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TOPIC OF INTEREST - "ANTIMICROBIALS - II"

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ANTIMICROBIALS - II

ESSENTIALS OF BLOOD CULTURE AND MINIMAL INHIBITORY CONCENTRATION

*Akshith Thimmaiah
**Impana BD

Abstract: *Blood culture is one of the most important tools in the diagnosis of sepsis. Whenever there is a clinical suspicion, it is pertinent to collect the sample aseptically at the right time and in appropriate volumes. In the past decade there has been a major improvement in the interpretation of antibiotic susceptibility of blood culture positive reports in terms of minimal inhibitory concentration, which is the in vitro levels of susceptibility or resistance of bacterial strains to specific antibiotic. Reliable assessment of minimal inhibitory concentration has a significant impact on the choice of a therapeutic strategy and efficacy of the antimicrobialtherapy. Standard procedures for the diagnosis of blood stream infection in pediatric population and the interpretation of antibiotic susceptibility pattern through minimal inhibitory concentration are reviewed.*

Keywords: *Pediatric bloodstream infection, Break point, Contamination, Minimal inhibitory concentration, Antibiotic.*

Severe sepsis is a major health problem in children.[1,2] SPROUT study, a point prevalence study spread across 26 countries, demonstrated 8.2% severe sepsis in children <18 years, admitted in pediatric intensive care units and this did not differ by age.[2] The most common primary site of infection is respiratory followed by blood stream.[1,2] In pediatric population Gram negative organisms predominated followed by Gram positives and fungi.[3] Blood cultures remain the mainstay of laboratory diagnosis of blood stream infections (BSIs) in infants and children, as it confirms the diagnosis of bacteremia and allows for identification and susceptibility testing on the organism to optimize antimicrobial therapy.[4] Continuous improvement

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of the whole BSI diagnostic process, based on sampling quality and time to result, should be a priority to improve patient outcome and avoid unnecessary antibiotic treatment.[5]

Sample collection

The impact of proper specimen management on patient care is enormous. It is the key to accurate laboratory diagnosis and confirmation, directly affects patient care / outcomes and influences therapeutic decisions. It impacts hospital infection control, patient length of stay, hospital and laboratory costs, influences antibiotic stewardship and drives laboratory efficiency.[6]

Timing

Although it has been common practice to obtain blood specimens for cultures at arbitrary 30-to-60-minute intervals, published studies show no difference in microbial recovery when blood specimens are drawn for culture simultaneously or at spaced intervals for up to 24 hours.[6,7] The timing of blood culture should be dictated by the clinical status. In urgent situations, 2 or more blood culture sets can be obtained sequentially over a short time interval, after which empiric therapy can be initiated.[6]

Sample volume and blood culture set

It is well accepted that the volume of blood collected is the single most valuable factor.[4] Though there are limited number of studies published about the ideal volume required in pediatric population, Bouza, et al in a multivariate analysis showed higher blood volumes were associated with positive blood culture sets independently of other variables studied. The increase in the detection rate of BSI was 3.3% for each extra millilitre of blood cultured.[8] Kellogg, et al found that the frequency of low level bacteremia in pediatric population is higher than that in other similar studies and found that the detection can be optimized by culturing up to 4 or 4.5% of a patient's total blood volume.[9] The recommended volume of blood for culture from infants and children as per Infectious Diseases Society of America (IDSA, 2018) (Table I). However, it should be noted that for initial evaluation of neonatal sepsis two site blood culture did not have a better yield in

Table I. Recommended volume of blood for culture from infants and children (IDSA, 2018)[6]

Weight of Patient, kg	Total Patient Blood Volume, mL	Recommended Volume of Blood for Culture, mL		Total volume for culture, mL	% of Total blood volume
		Culture set No. 1	Culture set No. 2		
<1	50-99	2		2	4
1.1-2	100-200	2	2	4	4
2.1-12.7	>200	4	2	6	3
12.8-36.3	>800	10	10	20	2.5
>36.3	>2200	20-30	20-30	40-60	1.8-2.7

pathogen detection. Sepsis in neonates can be detected with no loss of accuracy with a single site blood culture with blood volume of ≥1 mL.[10] For neonates and adolescents, an age and weight appropriate volume appropriate volume of blood can be cultured as proposed by IDSA. Only one set is recommended for children weighing <1 kg and an additional set is recommended in patients weighing >1 kg.[4]

Though weight based guidelines are simple on paper they are complicated to carry out in practice. In critically ill patients, collection of an adequate amount of blood, even when based on the patient weight, is often not feasible.[4] Ideal bottle inoculum should be based on clinical judgement and risk factors, drawing large volumes of blood should not unnecessarily increases the proportion of false-positive results and contributes to iatrogenic anemia without improving the rate of detection of BSI.[8]

Blood culture bottles

Pediatric blood culture bottles were developed to support the specific needs of pediatric patients, because of the small sample volume and for detection of fastidious organisms.[4] The reduced amount of broth optimizes the blood to broth ratio and improves the time to detection for culture of small blood volumes. The common practice is to have a blood broth ratio of 1:5 to 1:10 to optimize the growth of organism. However, a study found that common pediatric pathogens could be recovered without delay from volume of blood as small as 0.5 ml cultured at blood broth ratio 5 up to 1:100.[11] Of commonly used aerobic bottles, BD BactecPeds Plus/F Medium (Becton Dickin-son, Franklin Lakes, NJ, USA) and BacT/Alert PF (bioMeìrieux, Marcy I'Etoile, France) recommend a minimum of 0.5 ml of blood, while the VersaTREK Redox (Oakwood Village, OH, USA) claims it can detect bacteremia with as little as 0.1 ml of blood. Pediatric bottles also contain a different broth formulation to support the growth of fastidious pathogens in pediatric age group, such as *S. pneumoniae*, *H. influenzae* and *Neisseria meningitidis*, which are rarely detected from blood cultures these days due to widespread vaccination.[4]

Time to positivity

Time to positivity (TTP) was defined as the time interval between placement of the blood culture bottle into the automated system and detection of a positive signal.[12] A prospective study analysing time to positivity in children 0-16 years of age using automated blood culture system showed that blood cultures were positive within 36h of incubation in 90% of children with sepsis.[12] TTP was found to be <24 h in both children and adult population with sepsis.[8,11,12] Despite low probabilities a blood culture may incidentally become positive after more than 24 hours.[10] TTP should prompt re-evaluation of clinical stability, response to empirical therapy and consider alternate differential diagnosis.[12,13] The search for alternative causes of fever can be initiated more rapidly if the probability of bacteremia is incorporated in clinical reasoning. This may lead to better timed de-escalation, IV to oral switch and earlier hospital discharge.[13]

Blood culture contamination rate

Multiple blood culture sets can help to differentiate a 'true' pathogen from a 'contaminant'. Though optimal number of blood cultures to be drawn varies, a single blood culture clearly is inadequate. It has been demonstrated that positive blood cultures caused by skin contaminants usually result in a single positive blood culture when multiple sets were obtained.[14,15] Coagulase-negative staphylococci (CoNS) were the most commonly isolated contaminant, followed by non- pathogenic streptococci, bacillus species, micrococcus species and diphtheroids.[3] Blood culture contamination rates varies between 3.3%-6.6%.[3,9]

Antibiotic susceptibility testing and MIC

Once the significant bacterial isolate is determined, the testing proceeds to detect the antibiotic sensitivity pattern or an antibiogram. An antibiogram contains a qualitative assessment of a strain's susceptibility or resistance to antibiotics as well as information about the detected resistance mechanisms.[16] In-vitro antibiotic testing is either performed by disk diffusion method and expressed as zone diameter (mm) or by dilution method expressed as concentration (in mg/litre or g/mL) (Table II).[16,17] All susceptibility testing methods require breakpoints, also known as interpretive criteria, so that the results of the tests can be interpreted as susceptible, intermediate, or resistant and reported as such to a broad range of clinicians.[17] All breakpoints are either MICs or zone diameter values correlated with MICs.[17] A breakpoint is a chosen concentration (mcg/dL) of an antibiotic which defines whether a bacteria is susceptible or resistant to the antibiotic.

This is established by reference groups such as the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI). If the MIC is less or equal to the susceptibility breakpoint the bacteria is considered susceptible to the antibiotic, if MIC is more than the the break point, it indicates resistance. Intermediate (May be effective at higher doses) implies that the organisms are inhibited only by the maximum recommended dosage. In short, MIC should be interpreted in relation to break point.

Clinical breakpoints are set based clinical results from various types of study, wild type MIC distribution for relevant species of organisms [epidemiological cut-off value (ECOFF)], antimicrobial dosing, pharmacokinetic and pharmacodynamic aspects.[17,18,19] Currently clinical breakpoints are set and published primarily by two organizations in the world: the EUCAST and the American Clinical and Laboratory Standards Institute (CLSI) and partly by the Food and Drug Administration (FDA).[20,21]

Minimum inhibitory concentration (MIC) is defined as the lowest concentration of an antibacterial agent expressed in mg/L (mg/mL) which, under strictly controlled in vitro conditions, completely prevents visible growth of the test strain of an organism.[22] The determined MIC value must be compared with MIC clinical breakpoints to assess whether the strain is susceptible or resistant to the antibiotic.[16]

Relevance of MIC value in clinical practice

According to EUCAST[23,24] recommendations, MIC value can be interpreted as below

- Susceptible (S), standard dosing regimen: High likelihood of therapeutic success using a standard dosing regimen of the agent.

- Susceptible (I), increased exposure: High likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

- Resistant (R): High likelihood of therapeutic failure even when there is increased exposure.

MIC value allows to assess the degree of susceptibility or resistance to the antibiotic. The more susceptible the strain to the antibiotic, the greater the likelihood that its MIC is below the ECOFF and therefore the strain does not develop any drug-resistant subpopulation, so there is no increased risk of bacterial survival during treatment. In addition, high susceptibility of the strain increases the chance for reaching the therapeutic concentration of the antibiotic and for effective eradication of the pathogen using the standard dosage even in patients with significant changes in pharmacokinetic parameters.[16]

Limitations of MIC

While interpreting MIC, it should be noted that no current commercial system can determine 'true MIC', instead each measurement of an MIC generates a value

Table II. Methods to determine MIC

Methods	Techniques

1. Dilution methods	- in agar
	- in a liquid medium
	  • micromethod / microdilution
	  • macromethod / macrodilution

2. Gradient method	• strips impregnated with a predefined concentration gradient of antibiotic

that is a member of a probability distribution, which will vary in the range of 2 fold dilution. This may lead to significant dosing adjustment errors which may ultimately be harmful to the patient.[25]

Conclusion

This review summarizes the current literature regarding the sampling technique for blood culture and MIC interpretation. Blood culture is the single most essential investigation in diagnosis of BSI in pediatric population, a thorough knowledge of sampling techniques are required to optimize the culture results. Volume of blood is the single most critical factor which increases the sensitivity of the test. It is recommended to collect a weight or age-dependent blood volume and inoculate this sample into one pediatric blood culture bottle. We have not found many studies which highlight the advantages of paired sampling in pediatric and neonatal population.

MIC interpretation is important to recognize the sensitivity pattern of the strain and also to recognize emerging resistance pattern. Much of our MIC interpretations are based on EUCAST guidelines as the documents are freely available and the difference in interpretation between EUCAST and CLSI are outside the preview of this article.

Points to Remember

- *It is pertinent to collect the sample aseptically at the right time and in appropriate volumes.*

- *Volume of blood is the single most critical factor which increases the sensitivity of the test.*

- *A thorough knowledge of sampling techniques is required to optimize the culture results.*

- *MIC interpretation is important to recognize the sensitivity pattern of the strain and also to recognize emerging resistance pattern, which should be interpreted always in relation to break point.*

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CLIPPINGS

Association of breastfeeding with tidal breathing analysis in infants with bronchiolitis

This cross-sectional study aimed to assess the effects of breastfeeding on the TBFV (tidal breathing flow volume loops) measurements of infants who recover from acute bronchiolitis. TBFV analysis was performed in infants with bronchiolitis prior to hospital discharge.

The ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) at baseline and after the administration of 400 mcg salbutamol were analysed. A total of 56 infants aged 7.4 ± 2.8 mo, were included. Of them, 12.5% were exposed to tobacco smoke and 41.1% were breastfed less than 2 mo. There were no differences in baseline TBFV measurements between the breastfeeding groups; however, those who breastfed longer than 2 mo had a greater change in tPEF/tE after bronchodilation Moreover, there was a clear dose-response relationship between tPEF/tE reversibility and duration of breastfeeding (P < 0.001).

Infants who recover from bronchiolitis and have a shorter duration of breastfeeding or are exposed to cigarette smoke, have TBFV measurements indicative of obstructive lung disease.

Perikleous E, Fouzas S, Karageorgiou A, Steiropoulos P, Nena E, Chatzimichael A. Association of breastfeeding with tidal breathing analysis in infants with bronchiolitis. World J Clin Pediatr 2021 Nov 9; 10(6):168-176. doi: 10.5409/wjcp.v10.i6.168. PMID: 34868893; PMCID: PMC8603642.

ANTIMICROBIALS - II

SKIN, SOFT TISSUE AND JOINT INFECTIONS IN HOSPITALIZED CHILDREN

*Chetan Trivedi
**Helly Thakkar

Abstract: *Skin and soft tissue infections are the infections involving skin and underlying subcutaneous tissue, fascia or muscle. Hospitalization due to these infections is common. Skin and soft tissue infections can be classified into 'superficial' which includes erysipelas, cellulitis, bullous impetigo, bite infections, periorbital cellulitis and 'deeper' infections which include orbital cellulitis, necrotizing fasciitis and pyomyositis. Majority of community-acquired skin and soft tissue infections are caused by Gram positive organisms like Staphylococcus aureus and streptococci. Antibiotic therapy used in most of these conditions involve anti-staphylococcal penicillins or cephalosporin and clindamycin or metronidazole for covering anaerobes. In case of methicillin resistant Staphylococcus aureus, antibiotics such as linezolid, vancomycin and others are warranted.*

Keywords: *Skin infections, Soft tissue infections, Joint infections.*

Skin and soft tissue infections (SSTIs) comprise of variety of pathological conditions which involve skin and underlying subcutaneous tissue, fascia or muscle.[1] They are important causes for hospitalization in children. SSTIs can be classified according to the tissue level involved which includes 'superficial' and 'deep' infections. Superficial infections can be erysipelas, cellulitis, bullous impetigo, bite infections, and periorbital cellulitis whereas, deep-seated infections can be orbital cellulitis, necrotizing fasciitis, and pyomyositis that require surgical intervention in addition to parenteral antibiotic therapy. Different other classification systems are used to describe SSTIs based upon variables such as anatomic location, causative pathogen(s), rate of progression, depth of infection and severity of clinical presentation.[2]

In 2014, the Infectious Diseases Society of America (IDSA) updated practice guidelines for the diagnosis and management of skin and soft-tissue infections. The guidelines divided infections as purulent versus non-purulent, based on the severity (mild, moderate and severe) and tissue necrosis (necrotizing versus non-necrotizing). Non-necrotizing SSTIs include erysipelas, impetigo, folliculitis, simple abscess and complex abscess which can be treated by antibiotics and drainage. Necrotizing SSTIs (cellulitis, fasciitis, myositis, Fournier's gangrene) require surgical intervention including drainage and debridement of necrotic tissue as well as antibiotics.[3] Another method of classifying SSTIs is based on the type of acquisition. Community-acquired infections, usually have single responsible pathogen except in a bite /complex wound, whereas infections which are hospital acquired are usually polymicrobial.[2]

SSTIs can range in severity from minor infections to those that cause severe, life-threatening consequences which need hospitalization and management.

Need for hospitalization

- Patient presents with severe or uncontrolled infection despite outpatient antibiotics and drainage

- Patient is septic, dehydrated, acidotic or immunosuppressed

- Patient has organ dysfunction

- Appropriate follow-up is unavailable[4]

There is dramatic increase in the frequency, severity of infections and the emergence of resistance to many of the antimicrobial agents commonly used to treat SSTIs in the past. For example, there was a 29% increase in the total hospital admissions for these infections between 2000 and 2004. Some of this increased frequency is related to the emergence of community-associated methicillin resistant *Staphylococcus aureus*.[5]

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Organisms: Gram positive organisms like *S. aureus* and *streptococci* cause majority of simple community-acquired SSTIs. *S. aureus, P. aeruginosa, enterococcus and Escherichia coli* are the most common organisms isolated from hospitalized patients with SSTIs and empirical choice of antimicroials (Table I).[6]

We will be discussing here those SSTIs which might require hospitalization at length.

1. Cellulitis and erysipelas
2. Necrotizing fasciitis
3. Pyomyositis

Table I. Organisms and empirical antimicrobials in skin and soft tissue infections

Name	Organisms	Empirical choice of antimicrobials
Cellulitis and erysipelas	Group A streptococcus, *S. aureus*	• Moderate-IV penicillin, ceftriaxone, cefazolin or clindamycin. • Severe - Vancomycin plus either piperacillin - tazobactam or imipenem-meropenem
Preorbital cellulitis	*S. pneumoniae, S. aureus, H. influenzae*, GABHS	Cefuroxime or amoxicillin/clavulanic acid
Orbital cellulitis	*S. pneumoniae, S. aureus, H. influenzae, GABHS,* anaerobes	Cefotaxime plus clindamycin
Necrotizing fasciitis	*S. aureus*, streptococcal species, klebsiella species, *E. coli* and anaerobic bacteria	Vancomycin, linezolid, or daptomycin combined with one of the following options: (1) piperacillin-tazobactam, (2) a carbapenem (imipenem-cilastatin, meropenem or ertapenem), (3) ceftriaxone plus metronidazole, or (4) a fluoroquinolone plus metronidazole.
Pyomyositis	*Staphylococcus aureus*, Group A streptococci, *Streptococcus pneumoniae* and Gram-negative enteric bacteria	MSSA -Cefazolin/ nafcillin /oxacillinMRSA - Vancomycin/linezolid/ clindamycin
Infected animal bites	*Pasteurella multocida, S. aureus,* Streptococcus, *Capnocytophaga canimorsus, Eikenella corrodens* and other oral anaerobes	B-lactam/BLI combinations - (ampicillin/sulbactam, ticarcillin/ clavulanic acid or piperacillin/ tazobactam) or cefotaxime + clindamycin or metronidazole
Neonatal omphalitis	*S.aureus,* klebsiella *and E. coli*	Cloxacillin plus gentamicin/piperacillin-tazobactum
Staphylococcal scalded skin syndrome	Toxin producing strains of *S aureus*	Cloxacillin + gentamycin /cefotaxime+clindamycin
Toxic shock syndrome (TSS)	*Staphylococcus aureus, Streptococcus pyogenes*	Cefazolin + clindamycin
Postsurgical wounds	*S. aureus*, gram negative bacilli and anaerobes	Vancomycin + piperacillin-tazobactam or meropenem or ceftriaxone and metronidazole
Deep neck infections	Anaerobic organisms: Prevotella, porphyromonas, fusobacterium and *Peptostreptococcus* spp Aerobic organisms: group A streptococcus, *S aureus* and *H. influenzae* type b.	Ampicillin - sulbactam or penicillin G plus metronidazole or clindamycin

4. Infected animal bites

5. Neonatal omphalitis

6. Staphylococcal scalded skin syndrome

7. Toxic shock syndrome (TSS)

8. Postsurgical infection

9. Bone and joint infections

10. Deep neck infections

1. Cellulitis and erysipelas

Cellulitis and erysipelas present with skin erythema, edema and warmth. Erysipelas involves the upper dermis and superficial lymphatics due to which lesions are raised above the level of surrounding skin with clear demarcation between involved and uninvolved tissue. It causes acute onset of symptoms with systemic manifestations including fever and chills. Whereas, cellulitis involves the deeper dermis and subcutaneous fat having more indolent course and usually spreads with irregular margins with unclear demarcation. Cellulitis may present with or without purulent drainage or exudate. Lower extremities are most common sites for cellulitis, rarely it may be perianal, orbital, pre orbital or buccal.[7] Amongst all, orbital cellulitis is a medical emergency.

