tubular excretion) in neonates vary according to gestation and postnatal age, there is need for individualized therapy.

Though there are challaneges, there are opportunities too. As neonates at risk are kept under close observation in a controlled environment, the monitoring and implementation of antimicrobial stewardship actions is relatively easy.

Evidence favoring AMS program implementation

Cochrane review has shown that antimicrobial stewardship practices effectively increase compliance with antibiotic policy and reduce the duration of antibiotic therapy (10). Also, it was found that lesser use of antibiotics probably does not increase mortality but can reduce the length of stay. A systematic review from the pediatric population observed some evidence of a reduction in antibiotic consumption, costs, and use of broad-spectrum antimicrobials following ASP implementation (11,12).

As AMS principles are the same across populations, the results are likely to apply to neonates too. Very few studies have been done on neonates per se. A recent systematic review on antimicrobial stewardship in premature neonates (11 observational studies and one randomized clinical trial) observed that antimicrobial stewardship helps in reduction in initiation of antibiotics in low-risk infants, reduction in total days of antibiotics, reduction in infants receiving prolonged antibiotics without increasing risk of sepsis or mortality (13). Considering the growing evidence in favor of ASPs, CDC, IDSA, SHEA, PIDS, and the American Academy of Pediatrics (AAP) endorsed the development and implementation of ASPs across pediatric health care settings.

What are the Core Elements of the Antibiotic Stewardship Program?

Centers for Disease Control and Prevention (CDC) recommended implementing an antibiotic stewardship program (ASP) in all acute care hospitals. They outlined seven core elements that are necessary for implementing successful ASPs (14). These include leadership commitment, accountability, pharmacy expertise, action, tracking, reporting and education. CDC also advocates using a checklist to systematically assess all the essential elements and actions to ensure AMS in hospitals. Responsibilities need to be assigned to staff to ensure that the principles and actions to improve antibiotic use remain in place.

What should be the composition of the antimicrobial stewardship team ?

Successful implementation and sustenance of the AMS program require a coordinated team effort. The team should involve all the stakeholders involved in the policymaking, prescription, and dispensing of antimicrobials, testing of antimicrobial resistance, monitoring of asepsis activities, and regulatory powers (14,15). The team members may include physicians, pharmacists, microbiologists, nurses, representatives of hospital administration, infection control committee, quality impovement and information technology committees.

What are the goals of the Antibiotic Stewardship Program?

The broad goal of any AMS program is to achieve the best patient outcomes and deliver the best quality by optimizing the antimicrobial use of care with existing resources; without increasing costs and secondary damage.

Primary Goal
To improve the quality of care and patient outcomes by optimizing the appropriate use of antibiotics.

Secondary Goals
To reduce the antibiotics induced collateral damage

a) Less toxicity
b) To limit the further emergence, selection, and spread of antimicrobial resistance

c) To prolong the lifespan of existing antimicrobials

To reduce the health care expenses while maintaining the quality of patient care

a) Monetary benefit due to reduced collateral damage
b) Low antimicrobial usage

How to Implement AMS Program in a facility?

Steps in Implementing AMS Programs :

Understanding the pathogen profile and Antimicrobial use

The most important and the first step in building an AMS program is to identify current institutional microorganism profile, their sensitivity pattern and antimicrobials used to treat them. All facilities must have a local antibiogram for past 1-2 years. This antibiogram should be used to formulate a written antibiotic policy at the facility. This antibiotic policy formulation must involve clinicians, microbiologist, clinical pharmacologist, pharmacy, and infection control team.

Assess the available resources

The resource will include healthcare providers interested in AMS, availability of electronic records, standard prescription formats (antibiotic forms) for patients, and dispatch forms for pharmacy.

Decide your priority areas and act

Once you have data on antibiotic resistance pattern and antimicrobial use of your institution, engage your resources to identify the priority areas and actions to be taken. Priority interventions should best address gaps in antibiotic prescribing and recommendations.

Actions and Interventions for AMS program

All interventions should align with the local needs and available facilities of an institution.

