Nepal Paediatric Society Guideline for use of Antibiotics in Critically ill Children in the Pediatric Intensive Care Unit

Dhruba Shrestha[1], Puja Amatya[2], Arun Sharma[3], Shrijana Shrestha[4], Yograj Sharma[5], Santosh Pathak[6], Prakash Jyoti Pokhrel[7], Nipun Shrestha[1], Santosh Pokhrel[8], Srijana Dongol[9], Ganendra Bhakta Raya[1], Amrit Ghimire[10], Janak Koirala[11] and Sangita Basnet[12]

[1]Departmen of Paediatrics, Siddhi Memorial Hospital (for Women and Children), Bhaktapur, Nepal

[2]Department of Paediatrics, Patan Academy of Health Sciences, Lalitpur, Nepal

[3]Department of Paediatrics, Tribhuvan University Teaching Hospital and Secretary of NEPAS, Kathmandu, Nepal

[4]Department of Paediatrics and Dean of PAHS, Patan Academy of Health Sciences (PAHS), Lalitpur, Nepal

[5]Department of Paediatrics, Bharatpur Hospital, Chitwan, Nepal

[6]Department of Paediatrics, Chitwan Medical College, Chitwan, Nepal

[7]Department of Paediatrics, Civil Service Hospital, Kathmandu, Nepal

[8]Department of Paediatrics, Siddhartha Children and women Hospital, AMDA, Butwal, Nepal

[9]Department of Paediatrics, Kathmandu University, Dhulikhel Hospital, Nepal

[10]Department of Paediatrics, Grande International Hospital, Kathmandu, Nepal

[11]Department of Internal Medicine, Southern Illinois University School of Medicine, Consultant Nepal Health Research Council, Nepal

[12]Department of Paediatrics, SIU School of Medicine, USA

Correspondence:
Dhruba Shrestha
Siddhi Memorial Hospital (forWomen and Children)
Bhimsenthan-7, Bhaktapur, Nepal.
Mobile:9779851128629
Email: drdhrubashr@hotmail.com

Collaborators: Members of Nepal Paediatric Critical Care Network Working Group (NPCCWG) including Sangita Puri, Raju Kafle, Arun Giri, Yograj Sharma, Om Krishna Pathak, Asim Shrestha, Arun Neopane, Basant Rai, Jamun Singh, Nirajana Kayastha, Anita Lamichhane, Piyush Kanodia, Ruby Thakur, Sandeep Singh, Biraj Parajuli, Pawana Kayastha, Prakash Joshi, Sumit Agrawal, Henish Shakya, Vidhata KC, Kalpana Subedi, Shova Shrestha, Akhil Tamrakar, Anya Sharma, Prithuja Poudel, Amrit Dhungel

Acknowledgements: The authors are grateful to late Dr. Neelam Adhikari, who was a pioneer in establishing paediatric critical care delivery in Nepal. She participated in all Nepal Paediatric Critical Care Network Working Group (NPCCWG) meetings. Her dedication and encouragement were vital to this group. We thank Dr. Ezzeldin Saleh MD, Assistant Professor of Paediatrics, Division on Infectious Diseases, Southern Illinois University School of Medicine, Springfield, Illinois, USA, for his valuable input.

Funding: Nil
Conflict of Interest: None declared
DOI: 10.3126/jnps.v41i3.35051

To cite this article: Shrestha D, Amatya P, Sharma A, Shrestha S, Sharma Y, Pathak S, et al. Nepal Paediatric Society Clinical Nepal Paediatric Society Guideline for use of Antibiotics in Critically ill Children in the Pediatric Intensive Care Unit. J Nepal Paediatr Soc. 2021;41(3):307-14.

ABSTRACT

Justification: Overuse and administration of unnecessary and inappropriate antibiotics are the leading causes for the increased antimicrobial resistance worldwide. Judicious use of antimicrobials can prevent this phenomenon.

Objective: Create a collaborative outline for the use of antibiotics in the paediatric intensive care unit for various infections, based on evidence, taking into consideration local antimicrobial susceptibility patterns.