Organisms: The most common causes of cellulitis and erysipelas are Group A beta hemolytic streptococcus but it can also occur due to other *streptococci, Staphylococcus aureus* including methicillin resistant *Staph. aureus* (MRSA) and Gram-negative aerobic bacteria in minority of cases.[2]

Antimicrobial treatment: It depends on whether it is purulent or non-purulent cellulitis and the severity of presentation.

Purulent cellulitis: Whether the infection began as an abscess (with secondary cellulitis) or as the cellulitis (with secondary abscess) if purulent, majority are caused by Staph aureus (MSSA or MRSA) If infection is likely due to MRSA, pending culture results, antibiotics like vancomycin, clindamycin or linezolid should be started along with incision and drainage if infection is moderate/- severe in nature.

Non purulent cellulitis: Typical cellulitis / erysipelas with no focus of purulence should be treated with empirical antibiotics against infection due to beta hemolytic streptococci and methicillin sensitive *Staph.aureus* (MSSA). But, when cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection site infection, or systemic inflammatory response syndrome (SIRS), vancomycin or another antimicrobial agent effective against both MRSA and streptococci is recommended.

- **Mild infection:** Typical cellulitis/erysipelas without systemic signs of infection is considered mild and is treated with an oral antimicrobial agent like penicillin, amoxicillin, amoxicillin-clavulanate, dicloxacillin, cephalexin or clindamycin.

- **Moderate infection:** Typical cellulitis/erysipelas with systemic signs of infection is considered moderate and is treated with empirical parenteral antibiotics like IV penicillin, ceftriaxone, cefazolin or clindamycin.

- **Severe infection:** Patients who have failed oral antibiotic treatment; or those with systemic signs of infection (temperature >38°C, tachycardia, tachypnea or abnormal white blood cell count (>12000 or <400 cells/μL); are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension or evidence of organ dysfunction; or neonate with cellulitis except in mild cases are considered to have severe infection. They should receive antibiotics with broad coverage for polymicrobial infections such as vancomycin plus either piperacillin-tazobactam or imipenem-meropenem empirically.

Cellulitis of neonates usually requires hospitalization and initial parenteral therapy except in mild cases. Empirical therapy against group B streptococci in addition to MRSA and other group A beta hemolytic streptococci (GABHS) should be started with vancomycin plus cefotaxime or gentamicin for at least 7-10 days.

Duration of antibiotic therapy: The recommended duration of antimicrobial therapy is 5-10 days, but treatment should be extended if the infection has not improved within that time frame.[3]

Peri-orbital and orbital cellulitis

Under majority of situations, it is difficult to distinguish between orbital and periorbital cellulitis. Hence a broader antibacterial regimen such as cefotaxime or ticarcillin/clavulanic acid is recommended. Uncomplicated periorbital cellulitis can often be treated with oral antibacterial effective against *S.pneumoniae*, non-typable *Hemophilus influenza* and *Moraxella catarrhalis*. These antibacterials include amoxicillin/clavulanic acid or cefuroxime axetil whereas, antibacterials like cephalexin or clindamycin may be more appropriate when periorbital cellulitis occurs secondary to trauma

which is usually caused by organisms like *S. aureus* and GABHS.

The duration of therapy in orbital cellulitis is usually about 2-3 weeks provided there are no complications.[8]

2. Necrotizing fasciitis

Necrotizing soft-tissue infections (NSTIs) are aggressive infections involving one or all layers of the soft-tissue compartment, from the superficial dermis and subcutaneous tissue to the deeper fascia and muscle.[9] Hence, it is the most common life threatening and invasive infection requiring hospitalization and appropriate antibiotics.[10] It can be mono or polymicrobial.

Organisms: The usual pathogens are *S. pyogenes, S. aureus, Vibrio vulnificus, Aeromonas hydrophila* and anaerobic streptococci (Peptostreptococcus) in case of monomicrobial infection. Infection with *staphylococci* and hemolytic *streptococci* can occur simultaneously. Most of the infections are community acquired and most commonly affect lower extremities. Cases resulting after varicella infection or trivial injuries, such as minor scratches or insect bites, are usually due to *S. pyogenes* or less commonly, community-acquired MRSA.[11] The mortality rate is high in patients with group A streptococcal necrotizing fasciitis and those having hypotension, and organ failure which usually ranges from 30% to 70%.[12,13]

Polymicrobial infection is most commonly associated with four clinical settings:

(1) Perianal abscesses, penetrating abdominal trauma, or surgical procedures involving the bowel

(2) Decubitus ulcers

(3) Injection sites in illicit drug users and

(4) Spread from a genital site such as Bartholin abscess, or a minor vulvovaginal infection.

The organisms most commonly causing polymicrobial necrotizing fasciitis are *S. aureus, streptococcal* species, *Klebsiella* species, *E. coli* and anerobic bacteria. The development of crepitus indicates that the following gas producing organisms are involved: *Clostridium* spp or Gram-negative bacilli such as *E. coli,* klebsiella, proteus, or aeromonas.[3]

Antimicrobial therapy

- The use of antimicrobial therapy is an adjuvant treatment in case of necrotizing fasciitis and should be combined with early surgical debridement.

- Initial treatment should be empirical until definitive organism is identified.

- As it is impossible to exclude polymicrobial infection, an aggressive broad-spectrum empiric antimicrobial therapy should be given in order to cover Gram-positive, Gram-negative, and anerobic organisms until culture-specific results and sensitivities are available.

- Antibiotics, which cover MRSA with additional benefit of inhibiting invasive group A streptococci (GAS)virulence proteins should be used as empiric treatment.

- Among all the available treatment, most commonly used ones are vancomycin, linezolid, or daptomycin combined with one of the following options: (1) piperacillin-tazobactam, (2) a carbapenem (imipenem-cilastatin, meropenem, and ertapenem), (3) ceftriaxone plus metronidazole, or (4) a fluoroquinolone plus metronidazole.

- Once the organism is determined, antibiotic therapy should be changed accordingly.

- Penicillin plus clindamycin is the recommended treatment for group A streptococcal necrotizing fasciitis and/or streptococcal toxic shock syndrome (STSS). Clindamycin suppresses streptococcal toxin and cytokine production.[3]

- Vancomycin treatment should be avoided in patients with renal dysfunction and also when MRSA isolate requires MIC for vancomycin $\geq$ 1.5 mg/mL.

Duration of antibiotics: Antimicrobial therapy should be continued until further debridement is no longer necessary and the patient has improved clinically with no fever for 48-72 h.[2]

3. Pyomyositis

Pyomyositis is the presence of pus within individual muscle groups, caused mainly by *S. aureus*. It usually presents with localized pain in a single muscle group, muscle tenderness and fever. It typically occurs in an extremity, but any muscle group can be involved, including the psoas or trunk muscles. This infection is usually preceded by local trauma or vigorous use of muscles.[3]

Organism: *Staphylococcus aureus* is responsible for about 90% of cases of pyomyositis; community-acquired MRSA isolates in this infection have been reported in many non-tropical countries.[14] Group A *streptococci, Streptococcus pneumoniae* and Gram-negative enteric bacteria are other possible agents which can cause pyomyositis.

Antimicrobial treatment: Vancomycin is recommended for initial empirical therapy in case of suspected MRSA. Other agents active against MRSA include linezolid, daptomycin, telavancin, or ceftaroline; clindamycin can also be used. Cefazolin or anti-staphylococcal penicillin (nafcillin or oxacillin) is recommended for definitive therapy of pyomyositis caused by MSSA.[15] A broader spectrum of organisms causes pyomyositis in immunocompromised patients and empirical coverage with vancomycin plus one of the following is recommended: (a) piperacillin-tazobactam, (b) ampicillin-sulbactam or (c) a carbapenem.[14]

Duration of antibiotics: The recommended duration of therapy is two to three weeks.[3]

4. Infected animal bites

Children are more prone to animal bites like cats and dogs as well as human bites. These bite wounds may get infected and require hospitalization.

Organisms: Usually these infected bites of dogs and cats are polymicrobial in nature. Commonly found organisms are *Pasteurella multocida, S. aureus,* streptococcus and *Capnocytophaga canimorsus*. Human bites can get infected with *S. aureus, Eikenella corrodens* and other oral anerobes.[16] Generally, minor infections can be treated with oral antibacterials without need for hospitalization. Children with animal or human bites may need hospitalization when they show signs of sepsis, rapidly spreading deep seated infections like cellulitis, septic arthritis, or osteomyelitis.

Antimicrobial treatment: In hospitalized children empirical choice of antibiotics should be B-lactam/B-lactamase inhibitor combinations, such as ampicillin/sulbactam, ticarcillin/clavulanic acid or piperacillin/tazobactam or cefotaxime combined with clindamycin or metronidazole. Even if single microorganism is identified on culture, broad antimicrobial coverage is recommended to cover polymicrobial infection.[17]

Duration of antibiotics: The recommended duration of therapy is 7-10 days.[1]

5. Neonatal omphalitis

Omphalitis is characterized by inflammation and discharge at the umbilical stump and in the periumbilical area. Neonatal omphalitis can progress to life-threatening fasciitis if not recognized early. Other complications of omphalitis include intra-abdominal abscess and evisceration of the small bowel.[18]

Causative organisms: In a study, main bacteria involved in omphalitis are *S.aureus,* klebsiella, and *E. coli*.[19] Risk factors that lead to omphalitis are unhygienic birth and cord-care practices.[20]

Antimicrobial therapy: Empiric therapy for omphalitis includes an anti-staphylococcal penicillin, such as cloxacillin, combined with gentamicin. If Gram negative organisms or anaerobes are suspected, cloxacillin plus gentamycin in addition to metronidazole or a broadspectrum antibacterial such as piperacillin/tazobactam will provide coverage for Gram-positive as well as Gram-negative organisms and anaerobes.

Early surgical intervention should be done in order to manage the infection in case any complication arises. This may require drainage of the abscess or debridement of devitalized tissue.

Duration of therapy: Duration of antimicrobial treatment is for 10-14 days and should be continued until the infection is completely resolved with the neonate being clearly asymptomatic.

6. Staphylococcal scalded skin syndrome (SSSS)

SSSS is a superficial blistering skin disorder caused by the exfoliative toxins of certain strains of *S. aureus*. The condition is most commonly observed in neonates and children younger than 5 years with a peak between 2 and 3 years of age.

SSSS can have wide range of presentation from few localized blisters that burst and leave a tender erythematous base to exfoliation involving the entire body surface.

It is a potentially life-threatening disorder and a pediatric emergency. Early diagnosis and treatment are imperative to reduce the morbidity and mortality of this condition.

Organisms involved: Toxigenic strains of *S. aureus* most often belonging to phage group 2, less commonly phage 1 and 3. Patients with extensive exfoliation may get secondarily infected with Gram negative bacteria.

Antimicrobial therapy: Although no consensus exists about the role of antibacterial treatment in staphylococcal scalded skin syndrome, some authors maintain that early antibacterial therapy is important and may even halt the exfoliative process.

They should be treated as patients with burns.

Choice of antibiotics

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- Semisynthetic penicillinase resistant penicillin like nafcillin, cloxacillin or flucloxacillin and aminoglycoside like gentamicin

- If extensive exfoliation - 3rd generation cephalosporin like cefotaxime plus clindamycin to inhibit production of exfoliative toxin.

- If suspicion of MRSA - Vancomycin

- In case of penicillin allergy clarithromycin or cefuroxime should be used.

Duration of therapy: Once again, there is no consensus on the duration of treatment but 10 days of therapy is usually adequate if the skin appears to be improving.[21]

7. Toxic shock syndrome (TSS)

Toxic shock syndrome (TSS) is an acute illness which is characterized by fever, rash, hypotension, multi-organ system dysfunction and desquamation. TSS is most commonly caused by a toxigenic strain of *Staphylococcus aureus* or Group A streptococci (*Streptococcus pyogenes*). Staphylococcal TSS can be menstrual or non-menstrual. Nowadays both are seen in equal frequency. Out of all non-menstrual cases of TSS, 18.3% were reported after surgical procedures, 11.5% were post-partum or post-abortion and 23% were associated with nonsurgical cutaneous lesions.[22] Risk factors for non-menstrual TSS include colonization of a toxin-producing strain of *S. aureus*, absence of protective antitoxin antibodies and an infected site. Staphylococcal TSS is mostly likely seen along with any primary staphylococcal infection, after surgery, with any disruption of the skin or mucous membrane or placement of a foreign body and sometimes, no obvious site of infection.[23] Streptococcal TSS may result from bacteremia, necrotizing fasciitis, or cellulitis.

Causative organism

- *Staphylococcus aureus*

- *Streptococcus pyogenes*

Varicella is an important risk factor for invasive Group A streptococcal (GAS) infections in previously healthy children.[24] About 15% of children with invasive GAS disease had a history of varicella in the month prior to their illness.

Antimicrobial treatment: High-dose beta-lactamase-resistant anti-staphylococcal antibiotics are indicated to eradicate the organism and also to prevent its recurrences.[23] Nafcillin, oxacillin and first-generation cephalosporins (cephalosporins) are the first-line agents for *S. aureus*.

Vancomycin should not be used routinely as initial empiric therapy because methicillin-resistant *S. aureus* causes <1% of cases of staphylococcal TSS.[25] Clindamycin when used in combination with a beta lactamase-resistant anti-staphylococcal agent can result in a potentially helpful effect by decreasing the production of Toxic Shock Syndrome Toxin-1 (TSST-1).

8. Post-surgical wound

Local flora and colonization from nosocomial bacteria are responsible for surgical site infections in majority of cases. The predominant organisms involved are the ones that reside in mucus membrane close to surgical site.[26] The major categories of surgical site infections are superficial incisional SSI (involving only subcutaneous space occupying space between the skin and underlying muscular fascia), deep incisional SSI (involves deeper soft tissues like fascia and muscle) and organ/space SSI (an infection involving any organ or space, other than the skin, muscle, and surrounding tissue, which was site of original surgical incision). The presenting signs that help in diagnosis of surgical site infections are local pain, swelling, erythema and purulent discharge.[27]

Organisms: Surgical site infections are rarely the cause of fever within 48 hours of surgery and if at all occurs, likely causative organisms are *S. pyogens* or *Clostridium* species. When the fever occurs after 48 hours, careful inspection of the wound is required since surgical site infection is more likely during that time period.[28] MRSA should be suspected if patient has nasal colonization, or history of prior MRSA infection, recent hospitalization or recent antibiotics.[3] Surgical site infections located near mucus membrane like intestinal or genital tracts are usually polymicrobial infection involving Gram negative bacteria and anaerobes along with Gram positive bacteria.

Antimicrobial treatment: Antibiotic therapy along with opening of suture is recommended if the patient has significant systemic signs of infection. *S. aureus* and streptococcal species are the most common organisms responsible in clean surgeries without involvement of intestinal or genital tracts. In presence of high-risk factor for MRSA infection, one must use initial antibiotic like vancomycin, linezolid, daptomycin for MRSA coverage as well as one of the following for gram-negative and anaerobic coverage: (1) piperacillin-tazobactam, (2) a carbapenem or (3) ceftriaxone and metronidazole since most of surgical site infections are polymicrobial in nature.[29]

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Duration of therapy: The recommended duration of therapy is 10-14 days in uncomplicated cases.

9. Bone and joint infections

Acute osteomyelitis and septic arthritis are the two conditions that affect bone and synovium, usually caused by a bacterial infection (Table II).[30] Hip and knee are the most frequently involved joints. Other joints which are also affected include ankle, elbow, shoulder, sacroiliac and metatarsophalangeal joints.[31] Most cases are monoarticular (90%) although polyarticular presentations do occur.

Treatment of septic arthritis: Blood culture and culture of joint fluid aspirates is required before starting antibiotic therapy in order to determine the organism responsible. Empirical antibiotic therapy for most likely organism is usually initiated prior to definitive laboratory results.

Empirical antibiotics

- In neonates, empirical treatment with oxacillin or cefotaxime as well as gentamicin to cover Group B *streptococcus*, *Staphylococcus aureus* and Gram negative organisms is given.

- Whereas, in children >3 months, anti-staphylococcal penicillin (ASP) such as nafcillin or oxacillin or a first-generation cephalosporin such as cefazolin should be used to cover MSSA, *S. pyogenes* and *K. kingae*.[33]

- In case when there is high chance of MRSA infection (i.e., countries with a prevalence of MRSA >10%, patients previously hospitalized in the intensive care unit,immunocompromised patients), the recommended treatment is clindamycin, an antibiotic which belongs to the class of lincosamides.

- When there is resistance to clindamycin, most commonly used treatment is vancomycin.

- In children < 2 years clindamycin is added to first generation cephalosporin. In children 2 years of age and above, clindamycin alone can be given.

- In cases of MRSA that are unresponsive to clindamycin and vancomycin, an alternative option is linezolid which belongs to the class of oxazolidinones.

- Cefazolin should be added if *Kingella kingae* is also suspected in etiology since both vancomycin and clindamycin are not effective against it.

- The use of flucloxacillin, clindamycin or linezolid is recommended in cases where *S. aureus* produces Panton-Valentine leukocidin (PVL) and daptomycin is considered as a second-line antibiotic in such condition.

- Third-generation cephalosporin such as cefotaxime or ceftriaxone or a fluoroquinolone should be considered in sickle cell anemia patients with salmonella infection.

Table II. Causative organisms and empirical therapy in bone and joint infections

Infant:<3 month old	*Staphylococcus aureus* *Escherichia coli* and other Gram-negative bacteria GBS *Candida albicans* *Neisseria gonorrhoeae* (newborns)	Cefotaxime + Gentamicin
Young child: 3 months to 5 year old	*S. aureus* *Kingella kingae* GAS *Streptococcus pneumoniae* (especially under 2 yr old) *Hemophilus influenzae* type b (exceptional inwell-immunized populations)	Nafcillin/Oxacillin/Cefazolin +/- Clindamycin/Vancomycin
Older child: ≥5 year old	*S. aureus* GAS	Nafcillin/Oxacillin/Cefazolin +/- Clindamycin/Vancomycin
Adolescents	*N. gonorrhoeae* (in sexually active adolescents)	3rd Generation cephalosporin
Sickle cell disease	*Salmonella*	Ceftriaxone/Cefotaxime/Fluroquinolones

GAS indicates group A *Streptococcus*; GBS, group B *Streptococcus*[32]

- Finally, *Candida* spp. is another pathogen that may be identified from some cases of acute osteomyelitis (mainly spondylodiscitis) which requires a prolonged antifungal treatment and surgical debridement.[32]

- Once the definitive organism is identified and antibiotic sensitivity has been determined, the initial empirical antibiotics may be modified accordingly.

Duration of antibiotic therapy

The duration of total therapy which involves IV plus oral (PO), should be of 2-3 weeks for septic arthritis whereas it should be 3-4 weeks for osteomyelitis.

Duration of therapy may be prolonged in the following conditions

(Although practice varies, some centers may extend to 4-6 weeks):

- Resistant or unusual pathogens (e.g., MRSA, PVL+ and Salmonella)

- Newborns and young infants (i.e., <3 months)

- Slow/poor response or complications; complex infections

- Involvement of pelvis or spinal column

- Sepsis or in immunocompromised children

Switching to oral therapy following IV treatment

Early oral switch can be done if the child is showing clinical improvement as seen below

- Afebrile or decreased temperature for 24-48 hours

- Able to tolerate orally

- Improvement of clinical status-pain, range of movement and weight bearing status

- Decrease in CRP of about 30%-50% from maximum value

- No signs of complications, such as metastatic foci (endocarditis, pneumonia, etc.) or deep vein thrombosis (DVT)

- Absence of virulent pathogens, such as Salmonella, MRSA or PVL+

- Negative blood cultures if initially positive[34]

Surgery: Along with antibiotics, surgery plays a vital role in the treatment of acute osteomyelitis and septic arthritis in children. It is usually considered in patients who do not respond to antibiotic treatment for the suspicion of an underlying complication. Most commonly infections caused by MRSA or *S. aureus* producing PVL require surgical interventions as these bacteria are frequently associated with a more aggressive clinical course.[35]

10.Deep neck space infections

The submandibular space, parapharyngeal spaces and retropharyngeal space are the three spaces between the plane of cervical fascia holding major clinical importance. Infections in these spaces are known as deep neck infection which often have a rapid onset and can even lead to life threatening complications. Those infections are usually polymicrobial in nature representing normal resident flora of contiguous mucosal surfaces.[36]

Causative organisms: As mentioned earlier most infections are polymicrobial and the average number of isolates obtained is 5 (range, 1 to 10). Predominant anaerobic organisms isolated in these infections are *prevotella, porphyromonas, fusobacterium* and *Peptostreptococcus* spp whereas aerobic organisms found are group A *streptococcus* (*Streptococcus pyogenes*), *Staphylococcus aureus* and *Hemophilus influenzae*. More than two thirds of deep neck abscesses contain beta-lactamase producing organisms.[37]

Antimicrobial treatment: Depending on the location of the suspected infection and the overall state of the patient, empiric antimicrobial therapy is initiated.