Basic interventions

- Creating awareness among the health care professionals about antimicrobial stewardship
- Establishing basic microbiology laboratory facilities
- Basic point of care tests to exclude sepsis e.g. CRP, blood counts
- Sending blood culture before starting antibiotics
- Use of antimicrobial prescription charts mentioning indication, dose, duration, and route of therapy (including when to review)
- Cross-checking the dose and duration of antibiotics prescribed
- Reviewing the antimicrobial order forms for the patients getting more than two broad-spectrum antibiotics
- Reviewing the surgical antibiotic prophylaxis if it is prescribed for more than 24 hours
- Following the standard facility-based treatment guidelines for common clinical conditions such as community-acquired pneumonia, urinary tract infections, and skin and soft tissue infections.
- Improving the supply chain and management of essential antimicrobials
- Establishing regular surveillance activities

Advanced Interventions

These interventions require more resources and are useful in multi-discplinary health care facilities. All interventions should be used in combination rather than in isolation to harness the maximum benefits.

Interventions to Improve antibiotic prescription

Persuasive Actions: These are aimed at altering the prescriber's behaviour. They rely on education, training, and feedback to the healthcare providers.

Education and Training : The healthcare providers can be educated about AMS using case-based scenario, didactic, and significant event analysis. The education should include need for AMS program, facility-specific sensitivity pattern and local guidelines for managing common infections. AMS education can be given as a part of continuing medical education. Educational strategies should include clinician, clinical pharmacologist, pharmacist, microbiologist, and nurses.

Prospective audit and Feedback : It involves a review of antimicrobial therapy by an expert in antibiotic use, accompanied by suggestions to optimize use, at some point after the antibiotics have been prescribed. Regular audit with face-to-face feedback to prescribers can be an important way to improve the prescribing practices. This feedback can be during routine ward rounds, patient handover meetings, or during scheduled antibiotic rounds. Feedback should be constructive and based on real data. It also comprises reviewing antibiotic therapy after a fixed time (e.g., 24-48 hours), de-escalation of therapy, dose optimization as per clinical diagnosis and organism, intravenous to oral switch as per clinical indication, and reviewing the total duration of therapy based upon the organism and clinical response.

Restrictive Actions: They comprise of various strategies that regulate the physician to follow a specific protocol to decide, start, and stop the antibiotic. These include :

Formulation of facility-specific antibiotic policy : Facility-specific policy can be an effective way to standardize prescribing practices among physicians. Each unit should have a written antibiotic policy for empiric treatment, including when to stop or upgrade antibiotics, what should be the duration of therapy if the microbiological results are negative.

Pre-authorization and Formulatory Restrictions: Pre-authorization means prescribers need approval prior to the use of certain antibiotics (mostly higher antibiotics or those with very high propensity to toxicity). The AMS team should decide restrictions (with consultation to clinicians) based on the prevalent microorganism profile, resistance pattern, antimicrobial spectrum and toxicities associated with the given antibiotic. Formulatory restriction for higher antibiotics can be useful in reducing the overuse of higher antibiotics and can help in reducing AMR. However, this approach is labour-intensive, time-consuming, affects the autonomy of physician, and may delay the initiation of treatment. Therefore, there must be ongoing monitoring for potential unintended consequences of preauthorization, especially treatment delays.

Antibiotic Time-outs : An antibiotic timeout is a provider-led reassessment of the continuing need and choice of antibiotics when the clinical picture is clearer and more diagnostic information, especially results of cultures and rapid diagnostics, are available. This is commonly followed in scenario where empirical antibiotics are started while awaiting culture results. In this strategy the treating team itself reviews at scheduled time-points (48-72 hours after starting) or daily to reassess the need for continuing antibiotics keeping the clinical condition and test results in mind. In intensive care units. daily reviews of antibiotic selection, until a definitive diagnosis is

made can optimize treatment. The clinicians should ask themselves whether the patient has infection? If yes, did I send appropriate cultures or investigations ? Can I stop or use narrow-spectrum antibiotics? What will be my empirical duration of treatment if culture results are negative?