Process / Methods: Under the aegis of Nepal Paediatric Society, this guideline has been developed after several meetings of paediatricians working in various hospitals in different parts of Nepal, looking into the prevalent diseases and local sensitivity patterns of antibiotics.

Recommendations: This guideline will help standardize the treatment protocol in paediatric intensive care units in Nepal and help paediatricians decide the appropriate use of antibiotics promptly while managing critically ill children.

Keywords: Antibiotics; antibiotic sensitivity; antimicrobial resistance; critically ill child; Paediatric Intensive Care Unit

INTRODUCTION

Sepsis is the most common cause for admission in paediatric intensive care units (PICU) and antibiotic prescriptions worldwide.[1-3] Critically ill children require prompt antibiotic therapy. It is advised to start broad spectrum antibiotics empirically taking into consideration common infective organisms and local susceptibility patterns, and subsequently tailor them as specific organisms are identified.[4-7]

Antimicrobial resistance has been increasing rapidly. Inappropriate and expansive use of antimicrobials in our day-to-day practice has been linked to this rapid increase.[8] Judicious use of antimicrobials can prevent development of antimicrobial resistance.[4] Appropriate antibiotics use, in appropriate dosing and duration, is of utmost importance in order to achieve maximum benefit. Antibiotics should be prescribed taking into consideration common organisms prevalent in the area. Every attempt must be made to isolate causative organism, test for antibiotic susceptibility and administer antibiotics effective against those particular organisms for recommended durations. This will not only prevent development of resistance to the organism but also improve patient outcome and help cut down the cost of treatment in an efficient manner. Prompt treatment with effective antibiotics should be started in order to save critically ill children and prevent further deterioration.

This guideline is developed looking into prevalent diseases and local sensitivity patterns of antibiotics in Nepal. It could decrease variability in the PICUs in Nepal, assisting paediatricians to decide selection and use of antibiotics while managing the critically ill child.

PURPOSE

The primary objective is to develop a consensus guideline involving paediatricians working in PICUs in various part of Nepal that would:

1. Standardise antibiotic prescription in PICUs in Nepal.
2. Reduce inappropriate use of antibiotics in critically ill children

This guideline is mainly for management in the PICU and high dependency unit (HDU). However, it is targeted towards all physicians and healthcare workers managing children in inpatient, emergency, urgent care settings all over Nepal. In facilities that lack PICUs or HDUs, this document should guide appropriate antibiotic administration prior to transport to a higher level of care.

METHOD

Nepal Paediatric Society (NEPAS) is an umbrella organization of all paediatricians working in Nepal. NEPAS not only works for the welfare of paediatricians, it is actively involved in the betterment of child health in Nepal. Under the aegis of NEPAS, paediatricians working in PICUs from different parts of Nepal gathered and formed a critical care working group. The objective of this Nepal Paediatric Critical Care Working Group (NPCCWG) was to develop guidelines essential for the management of common conditions in critically ill children in Nepal. One of the major issues identified was use of antibiotics in PICUs. After extensive discussions, expert opinions and literature reviews,[9] an initial draft was prepared. Experts working in infectious diseases, paediatric intensive care and microbiology were involved in preparing this document. Due consideration was given to local antimicrobial sensitivity patterns of common organisms prevalent in various institutions.

Second revision was done at a meeting of the NPCCWG, after a year of initial preparation. Finally, at the third meeting of the NPCWG, the protocol was discussed in detail and the final collaborative protocol was finalized for publication and dissemination.

Steps in appropriate administration of antibiotics[8, 10] (Table 1 and Appendix)

Table 1 Outlines the procedure used to create this guideline. Making a clinical diagnosis is the first step, where attempt needs to be made to confirm true or suspected infection and the source of the infection. Choice of antibiotic is the next step. Initially broad-spectrum empiric antibiotics may be prescribed; these are ultimately narrowed or replaced by specific antibiotics once the culture and sensitivity results become available. In addition to de-escalation / modification, the duration of antibiotics needs to be decided. The type and number of antibiotics and duration of treatment do not need to be longer than required according to type and site of infection and infecting organism. Monitoring conditions that may affect the delivery and excretion of antibiotics, and the adverse effects and efficacy of the antibiotics is of utmost importance.