- For peritonsillar abscess, ampicillin-sulbactam or penicillin G plus metronidazole or clindamycin.

- For retropharyngeal and parapharyngeal infections, treatment depends upon the mode of spread. If odontogenic spread then ampicillin-sulbactam or penicillin G plus metronidazole or clindamycin. Whereas, in case of rhinogenic or otogenic spread then ampicillin-sulbactam or ceftriaxone plus metronidazole or clindamycin. *S.aureus* being the most common pathogen in patients younger than 2 years having parapharyngeal infection, cefazolin and nafcillin are preferred antibiotics.[38]

Surgical source control and adequate antibiotics are needed in case of loculated collections for successful management of such infections.

Duration of antimicrobial treatment: The duration of treatment is often 2-3 weeks depending upon severity of infection.

Antimicrobials commonly used in SSTI and their dosage are summarized in Table III.

Table III. Dosage guide for commonly used antimicrobial agents in skin and soft tissue infection

Antibiotic	Pediatric dose
Amoxicillin-clavulanate (Co-amoxiclav)	Neonates: 30 mg/kg/24 hr divided q 12 hr POChildren: 20-45 mg/kg 24 hr divided q 8-12 hr PO.
Ampicillin-sulbactam	100-200 mg/kg/24 hr divided q 4-8 hr IV or IM
Cefadroxil	30 mg/kg/day in 2 divided doses,max 2 gm/day
Cephalexin	Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO
Cefazolin	25-100 mg/kg/day in 3-4 divided doses; 100-150 mg/kg daily for severe infections
Cefuroxime	Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IMChildren: 200-240 mg/kg/24 hr divided q 8 hr IV or IM;PO administration: 20-30 mg/kg/24 hr divided q 8 hrPO
Ceftriaxone	50-75 mg/kg/day , max 2 gm/day 12-24 hourly
Ciprofloxacin	15-30 mg/kg/24 hr divided q 12 hr PO or IV;
Clindamycin	10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO
Cloxacillin	50-100 mg/kg/day in 3-4 divided doses
Cotrimoxazole	6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO
Daptomycin	12-17 years: 5 mg/kg IV Q 24 hours; 7-11 years: 7 mg/kg IV Q 24 hours; 2-6 years: 9 mg/kg IV Q 24 hours; 1 to <2 years: 10 mg/kg IV Q 24 hours; <1 year: safety and efficacy not established
Linezolid	10 mg/kg q 12 hr IV or PO
Imipenem	60-100 mg/kg/24 hr divided q 6-8 hr IV or IM
Meropenem	60 mg/kg/24 hr divided q 8 hr IV meningitis:120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV
Metronidazole	30 mg/kg/24 hr divided q 6-8 hr PO or IV
Piperacillin-tazobactam	300-400 mg/kg/24 hr divided q 6-8 hr IV or IM
Vancomycin	45-60 mg/kg/24 hr divided q 8-12 hr

Source: (adopted from Nelson Textbook of Pediatrics, South Asia 1st edition pg1301-1311)

Points to Remember

- *Skin and soft tissue infections are very common in children and are classified based on the site, severity, purulence and extent of spread.*

- *The common organisms in community acquired infection are Gram positive bacteria such as Staphylococcus aureus and streptococci, whereas S. aureus, P. aeruginosa, enterococcus and Escherichia coli are the most common organisms in hospital acquired infections.*

- *The choice of antibiotics and duration depends on the site and severity, the empiric choice of antibiotics for the common infections includes penicillins and cephalosporins.*

- *Timely treatment with appropriate antibiotics plays an important role in their management along with surgical intervention in some conditions.*

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CLIPPINGS

Successful use of telemedicine for evaluation of infantile hemangiomas during the early COVID-19 pandemic: A cross-sectional study.

The COVID-19 pandemic prompted a rapid expansion in the use of telemedicine. This study aimed to assess the experiences of hemangioma specialists utilizing telemedicine during the COVID-19 pandemic to evaluate and manage infantile hemangiomas (IH), including perceived effectiveness of different modalities and barriers to care delivery. Multicenter cross-sectional study asking providers to describe their experiences using telemedicine for initial evaluation of IH from March to September 2020.

The study included 281 patients from 15 medical centers internationally. Median time from referral to evaluation was 17 days. Median physician confidence in performing evaluations via telemedicine was 95.0 (IQR 90.0-100.0). Most evaluations were performed via video communication with photographs or audio communication with photographs; when not initially available, photographs were requested in 51.4%. Providers preferred follow-up modalities that included photographs.

Physicians with extensive expertise in managing IH were confident in their abilities to assess and manage IH via telemedicine including initiating treatment in patients without risk factors for beta-blocker therapy. There was a preference for hybrid modalities that included photographs. The data suggest that telemedicine can be effective for managing IH and may decrease wait times and improve specialist reach to underserved areas.

Kittler NW, Frieden IJ, Abuabara K, Siegel DH, Horii KA, Mathes EF, et al. Pediatr Dermatol 2022 Jun 22. doi: 10.1111/pde.15040. Epub ahead of print. PMID: 35734850.

Factors Predicting Blood Culture Positivity in Children With Enteric Fever.

Blood culture, despite low sensitivity, is the gold standard for enteric fever diagnosis. Predictors of blood culture positivity may help design strategies to optimize enteric fever diagnosis. A cohort of 6760 children aged 0.5-15 years was followed for 3 years for enteric fever with blood cultures in an automated system, for fevers >3 days. Factors affecting test positivity in fevers and participant-level predictors for culture refusals were analyzed using regression models.

6097 suspected typhoid/paratyphoid fever (STF) episodes were reported, of which 5703 (93.5%) STFs had sampling for blood cultures, with 394 (6.5%) refusals. Salmonella enterica serovar Typhi/Paratyphi positivity was culture-confirmed in 3.8% (218/5703) of STF episodes. Older children, larger blood volume inoculated, higher temperatures during fever, and fevers diagnosed as suspected typhoid or acute undifferentiated fever had a higher probability of culture positivity. Antibiotics before culture did not decrease culture positivity. Blood culture refusals were higher for children from wealthier households or with milder illness.

Performing blood cultures in older children with fever, especially those fevers with toxic presentation and increasing blood volume for inoculation are strategies to improve enteric fever detection in surveillance settings.

Srinivasan M, Sindhu KN, Ramanujam K, Ramasamy RK, Subramaniam S, Rose W, et al. Factors Predicting Blood Culture Positivity in Children With Enteric Fever. J Infect Dis 2021 Nov 23; 224(Supple 5):S484-S493. doi: 10.1093/infdis/jiab357. PMID: 35238358; PMCID: PMC8892536.

ANTIMICROBIALS - II

ANTIMICROBIAL THERAPY OF CENTRAL NERVOUS SYSTEM INFECTIONS

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Abstract: *Intracranial infections are always considered to be a critical emergency in pediatric patients, more so in neonates and infants. Depending upon host immune status and the virulence of infecting agent, it can lead onto rapid, permanent damage to the brain with resultant higher mortality and morbidity. This article will guide us through etiology, risk factors and types of various central nervous system infections with protocolized treatment for the same and is restricted to non tuberculous bacterial infections.*

Keywords: *Children, Central nervous system infections, Antibiotics.*

The central nervous system (CNS) infections are higher in low-income countries than in high income countries.[1] The CNS infections are caused by bacteriae, viruses, fungi and parasites with their predilection based upon host and environmental factors. Bacterial CNS infections are more common in neonates and in early infancy than later ages. Choice of the right antibiotic for an individual patient with CNS infection is determined by many factors such as age of the child, local epidemiology, immune status of the patient, existing co-morbidity, etc. Apart from the right choice of an antimicrobial, appropriate dose, route and duration are also extremely important for complete recovery. To choose appropriate antibiotics, one needs to understand the microbiology, pathology, pharmacokinetics (PK) and pharmacodynamic (PD) principles of drugs used for CNS infections.

Based on pathological and anatomical localization,

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CNS infections are listed as below

1. Meningitis
2. Encephalitis
3. Cerebritis and brain abscess
4. Subdural abscess/empyema
5. Ventriculitis

Etiology

The common microbes causing community acquired CNS infections, in otherwise healthy children are *S. pneumoniae* (SP) and *H. Influenzae b (HI)*. *Neisseria meningitidis* is not a very common microbe in India, unlike the western world. Health care associated infections and infections in immunodeficient children are caused by all opportunistic commensals or resistant organisms.

Predisposing factors

Following factors determine the probable infecting organism:

1. Age of the child

Causative organisms depending on age group are given in Table I.

2. Predisposing factors

Various predisposing factors are fractures, congenital anatomical defects (Table II) and immunodeficiency.

Table I. Age group and causative organisms

Age group	Organism
Neonate	*Group B streptococci, E. coli, Listeria monocytogenes. Staphylococci, Klebsiella* from maternal birth canal flora.
1-3 months	*S. pneumoniae, H. influenza, Meningococci*
3 months to 5 years	*S. pneumoniae, H. influenza*
More than 5 years	*S. pneumonia*

Immunodeficiency

- Complement defects predispose to infections by capsulated organism.

- Malnutrition and asplenia are other immune suppressed states in children.

- Immunodeficiency will also predispose to opportunistic infection from commensals like enterococci, skin commensals, fungus, etc.

3. Vaccination status

- *H.influenza b (Hib)* vaccine has drastically decreased the *Hib* CNS infection rate from 25% in pre-vaccination era to 2% in post vaccination era in Mongolia.[2] Invasive pneumococcal disease rate also declined significantly with the advent of PCV 7 and further with PCV 13 vaccine. Despite this improvement, infections due to uncovered strains of *pneumococci* increased or remained the same.[3] The new PCV 10 in India nearly equals in coverage with the existing PCV 13 at almost half the cost. Children receiving new PCV 10 (10vPCV) or old PCV 13 get nearly 80% protection against covered strains and 56% against the non-covered strains.[4,5]

4. Healthcare associated infections

Health care associated or hospital acquired infections commonly present two days after hospitalization or health care visit until 30 days after the visit.[6] The spectrum of the causative organisms is wide and depends on the type of exposure, immune status of the patient and type of interventions the patient received during hospitalization.

Clinical presentation

Classical clinical presentation generally depends on the common organisms for the age. Clinical presentation will vary according to the age and immune status.

Table II. Anatomical defects and probable organisms

Anatomical defects	Probable organism
Basal skull fracture	*S. pneumonia*
Pilonidal sinus and congenital midline defects	*S. aureus*
Neuro-enteric sinus	Intestinal Gram-negative commensals, *Enterococci*
Cyanotic heart diseases	Opportunistic and anaerobic bacterial infections.

In neonates and early infancy the blood brain barrier (BBB) is immature. Hence, bacteriae from systemic bacteremia easily get access into the CNS and on many occasions CNS manifestations may be the earliest symptoms even before fever. Infants and children present with headache, vomiting, irritability, seizures, altered sensorium on day 2 to 3 with rapid deterioration, if treatment is delayed or inappropriate. It is not easy to differentiate bacterial from viral infections.

Investigations

Cerebrospinal fluid (CSF) examination

In a given clinical background, CSF examination showing neutrophilic cell counts more than 5 cells / mm^3, proteins more than 40 mg / dL and sugar levels less than 60% of blood sugar from simultaneously collected samples favour the diagnosis of bacterial meningitis. In neonates the normal CSF contains as many as 15 cells/mm^3 and protein as high as 120 mg/dL.[7] Gram stain of CSF and culture should always be the norm. In the presence of suspected or confirmed features of raised intracranial pressure (ICP), diagnostic CSF examination is to be deferred, till control of ICP. Empirical antibiotics based on epidemiology and child's age are recommended till then. Studies show that blood and CSF can become sterile after two hours of institution of first dose of appropriate antibiotic. So empirical antibiotics before lumbar puncture may reduce chances of CSF culture positivity, but rest of the picture in the CSF usually doesnot change in first 48 hours of antibiotic therapy.[8] Delay in institution of antibiotic for more than 2 hours increases morbidity and mortality exponentially.[9]

Blood culture

Blood culture should always be sent for cases of suspected pyogenic meningitis. Some of the western studies report blood culture yield as high as 40-90% in those who have not received antibiotics. In neonates, the blood culture yield in similar situation is 70-85%.[7]

Other diagnostic tests

Availability of newer polymerase chain reaction (PCR) based microbiological detection techniques, bacterial diagnosis may be possible early within 12-24 hours, with 85-100% sensitivity and specificity for *S. pneumoniae, H. influenzae* and *Meningococci*, as there are many occasions when Gram stain of CSF may not reveal organisms and culture may take upto 48 to 72 hours.[10] But these tests lack the ability to show antimicrobial sensitivity pattern of the bacteria which is very important in case of unusual organisms or resistant organisms.

Newer methods of microbial recognition in matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and 16SrRNA have reduced the microbial recognition time. Newer methods for recognition of genetic susceptibility or resistance patterns of micro-organisms in pyrosequencing is the future of rapid microbial detection of organisms and their antibiotic susceptibility.

Empirical antimicrobial therapy

Empirical antibiotics need to be used till a definite pathogen is identified either by culture tests or by PCR. Empirical choice depends upon epidemiology, risk factors, possible source of infection and historical evidence of local sensitivity pattern.

- *S.pneumoniae* (SP) meningitis strains are sensitive to penicillin. However, few penicillinase producing strains are resistant to both penicillin and cephalosporin.[11] Thus, empirical choice for bacterial meningitis in India should be ceftriaxone which acts against *Hib* and vancomycin which acts against resistant *SP*. After positive culture results and specific antibiotic sensitivity pattern it can be modified accordingly.

- If a resistant organism is identified, the choice of antibiotics becomes more difficult and expert guidance from infectious disease specialist is desirable.

Factors determining the use of antibiotic

1. Pharmacodynamics

- The agent should be bactericidal.

- The minimum inhibitory concentration should be lower than the breakpoint recommended by Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility testing (EUCAST) guidelines. If multiple antibiotics are showing susceptibility, the one with lowest MIC/break point ratio and favourable pharmacokinetics for the given patient is best suited.

2. Pharmacokinetics

- Lipophilic agents are preferred: Lipophilic agents like rifampicin, quinolones, chloramphenicol, sulphonamides penetrate blood brain barrier (BBB) rapidly irrespective of inflammation. Hydrophilic agents like beta-lactams, vancomycin penetrate BBB better if inflammation is present. Most antibiotics cross BBB during inflammation and penetration decreases as inflammation subsides.

- Low molecular weight agents penetrate CSF better.

- Antibiotics in protein bound state cannot enter CSF.

- Antibiotic concentration in CSF should be adequate.

- Antibiotic should be effective both in CSF and brain parenchyma.

Basic principles of pharmacodynamics and pharmacokinetics in antibiotic efficacy:

β-lactam antibiotics work with principle of maintaining drug levels above MIC for longer time. This can be achieved by highest possible dose to be delivered over longer hours of infusion. Classically, meropenem can be given as 40 mg/kg/dose as infusion for 3-4 hours, three times a day. Aminoglycosides work on principles of highest peak level to inhibit the bacteria and hence once a day dose is ideal way of delivery.

Choice of antibiotics

1. Penicillins

Penicillins had proven to be the mainstay of treatment of CNS infections. This group has favourable safety profile and better CNS penetration, across inflamed meninges. With increasing instances of resistance and less availability of penicillins, it is no longer considered first drug of choice in clinical practice.

2. Third generation cephalosporins

This group is still the commonest first line empirical choice for community acquired CNS infections currently. Cefotaxime, ceftriaxone are the commonly used agents. Penetration is good through inflamed meninges. Cephalosporins are effective against few beta lactamase (BL) producers, but extended spectrum beta lactamase (ESBL) producing organisms are resistant to cephalosporins. It is effective against *Hib* and most of the *S.pneumoniae*.

3. Carbapenems

This group is effective empirical choice especially when ESBL producers are suspected. They are good broad-spectrum agents working against non-MRSA Gram positive, almost all Gram negative, ESBL producers and anaerobes. Imipenem has seizure potential and needs to be combined with cilastatin to prevent rapid excretion through renal tubules, hence meropenem is the preferred agent. Present break point by CLSI guidelines is 8 mcg/mL.

4. Aminoglycosides

This group of agents are used in combination with B-lactam antibiotics for synergism, better efficacy and to achieve good concentration in CSF. The renal toxicity and ototoxicity are the side-effects and are to be monitored.

Antimicrobials for resistant pathogens

a. Gram positive organisms

Resistant *S. pneumoniae* and MRSA are growing concern. VRSA and VRE are less common in India.[12]

1. *S.pneumoniae* resistance to penicillin groups in India is a growing concern and Vellore study[11] has highlighted that fact. MIC more than 1 mcg/mL for cefotaxime is considered cefotaxime resistance and vancomycin is indicated.

2. Linezolid being bacteriostatic and its role as anti-tubercular drug has prevented its use in MRSA infections. It has good CNS penetration and can be used in vancomycin resistant Gram positive CNS infections. Side effects like optic neuritis, peripheral neuropathy and bone marrow suppression need to be monitored.

3. Clindamycin or daptomycin may be used sparingly in specific situations. Daptomycin is more effective against *S. aureus* than vancomycin. It is as effective as vancomycin in *S.pneumoniae* infections. Being a large molecule, its penetration in CSF is not very good.

4. Quinolones like moxifloxacin have better penetration in non-inflamed meninges. They are effective in resistant *S. pneumoniae*. Tigecycline, a semisynthetic derivative of tetracycline has poor CSF penetration.

b. Gram negative organisms

1. Resistant Gram-negative infections are a cause of concern world over. The resistance is mainly due to B-lactamase producing organisms which damage the B-lactam ring of first line drugs. With increasing rate of resistance from B-lactamases and extended spectrum B-lactamases (ESBL) in the context of non-availability of newer research molecules, it has become extremely difficult to treat such infections. They are predominantly seen in hospital setup and in patients with predisposing risk factors. They are also found in community settings, more often in neonates.

c. ESBL producers

1. ESBL/carbapenemase producers are categorized by Ambler classification as A, B, C, D. C and D are phylogenetically derived from A and has genetic structure like A.

2. Ambler class C is basically cephalosporinase producers from SPICE (Serratia, Pseudomonas, Indole positive Proteus, Citrobacter, Enterobacter) and carbapenem is effective in such infections.

3. Ambler class B are NDM (New Delhi metallo-beta-lactamase) organisms and are almost pan drug resistant. Combinations of high dose carbapenem with colistin/polymyxin are useful: occasionally tigecycline may work

4. Following drugs may be useful in such infections

   i. Fosphomycin: Formerly used in UTI,is now finding its utility in resistant ESBL producers

   ii. Ceftazidime-avibactam

   iii. Meropenem-verobactam

   iv. Rifampicin

   v. Co-trimoxazole

   vi. Quinolones

While using such drugs in resistant infections, MIC, break point, CSF penetration of these drugs in such infections need to be studied and poly therapy may be instituted when appropriate. Sometimes, short course of these drugs given intrathecally may complement the IV course (especially when primary drug is a poor CSF penetrator).