Microbiology-based Interventions

The microbiology department plays a crucial role in AMS program and can have restrictive strategies in ensuring optimum and judicious antimicrobial use.

Selective reporting of antimicrobial susceptibility testing results: Selective reporting is the practice of reporting susceptibility results for a limited number of antibiotics (first line, narrow spectrum) instead of all tested antibiotics. For example, the microbiology will report the linezolid sensitivity to enterococcus only if it is resistant to ampicillin and vancomycin. Cascade reporting is a subtype of selective reporting in which susceptibility results of higher antibiotics (more costly or broader spectrum) are only reported if an organism is resistant to the primary antibiotic within the particular antibiotic class. Most of the laboratories follow the Clinical and Laboratory Standards Institute guidelines for testing and reporting susceptibilities, but this guidance is not exclusive and should be used in conjunction with local susceptibility pattern. This approach requires constant support from the laboratory and may not be feasible in resource constrained settings.

Using Stratified Antibiograms : As the microorganism profile and sensitivity pattern may vary across age-groups (neonates versus adults), units (surgical vs medical) within an institution; stratified antibiograms might be helpful in highlighting the differences. In clinical settings with adequate support and resources, this approach might be used.

Pharmacology-based Interventions

Switch from intravenous to oral antibiotic therapy: In hospitalized settings, initially the antibiotics are given by parenteral route and as the patient's condition improves, they are switched to oral route. In adults, IV to oral switch after initial 3-5 days of therapy is shown to reduce costs and length of hospital stay without increasing adverse effects. However, the evidence in neonatal population is lacking. Three large community based RCTs in young infants (0-59 days old) have shown that a short course of parenteral therapy (2 days) followed by oral therapy is as effective and safe as total parenteral therapy. However, there is no evidence about this strategy in hospitalized sick or preterm neonates and hence cannot be recommended.

Time sensitive automatic stop orders: This approach might be useful for conditions like surgical prophylaxis, community-acquired pneumonia, uncomplicated UTI, etc.

Dose adjustments and Dose-Optimization: We suggest using appropriate dose adjustments in organ dysfunctions (renal and hepatic dysfunction). In certain situation (infection with MDR pathogen, lack of clearance of organism despite standard dose, poor penetration of antibiotics) and with certain antibiotics (vancomycin, Amikacin) we suggest a case to case based discussion with pharmacology team to ensure dose optimization for a given individual.

Diagnostic stewardship

Diagnostic stewardship comprises of the use of clinical judgement and rapid diagnostic tests for risk stratification. In preterm neonates >35 weeks, careful serial examinations and/ or sepsis calculators (in selected situations as suggested in sepsis guidelines) can help in reducing antibiotic use.

Biomarkers: C-reactive protein and procalcitonin are the commonl used inflammatory markers in neonates. Unfortunately, neither of the index tests (CRP and PCT) are optimal as a screening test for LONS. However, they can be used to exclude sepsis in low-risk neonates. NNF Sepsis guideline conditionally recommends the use of serum CRP as a screening tool to rule out sepsis in neonates with a low risk of late-onset sepsis (for example, neonates with apnea, feed intolerance, or fast breathing) admitted to level-2 neonatal units with no facilities for blood culture. However, one should use gestation and age-appropriate cut-offs to interpret the results.

Rapid blood culture methods: Blood culture must be sent before starting antibiotics in all cases. Rapid blood culture methods have been associated with significantly faster identification of the organisms, shorter time to initiation of appropriate antibiotic therapy, and shorter time to escalation/de-escalation of antibiotic therapy. However, the effect on mortality, length of stay, and hospital costs has not consistent. The optimal implementation of rapid culture methods requires increased laboratory resources and additional costs. We suggest using rapid culture methods if resources are available.

How to Measure the Implementation Success of AMS Program?