CONCLUSIONS

This guideline is a consensus document created by the NPCCWG after discussions at several meetings, and is based on international recommendations as well as local antimicrobial susceptibility patterns and resources. It is recommended that this guideline be referred to when antibiotics are considered in critical care facilities in Nepal. Guideline may need to be updated as new evidence and data are produced. Judicious and appropriate use of antibiotics can mitigate and even prevent antimicrobial resistance. Additionally, if antibiotics are used only when necessary, unwanted adverse effects can be minimized leading to increased patient safety and decreased morbidity.The outcome and challenges of implementation of the guideline will be analyzed after dissemination and implementation.

Table 1. Steps in appropriate administration of antibiotics (See Appendix for further information)

1. What is the diagnosis?

1. If it is an infection:
   A. What type of infection?
   B. What are the common causative organisms?
2. Consider possible non-infectious causes.
3. Make sure cultures are taken according to the type of infection to reach an ultimate final diagnosis.

2. Only critically ill children, and those with signs of probable infection should receive empiric antibiotics

1. Those admitted to PICU with septic shock, meningitis, necrotizing fasciitis, Xray confirmed and / or severe pneumonia, febrile neutropenia particularly with malignancy. (Note: start antibiotics within one hour in patients with septic shock and within three hours in patients with sepsis associated organ dysfunction without shock).[10]
2. Non-critical patients or those not in shock can wait a few hours to receive antibiotics until further confirmation from laboratory results or other signs or symptoms are received.

3. Choice of antibiotics

1. Choose antibiotics according to the most common organisms for the identified source and site of infection
2. Know your institution's local susceptibility / resistance patterns
3. Decide on the appropriate dose and duration
4. Decide on the best route of administration

4. De-escalation and modification (Refer to Appendix for appropriate antibiotics)

1. Make every effort to identify organism
2. Once organism is isolated, change / narrow antibiotics and dose according to the isolated organism
3. Consider your institution's antimicrobial susceptibility patterns
4. If appropriate, change parenteral to oral antibiotics, when patient is able to take it orally
5. Monitor the status of your patient - if improved, you may be able to discontinue antibiotics altogether

6: Some clinical conditions do not require antibiotic therapy

1. Viral pharyngitis, viral rhinosinusitis, viral bronchitis
2. Asymptomatic bacteriuria and pyuria
3. Culture reports with suspected contamination and colonization

7: Optimize duration of therapy (Refer to Appendix for suggested durations)

1. Follow standard national and international guidelines to determine the optimum and minimum duration of therapy
2. Document planned duration of therapy to prevent discrepancy among providers and continuity of care
3. Do not keep continuing antibiotics just to feel safe - base it on the patient status. Prolonged use of antibiotics can be more harmful to the patient.

8: Monitor for conditions that may affect the choice and dose of antibiotics

1. Compromised renal or liver function which may decrease excretion of antibiotics
2. Other drugs that may interact with the antibiotics
3. Adverse effects of antibiotics
   A. For example: Vancomycin levels to prevent nephrotoxicity
   B. If levels not available then monitor creatinine levels when using nephrotoxic drugs
   C. If antibiotic not showing effect discontinue it.

APPENDIX: CLINICAL GUIDELINE

Antibiotic protocol for PICU patients with sepsis

1. Establish sepsis: Clinical diagnosis of sepsis

1. Suspected infection manifested by hypothermia (< 96˚F) or hyperthermia (100.4˚F) **AND**
2. Clinical signs of inadequate tissue perfusion including any of the following:
   A. Decreased or altered mental status
   B. Prolonged capillary refill greater than two seconds
   C. Diminished pulses, mottled cool extremities
   D. Flash capillary refill, bounding peripheral pulses and wide pulse pressure
   E. Decreased urine output less than 1 ml / kg / hour