Timing and duration of antibiotic treatment

In all infections, delayed institution of antibiotics leads to poor outcome, and hence the following points are to be borne in mind. Based on the clinical features, such as with hemodynamic instability, encephalopathy, seizures, etc. The disease can be categorized as stage I, stage II and stage III. In adults, institution of antibiotics prior to stage I has 9% adverse outcome as compared to 33% in stage II and 56% in stage III.[13] One needs to ensure CSF sterility and absence of complications such as abscess, subdural empyema. Usually, 10-14 days duration is recommended for bacterial meningitis in children.[14] Repeat CSF examination is not essential if rapid clinical recovery without focal signs or symptoms is achieved. Repeat CSF examination, with or without neuroimaging is essential if clinical response is not seen within 3 days of antibiotic therapy or with deterioration. In case of neonatal bacterial meningitis with Gram negative infection, appropriate antibiotics for three weeks is recommended. In case of fungal meningitis, 4-6 weeks of IV antifungal therapy is

recommended. CSF parameters may linger for longer duration in neonates and CSF sugar and CSF cell count may take long time to normalise, after completion of antibiotic course. Once the stipulated course is completed and baby is clinically normal, antibiotics should be stopped irrespective of CSF sugar levels.

Antimicrobial therapy beyond neonatal period

Standard recommendation for empirical choice of antibiotics in diagnosed case of bacterial meningitis in different age groups beyond neonatal period is shown in Table III.

Antibiotic choices for neonatal meningitis

Common organisms involved are *Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella species and* occasionally *Acinetobacter.*

Choice of antibiotics include ampicillin and gentamicin or cefotaxime. For infants younger than 7 days old, the dose for Ampicillin is 150 mg/kg per day divided every 12 hours, plus gentamicin 4 mg/kg daily once a day or cefotaxime 100 to 150 mg/kg per day divided every 12 hours. From 8 to 28 days old, the antibiotics are the same, but the dosing is slightly different. The ampicillin dose is 200 mg/kg/day divided q6 hours, plus the same dose for gentamycin or cefotaxime 150 to 200 mg/kg per day divided every 6 to 8 hours.[15]

In Indian scenario with growing incidence of community acquired ESBL producers and resistant Gram-positive organisms, vancomycin with meropenem can be justified as first line empirical choice for a sick baby with neonatal meningitis. It should be de-escalated as per culture reports. In instances where CSF has not grown any bacteria and blood culture is positive for an organism

Table III. Antimicrobial therapy beyond neonatal period in different age groups

Age groups	Common organisms	Empirical antibiotics (should be given intravenously)
1-23 months	*Streptococcus pneumoniae, Neisseria meningitidis, Strep. agalactiae, Haemophilusinfluenzae, E. coli*	Vancomycin(10-15 mg/kg/dose 6 hourly) plus a third-generation cephalosporin (e.g., ceftriaxone 50 mg/kg/dose 12 hourly, cefotaxime 75 mg/kg/dose 8-12 hourly)
2-18 years	*N. meningitidis, Strep. Pneumonia*	Vancomycin plus a third-generation cephalosporin
Special conditions		
Head trauma basilar skull fracture and penetrating trauma	*H. influenzae, Strep. pneumoniae, Staphylococcus aureus, coagulase-negative staphylococci (especially Staphylococcus epidermidis), gram-negative bacilli (including Pseudomonas aeruginosa)*	Vancomycin plus cefepime (50 mg/kg/dose 8-12 hourly), vancomycin plus ceftazidime (100 mg/kg/dose every 8 hourly) (duration 10-14 days)
Post-neurosurgery	*Gram-negative bacilli (including P. aeruginosa), S. aureus, coagulase-negative staphylococci (especially S. epidermidis)*	Vancomycin plus cefepime, vancomycin plus ceftazidime (duration 14 days)
CSF shunt	*Coagulase-negative staphylococci (especially S. epidermidis), S. aureus, aerobic gramnegative bacilli (including P. aeruginosa)*	Vancomycin plus cefepime, vancomycin plus ceftazidime (duration 2-3 weeks)

Note: Consider addition of injection azithromycin in 8-years and above for rickettsial infections.

Source: Lingappa L, Patel H, Sharma D. Acute Bacterial Meningitis. IAP Standard Treatment Guidelines 2022.

the same organism is considered to be the pathogen and antibiotics are continued accordingly.

Tackling resistant organisms

Infectious diseases expert opinion is desirable in resistant infections. Know the MIC/break-point from report provided and CLSI/EUCAST guidelines.[16] Ensure that the minimum inhibitory concentration (MIC) is less than break point and the antibiotic has favourable PK/PD criteria for CNS infections.

- Resistant Gram-positive infections

1. Vancomycin as empirical choice is justified. Once report shows sensitivity to B-lactam, ceftriaxone alone can be given.

2. Resistant staphylococci need vancomycin in case of MRSA. Linezolid penetrates CNS but it is a bacteriostatic drug.

- Resistant Gram-negative infections

These are predominantly ESBL producers. Common organisms being *E. coli, Klebsiella, Pseudomonas, Acinetobacter, Strenotrophomonas, E.kingi,* etc. These bacteria are seen in high-risk susceptible population, commonly seen in health care associated infections in neonates and immunosuppressed patients.

Carbapenems in high dose with prolonged infusions is the mainstay of treatment. Polymyxins are more commonly used in combination. Colistin has renal toxicity, thus polymyxin B is the preferred molecule from the group and has better safety profile. Polymyxin cannot be used alone, thus they are always part of polytherapy. Colistin has poor BBB penetration, thus short duration intrathecal or intraventricular injections can be used in sensitive organisms.

Complicated CNS infections

Brain abscess[17]

Brain abscess is localized capsulated collection of pus in brain. It has various stages starting from early cerebritis,late cerebritis to abscess formation. Cerebritis is localized infective inflammation which has high chances of total resolution with appropriate antibiotic therapy for appropriate duration.

Treatment

Abscess generally needs evacuation and prolonged antibiotic therapy.

- Evacuation: Needle aspiration or surgical removal.

- Antimicrobial therapy: Empirical choice can be decided from probable source of infection. For blood stream infection, ceftriaxone with metronidazole can be empirical choice till definitive pathogen is identified. For contiguous infections, vancomycin with ceftriaxone can be empirical choice. Prolonged course, generally 6-12 weeks based on type and sensitivity pattern of organism detected and clinical response, is often needed.

- Radiological recovery may take months. antibiotics can be stopped after 6-8 weeks once clinical recovery and reduction in size of lesion is noticed. Subsequently child needs to be clinically monitored for 6-12 months for any deterioration.

Ventriculitis

Commonly seen in neonatal meningitis (almost 20%). Clinically presents with non-responding fever or re-appearance of fever, seizures, increasing head circumference, bulging fontanel or irritability with poor feeding and vomiting after primary response. It is a localized lesion and at times, CSF from lumbar puncture may be normal. Antibiotics according to culture sensitivity should be given for 6-8 weeks. Few studies have shown role of intraventricular antibiotics, especially for resistant organisms showing colistin sensitivity. CSF sterility and total recovery needs to be ensured to reduce long term sequel.

Recurrent meningitis

This is a rare problem which needs further investigation for a probable cause. There can be anatomical defects or it may be due to immunodeficiency disorders. CSF culture may give a clue as to the possible defect. Treating the underlying defect will lead to permanent cure.

Localized meningitis / Spinal meningitis

Sometimes meningitis may be localized to certain pockets in cranium or in spinal canal due to fibrinous septa formation. This can be a true infection or just local inflammation and needs prolonged antibiotic course and sometimes surgical debridement.

Subdural empyema

This is also a complication of bacterial meningitis. It is commonly seen in infantile age group. Microbes are same as for bacterial meningitis. It presents with fever and features of raised ICP, seizures, idiopathic irritability. It is diagnosed by USG or CT and drained with needle or surgical evacuation with an external ventricular drain (EVD) followed by antibiotics for 4-6 weeks.

Points to Remember

- *Common organisms in the community acquired CNS infections are S. pneumoniae and H. influenzae.*

- *Understandingthe microbiology, pathology and pharmacokinetic and pharmacodynamic principles of drugs is essential in treating CNS infections.*

- *Choice of antibiotic for CNS infection is determined by age, epidemiology, source of infection and immune status of the host.*

- *Newer resistance patterns are being recognized in CNS infections in India.*

- *The complications like brain abscess, ventriculitis and recurrent meningitis must be treated adequately.*

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ANTIMICROBIAL THERAPY OF URINARY TRACT INFECTION

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Abstract: *Urinary tract infections in young children are more often associated with underlying abnormalities and can cause permanent renal scarring. Diagnosis is based on a combination of clinical and laboratory parameters. Initial empiric therapy is guided by knowledge of common local pathogens and sensitivity patterns, followed by targeted therapy based on urine culture and sensitivity reports.*

There is conflicting evidence regarding use of continuous antibiotic prophylaxis. Although there is a reduction in recurrent febrile UTI with antibiotic prophylaxis, infections with resistant strains increase with no proven benefit on scarring. Individualized decisions need to be taken and other modifiable risk factors corrected.

The principles of good antibiotic stewardship need to be followed to avoid increasing prevalence of UTI due to resistant organisms.

Keywords: *Cystitis, Pyelonephritis, Antibiotics, Antimicrobial stewardship.*

Infection of the urinary tract is a common cause of morbidity in children, with reported prevalence rates of 4 to 8%.[1] They are more common in males in the first year of life and in females thereafter. Pediatric urinary tract infections (UTIs) have a significance beyond the acute illness, as they may be the first presenting feature of an underlying anatomical or functional anomaly of the urinary tract (AFAU). Commonest of these are vesicoureteric reflux, obstructive uropathies like posterior urethral valves and bladder-bowel dysfunctions (BBD).[2] Therefore, apart

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from immediate management, diagnostic work up should include tests which rule out such anomalies.

In addition, febrile UTI in young children, particularly if recurrent and /or associated with AFAU, can result in permanent renal parenchymal scarring.[3] Such scarring has been associated with hypertension and risk of chronic kidney disease(CKD).[4,5] It is therefore vital that antimicrobial therapy is used early in an effective and safe manner, but also important that resistant strains do not emerge due to inappropriate therapy.

Anti-microbial therapy in the form of continuous antibiotic prophylaxis (CAP) is also indicated in some circumstances to prevent recurrence of UTI.

Diagnosis

ISPN guidelines consider growth of a single organism of >1 lakh cfu/mL in the presence of symptoms as diagnostic of UTI.[6] A mid-stream clean catch sample after local cleansing, is preferred to samples from collection bags. If there is suspicion of contamination, confirmation from a suprapubic aspirate or a sample obtained by trans-urethral bladder catheterisation is required. Urinalysis should be performed within 1 hour of voiding urine. For culture, the urine sample should be plated within one hour of sample collection, if not possible it may be stored at 4°C upto 24 hours.[6] Mis-match with clinical symptoms (for example symptoms subsiding rapidly without antimicrobial treatment before urine results are available), absence of pyuria, presence of large number of epithelial cells, low colony counts or mixed growths suggest contamination. Laboratory diagnostic criteria for UTI based on various methods of urinary sampling are given in Table I.[6,7]

Urinary pathogens

The commonest organism grown in 70-90% of urine cultures is *Escherchia coli*.[8,9] This predominance is due to its ability to attach to urinary tract urothelium, invade cells and form an intracellular biofilm that protects it from the host immune system. Other Gram negative organisms like *Klebsiella spp., Pseudomonas spp., Enterobacter spp.* and *Proteus spp.* are grown less commonly. *Proteus spp.* are common prepuceal contaminants in uncircumcised boys.

Table I. Laboratory diagnosis of UTI[6,7,11,17]

Test	Criteria	Sensitivity % (95% CI)	Specificity % (95% CI)
Urine dipsticks	Nitrite positive	53 (15-82)	98 (90-100)
	Leucocyte esterase positive	83 (67-94)	78 (64-92)
Urine microscopy	WBC > 5/HPF of centrifuged urine >10/µL uncentrifuged urine	73 (32-100)	81 (45-98)
	Bacteria present	81 (16-99)	83 (11-100)
Urine culture	Growth of single organism :		
Clean catch specimen	$\geq 10^5$ CFU/mL	75-100%	57-100%
Catheter specimen	$\geq$50,000 CFU /mL	95%	99%
Supra-pubic aspirate	Any growth	gold standard	

CFU: colony forming units, HPF : high power field

True UTI due to *Proteus* organisms may be associated with nephrolithiasis and triple phosphate (struvite) stones. UTI due to Gram positive organisms like *Enterococci spp.* is occasionally detected, while *Staphylococcus saprophyticus* UTIs are more common in adolescent girls.[9] Non-*E Coli* and extended spectrum beta lactamase (ESBL) producing (atypical) organisms are more common in patients with previous infection, recent hospitalisation, short-term antibiotic exposure, CAP, AFAU or indwelling catheter/devices. In a retrospective study, febrile UTIs caused by *Enterococcus* were more common in males, children with VUR and recent antibiotic use.[10]

The commonest source of infection is ascending infection from the perineum, therefore UTIs are more common in girls who have shorter urethra. In infants and younger children hematogenous spread can also happen.

Management of acute UTI

The decision to hospitalize depends on general condition, compliance, age, ability to take fluids and medications orally and need for parenteral therapy along with risk identification. Children with systemic signs like high grade fever, loin pain and vomiting are considered to be suffering from upper renal tract infection or pyelonephritis and are at higher risk. Risk is also increased in infants and those with AFAU. Risk is assumed to be less in older children with lower urinary tract symptoms or cystitis features.

Specific management with antimicrobial therapy

This is usually planned in two stages:

1) **Empirical treatment** - When clinical features as well as preliminary urinalysis are strongly suggestive of an UTI, antibiotics are commenced as early as possible, without waiting for urine culture reports. Delay in initiating treatment has been associated with increased risk of developing renal scars.[3] The knowledge of commonly grown local urinary organisms and their sensitivity pattern is required to guide this initial therapy and formation of local guidelines accounting for these are useful (Table II and III).[6,11,12]

2. Definitive / targeted treatment, is management as per urine culture report - once the culture reports are attained, the antibiotic regime can be tailored and narrowed down as per the report.

Anti-bacterial therapy

Common choices for initial empirical therapy are 3rd generation cephalosporins, aminoglycosides (if normal renal function) and amoxicillin-clavulanic acid. (Table II, III). Drugs like nalidixic acid or nitrofurantoin, are rapidly eliminated in urine and do not achieve therapeutic concentrations in serum or renal parenchyma, therefore they are avoided in the therapy of febrile UTI.[11] One study suggests that oral nitrofurantoin treatment could be an option for lower UTI caused by ESBL-producing E. coli.[13]

Quinolones (which are not licensed for use in prepubertal children), are highly efficient against most uropathogens. However, their use should remain limited to multidrug-resistant pathogens, since development of quinolone-resistance occurs rapidly.[14]

Table II. Commonly used antibiotics for UTI

Drug	Dose (mg/kg/day)
Therapeutic (parenteral)	
Ceftriaxone	75-100, in 1-2 divided doses IV
Cefotaxime	100-150, in 2-3 divided doses IV
Amikacin	10-15, single dose IV or IM
Gentamicin	5-6, single dose IV or IM
Amoxicillin-clavulanic acid	75-100 of amoxicillin, in 3 divided doses IV
Therapeutic (Oral)	
Cefixime	8-10, in 2 divided doses
Amoxicillin-clavulanic acid	30-35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10-20, in 2 divided doses
Ofloxacin	15-20, in 2 divided doses
Cefalexin	50-70, in 2-3 divided doses
Prophylactic antibiotics, single bedtime oral dose	
Trimethoprim-sulphamethoxazole	1-2 (trimethoprim component)
Nitrofurantoin	1-2
Cephalexin	10
Cefadroxil	5

Aminoglycosides achieve very good concentrations in renal parenchyma, once daily administration is effective[15] however it must be remembered that they have nephrotoxic potential and a narrow therapeutic index (difference between efficacious and toxic drug levels) and drug levels are monitored less often in practice. Patients may be dehydrated or have pre-existing AFAU which predispose them to develop AKI and hence aminoglycosides are best avoided unless there are no other options.

On days 2-3[16,17] after initial diagnosis and start of empirical antibiotic therapy, the situation should be reviewed to assess response, confirm diagnosis and narrow down to targeted antibiotics as per sensitivity reports. If there is no significant growth in urine, the empiric antibiotic should be stopped and an alternative diagnosis evaluated. If there is significant growth and the clinical condition has not improved, change of antibiotic as guided by culture report and exclusion of factors such as obstruction, stasis, pyonephrosis or perirenal abscess is indicated.

The problem of resistant organisms

In recent times, anti-microbial resistance has become a major issue. Extended spectrum beta lactamase (ESBL) strains of Gram negative bacteria are increasingly seen, even in patients without risk factors.[9,18] This often necessitates use of antibiotics like piperacillin-tazoabactam, cefoperazone-sulbactam, quinolones, aminoglycosides or carbapenems. Antibiotic combinations may increase effectiveness and a recent study found that bacterial sensitivities improved from 47.8% when amoxicillin-clavulanic acid was used alone to >96% when used in combination with gentamicin.[19]

However, ESBL organisms are also resistant to drugs like aminoglycosides, fluoroquinolones and sulphonamides quite often.[20] In addition, carbapenemase-producing strains are rising particularly in hospital acquired UTI or in patients who have obstructive uropathies or indwelling catheters. Colistin and polymyxin B are then chosen despite their nephrotoxic profiles. In using nephrotoxic agents in such situations, it is important to maintain hydration, to regularly check kidney function and reduce doses if GFR is impaired. Imepenem-cilastin, tigecycline, fosfomycin and other newer agents, have also been used in children in salvage scenarios.[20,21]

In-vivo and in-vitro antibiotic response may sometimes be divergent, and clinical response to standard

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Table III. Empiric antibiotic therapy - comparison of guidelines

Guideline	ISPN 2011[6]	NICE 2007 updated 2017[12]	SWISS 2020[17]	ASIAN 2021[11]
Choice of antibiotic	Guided by local sensitivity patterns **or** 3rd generation cephalosporin ± aminoglycoside (AG)	**Pyelonephritis/upper UTI**: age <3 months: IV 3rd generation cephalosporin + ampicillin/amoxicillin age >3 months: oral cefalexin/AC IV: AC/cefuroxime/ ceftriaxone/AG **Cystitis/lower UTI**: >3 months: NF/ TMP/ NF/ TMP/ cefalexin/amoxicillin	**Febrile UTI/ pyelonephritis** aged ≤ 30 days: IV amoxicillin + AG, can switch to oral on improvement age 31-60 days: IV amoxicillin + ceftriaxone, can switch to oral on improvement age >61 days: oral AC or 3rd generation cephalosporin / IV ceftriaxone **Afebrile UTI/ cystitits**>6 months : Oral TMP or AC	Guided by the expected pathogen and the local resistance patterns
Duration (total)	**Infants/children with complicated UTI**: 10-14 days **Uncomplicated UTI**: 7-10 days **Adolescents with cystiti**s: 3 days	**Pyelonephritis/upper UTI**: 7 to 10 days **Cystitis/lower UTI**: 3 days	**Febrile UTI/ Pyelonephritis:** 7-10 days **Afebrile UTI/ Cystitits** age>6 months: 3 days	**Febrile UTI**: 7-14 days **Afebrile Cystitis**: 2-4 days

NF-Nitrofurantoin, TMP-Trimethoprim, AG-Aminoglycoside, AC- Amoxycillin-Clavulanic acid

therapy may be seen even when the culture report indicates a resistant strain. In such cases, there is no harm in completing the course with the antibiotic that has achieved clinical response.

"Antibiotic stewardship" is adhered to while planning and following rational antibiotic guidelines depending on local epidemiology and sensitivity patterns. Avoiding use of broad spectrum antibiotics for non-bacterial or trivial diseases, discerning between contamination and true UTI before starting management, deescalating antibiotics as per the culture results, or stopping antibiotics if cultures are negative and clinical symptoms resolve, are all essential practices that need to be followed to prevent further magnifying this problem.

Route of administration

The Cochrane meta-analysis compared children with pyelonephritis, who received initial IV therapy followed by oral regimes to those who received oral therapy alone.[15] There was no difference in outcome measures in this study, suggesting that therapy can be changed to oral, once acute symptoms like fever and vomiting subside. However, the

data was insufficient to account for children <1 month age or with dilating VUR. The AAP guidelines suggest that the majority of children can be treated with oral medications,[16] however, these guidelines are applicable to patients between 2 months and 2 years only.