AMS programs require regular assessment of process and outcome measures to reach the desired goals. The data is aimed to identify the problems as well as to evaluate the benefits of AMS interventions. It also has structural, process, and outcome measures (Table 1).

Table 1: Indicators for Monitoring the Impact of Antimicrobial Stewardship Program in Neonates

Indicators	Explanation
Structural Indicators	• Availability of a dedicated antibiotic stewardship team • Availability of written facility-specific policy for empirical treatment and surgical prophylaxis • Provision of antimicrobial stewardship education at regular intervals
Process Indicators	• Percentage of documented indication for antibiotic use • Compliance with empirical antibiotic guidance • Compliance with current guidelines for surgical prophylaxis • Percentage of 48-hour review • Percentage of appropriate de-escalation • Proportion of patients with change of antimicrobials based on the culture reports • Compliance with care bundles
Outcome Indicators	Related to antimicrobial use • Days of treatment (DOT) per 1000 patient days Related to Patient • In-hospital mortality rate • Readmission rates within 30 days of discharge • Surgical site infection rates • Proportion of patient with clinical failure • Treatment-related toxicity • Costs of treatment Microbiological Outcomes • Multidrug-resistant organism growth rates

The choice of measures and methods for measurement depends upon the available infrastructure, resources and manpower. Defined daily doses (DDDs) has very limited role in neonates as drug doses very greatly as per weight and gestation. Therefore, it is preferred to use days of therapy (DOT) in pediatric and neonatal population. DOT is an aggregate sum of days for which any amount of a specific antimicrobial agent is administered to a particular patient (numerator) divided by a standardized denominator (e.g., patient days, days present, or admissions). If a patient is receiving two antibiotics for 10 days, the DOT numerator would be 20. Many other measures of antibiotic consumption have been tested in neonates and may offer certain advantages, e.g. antibiotic spectrum index.

Tracking: If a hospital has an electronic health system integrated at all levels continuous measurement of process and outcome measures is most desirable. However, in facilities with manual records periodic assessments of the use of antibiotics in the form of point prevalence surveys (PPS) can be used.

Quality Improvement approach in Implementing AMS program in a facility : Evidence from adult and neonatal population suggests that QI approach is effective in successful implementation of ASP in a facility. We suggest using QI approach in each facility using a structured framework based on standard principles.

Antimicrobial Stewardship in Outpatient Setting

Unlike older age, antimicrobial use in the outpatient setting is very limited in neonates. However, the situation in the outpatient setting is quite different from the inpatient setting. Access to rapid diagnostic tests, pre-authorization, prospective audit, and feedback may not be practical in the ambulatory setting. There is a need for different approaches in the outpatient setting.

Clinical circumstances: The common clinical conditions in which antibiotics are prescribed in neonates in outpatient are upper respiratory tract infection, acute gastroenteritis, bronchiolitis, conjunctivitis, Antenatal hydronephrosis, and urinary tract infection.

Prescription stewardship : As most of the clinical conditions mentioned above are non-bacterial, the primary goal should be to avoid antibiotic prescription unless the neonate is sick or has grown some organism. Clear, detailed communication between physicians and parents is crucial in viral illness and can help avoid over-the-counter antibiotic use. Furthermore, educating parents about the natural course of viral and bacterial infections can foster an understanding of expectations and shorten antibiotic exposure. If the clinician has started empiric antibiotics while awaiting test results, the caregivers must be advised to stop the antibiotics if the results are negative. Even if required, the choice, dose, and duration of therapy should be according to standard guidelines.

Diagnosis Stewardship : Availability of rapid diagnostic tests like CRP, CBC, PCT, urine dipsticks can be helpful in the ambulatory setting and might help reduce antibiotic prescriptions.

Antibiotic choice and duration : The clinicians should choose narrow-spectrum antibiotics as per the previous culture-sensitivity pattern of the local health system or community setting (as applicable). The duration of therapy should be as per the guidelines for common diseases (mostly 3-5 days). Intravenous antibiotics should be used only if the oral antibiotics are less effective or the patient cannot take oral medications.

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