2. Diagnostic work up

1. Blood culture
   A. Minimum 2 - 5 ml for older children,1 ml for neonates (Blood broth ratio 1:5 to 1:10)
   B. Preferably obtain blood cultures before starting antibiotic
   C. See blood cultures drawing technique in the box
   D. Repeat blood cultures before starting and escalation of antibiotic
   E. Blood cultures should be done preferably using BACTEC (or other automated system).
2. Urine for urinalysis and culture
3. Chest X-ray
4. Other tests based on patient presentation and clinical suspicion, e.g. Meningitis - CSF analysis and culture, Scrub Typhus serology, Dengue (NS1 antigen test and serology), malaria (optimal test and PS for MP)

Blood culture drawing technique
- Apply a tourniquet
- Palpate for vein before disinfection
- Clean site for 15 seconds with chlorhexidine OR 70% alcohol followed by 2% tincture of iodine
- The disinfectant should be allowed to dry before blood is drawn
- If further palpation of the vein is necessary after skin preparation, wear sterile gloves
- Disinfect the bottle cap before piercing

5. ET secretion culture if intubated, central line culture if central line catheter is used*.
6. Mention antibiotics being used while sending culture. Sensitivity should be organism specific.
7. CSF analysis / culture is mandatory for less than two month child unless contraindicated.
8. Send nasopharyngeal swab for influenza and SARS-CoV-2, if suspicion or during epidemic.

*ET culture may lack diagnostic specificity and clinical correlation is required to distinguish between colonization and true infection

3. Initial empiric antibiotic therapy

1. Initiate antibiotics as soon as possible, ideally within one hour if shock present and after collecting culture samples.
2. Change antibiotics to pathogen specific agents when culture results become available
3. Antibiotics should be changed if patient continues to deteriorate or does not show response to treatment in 48 - 72 hours after initiation of antibiotic therapy.
4. Response to therapy should be evaluated by
   A. Clinical assessment
   B. Indicators such as blood pressure, temperature and WBCs.
   C. Quantitative CRP. (Qualitative CRP has no clinical value).
5. Duration of treatment should be determined based on final diagnosis. Unnecessary antibiotics should be discontinued when infectious agent is identified by culture or other methods.

Following antibiotic recommendations are based on currently available local microbiological data and collective experience in paediatric intensive care units of Nepal

These recommendations should be used only as guidelines and adapted based on local prevalence of pathogens, microbiologic data and resistance pattern

Specific conditions and antibiotic:

A. Under two months of age group:

Common pathogens: *E coli, Listeria Monocytogenes*, Streptococci (Group B streptococcus), *Klebsiella spp*, Staphylococci

Recommended antibiotics-

First line agents:

- Ampicillin plus Aminoglycoside (Gentamicin / Amikacin) OR
- Cloxacillin plus Aminoglycoside (Gentamicin / Amikacin)

Note: Cloxacillin should be used if MSSA is suspected

Second line agents:

- Cefotaxime plus aminoglycoside (Amikacin or Gentamicin) OR
- Cefotaxime plus fluoroquinolone* (Ciprofloxacin or Ofloxacin)

Note: Add vancomycin if MRSA is suspected

Add Ampicillin if group B streptococcus or Listeria is suspected

Fluoroquinolones should be used only in absence of any other alternatives

Third line agents: MDR organisms and nosocomial infections: *Acinetobacter spp*, *Klebsiella spp*, MRSA

- Meropenem + vancomycin **OR**
- Chloramphenicol + Vancomycin

Note: Keep Colistin and Piperacillin-tazobactam as reserve drug

Add Clindamycin for suspected toxic shock syndrome

Duration of antibiotics: should be decided based on causative organisms, severity of disease and treating physician's decision.