The group of children <2-3 months of age are found to be at higher risk of urosepsis and more often affected by UTI due to atypical organisms. Therefore the preference is often to treat this age group with parenteral antibiotics.[6,12] However, a recent survey showed that prescriptions of IV antibiotics for > 4 days for this age group have decreased from 50% in 2005 to 19% in 2015 and this did not cause increased re-admission.[22] A systemic review similarly indicated that switching from early parenteral to oral therapy did not increase recurrence of UTI in children <3 months.[23] Thus initial parenteral therapy (usually 48-72 hours) is followed by oral therapy after resolution of fever and acute symptoms may also be satisfactory in this age group and should be decided on an individualised manner depending on the condition of the baby.

Duration of antibiotic therapy

Children with febrile UTI should be treated for at least 7 to 14 days. Shorter courses have not been shown to be effective.[24] Only afebrile adolescents with lower urinary symptoms have been reported to do well with short courses of antibiotics of 3-5 days in a relatively older metanalysis.[25] Fever is expected to resolve within 48 to 72 hours with appropriate therapy.[6] If there is rapid resolution of symptoms, there is no requirement to repeat urine tests after completion of therapy.

In children with acute and/or chronic renal failure, AFAU or presence of foreign material, a more severe course of UTI is expected. In such cases, longer treatment duration may be required and the optimal management strategy should be determined after a multidisciplinary discussion involving nephrologists, urologists and infectious disease specialists.

Fungal UTI

Fungal UTIs are more common in low birth weight neonates, immune-compromised patients, patients who have been treated with antibiotics for long durations and who have had prior surgical procedures or indwelling urinary devices. Neonatal candiduria can indicate contamination or infection. For asymptomatic patients, elimination of risk factors, such as removal of bladder catheters, is recommended if feasible and if not feasible, treatment is not recommended unless the patient is at high risk for dissemination.

For symptomatic candida UTI, fluconazole is preferred for susceptible strains; alternatives like amphotericin B or flucytosine may be used as per sensitivity patterns.[26] Amphotericin B is nephrotoxic and requires renal functional monitoring and dose adjustments in the case of reduced GFR. The liposomal amphotericins are not nephrotoxic since they are not concentrated well in renal parenchyma, for the same reason they are usually not effective in fungal pyelonephritis.[27] The newer antifungals like caspofungin or micafungin may be used in case of resistant strains and have been shown to be safe and effective in children. Echinocandins may be used only in pyelonephritis, since renal parenchymal concentrations are adequate, but urine concentrations are poor, so they are ineffective in fungal cystitis.[28] In fungal pyelonephritis with or without fungus balls, elimination of urinary tract obstruction and sometimes surgical intervention is recommended.

Tuberculous UTI

Tuberculous pyelonephritis is rare in children, affecting <5% of cases with extrapulmonary tuberculosis. Diagnosis is often delayed because of nonspecific symptoms and late presentation and many children present with cicatrization sequelae. Anti-tubercular therapy is the cornerstone of treatment, although surgical intervention is required in a minority of the cases.[29]

Asymptomatic bacteriuria

Several reports have shown that patients who have significant bacterial growths in urine, without any symptoms, do not have risk of renal parenchymal damage.[6,11] This suggests that the virulence of the organism has been attenuated by host immune factors, or that it is due to colonisation by non-virulent strains. If treated, the organisms may be replaced by more aggressive bacteria. Thus asymptomatic patients should not be treated. This is true even for patients with AFAU (who may even have significant associated leucocyturia), immunosuppressed patients such as those with renal transplants[30] and patients on clean intermittent catheterization. Asymptomatic bacteriuria should be treated only in pregnant women, because in them it is a risk factor for pyelonephritis and premature delivery.

Prophylactic antibiotics and prevention of UTI recurrence

In long term management of patients with UTI, CAP for several months to years, is often considered in an attempt to prevent recurrent UTI, which is associated with increased risk of permanent renal scarring.[3]

Table IV. Continuous antibiotic prophylaxis (CAP), comparison of guidelines

Guideline	ISPN 2011[6]	NICE 2007 updated 2017[12]	SWISS 2020[17]	ASIAN 2021[11]
Indication	Infants: while awaiting imaging studies, VUR, recurrent febrile UTI even if the urinary tract is normal	Recurrent UTI, peri-MCUG	Complex CAKUT / BBD/VUR grades IV-V/peri-MCUG	VUR grades III-V, recurrent pyelonephritis, significant urinary tract obstruction.
Choice of antibiotics	aged ≤ 3-6 months: cefalexin/ cefadroxil age >3 months: TMPS /NF* (avoid in G6PD deficiency, renal insufficiency*)	Age>3 months First line: TMP/ NF Second line: cefalexin / amoxicillin	Amoxicillin (neonates), TMP/ TMPS/NF	TMP/TMPS/ NF/ cefalexin
Duration	VUR grades I-II: until 1 year old, restart if breakthrough febrile UTI occurs. VUR grades III-V: up to 5 years of age. Consider surgery if breakthrough febrile UTI occurs. Beyond 5 years: if BBD.	Individualised, review every 6 months	Individualised, review after 6-12 months	Not specified

NF: nitrofurantoin, TMP: trimethoprim, TMPS: trimethoprim-sulphamethoxazole, VUR: Vesicoureteric reflux, MCUG: micturating cysturethrogram, CAKUT: congenital anomalies of kidney and urinary tract, BBD: bladder bowel dysfunction.

RIVUR study has shown in patients with grades 1-4 VUR that there was 50% reduction in the occurrence of recurrent UTI, but scarring incidence remained the same in CAP group. Also, the incidence of resistance to CAP drugs was found to be increased.[31]

In contrast, a smaller RCT from India, found an increased risk of symptomatic UTI in patients on CAP in patients with grade 1-4 VUR. In contrast, a smaller RCT from India, found an increased risk of symptomatic UTI in patients on CAP in patients with grade 1-4 VUR with no difference in new scar formation. However subjects were dissimilar in these two studies, and the time to develop scarring was short.[32]

Considering these and previous RCTs, a Cochrane updated meta analysis in 2019 suggested a small benefit of using CAP to prevent recurrent symptomatic UTI. This effect was similar in children with or without VUR. However benefit of CAP used should be balanced against the risk of developing microbial resistance.[33] A systematic review of 7 RCTs showed no effect of CAP in preventing renal scarring, however follow up duration was short and limited in number of children with high grade VUR.[34]

Utility of CAP showed no benefit in patients with antenatally diagnosed hydronephrosis of diverse etiologies.[35]

In view of such conflicting data, the common sense practice seems to be to individualise the decision to use CAP depending on patient characteristics. In addition, a careful search should be made for any underlying correctable UTI risk factor. Constipation and urinary stasis, should be treated optimally. Good fluid intake, perineal hygiene and frequent and complete bladder voiding, should be attempted. Most guidelines continue to recommend CAP for infants with VUR, children with higher VUR grades, BBD and recurrent UTI (Table IV). In patients with dilating VUR, CAP is often prescribed until the patient is symptom free for about 2 years. If there are repeated breakthrough UTIs despite CAP, VUR surgery may be advised.

Short courses of antibiotic prophylaxis to cover procedures like micturating cystourethrogram (MCUG) was shown to significantly reduce post-MCUG UTI especially in those with dilated VUR or bilateral VUR, but made no difference in patients already on CAP.[36]

Intra-vesical instillation of gentamicin has been proven to be safe and effective in small series of patients with complex urological abnormalities,[37] but may have a detrimental effect on the bladder in the long term.

Choice of antibiotic for prophylaxis

If CAP is contemplated, a narrow spectrum antibiotic which concentrates well in the urine is selected (Table IV). Trimethoprim or nitrofurantoin are suggested first-choice antibiotics for prophylaxis. These antibiotics have less effect on the normal intestinal microflora and reduced emergence of resistance. Trimethoprim alone is not available in India and trimethoprim-sulphamethoxazole, which is used in its place is contraindicated below 3 months of age.

Broad-spectrum agents should not be used for CAP since they result in higher rates of resistance and kill normal commensal flora and increase susceptibility to antibiotic-resistant strains. Neonates are an exception, where amoxicillin and cephalexin are accepted as prophylactic agents.

Miscellaneous anti-microbial modalities to prevent UTI recurrence

In a meta analysis of 10 studies (2865 children), probiotic (lactobacillus) treatment was shown to have a small effect in preventing UTI when used along with antimicrobial agents, but not when used alone.[38] Cranberry use reduced UTI occurrence in healthy children and had similar efficacy as CAP in patients with urogenital abnormalities, however dosages varied widely and no standardisation of treatment is yet available.[39] Utilisation of steroid cream in physiological phimosis of infants and circumcision in young boys with underlying anatomical abnormalities are reported to reduce UTI recurrence rates.[2]

Supportive management

This includes adequate hydration, antipyretics and maintaining electrolyte balance. Blood pressure and renal function are monitored. In addition children with obstructive uropathies may require relief of obstruction, without which the infection may not be adequately cleared

Conclusions

Urinary tract infections are common in children. They may be the first symptom of an underlying urinary tract anomaly and be associated with permanent renal scarring. The current UTI guidelines are focused on identifying the children with risks of renal damage, treating them effectively and on protecting them from unnecessary,

painful and potentially harmful investigations as much as possible. Over-diagnosis of UTI is a common problem since urinalysis and urine cultures often give non specific results. Clinical clues, urinalysis and culture results should be considered together in making an UTI diagnosis.

The choice of antibiotics for treating symptomatic UTI should be guided by good antibiotic stewardship. In case of pyelonephritis, a critically sick child, infants and/or underlying urogenital anomalies, parenteral antibiotics may be required initially, before shifting to oral antibiotics on improvement of symptoms. Rapid and effective anti-microbial treatment of the acute UTI should be followed by consideration of underlying risk factors and efforts to prevent recurrence.

Criteria for using prophylactic antibiotics continue to face controversies because of lack of irrefutable evidences and it has to be viewed on case by case basis. Control of modifiable risk factors like constipation, voiding anomalies and urinary stasis should be looked into first. Individualising CAP decision with restriction to those with recurrent UTI, high grade VUR, BBD and in infants is advisable. Asymptomatic bacteriuria is not an indication for treatment or follow-up.

Points to Remember

- *Urinary tract infections are common and require early but specific diagnosis and prompt treatment.*

- *Empiric therapy is based on knowledge of common local uropathogens and their sensitivity patterns.*

- *Targeted antibiotic therapy, based on culture and sensitivity results should be as narrow spectrum as possible.*

- *Discontinuation of unnecessary antibiotics is an essential opportunity for improved antimicrobial stewardship.*

- *The benefits of using a prophylactic antibiotic should be judged against the potential risk of UTI due to resistant organisms.*

- *Modifiable risk factors like constipation, voiding anomalies and urinary stasis should be looked for in all patients and managed.*

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ANTIMICROBIALS IN PEDIATRIC INTENSIVE CARE UNIT

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Abstract: *Severe infections in children are the most commonly encountered situation in pediatric intensive care units and therefore, antimicrobial agents are the most frequently used medications. The treatment of these patients poses challenges for various reasons like delayed diagnosis, prior use of antibiotics, difficulties in identifying causative microorganisms and the high prevalence of antibiotic-resistant strains. Therefore, appropriate use of antimicrobials is the cornerstone to ensure positive clinical outcome. On the other hand, inappropriate use of antimicrobials may lead on to the increase in hospital stay, increasing cost, emergence of multi-drug resistant organisms and mortality. The pediatric intensive care unit should evolve and implement standardised guidelines for antimicrobial use based on local susceptibilities and hospital based antibiograms. This article will review the appropriate use of antimicrobial in pediatric intensive care unit especially as the empirical therapy for commonly encountered infections.*

Keywords: *Antimicrobial therapy, Antibiotic use, Critical care.*

Majority of patients admitted in the pediatric intensive care units (PICUs) are admitted with infections or develop it during the hospital stay. The reason for this is either there is primary infection at admission or secondary infection develops due to malnutrition or suppression of immunity following severe illness, use of invasive devices or a possibility of cross infection. The early and appropriate use of antimicrobials has proved to be the most important decision in the management of septic patients. This looks like a promising prospect, but, there is a constant clinical challenge for intensivist due to the increasing prevalence of new multi-drug resistant pathogens and complexity of the factors involved in the selection of drugs keeping in mind the changing pharmacodynamics and pharmacokinetics of the drugs and to match it with the patient's clinical response.[1,2] The lack of protocolised treatment for critically ill children could lead to an increase in inappropriate antimicrobial usage. An estimated 25-50% of antimicrobials used are unnecessary or inappropriate, directly impacting antimicrobial resistance.[3]

Factors determining initiation of antibiotics

1. Establishing the factor that it is bacterial infection: Antibiotics should not be started for probable viral infections like common cold or diarrhoea.

2. Consideration of biomarkers for starting antibiotics prevents nonessential antimicrobial exposure and reducing treatment failure rates.

3. Source of the organism whether originating from community or health care associated infection is assessed.

Golden rules to for antibiotic usage.[4]

a) Appropriate cultures before starting antibiotics (blood, urine, throat swab, tracheal aspirate +/- BAL, pus, wound swab) should be taken.

b) Two sets of cultures with appropriate amount of blood are taken. Sample should not be taken from central or arterial line (unless checking for central line mediated infection).

c) Timing of blood cultures with fever is not critical.

d) Delay in the administration of antibiotics must be avoided.

e) Empirical therapy is started first the spectrum is narrowed narrow later.

f) Initial doses must be appropriate under dosing avoided.

g) Monotherapy used wherever possible (reduces cost and toxicity).

h) If the microbiology results suggest decreased susceptibility, one should consider whether the antibiotics are working well based on the response.

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If there is direct bedside evidence that they are working, then they are continued in spite of laboratory evidence. In vitro sensitivity does not always predict in vivo effect.

i) A shorter course (e.g. 7 days) is probably as good as a standard 2-week course in most cases.

j) Infectious diseases specialists should be consulted when managing serious infections.

k) Antimicrobial pharmacokinetics and pharmacodynamics must be known tissue penetration and dose adjustment considered to correct for altered clearance.

l) Antibiotic levels monitored when available.

m) "Prophylactic" use limited to appropriate situations.

n) Non-infective causes of inflammation considered as sepsis mimics are surprisingly common

o) Antimicrobial stewardship program in the PICU is essential.

Common errors committed during antibiotic therapy

- Delay in antibiotic administration in severe sepsis.

- Antibiotics given before cultures taken

- Contaminated or insufficient blood sample

- Excessively long courses of antibiotics

- Erratic changes of antibiotics in non-resolving sepsis

- Inadequate doses

- Poor choice of empirical antibiotics, failing to account for resident flora

- Failure to predict toxicity or account for interactions

- Failure to consider tissue penetration of different antibiotics

- Inappropriate use of antibiotic polypharmacy or failure to de-escalate to monotherapy

Factors affecting antibiotics effectiveness.[5]

a) Pharmacokinetics (PK)

- PK parameters, together with dosage strategy, determine drug serum concentrations and consequently concentrations in tissues and body fluids.

- The modified PK in the PICU patient, namely in terms of altered volume of distribution (Vd) and drug clearance (Cl) are the two most important kinetic challenges.

- Intravenous fluid loading, hypoalbuminemia and endothelial dysfunction with consequent capillary leakage contribute to interstitial space expansion in the critically ill children. Diseases with exuberant systemic inflammation accentuate this effect, such as burn victims and patients with sepsis. In the case of hydrophilic antibiotics (beta-lactams, aminoglycosides, daptomycin, glycopeptides), this can potentiate Vd.

- For protein-bound antibiotics (ceftriaxone, ertapenem, flucloxacillin, daptomycin), an increase in their unbound fraction, due to hypoalbuminemia, causes greater distribution and clearance (Cl)

- Many critically ill children demonstrate increased Cl despite normal serum creatinine values. This is called as augmented renal clearance (ARC) and is thought to occur after an acute insult. ARC poses the risk of suboptimal antibiotic concentrations and subsequent treatment failure.

- In critically ill children requiring renal replacement therapy (RRT) for acute kidney injury, clearance will depend essentially on the dialysis dose of RRT (mode of RRT, filter porosity, protein binding, molecular weight, blood flow and effluent rates) and eventual residual native renal function.

b) Pharmacodynamics (PD)

- The PD of a drug reflects parameters of antimicrobial activity (capacity to kill or inhibit microbial growth) and toxicological effects of the drug.

- Concentration-dependent patterns of bactericidal activity are observed with fluoroquinolones, aminoglycosides, and metronidazole's effect on anerobic bacteria. For these antibiotics, a high initial concentration is required to ensure maximum bacterial kill.

- Time-dependent patterns rely on minimal concentration-dependent activity. Bactericidal saturation occurs at low multiples of minimal inhibitory concentrations (MIC). This pattern is observed in beta-lactams, clindamycin, vancomycin, and macrolides. Consequently, dosage optimization implies increasing duration of time the serum levels exceed the MIC so timely doses of the drug required.

- Beta-lactams, the most commonly prescribed antibiotic, are hydrophilic drugs with consequent extracellular distribution, a small Vd and renal excretion. Risk of sub-therapeutic concentrations with increased Vd and ARC could be overcome with prolonged infusions.

Factors determining initial choice of antibiotics

1. Travel history

- Geography of endemic region

- Known ongoing outbreaks (like COVID)

2. Empiric vs definitive

- Are we convinced of the diagnosis?

- Is there a need to cover broadly?

3. Urgency and timing

- In patient with sepsis (every hour delay is associated with a 1% mortality increase)

4. Reliability of cultures

- Are we sure that the correct pathogen is cultured?

- Is a polymicrobial infection possible

5. Drug factors

a. Site penetration

- Penetration to the CSF (lipophilicity)

- Exclusive distribution into the circulating volume, (hydrophilicity, or high serum protein binding)

- Exclusion of a drug from a specific organ (eg. the inactivation of daptomycin by lung surfactant)

b. Synergistic combination

- Need for multiple agent therapy (e.g. in *Pseudomonas*)

- Unquestioned need for synergy (e.g. cocktail for TB)

- Advantage from synergy (e.g. ampicillin with gentamicin for enterococci)

Timing of antibiotic

- Early antibiotics, prevent injury caused by microbial activity and toxin production.

- Administration of antibiotics, by killing the causative micro-organism, may halt or ameliorate physiologic progression to multi-organ dysfunction syndrome (MODS).

- Microbial load increases as the infection progresses over time and the cytokine release that occurs when antibiotics are given may be more severe and increase the likelihood of progression to MODS.

Guidelines for antibiotic prescription[6]

1. Community acquired pneumonia (CAP)

- A non-pseudomonal beta-lactam (cefotaxime, ceftriaxone, or amoxicillin-clavulanic acid) plus a macrolide (azithromycin or clarithromycin).

- For penicillin-allergic patients, a respiratory fluoroquinolone (levofloxacin, moxifloxacin or ciprofloxacin).

- If *P.aeruginosa* is an etiological consideration, antipseudomonal antibiotic (like ceftazidime, cefoperazone, piperacillin-tazobactam, cefoperazone–sulbactam, imipenem, meropenem or cefepime) should be used.

- If Staphylococcus infection [Methicillin resistant Staphylococcus aureus(MRSA)] is suspected, empiric vancomycin or teicoplanin to be added. Linezolid used for vancomycin intolerant patients, vancomycin-resistant *Staphylococcus aureus* (VRSA), or patients with renal failure.

- Duration : Usual 7 to 10 days. For CAP due to *Pseudomonas* or aspiration pneumonia : 14 days. Necrotizing pneumonia due to *Staphylococcus* or anerobes : 14 to 21 days

2. Ventilator associated pneumonia (VAP)

- Monotherapy with piperacillin-tazobactam or cefoperazone-sulbactam, cefepime, levofloxacin, imipenem, or meropenem. For treatment of VAP due to MRSA, vancomycin or linezolid.

