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

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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 critically ill children.

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, 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)
   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

Third line agents: MDR organisms and nosocomial infections: *Acinetobacter spp*, *Klebsiella spp*, MRSA
- Meropenem + vancomycin OR
- Chloramphenicol + Vancomycin

Note:
- Use Cloxacillin if MSSA suspected or Vancomycin if MRSA suspected
- Use chloramphenicol / Doxycycline instead of cloxacillin if scrub typhus is suspected
- Use azithromycin if Cloxacillin cannot be administer

Third line agents: MRSA prevalence is high
- Meropenem + Vancomycin / Linezolid / Teicoplanin

B. Two months or older age group:

1. Undifferentiated sepsis (sepsis of unknown origin)

Common pathogens: *Staphylococcus aureus*, *Strep pneumoniae*, *E coli*, *Klebsiella spp*, *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
- 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*, MRSA
- Meropenem + Vancomycin / Linezolid / Teicoplanin

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
Note:
• Keep Tigecycline and Colistin as reserve drugs
• Add Vancomycin if MRSA is suspected
• Consider antimarials 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 Vancomycin
  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 / Fluoroquinolones +/- 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
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