- Suspected sepsis and ruled out: 72 hours and stop if blood culture is sterile
- Probable sepsis (culture negative sepsis): 7 days
- Culture proven sepsis: Gm negative sepsis: 14 days
- Gm positive sepsis: 10 - 14 days (for Staph aureus 14 days at least)
- Neonatal meningitis: Penicillin and cephalosporin for three weeks and aminoglycoside for two weeks

This duration may be longer if there is persistence of bacteremia or symptoms

B. Two months or older age group:

1. Undifferentiated sepsis (sepsis of unknown origin)

Common pathogens: *Staphylococcus aureus, Strep pneumoniae, E coli, Klebsiella spps, S enterica, Scrub typhus*

Recommended antibiotics:

First line agents:

- Ceftriaxone + Cloxacillin OR
- Ceftriaxone + Vancomycin

Note:

- Use Cloxacillin if MSSA suspected or Vancomycin if MRSA suspected
- Use chloramphenicol / Doxycycline instead of cloxacillin if scrub typhus is suspected and Azithromycin can be used in place of chloramphenicol if it is contraindicated.
- Vancomycin as the first line antibiotic should be used in tertiary level PICU or where MRSA prevalence is high

Second line agents:

- Piperacillin-Tazobactum / Chloramphenicol + Vancomycin OR
- Piperacillin-Tazobactum / Chloramphenicol + Aminoglycosides OR
- Piperacillin-Tazobactum / Chloramphenicol + Fluroquinolones*

Note: Use azithromycin if Chloramphenicol cannot be administer

* Fluoroquinolones should be used only in the absence of any other alternatives

Third line agents: MDR organisms and nosocomial infections: *Acinetobacter spp, Klebsiella spp*, MRS0

- Meropenem + Vancomycin / Linezolid / Teicoplanin

Note:

- Keep Tigecycline and Colistin as reserve drugs
- Add Vancomycin if MRSA is suspected
- Consider antimalarials in malaria endemic regions
- Consider Linezolid / Teicoplanin if renal function is deranged
- Renal function should be monitored closely if Vancomycin is used
- Add Clindamycin for suspected toxic shock syndrome

Duration of antibiotics:

- Sepsis of unknown origin: 10-14 days based on suspected causative organism and / or severity of disease.

2. Sepsis of respiratory tract origin

Common pathogens: *Streptococcus pneumoniae, Staphylococcus aureus*, Atypical pathogens, Viruses (Influenza, SARS-CoV-2)

Recommended antibiotics:

First line agents:

- Ceftriaxone + Azithromycin +/- Cloxacillin or Vancomyci

Note:

- Add Cloxacillin or Vancomycin in severely ill patients
- Use Cloxacillin if MSSA or Vancomycin if MRSA suspected
- Vancomycin as a first line agents should be started in tertiary PICU
- Monitor renal function test frequently if Vancomycin is used

Second line agents:

- Piperacillin-Tazobactum / Chloramphenicol +/- Cloxacillin OR Vancomycin **OR**
- Piperacillin-Tazobactum / Flouroquinolones +/- Cloxacillin OR Vancomycin

Third line agents: MDR organisms and nosocomial infections: *Acinetobacter spp, Klebsiella spp*, MRSA

- Meropenem + Vancomycin/Linezulid

Note:

- Avoid using combinations of Vancomycin with Aminoglycosides or Colistin
- Add Chloramphenicol or Levofloxacin* or Azithromycin if atypical organism suspected
- Add Oseltamivir if influenza test (including H1 N1) is positive
- Consider Remdesivir if SARS-CoV-2 test positive

Duration of antibiotics:

- *Streptococcus pneumonia*: 7 - 10 days
- *H. influenzae*: 7 - 10 days
- *Staphylococcus aureus*: 2 weeks (longer course ~ 21-28 days for lung abscess / necrotizing pneumonia)

3. Meningitis / CNS infection

Common pathogens: *Streptococcus pneumoniae, N meningitidis, H. influenzae*

First line agents:

- Ceftriaxone (add Chloramphenicol or Azithromycin if scrub typhus is suspected)

Second line agents:

- Ceftriaxone / Chloramphenicol +/- Vancomycin

Note:

- Use Vancomycin if MRSA is suspected such as children with head trauma or who are post-operative for CNS
- Use IV doxycycline for scrub typhus if chloramphenicol cannot be used due to allergy, neutropenia (< 1000 ANC) in children under eight yrs (safe for < 21days)
- If MDR pathogens suspected use Meropenem + Vancomycin
- Drugs should be used in meningitis doses

Duration of antibiotics:

- Uncomplicated penicillin-sensitive *S. pneumonia*: 10-14 days
- Uncomplicated *N. meningitides*: 5-7 days
- Uncomplicated *H. Influenzae* type b: 7-10 days

- No identifiable pathogen but does have evidence of acute bacterial meningitis: 7-10 days

4. Sepsis of Urinary Tract origin

Common pathogens: *E coli*

First line agents:

- Ceftriaxone **OR**
- Aminoglycosides **OR**
- Fluoroquinolone*

Note:

- *Fluoroquinolones should be used only in the absence of any other alternatives
- If MDR suspected- use Meropenem +/- Colistin

Duration of antibiotic:

- Culture negative UTI without fever in immune-competent children: 5-7 days
- Culture negative UTI with fever: 7-10 days
- Culture positive UTI: 10-14 days based on causative organism
- UTI suggesting clinical pyelonephritis: 10-14 days (10 days for pyelonephritis and 14 days for urosepsis (associated with bacteremia)

Adapted from UptoDate[11]

NOTES:
• MRSA infection may be suspected if there is:
Invasive devices at the time of onset of infection
History of previous MRSA infection
History of surgery, hospitalization or dialysis
•Risk factors for Fungal infections include:
Malignancy
Age < 1 month
Recent abdominal surgery
Presence of CVC particularly if TPN administered
Prolonged use of broad-spectrum antibiotics and patient condition do not resolve or get worse.
Mucosal candidal colonization
Renal failure
•Anaerobic coverage should be added in conditions such as abdominal surgeries and necrotizing enterocolitis: Metronidazole / Clindamycin

REFERENCES

1. Carcillo JA, Han YY, Kissoon N. Sepsis guidelines and the global pediatric sepsis initiative: implications for treatment. Therapy. 2008;5:391-4.10.2217/14750708.5.4.391
2. Mathias B, Mira JC, Larson SD. Pediatric sepsis. Curr Opin Pediatr. 2016;28:380-7. https://doi.org/10.1097/mop.0000000000000337
3. Randolph AG, McCulloh RJ. Pediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children, and adolescents. Virulence. 2014;5:179-89. http://dx.doi.org/10.4161/viru.27045
4. Croche SB, Campos AE, Sánchez CA, Marcos FL, Diaz FI, Vargas JC, et al. Appropriateness of antibiotic prescribing in paediatric patients in a hospital emergency department. Anales de Pediatría (English Edition). 2018;88:259-65.
5. Canadian Pedaitric Society. Prophylactic antibiotics in children. Paediatr Child Health. 1999;4:490-4. https://doi.org/10.1093/pch/4.7.490
6. Bradley JS, Nelson JD.editors. Nelson's Pediatric Antimicrobial Therapy. 25th ed. Itasca (IL): American Academy of Pediatrics; 2019
7. Summary of antimicrobial prescribing guidance – managing common infections. National Institute for Health and Care Excellence(NICE): 2020. [cited 2021 January 19]
8. Gangakhedkar RR, Walia K, Aggarwal S, Madhumathi J, Vijay S. Treatment Guidelines for Antimicrobial Use in Common Syndromes.2nd Edition. Indian Council of Medical research; 2019. [cited 2021 January 19]
9. Fuchs A, Bielicki J, Mathur S, Sharland M, Van Den Ankera JN. Antibiotic use for sepsis in neonates and children: 2016 Evidence Update. WHO Reviews. [cited 2020 November 2020]
10. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med. 2020;21:e52-e106. https://doi.org/10.1097/pcc.0000000000002198
11. Kaplan SL. Staphylococcus aureus in Children: Overview of treatment of Invasive infections. In: UpToDate, Edwards MS (Ed), UpToDate, Waltham, MA [cited 2021, January 16