- Duration : 7 to 8 days

3. Catheter related blood stream infection (CRBSI)

- Empirical antibiotic regimen for CRBSI should include coverage for both Gram-positive and Gram-negative organisms.

- Vancomycin or teicoplanin is the recommended firstline drug for the empiric treatment of CRBSI for MRSA.

- Empiric coverage for gram-negative bacilli should include a fourth-generation cephalosporin, a carbapenem, or a â-lactam/â-lactamase inhibitor combination, with or without an aminoglycoside.

- Echinocandin or fluconazole should be used as empirical antifungal agents for the treatment of suspected central line-associated candidemia.

4. Urinary or urogenital sepsis

- The antibiotics should cover for ESBL producing Gram-negative organisms: aminoglycosides, beta-lactam along with a beta-lactamase inhibitor or carbapenems.

5. Peritonitis

- Third-generation cephalosporins (such as cefotaxime and ceftriaxone) for 7 to 10 days in patients with primary peritonitis.

6. CNS infection

a) Meningitis: Community acquired

- Third-generation cephalosporin (preferably ceftriaxone) plus vancomycin as empirical antibiotics of choice for community-acquired meningitis.

- Duration :10 to 14 days for *Streptococcus pneumoniae,* 14 to 21 days for Streptococcus agalactiae, 7 days for Neisseria meningitides or *Haemophilus influenzae*, 21 days for aerobic Gram-negative bacilli and 21 days or more for *Listeria monocytogenes*. If no microorganism is identified, treatment should be given for at least 10 to 14 days.

b) Meningitis: Nosocomial

- Vancomycin in combination with cefepime, ceftazidime or meropenem.

c) Brain abscess

- Third generation cephalosporin combined with metronidazole.

7. Skin and soft tissue infection (SSTI)

- For moderate SSTI, penicillin or clindamycin.

- Severe SSTI, combination of piperacillin-tazobactam with vancomycin, teicoplanin or linezolid.

- Concomitant surgical examination and/or debridement should be considered.

- Sepsis of unknown origin

  - Combination of ceftriaxone and doxycycline or macrolide for community-acquired sepsis of unknown origin.

  - Beta-lactam/beta-lactamase inhibitor and a fluoroquinolone or aminoglycoside for nosocomial sepsis of unknown origin.

  - Duration of therapy is 7 to 10 days.

Stopping antibiotics or de-escalating antibiotics

- Antibiotics should be ceased after 48-72 hours if cultures are negative.

- Antibiotics should be tailored specifically according to cultures at 48-72 hours.

- If it is not appropriate to stop antibiotics (because of a high probability of bacterial infection or signs of severe sepsis), antibiotic therapy can be de-escalated when 48-hour cultures are negative.

Conclusion

- Treatment of infection in PICU is a very challenging task.

- The choice of antibiotic and the duration of therapy has to be individualized for each patient, taking into consideration the disease severity, etiological organisms and local resistance patterns.

- A responsible antibiotic prescribing may help reduce antibiotic pressure and development of antibiotic resistance.

Points to Remember

- *Antimicrobials are the most commonly used drugs in PICU and appropriate use helps reducing mortality in critically ill child.*

- *Antibiotics should be monitored for dosage, indication and early de-escalation must be done.*

- *Pharmacodynamics and pharmacokinetics are the factors which determine the effectiveness of antimicrobials.*

- *The choice of antimicrobial is decided by the site of infection and whether it is community acquired or hospital acquired.*

- *Initiation, de-escalation, or escalation of antimicrobials should be done based on the culture sensitivity results.*

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ANTIMICROBIALS - II

MANAGEMENT OF HIV IN CHILDREN - AN UPDATE

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Abstract: *Management of human immunodeficiency virus infection, especially in the pediatric population is constantly evolving. As newer drugs are being introduced and safety profile established for children, there has been a change in guidelines. With the onset of the COVID - 19 pandemic, it is essential that the management of human immunodeficiency virus infection in children, including early diagnosis, medications and follow up is not disrupted. This article reviews the recent updates in human immunodeficiency virus infection care and hopes to equip the practicing pediatrician with a tool for basic care and management of children living with HIV infection.*

Keywords: *Human immunodeficiency virus infection, Antiretroviral therapy, Prevention, Transmission, Acquired immunodeficiency syndrome.*

With the introduction of antiretroviral therapy (ART), human immunodeficiency virus *(*HIV) infection is no longer considered a disease with definite mortality; but a chronic, manageable illness with reduced morbidity. Although great strides of improvement were witnessed in the epidemiology of HIV since 1997, people living with HIV (PLHIV) now face multiple problems because of the Covid-19 pandemic especially access to medicines and healthcare.

The latest technical brief estimated the total number of PLHIV in India at 23.19 lakh in 2020. Children (<15 years) accounted for 3.5% of the total infections.[1]

There has been a decline of around 55% annual new HIV infections among children between 2010 and 2020.

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Still, the MTCT (mother to child transmission) rate was approximately 27.45% in 2020 against the target of 5%. The slow PMTCT (prevention of mother to child transmission) response was observed during the COVID-19 pandemic and is expected to be further affected due to disruption of services.[1]

This review aims at equipping pediatricians, general practitioners and students with a brief guide in the management of HIV in children and to prevent mother to child transmission at the background of an ongoing COVID pandemic.

Maternal testing[2]

Pregnant women should be tested as soon as possible during each pregnancy.

Repeat testing is recommended for pregnant women with negative initial HIV tests in the 3rd trimester in the following situations

a) Increased risk of acquiring HIV, especially in those facilities where HIV incidence is >1/1000 pregnant women/year.

b) Pregnant women with sexually transmitted infections (STI's), or with signs and symptoms of acute HIV infection, or ongoing HIV exposure.

c) HIV testing should be fast-tracked for those who have undocumented status during pregnancy or delivery and those who have tested negative in early pregnancy but were not re-tested in the third trimester.

If results are positive, intrapartum antiretroviral (ARV) treatment should be initiated immediately.

Viral load testing for mother and updated prophylaxis of infants

HIV risk categorization of infants is done on the basis of viral load (VL) of the mother tested during 32 to 36 weeks of pregnancy (Table I).

• Zidovudine (ZDV) prophylaxis regimen is recommended for infants born to mothers with HIV-2 mono-infection.

Table I. Risk categorization and treatment of infants born to mothers with HIV

Category	Options for prophylaxis
Low - Risk - Infants born to mothers with VL <1000 copies/ml at any time from 32 weeks up to delivery	Syrup nevirapine or syrup zidovudine Indications for syrup zidovudine - 1) Infants born to mother with confirmed HIV-1 or HIV-2 or combined infection 2) Mothers who have received a single dose of nevirapine during previous pregnancy or delivery 3) Mother on a PI (Protease inhibitor) based regimen due to treatment failure Duration - birth to 6 weeks
High risk mothers - • Mothers not on ARV • Maternal viral load not done from 32 weeks up to delivery • Maternal viral load not supressed to <1000 copies/ml after 32 weeks of delivery to delivery • Newly identified HIV positive within 6 weeks of delivery	Dual prophylaxis - syrup nevirapine (NVP) and syrup zidovudine (ZDV) Duration - If exclusive replacement feeding (ERF) - 6 weeks If exclusive breast feeding (EBF) - 12 weeks NOTE - If syrup zidovudine is unavailable - syrup nevirapine can be used for 14 days and then syrup lopinavir/ritonavir or pediatric formulation of zidovudine+lamivudine+nevirapine (ZLN) can be used

Table II. Dosing of zidovudine and nevirapine

Infant age	Daily dosing (Nevirapine)	Daily dosing (Zidovudine)
Birth* to 6 weeks		
Birth weight 2000- 2500 g	10 mg (1 ml) Once daily(OD)	10 mg (1 ml) twice daily(BD)
Birth weight > 2500 g	15 mg (1.5 ml) OD	15 mg (1.5 ml) BD
> 6 weeks – up to 6 months	20 mg (2 ml) OD	
> 6 months – up to 9 months	30 mg (3 ml) OD	
> 9 months - until breast feeding ends	40 mg (4 ml) OD *Infants weighing < 2000 g; dose is 2 mg/kg OD	<2000 grams - 5 mg (0.5 ml) BD

• If the mother has HIV-1 and HIV-2 infection, the infant ART regimen should be based on the determination of low or high risk of HIV-1 transmission as described in the Table I. Raltegravir (RAL) may be considered for infants with HIV-2 exposure as it is not susceptible to nevirapine (NVP).[3]

• Daily dose of Zidovudine and Nevirapine as given in Table II.

Note - According to National institute of health (NIH) - 2021, in situations where ZDV is unavailable or the infant has ZDV-associated toxicity - neutropenia or anemia, abacavir (ABC) can be considered as an alternative to ZDV. Prior to initiating ABC, HLA B5701 allele should be done to prevent ABC-associated hypersensitivity.[3]

Dosing of ABC - ≥ 37 weeks' gestation at birth

Birth to 1 month:

- ABC - 2 mg/kg per dose orally BD

Age 1 month to <3 months:

- ABC - 4 mg/kg per dose orally BD

Diagnosis of HIV infection in infants and children[4]

Salient features

1) <6 weeks

- Serologic tests are not recommended according to National AIDS Control Organization (NACO). 6 weeks or above is the optimal age for a routine HIV-PCR test.

- Virologic testing at birth, as per NIH, may be done for babies born to mothers who-

  - Did not receive antenatal care;

  - Received no antenatal or only perinatal ART

  - Initiated ART late in pregnancy (during the late second or third trimester);

  - Received a diagnosis of acute HIV infection during pregnancy or in labour; and/or

  - Had detectable HIV viral loads ($\geq$1000copies/mL) close to the time of delivery, including those who received ART and did not have sustained viral suppression

If negative, ART prophylaxis should be initiated for such infants as per Table I after risk stratification. Blood samples from umbilical cord may get contaminated with maternal blood, hence they should not be used for diagnosis.

2) 6 weeks to < 6 months

a) Human Immunodeficiency Virus Deoxyribonucleic acid Polymerase chain reaction (HIV DNA PCR) via dried blood spot (DBS) method is conducted at 6 weeks of age. If positive, a repeat test is done for confirmation. If the second test is positive - ARV is initiated.

If there is discordance between the 1st and 2nd test, a third test is done and the result of this test is taken as final.

b) If the 6 weeks DBS- HIV DNA PCR is negative, the infant is screened at 6 months or 12 months or 6 weeks after stopping breast-feeding, whichever is earlier.

If the infant gets symptomatic, repeat testing can be done based on the age - HIV DNA PCR for <6 months and HIV antibody + HIV DNA PCR for 6 months to 18 months.

3) >6 months to 18 months

a) Collect blood for HIV antibody tests and use 3 serological tests.

b) If any one of the tests are positive, follow point 2a.

c) If all three tests negatives, follow up for screening as per point 2b.

4) >18 months

a) Test for HIV antibody with 3 serological tests

b) If all three positive - initiate lifelong ARV treatment

c) If all three negative - HIV not detected

d) If any one or two reactive, repeat antibody testing after 2 weeks

Antiretroviral management of infants with perinatal HIV exposure or HIV infection

All newborns who have perinatal exposure to HIV should receive post-partum antiretroviral therapy (ART) to reduce chances of perinatal transmission within 72 hours of delivery or as close to the time of birth as possible. NACO recommends ART initiation even after 72 hours as ART will reduce the transmission via breastfeeding.[5]

ARV management depends on maternal and infant risk factors that influence transmission. It includes

a) ART prophylaxis -newborns without documented HIV infection

b) HIV therapy - ART with documented HIV infection

c) Opportunistic infection prophylaxis

b) HIV - Choice of therapy

NACO and NIH recommend initiating ART as soon as possible irrespective of CD4 count, WHO stage and age; except in the setting of opportunistic infections; where the infections should be stabilised prior to initiating ART.

Exceptions to this - progressive multifocal leukoencephalopathy and mycobacterium avium complex infections (MAC) where MAC treatment may not be available.[6]

Based on the age, hemoglobin levels and renal function, NACO (National AIDS Control Organization (2021). National Guidelines for HIV Care and Treatment, 2021. New Delhi: NACO, Ministry of Health and Family Welfare, Government of India.) recommends the following

ARV medications

1) <6 years and weight <20 kg

Abacavir (ABC) + lamivudine (3TC) + lopinavir/ritonavir

If child is on rifampicin containing anti-tubercular therapy (ATT) - super-boosted ritonavir or body surface area based dose of nevirapine should be used up to 2 weeks after stopping rifampicin.

2) 6-10 years and weight 20-30 kg

ABC + 3TC + Dolutegravir (DTG)

Note - If a child <10 years has intolerance to both ZDV and ABC, stavudine based regimens can be used

3) >10 years and >30 kgs

Tenofovir + 3TC + DTG

But from April 2020 onwards, there has been a gradual shift of current regimen to dolutegravir based ART regimen.

For those children on ALE (ABC + 3TC + EFV) and ZLE (ZDV + 3TC + EFV) regimens, >10 years and >30 kgs and suppressed viral load (viral load <1000 copies/mL), NACO recommends transition to tenofovir (300mg) + lamivudine (300 mg) + dolutegravir (DTG) (50 mg) OD.

If the child is also on rifampicin containing ATT (Anti-tubercular therapy) NACO recommends taking one additional tablet of dolutegravir 50 mg OD.

If the child is on bedaquiline/delaminid containing ART, dolutegravir can be given safely with close monitoring as per NACO.

Children receiving anticonvulsants, require expert opinion and those on antacids should have a time gap of 2-4 hours between antacids and dolutegravir.

Children initiated on ART should be regularly followed up.

Clinical and laboratory monitoring of children living with HIV

NACO recommends

Clinical monitoring - monthly

- Monthly clinical evaluation of growth, development and nutrition
- Tuberculosis (TB) screening

- Adherence check
- For adverse reactions / opportunistic infections
- For drug interactions
- For IRIS (Immune reconstitution inflammatory syndrome)

Immunological monitoring

CD4 count (%) should be monitored every six months for children upto 5 years. Initial CD4 prior to initiating therapy is not compulsory. Beyond 5 years, adult guidelines have to be followed

Virological monitoring

Viral load testing is to be done 6 months and 12 months after ART initiation and then once every year. 'Adherence counselling' must be reinforced at every visit.

Note - If child is above 5 years, CD4 >350 cells/cmm. and viral load <1000 copies/ml testing can be discontinued until viral load is >1000 copies/ml.[7]

With the onset of pandemic - telemedicine and telehealth are growing areas of easy access to health services and has been shown to produce similar outcomes as those associated with in-person care. The advantages of telemedicine include patient and caregiver convenience, lack of travel, flexibility and ability to visualize ART handling/swallowing and conduct directly observed therapy at home.

Telemedicine visits, however, require technological access/capacity and limit the health care professionals' ability to conduct physical examinations and obtain laboratory testing on site.[8]

What's new in ART drugs?

Updated NIH recommendations[9]

- NIH recommends use of DTG (dolutegravir) for children aged 4 weeks and >3 kgs
- Bictegravir (BIC) containing FDC (Bictegravir/emtricitabine and tenofovir) is preferred ART regimen for children >6 years and >25 kg
- Alternative integrase inhibitor now recommended is raltegravir (RAL) with 2 NRTI as they have lower barrier to resistance compared to DTG and BIC
- FDA has approved ABC for infants >3 months with lamivudine or emtricitabine as preferred nucleoside reverse transcriptase inhibitors (NRTI). Zidovudine is

now recommended as alternative NRTI for use in infants and children. NIH recommends use of ABC >1 month.

- Maraviroc is not recommended for use in children

These recommendations are yet to be included and adapted by NACO.

c) Opportunistic infections prophylaxis

1) Cotrimoxazole Preventive Therapy (CPT)

CPT is recommended for all infants exposed to HIV from the age of 4-6 weeks till HIV is reliably excluded. If found to be HIV positive, it is continued until 5 years of age and until CD4 >350 cells/cmm.[10]

For children >5 years, it is initiated at WHO stage 3 and 4 and CD4 count <350 cells/cmm. It is stopped when CD4 count is >350cells/cmm at two different occasions, 6 months apart and WHO Stage 1 and 2.

WHO recommends cotrimoxazole prophylaxis to continue till adulthood if prevalence of malaria and other bacterial infections is high. In areas of low prevalence of malaria and serious bacterial infections, prophylaxis may be discontinued for children >5 years who are clinically stable, on ART for at least 6 months and a CD4 count >350 cells/cmm.[10]

Dose - 5mg/kg/day of trimethoprim

If child is allergic to co-trimoxazole or suffers from G6PD deficiency, dapsone at 2 mg/kg/day (max - 100 mg) may be given.

2) Isoniazid preventive therapy (IPT) and tuberculosis

Tuberculosis (TB) is one of the most common opportunistic infections associated with HIV. NACO recommends IPT for all children with HIV, irrespective of CD4 count and stage of the disease as it helps prevent progression of latent tuberculosis to active disease and reinfection post-exposure to an open case of tuberculosis. IPT is instituted only after ruling out active disease.

Indications

- Children >1 year who do not have fever, cough, poor weight gain.

- Children with no history of contact with tuberculosis

- Active TB to be ruled out (X-ray chest and tuberculin skin test)

Contraindications

- Active tuberculosis

- Active hepatitis

- Signs and symptoms of peripheral neuropathy

- Poor adherence to CPT

- Contacts of MDR-TB

- Children who have completed DR-TB treatment

Dosage - 10 mg/kg/day of isoniazid (max 300mg)

Pyridoxine must be given along with IPT

Dosage - 50 mg OD for >25 kg

25 mg OD for 14-25 kg

12.5 mg OD for 1-13.9 kg

WHO recommends for those CLHIV, with signs and symptoms of disseminated tuberculosis, Xpert Tb/MTB Rif of blood specimens for diagnosis of the same.

If a child is diagnosed with HIV and tuberculosis, WHO recommends initiating ART 2 weeks after anti-tubercular therapy (ATT). If a child is diagnosed with HIV and TB meningitis, WHO recommends initiating ART 4 weeks after ATT.[10]

Feeding of infant born to mother with HIV

The National AIDS Control Organization advises exclusive breast feeding (EBF) for first 6 months of life. If parents are willing, exclusive replacement feeding (ERF) may also be instituted.

Health care workers should encourage EBF or ERF and not mixed feeding.

Maternal ART reduces the risk of postnatal HIV transmission in the context of mixed feeding as well.

Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond with adequate adherence to ART.

For breast-fed babies, NIH recommends three monthly HIV viral testing while breast-feeding and three monthly testing up to 6 months after stopping breast feeds, whereas NACO recommends HIV testing after 6 weeks of stopping breast feeds.[4,5]

Immunization, growth and development of all infants and children born to mothers with HIV should follow

national guidelines as recommended by NACO and NIH. Inactivated vaccines can be given at all ages; but live vaccines are contra-indicated for CD4 <15%.[11]

Points to Remember

- *Pregnant women should be tested as soon as possible during each pregnancy.*

- *HIV DNA PCR for newborns to be done 6 weeks after birth, after 6 months to 18 months, HIV antibody test is recommended and beyond 18 months, serological tests to be done three times.*

- *NACO recommends exclusive breast feeding for the first 6 months or exclusive replacement feeding if parents are willing but not both.*

- *Maternal ART reduces the risk of post natal HIV transmission.*

- *ART therapy should be given based on age, haemoglobin and associated renal disease.*

- *INH preventive therapy with pyridoxine is given as recommended by NACO and cotrimoxazole preventive therapy as advised by WHO.*

- *Inactivated vaccines can be given but live vaccines are contraindicated if the CD4 count is less than 15%.*

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NEWS AND NOTES

NCPID 2022

24th National Conference of Pediatric Infectious Diseases

IAP-ID Chapter

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ANTIMICROBIALS - II

MANAGEMENT OF INVASIVE FUNGAL INFECTIONS

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Abstract: *With the advancement of medical science, there is increase in incidence as well as recognition of invasive fungal infection in children. The introduction of new antifungal agents has increased treatment options for fungal infections. Simultaneously many species have acquired resistance to common antifungal agents. Newer broad-spectrum azoles and echinocandins have revolutionized antifungal treatment. This article summarizes the treatment options for different invasive fungal infections in children.*

Keywords: *Azoles, Amphotericin, Echinocandin, Flucytosine.*

Advancement in medical science in various fields has resulted in increased survival, of neonates and children with increased vulnerablity to invasive fungal infections. Pharmacokinetics and pharmacodynamics of antifungal agents differ in children than in adults.[1] Despite availability of more number of antifungal agents, very few clinical trials have evaluated their clinical safety and efficacy in children and hence limited drugs are being used.

Spectrum of candida infections includes the following

- Local mucocutaneous infections: Oropharyngeal candidiasis, esophagitis, vulvovaginitis, balanitis, chronic mucocutaneous candidiasis

- Invasive Infections: Disseminated infection occurs in high risk patients such as hematological malignancies, recepients of solid organ and stem cell transplants and those on chemotherapy. Invasive focal infections include urinary tract infection, endophthalmitis,

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Box 1. Invasive fungal infections

- Candidemia and invasive candidiasis
- Cryptococcal infections
- Histoplasmosis disseminated
- Histoplasmosis acute pulmonary infections and disseminated infections
- Invasive aspergillosis
- Mucormycosis

Box 2. Antifungal drugs

1. Triazole antifungals: Fluconazole, itraconazole, posaconazole, voriconazole.

2. Polyene antifungals: Amphotericin B, lipid formulations of amphotericin

3. Echinocandin antifungals: Echinocandin, anidulafungin, caspofungin, micafungin

4. Other antifungals: Flucytosine

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osteoarticular infections, meningitis, endocarditis, peritonitis and intra-abdominal infections, empyema, mediastinitis, pericarditis and chronic disseminated hepatosplenic candidiasis (Box.1).

Following are the antifungal drugs used in invasive infections (Box 2).

Amphotericin B and lipid formulations of amphotericin B: Liposomal amphotericin B is a unique lipid formulation of amphotericin B prepared by its incorporation into a liposome bilayer or unilamellar liposomes. This alters the pharmacokinetic properties of the drug, where in antifungal activity of amphotericin B is retained, but its toxicity is significantly reduced. Acute infusion-related reactions, electrolyte disturbances and nephrotoxicity are associated with the use of amphotericin B, which often prevents completion of the course. Lipsomal preparations of Amphotericin B has comparable efficacy with less side effects and hence this is used more frequently now, despite its higher cost compared to conventional preparations.

Candidiasis

Invasive candidiasis caused by *C. albicans* is the most common systemic mycotic infection reported throughout the world. Candida is a small oval shaped yeast which normally inhabits the gastrointestinal tract, female genital tract and the skin which causes superficial as well as invasive infection. Invasive candidiasis usually results from hematogenous spread in an individual with risk factors. But it can also result from contiguous spread from deep wounds, catheter related or following abdominal surgery. It can involve any system or organ starting from nervous system, pulmonary, gastrointestinal, urinary tract, liver, spleen, heart and eyes. The incidence and spectrum of candidiasis has changed dramatically in recent years. There is an overall increase in the incidence of non albicans candida species such as *C. tropicalis Candida parapsilosis* and *C. glabrata* globally.[2]

Treatment: Antifungal therapy is the mainstay of treatment for invasive candidiasis. In addition, the probable source of infection like, indwelling catheter, or infected prosthetic heart valves should be removed. While selecting the antifungal therapy for invasive candidiasis following points should be considered.

- Organ or system involved
- Severity of the disease
- Species involved and the sensitivity pattern
- Immune status of children
- Previous use of azoles

Antifungal therapy in different clinical situations are discussed below.

a) In non-neutropenic children, fluconazole is used as a first line drug. Echinocandins may also be used. Amphotericin B is used as an alternative drug only if there is intolerance or resistance to other agents.

b) In neutropenic children echinocandins or liposomal amphotericin B is used as the first line drug. Azoles are used only if the patient is not critical or there is no previous azole exposure.

c) In neonates, amphotericin B or fluconazole is recommended. Echinocandins are used only if intolerance or resistance to other antifungal agent and after ruling out central nervous system (CNS) infection. The penetration of echinocandins in CNS is low and thus the clinical value of the use of echinocandins for CNS infections remains to be established.[3]

d) In CNS candidiasis, amphotericin B is the drug of choice. Flucytosine is added if no improvement occurs with initial therapy. Switchover to fluconazole may be done if the species are susceptible to it. Echinocandins has limited penetration in CSF and should not be used.

e) In hepatosplenic candidiasis, amphotericin B and echinocandins are used as first line drug. Switchover to fluconazole is done in the consolidation phase if the species are susceptible to it. The dosage schedule of different antifungals is given in Table I.

f) Drug of choice for *Candida krusei* is echinocandins as this species is intrinsically resistant to fluconazole and itraconazole.[4] *Candida glabrata* are also often resistant (both intrinsic and \ acquired) to fluconazole. Voriconazole or amphotericin B is an alternative drug for these two species. Over 90% of *Candida auris* isolates are

Table I. Dose of different antifungals in pediatric age group

Antifungals	Neonates	1 month - 2 years	3-17 years
Amphotericin B deoxycholate	0.7- 1 mg/kg/day	0.7- 1 mg/kg/day	0.7- 1 mg/kg/day
Liposomal amphotericin B	3-5 mg/kg/day	3-5 mg/kg/day	3-5 mg/kg/day
Fluconazole	12 mg/kg/day	12 mg/kg/day	8-12 mg/kg/day
Voriconazole	4-6 mg/kg 12 hrly loading, 2-3 mg/kg 12 hrly maintenance	4-6 mg/kg 12 hrly loading, 2-3 mg/kg 12 hrly maintenance	7-9 mg/kg IV 12hrly 200-400mgoral12hrly
Caspofungin	25 mg/m2/day	50 mg/m2/day	70 mg/m2/day loading 50 mg/m2/day maintenance
Micafungin	10 mg/kg/day	2-4 mg/kg/day	2-4 mg/kg/day

intrinsically resistant to fluconazole and 50-55% to voriconazole. *Candida lusitaniae* is notorious for intrinsic resistance to amphotericin B.[5]

Duration of therapy: For candidemia without any obvious metastatic complication it should be given for 2 weeks after documented clearance of candida from bloodstream.

For candidiasis with end organ involvement like osteomyelitis, arthritis, carditis-prolonged course for at least 4-6 weeks is required.

In hepatosplenic candidiasis - The optimal approach to treatment of chronic disseminated candidiasis is uncertain. Antifungals are continued till lesions disappear. Follow-up computed tomography imaging should be obtained every two to three months. Therapy should be continued until there is persistent resolution or calcification of the lesions on imaging, which usually takes approximately six months.

The pediatric dose of different antifungal agent usually used in children is given in Table I.

Cryptococcosis

In general, cryptococcosis is less common in children than in adults. It is mainly caused by two species of cryptococcus namely, *C.neoformans* and *C.gattii*. Cryptococcosis predominantly occurs in immunocompromised hosts but may also occur in immunocompetent individual. Meningitis and pneumonia are the two common forms of infection. The choice of treatment depends on the site of infection as well as the host immune status.

a) The immunocompetent patients with asymptomatic or mildly symptomatic pulmonary diseases should be treated with oral fluconazole (6 to 12 mg/kg/day) for 6 to 12 months to prevent dissemination of the disease. Any other azole drugs like itraconazole, voriconazole and posaconazole can also be used.

b) Immunocompromised patients with asymptomatic infection or mildly symptomatic isolated pulmonary disease without any evidence of dissemination (backed up by a negative blood culture as well as negative CSF report) can also be treated with long term fluconazole monotherapy. But inadequate response and possible dissemination need more intensive therapy.

c) More severe form of disseminated disease mainly occurs in immunocompromised hosts. For this more severe form of disease (like severe pneumonia, meningitis, sepsis, disseminated cryptococcosis involving two or more organ system) more intensive antimicrobial therapy is needed.

It usually consists of an induction therapy followed by a consolidation/maintenance therapy.

Induction therapy: It consists of amphotericin B (1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hr assuming normal kidney function) for a minimum of 2 weeks. Flucytosine is always used as combination therapy with amphotericin B for invasive infections.

Longer periods of induction (4-6 wk) should be considered in the following scenarios:1) Immunocompetent patients with cryptococcal meningitis; 2) Meningitis secondary to *C. gattii*; 3) Neurological complications (including cryptococcomas) and 4) Absence of flucytosine in the induction regimen. Lipid-complex amphotericin B (3-6mg/kg/day) can be used in place of amphotericin B for patients with underlying renal injury or those receiving nephrotoxic drugs.

Consolidation therapy: Following induction, consolidation therapy with oral fluconazole (pediatric dose 10-12 mg/kg/day, adult dose 400-800 mg/day) should be given for 8 weeks.

In patients with ongoing immunosuppression, maintenance fluconazole should be used to prevent recurrence. Maintenance fluconazole for 6 to 12 months is recommended for organ transplant patients.

d) In pediatric AIDS patients with disseminated or severe cryptococcosis, after the initial induction therapy consolidation/maintenance therapy should be given for at least one year.[6]

Aspergillosis

Aspergilli are ubiquitous fungi which have almost 250 species, where only 5 species (*A.fumigatus, A.flavus, Aniger, A.terries and A.nidulans*) are responsible for most of the human infections, predominantly in the immunocompromised. Aspergillus can cause different types of diseases depending upon the characteristics and immune status of the host. It can cause allergic (hypersensitive) disease, invasive disease, saphrophytic (non-invasive disease) and chronic diseases. Immunodeficient hosts develop invasive diseases.

The choice of treatment depends on the type of disease and on host immune status.

I. Allergic disease (Hypersenisitivity syndrome)[7,8,9]

1. Allergic bronchopulmonary aspergillosis (ABPA): ABPA is a not a pure infection, it is a mixed immunologic hypersensitivity reaction in the lungs and bronchi in response to colonization of Aspergillus species, presenting like difficult-to-treat asthma. Hence the treatment is also complex, which depends on the stage of the illness. Therapy comprises of systemic steroids, antifungal medications and anti-IgE therapy with omalizumab.

a) Steroid therapy: This depends on the stage of the disease. Exacerbations in stages 1 and 3 are treated with 0.5-1 mg/kg of glucocorticoid for 14 days, followed by every-other-day usage and tapering over 3 months or as long as 6 months. Stage 2 remission phase and stage 5 where fibrosis has occurred do not require steroid therapy.

b) Antifungal therapy: This is needed in stage 4 where steroid weaning has not been successful and continued long-term therapy is required. A 16 week course of itraconazole improves the response rate during exacerbations allowing the reduction of glucocorticoid dosage by 50% and resulting in a reduction of total serum IgE of 25% or more. The adult dosage recommendation for itraconazole is 200 mg 3 times per day for 3 days followed by 200 mg twice daily for the remainder of the 16 wk. Children should receive 5 mg/kg/day in a single dose. If the proper calculated dose exceeds 200 mg, then the total dose should be divided equally and given twice daily. Serum levels of itraconazole are necessary to ensure proper absorption of capsule form. The liquid form is more readily absorbed and has achieved substantially higher levels. Voriconazole has been used as a substitute antifungal medication.

c) **Anti-IgE therapy** - Omalizumab (300-375mg every 2 weeks by subcutaneous injection), a humanized monoclonal antibody against may be beneficial in the treatment of ABPA in the setting of poorly-controlled asthma.

2. Allergic aspergillus sinusitis: Surgical drainage is the mainstay of therapy coupled with oral steroids and antifungals.

II. Invasive disease

Invasive aspergillosis (IA) is a disease of the immunocompromised hosts IA can affect any organ (like lungs, CNS, heart, eye, bone), but invasive pulmonary aspergillosis (IPA) is and most common form Voriconazole is the drug of choice for IPA as well as for other forms if IA. Echinocandin is considered as a second line agent where voriconazole is contraindicated.[10]

III. Saprophytic (non-invasive) syndromes

These syndromes usually manifests in the form of pulmonary aspergilloma or chronic pulmonary aspergillosis. These are extremely rare in pediatric age group and needs surgical excision along with systemic antifungal therapy with azoles.

Histoplasmosis

Histoplasmosis is caused by the fungus *Histoplasma capsulatum* and usually causes acute and chronic pulmonary histoplasmosis.

Acute pulmonary histoplasmosis does not require antifungal therapy for asymptomatic and mildly symptomatic patients. If the acute pulmonary infection fails to improve spontaneously in 4 to 5 weeks,then oral itraconazole therapy for 6 to 12 weeks should be given (4 to 10 mg/kg/day in 2 divided doses, not to exceed 400 mg/day).

For more sick patients with acute pulmonary histoplasmosis who becomes hypoxic or needs mechanical ventilatory support treatment should be initiated with injectable amphotericin B or amphotericin B lipid complex for 3 to 4 weeks followed by oral itraconazole for at least 12 weeks.

Patients with obstructive mediastinal disease should be treated with oral itraconazole.

Progressive disseminated histoplasmosis needs intravenous amphotericin B for 2 to 4 weeks followed by oral itraconazole for 3 to 4 months.

Severely immunosuppressed patients need more prolonged therapy and if immunosuppression persists then they need lifelong itraconazole prophylaxis.[11]

Blastomycosis

Blastomyces dermatitidis and Blastomyces gilchristi are the main human pathogen involved in causing blastomycosis. They can cause subclinical infection, symptomatic pneumonia as well as disseminated disease depending upon the host immunity.

Treatment of blastomycosis depends on the severity of the infection and status of the host immune system. Neonates with blastomycosis should be treated with IV amphotericin B.

Children with mild to moderate disease can be treated with oral itraconazole 10 mg/kg/day for 6 to 12 months.

Severe and disseminated disease with immune suppression needs treatment with IV amphotericin B for 2 to 3 weeks allowed by oral itraconazole for 8 to 12 months.

CNS blastomycosis requires therapy with IV amphotericin B for 4 to 6 weeks followed by oral Itraconazole for more than one year.[12]

Coccidiodomycosis

Coccidiodomycosisi is caused by Coccidioides spp, a soil dwelling dimorphic fungus. The infection usually results from inhalation of aerosolized spores. Pulmonary infection is the main manifestation and extra pulmonary infection occurs only in 5% cases.

Oral fluconazole or itraconazole are the drug of choice for mild to moderate infection where inj.amphotericin is used for severe infections.[13]

Paracoccidioidomycosis: A systemic fungal infection caused by Paracoccidiodes brasiliensis. There are 2 forms of disease, acute and chronic. Acute infection occurs in children and is manifested as fever, hepatosplenomegaly, lymphadenopathy pulmonary symptoms and multifocal osteomyelitis.

Oral itraconazole for 6 months is the drug of choice, failure of which may need treatment with IV amphotericin B. Sometimes oral steroids are being added to reduce inflammation. Trimethoprim-sulfamethoxazole had been found to be effective in few studies. Other experimental therapies include cyclosporine and curcumin.[14]

Mucormycosis

Predisposing factors include uncontrolled diabetes, hematological malignancy, post transplant patients and use of corticosteroids. Most common forms are the sinus and rhino cerebral mucormycosis followed by pulomonary mucormycosis.

Systemic mucormycosis is a fatal disease and very much resistant to anti-fungal therapy. The treatment includes both extensive surgical debridement along with systemic antifungals.

Injectable amphotericin B (lipid preparations are preferred) is the drug of choice. The dose is usually 5 mg/kg/day and up to 10 mg/kg/day. Duration of therapy is individualised, but usually a 2 to 6 weeks therapy is recommended.[15]

Most of the azoles are ineffective except posaconazole and isavuconazole.[16]

Points to Remember

- *The choice of antifungal agents depends upon the infecting species, organ or system involved and host immune status.*
- *Duration of antifungal therapy depends upon host immune status and response to treatment.*
- *Due to increase in fluconazole resistance amongst candida species, amphotericin B or echinocandins are often used as the first line drug for invasive candidiasis especially in critical, neutropenic patients or with children with azole exposure.*
- *Expansion of azole group of antifungals to voriconazole and posaconazole has added significantly to the treatment of invasive aspergillus species and some emerging fungal pathogens.*
- *Flucytosine is always used as combination therapy with amphotericin B for invasive cryptococcal and some candida species infection.*

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CLIPPINGS

SARSCoV2 neutralising monoclonal antibodies to prevent COVID-19.

Monoclonal antibodies (mAbs) are laboratory produced molecules derived from the B cells of an infected host. They are being investigated as potential prophylaxis to prevent coronavirus disease 2019 (COVID-19). The objective of this study was to assess the effects of SARSCoV2neutralising mAbs, including mAb fragments, to prevent infection with SARSCoV2 causing COVID-19; and to maintain the currency of the evidence, using a living systematic review approach. Randomised controlled trials (RCTs) that evaluated SARSCoV2neutralising mAbs, including mAb fragments, alone or combined, for preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) of COVID-19. Studies of SARSCoV2neutralising mAbs to treat COVID-19 were excluded.

For PrEP, there is a decrease in development of clinical COVID-19 symptoms (high certainty), infection with SARSCoV2 (moderate certainty), and admission to hospital (low certainty) with tixagevimab/cilgavimab. There is low certainty of a decrease in infection with SARSCoV2, and development of clinical COVID-19 symptoms; and a higher rate for allgrade adverse events (AEs) with casirivimab / imdevimab.

For PEP, there is moderate certainty of a decrease in infection with SARSCoV2 and low certainty for a higher rate for allgrade AEs with bamlanivimab. There is high certainty of a decrease in infection with SARSCoV2, development of clinical COVID-19 symptoms, and a higher rate for allgrade AEs with casirivimab / imdevimab.

Although there is hightomoderate certainty evidence for some outcomes, it is insufficient to draw meaningful conclusions. These findings only apply to people unvaccinated against COVID-19. They are only applicable to the variants prevailing during the study and not other variants (e.g. Omicron). In vitro, tixagevimab / cilgavimab is effective against Omicron, but there are no clinical data. Bamlanivimab and casirivimab/imdevimab are ineffective against Omicron in vitro. Further studies are needed and publication of four ongoing studies may resolve the uncertainties.

Hirsch C, Park YS , Piechotta V, Chai KL, Estcourt LJ, Monsef I, et al. SARSCoV2 neutralising monoclonal antibodies to prevent COVID-19. 17 June 2022, https://doi.org/10.1002/14651858. CD014945.pub2.

ANTIMICROBIALS - II

HEALTH CARE ASSOCIATED INFECTIONS AND ANTIMICROBIALS

Naveen Jain

Abstract: *Microbes causing healthcare associated infections are often resistant to commonly used antibiotics. This leads to use and often overuse of combination of antibiotics, resulting in further resistance of microbes. The decision to start a new antibiotic in healthcare associated infections setting should be based on the severity of new signs. If there is organ failure and threat to life, the antibiotics must be urgently administered, and must address most organisms possible. If the antibiotics were prescribed for early warning signs, a combination of signs or persistent abnormal sign must be observed, before making the choice. Overuse of antibiotics can be curtailed by simple measures like hospital policies and ensuring compliance. Shorter courses of antibiotics can be guided by use of biomarkers.*

Keywords: *Healthcare associated infections, Antimicrobials, Children, Neonatal.*

Infections that harm a child / neonate which were not present before health care was initiated; typically, an infection that manifests 48 hours after a procedure or hospital admission is considered as healthcare associated infection (HAI). The risk of HAI is greater among children / neonates following a major procedure or surgery, those who require more than one device or organ system support (ventilator / central catheter, etc.), those with longer hospital stay, among babies who are more sick at admission to hospital, born preterm and younger infants.

HAIs increase the co-morbidities by several fold as well the length of hospital stay[1] and are possibly a contributing cause of preventable death among sick hospitalized children and neonates. The suspicion of HAI results in increased use of antibiotics, often broad spectrum antibiotics and combination of antimicrobials (including anti-fungal),[2] further increasing the risk of antimicrobial resistance (AMR).[3]

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Justification to consider newer antibiotics in suspected HAI

Following hospitalization with or without an invasive procedure, 24-48 hours after hospitalization, any change in clinical status [(sensorium, temperature, oxygenation, perfusion, sugars (STOPS)] for worse or any increased need for ICU supports (ventilation, inotrope, blood products, glucose infusion rates) should be considered as possible HAI. In children, fever is a common pointer to a new infection, which is not the case in neonates. Decision to start / change an antimicrobial in a child / neonate who is hospitalized must be based on potential hazard of the infection. The clinician must be willing to stop, if cultures, biomarkers and clinical findings exclude serious infection.

1. Start new antimicrobial urgently in setting of HAI, in case of organ failure: Shock needing inotropes for hypotension, persistent unexplained tachycardia, poor respiratory efforts / severe respiratory distress, hypoxia despite 40% or more FiO2 / hypercarbia ($PCO_2 > 50$ mmHg) despite optimal ventilation, moderate / severe encephalopathy (seizures), fever $> 38°$ C or hypothermia not corrected after 30 minutes of rewarming, hyperglycemia while on standard glucose infusion rates, hypoglycemia requiring high glucose infusion rates, coagulopathy or oliguria.

2. Consider antibiotics for HAI if early warning signs are identified: more than two abnormal STOPS signs or if one sign persists for more than 6 hours; or persistent increased need of ICU supports (ventilation / inotropes)

3. *High alert for HAI* among children / neonates on more than one device or longer than 48 hours on device (ventilator, central catheter)

4. Children / neonates at higher risk of HAI: Preterm neonates, infants less than 3 months old, extensive skin losses (burns), malnutrition (poor oral intake for 1 week or more), children / infants on parenteral antibiotics for more than 5 days, any health condition requiring repeated hospitalization, infants in foster care (parents not available always) for more than 48 hours

Interventions to minimize HAI?

- Optimize the use of devices[4]: Replace invasive ventilation (intubation) with nasal CPAP / non-invasive ventilation; remove central catheters / urinary catheters

- Replace intravenous fluids with enteral feeds

- Skin care - Protect skin from large adhesive tapes, minimize skin punctures, avoid pressure sores. Prepare skin with disinfectant before skin is breached.

- Decrease unnecessary skin / mucosa handling: Touch charts may restrict the frequent touch opportunities to minimum

- Cohort patients with confirmed infection and limit cross infection

- Hand hygiene: Reinforce wash hands (use alcohol / chlorhexidine hand rubs)

- Disposables to reduce cross infections.

- Optimizing staff pattern - Sickest of infants may require 1: 1 nursing or more. Inadequate staffing results in poor asepsis practices.

- Reduce hospital stay - Ask yourself every day: can the child / neonate be managed at home; can we return the child / neonate from ICU to the room in the ward with the / mother/ caregiver .

- Minimizing work - Workload of the health care personnel can be reduced by decreasing non-critical / non-beneficial processes; example frequency of documentation can be once in 2-3 hours than hourly, in stable ICU patients.

- Have protocols for hygiene of health care facility and equipment disinfection[5]

Managing suspected HAI

Breaking news - It is best to be honest to the families (parents), that a new infection is possibly needing testing and treatment and that this may be associated with health care. This is better than the families asking the same question.

Investigations to confirm new infection

- Blood culture / (urine or CSF as appropriate) - Identification of the microbe has benefits beyond managing the HAI with appropriately chosen antibiotic. The knowledge of common microbes guides choice of empirical antibiotics in the unit.

- Biomarkers (sepsis screen) - The role of CRP, complete blood count, procalcitonin or similar inflammation markers increase the clinician's confidence in stopping an empiric antibiotic. Their role in guiding start of new antibiotics is debatable.

- Unconventional tests

  • Endotracheal culture in suspected ventilator associated pneumonia: Although the aspirates may give a clue to the microbe, a commensal misguiding the clinical decision is more common.

  • PCR of blood / CSF has advantage that the test is not negated by antibiotics; but the amplification of genetic material increases risk of false positives.

  In both the above tests, the reports must be interpreted in context with clinical scenario.

  • Abscess search: Bedside ultrasound can detect deep seated abscess in kidney, liver (especially if a catheter has been in place); ultrasound chest for empyema in a child with pneumonia

Choice of antimicrobials in the setting of HAI

1. Antibiotic choice based on BUG factor: (Expected microbe)

   a. Knowledge of common microbes causing HAI in the region is equally important as the clinical setting.[6] In India, Gram negative bugs have dominated all late infections (HAI); sadly most of them are resistant to frequently used antibiotics.[7] In neonates with suspected HAI in Asian setting, meropenem was found to be far more effective[8] as compared to penicillin / gentamicin or cefotaxime.

   b. An extreme preterm baby with a central catheter and already on antibiotics (especially ampicillin or cefotaxime) must be protected against fungal infections.

2. Antibiotic choice based on HOST factors: (Seriousness of the illness)

   a. If the child / neonate has life threatening (red flags: shock, seizure/ severe encephalopathy, need for ventilation, coagulopathy) / organ threatening health change then antibiotics must cover Gram negative and Gram positive organisms. One may de-escalate to a narrow spectrum antibiotic after the neonate / child is stabilized and culture reports are available). Example of antibiotic choice-meropenem + vancomycin (± anti-fungal, amphotericin).

   b. Early warning signs (two or more / persisting > 6 hours), no red flags as mentioned earlier.

Poor sensorium, persistent/ high grade fever or hypothermia, high Fio2 need or severe distress despite non-invasive ventilation, persistent severe tachycardia, fall in urine output, glucose disturbances, severe feed intolerance. (choose a broad spectrum like piperacillin tazobactum or cefoperazone - sulbactum; CONS is not as common in Asia, as is in the Western population).

c. Sepsis biomarker positive (CRP > 15 - 20 mg / L, or low total / absolute neutrophil counts) in the presence of a new sign (one may choose a narrow spectrum antibiotic if there are no red flags / warning signs; one may even wait and watch) (example amikacin alone)

The suggested antimicrobial combinations have to be adapted as per local / clinical scenarios; they are illustrative examples from the authors unit

3. Antibiotic choice based on DRUG factors

a. If there is severe renal dysfunction, nephrotoxic antibiotics like vancomycin, amphotericin, aminoglycosides, colistin may be used only if indicated. Drug dose modification must be made as indicated.

b. Site of infection: Encephalopathy / seizures, mandates use of antibiotics that cross meninges like meropenem or cefotaxime. If cultures suggest antibiotics that are not expected to cross meninges as the only choice, one may still use them in maximal doses. When the meninges are inflamed, they allow most antibiotics to cross.

Minimizing antimicrobial overuse (and AMR) in HAI - Quality initiative examples

1. Preventing spread of multi-drug resistance (MDR) microbes: [10] Even a single microbe that is MDR must trigger a comprehensive control plan that includes cohorting patients, reinforcing hand hygiene, environment control and surveillance.

2. Restricting antibiotic misuse: [9] In most outpatient settings (children without serious illnesses) there is a potential to decrease antibiotic prescription to a great extent. HAI often result from incorrect use (example fungal and clostridial infections, following antibiotic misuse).

3. Reducing the duration of antibiotic therapy: [11] Shorter courses of antibiotics for urinary infections, ear infections and many other settings have been proven to be safe and effective and adults. Shorter courses in children and neonates need to be tested and validated. Biomarker have shown to be promising.[12]

4. Empower labs and clinical pharmacists: [13] The labs must flag detection of microbes directly to the clinician and the response to report must be documented and audited. The clinical pharmacist can help in evaluating the right dose, combinations and limit the use of "higher antibiotics", when not indicated. These practices have a direct effect in cost- saving.

5. Parents in ICU: [14] Strict hand hygiene practices are very labour intensive and fail due to worksite fatigue among doctors and nurses. Involving parents / families in care processes that place lower risk and that do not require skill acquisition have many benefits (example diaper change, oro-gastric feeding, calming the child, giving oral medications not requiring accurate doses). The parents are more likely to adhere to hand hygiene when caring for their own child; they often do not harbour MDR. They also act as "surveillance cameras" (Families not allowed to be near their child is more likely to trigger medico-legal situations).

6. Role of leadership (state / hospital administration):[15] Having standard treatment guidelines - choice, dose, duration, dispensing anti-microbials and audits is a low investment high output strategy in improving anti-microbial behaviours.

7. Engineering solutions: They appear attractive, but are expensive and often not as effective.[16]

HAI prevention is of medical and medicolegal importance; the use of antibiotics for suspected HAI results in resistance and increasing resistance forces clinicians to use more antibiotics. This vicious cycle leading to MDR will pull us back to pre-antibiotic era, where infections were uniformly fatal. We must act fast and at different points. This article has many suggested solutions; one may choose and adapt the principles mentioned.

Points to Remember

- *New STOPS signs (2 or more / persistent sign) that suggests possible infection in a child / neonate after an invasive procedure / device use should alert possibility of HAI.*

- *Severe (organ failure) infection must cover all possible microbes (including fungus) and de-escalate after cultures point to a specific microbe.*

- *If HAI is suspected, but not life or organ threatening, biomarkers may guide to a shorter course of anti-microbials.*

- *Involving parents in care of sick children in ICU can decrease the risk of HAI.*

- ***Measures to control HAI and compliance to policies on appropriate antibiotic use can slow down the problem of antimicrobial resistance.***

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NEWS AND NOTES

MADURAI PEDICON 2022

46th Annual Conference of IAP-TNSC

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ANTIMICROBIALS - II

UNCOMMON PEDIATRIC INFECTIONS

Valsan Philip Verghese

Abstract: *Brucellosis, Melioidosis and Lyme disease are increasingly being recognized as causes of acute febrile infection in children. Vital clues to diagnosing these infections include history of exposure to livestock or consumption of unboiled milk for brucellosis, exposure to soil or surface water for melioidosis, and exposure to ticks for Lyme disease. As the clinical manifestations of these infections can mimic typhoid, tuberculosis, rheumatic fever and systemic-onset juvenile idiopathic arthritis, they need to be kept in mind whenever there is failure to respond to therapy. Early diagnosis and appropriate therapy, although often prolonged in duration, is associated with good outcomes in children.*

Keywords: *Brucellosis, Melioidosis, Lyme disease*

Brucellosis

Brucellosis is a zoonotic disease in which children acquire the infection most commonly by ingestion of unpasteurized milk or through direct contact with an infected animal.

Etiology and pathogenesis

Brucella was first isolated from humans by Sir David Bruce and later found to be carried by goats on the island of Malta (*Brucella melitensis*), after which other *Brucella* species were identified from the aborted fetuses of cattle (*Brucella abortus*), swine (*Brucella suis*) and dogs (*Brucella canis*). These animals serve as a reservoir for the organisms and are transmitted to humans through ingestion of contaminated milk or meat, inoculation through abraded skin or the conjunctiva, or inhalation of aerosolised infectious particles. *Brucella* are facultative intracellular aerobic Gram-negative partially acid-fast

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coccobacilli that have the ability to evade the body's natural defense mechanisms including stomach acid on ingestion, leading to intracellular survival of the organism followed by replication and seeding of macrophages within the reticuloendothelial system including the liver, spleen, lymph nodes and bone marrow via the lymphatics.[1]

Epidemiology

Brucellosis has been reported in humans and domestic animals in India from the beginning of the century. Although commonly reported in rural communities where people live in close proximity to animals from various states including Karnataka, Goa, Rajasthan, Uttar Pradesh, Bihar and West Bengal, Assam and Kashmir, the true population incidence of disease is unknown.[2-8] Children account for a third of the cases of human brucellosis, usually in those taking care of cattle or sheep and/or consuming raw or unpasteurized milk or poorly cooked meat.[9] While most human brucellosis in India is due to *B.abortus* and *B.melitensis*, pediatric cases are reported to be more common in areas where *B.melitensis* is endemic.[2] Males and children older than 6 years of age are more commonly affected than females or younger children and more than half of pediatric cases are over the age of 11, reflecting the sex and age groups of those most likely to have occupational exposure.[2,8]

Clinical manifestations

Brucellosis in adults can present as an acute illness with symptoms for < 2 months after an incubation period of 2-3 weeks, a subacute illness with insidious onset and symptom duration of 2-12 months, or a chronic illness lasting for > 1 year associated with complications and debilitation ("chronic fatigue syndrome").[1]

Children tend to have an acute febrile illness, usually associated with *B.melitensis* infection.

Common clinical manifestations documented in children from India (Table I) are

- fever and arthralgia, associated with

- hepatic and/or splenic enlargement and

- generalized lymphadenopathy that is discrete, involving the cervical, submental, submandibular and axillary nodes.

Table I. Clinical manifestations of brucellosis in Indian children[2,4,8,10]

Symptoms and signs of brucellosis	Findings in children from various studies, in percentages
Symptoms	
Fever	73-100%
Arthralgia / myalgia	22-39%
Sweating / chills	32-42%
Abdominal pain	13-33%
Backache	10-20%
Signs	
Hepato/splenomegaly	53-67%
Generalised lymphadenopathy	3-33%
Arthritis	7-39%
Rash	3-13%
Meningitis	1-7%
Epididymo-orchitis	7%
Carditis	2%
Peripheral neuritis	1%

Arthritis, when present, is often monoarticular mimicking septic arthritis with the knee most commonly involved, and involvement of the hip, ankle, elbow and shoulder less commonly seen. Sacroiliitis, spondylitis and osteomyelitis have been described in adults.

Rash when present is seen as non-pruritic, erythematous, discrete papules measuring 2-4 mm over the face, trunk and the extremities and associated with positive blood cultures.

CNS involvement (neuro brucellosis) is seen in about 5% of cases and presents as meningitis or meningo encephalitis, while chorea, facial palsy and peripheral neuritis have also been described.

Carditis is rare and manifests as endocarditis, with mitral mid-diastolic or pansystolic murmurs on clinical examination, vegetations on the mitral valve on echocardiogram and blood cultures positive for *B.melitensis*.[2]

Pulmonary involvement with pneumonia or bronchitis, and rarely pleural effusions, has been described[10] and is probably due to inhalation of aerosolized bacteria, while epididymo-orchitis has been described in adolescent males.[8]

Congenital brucellosis that presents with a clinical picture of neonatal sepsis and meningitis has also been described in babies born to infected mothers, in whom the infection can also lead to stillbirths and preterm deliveries.[11]

Laboratory investigations[1,12]

Culture: Definitive diagnosis of brucellosis is based on a positive culture from the blood, tissue or fluids such as CSF or synovial fluid. However, as Brucella are fastidious slow-growing organisms, blood and other cultures tend to be positive in only about 50% of specimens. As Brucella bacteremia becomes low-grade and intermittent after the organism gets sequestered in the macrophages, repeating blood cultures can improve the yield to over 80%. Use of rapid isolation method such as Bactec / BacTAlert or MALDI-TOF, prolonged incubation for 30 days and culture of bone marrow also improve culture positivity.[12]

Serology: As Brucella manifest slow growth in culture, serological tests to detect IgM antibodies to Brucella that appear by the end of the first week of illness, followed by IgG, are the most useful tools for diagnosis. Serological tests include the Rose Bengal test which is used as a rapid screening test. With its high sensitivity but poor specificity it has a high negative predictive value, but a positive test has to be confirmed by a more specific test such as the serum agglutination test (SAT) which is diagnostic at titres of 1:160 or above in a symptomatic patient or 1:320 in an asymptomatic individual from an endemic area. Other serological tests include the Brucella IgM/ IgG ELISAs, point-of-care tests such as the IgM / IgG lateral flow assays and the latex agglutination tests that have sensitivity and specificity of 90-95%.

Molecular methods: Polymerase chain reaction / PCR tests are rapid and can be done on any specimen. These include real-time PCRs and the multiplex PCRs for rapid confirmation of *Brucella* with identification of the species. Although more sensitive than the culture and more specific than serology, standardization of the test and its clinical significance, including defining a threshold to differentiate active infection from low-level DNAemia in asymptomatic individuals, still needs to be established.[1,12]

Other lab tests: Hematological findings in brucellosis may be normal or include anemia, leukopenia, neutropenia, thrombocytopenia, and pancytopenia.[4,13] Liver function

tests are often normal, or may show mild to moderate elevation of liver enzymes.[10,13] Bone marrow and liver biopsies may show ill-defined epithelioid granulomas without caseous necrosis.[10,14]

Synovial fluid in children with arthritis has shown lymphocytic pleiocytosis.[8] Children with neurobrucellosis have CSF pleiocytosis, low sugar and elevated proteins similar to pyogenic meningitis.[2,8] Neuroimaging findings can be normal or reveal inflammatory changes and raised intracranial pressure with ventricular dilatation or rarely, a ring-enhancing lesion with surrounding vasogenic edema.[15]

Treatment[16,17]

The principles of brucellosis treatment include prolonged use of antibiotics with intracellular activity such as doxycycline and rifampicin in combination together or with trimethoprim-sulphamethoxazole (TMP-SMX) or an aminoglycoside, to prevent relapses.

Recommended treatment regimens are as follows, given in Box 1.

Prevention

Ensuring pasteurization of milk and complete cooking of meat as well as eradication of the organism from livestock remain the essential steps in prevention of human brucellosis.

Box 1. Various treatment regimens for Brucellosis

1) For Brucellosis without carditis, neurobrucellosis or spondylitis

< 8 years of age

TMP-SMX (oral) at 10 mg/kg/day of trimethoprim (maximum 320 mg/day) in 2 divided doses for 6 weeks
PLUS
Rifampicin (oral) 15-20 mg/kg/day (maximum 600-900 mg/day) once daily for 6 weeks.

≥ 8 years of age

Doxycycline (oral) 4.4 mg/kg/day (maximum 200 mg/day) in 2 divided doses for 6 weeks
PLUS
Rifampicin (oral) 15-20 mg/kg/day (maximum 600-900 mg/day) once daily for 6 weeks.

Alternative regimen for ≥ 8 years of age

Doxycycline (oral) 4.4 mg/kg/day (maximum 200 mg/day)in 2 divided doses for 6 weeks
PLUS Either of:
Streptomycin IM 15-40 mg/kg/day (maximum 1 gm/day) IMonce daily for 14-21 days

Or

Gentamicin IM/ IV 5 mg/kg/day IM / IV once daily for 7-10 days.

2) For brucella carditis (endocarditis)

Doxycycline (oral) in children **≥ *8 years of age*** **OR** TMP-SMX (oral) in children **< *8 years of age***
PLUS Rifampicin (oral); all doses as previously mentioned, for 12 weeks ***PLUS*** **either of:**
Streptomycin IM **OR** Gentamicin IM/ IV, doses as previous, for 4 weeks.

3) For brucella spondylitis (rare in children)

Doxycycline (**age ≥ *8 years)*** **OR** TMP-SMX (**age < *8 years)*** **PLUS** Rifampicin (as mentioned above) **PLUS**
Streptomycin IM, dose as previous for 14-21 days **OR** Gentamicin IM/IV, dose as previous, for 7-14 days.

4) For neurobrucellosis / Brucella meningitis

Ceftriaxone 100mg/kg/day in 2 divided doses (maximum 4 gms/ day) for 4-6 weeks
PLUS
Doxycycline (**age ≥ *8 years)*** **OR** TMP-SMX (**age < *8 years)*** **PLUS** Rifampicin (as mentioned above), for at least 12 weeks.

For Brucella carditis and neuro brucellosis, treatment may be extended for 4 to 6 months.

Melioidosis

Melioidosis in children is due to infection with the soil saprophyte *Burkholderia pseudomallei* through inhalation, ingestion or skin inoculation via soil and surface water.

Etiology and pathogenesis

Burkholderia pseudomallei is a facultative intracellular motile Gram-negative bacillus with bipolar staining and rounded ends, the "safety pin" appearance. It is an environmental saprophyte found in soil and surface water in endemic regions that can survive in the soil for many years under harsh environmental conditions including high temperatures and soil desiccation. Although it can be aerosolised in dry dust, most acquisition of infection is through occupational and recreational exposure to moist soil and pooled surface water. While most abundantly found in soil at a depth of >10 cm from the surface, rainfall allows the organism to move closer to the surface and multiply leading to seasonal increases of infection during the rainy season. A host of virulence factors and intrinsically broad drug resistance to aminoglycosides, fluoroquinolones and tetracyclines enable *B.pseudomallei* to survive and multiply within phagocytic and non-phagocytic cells of the human host. Intercellular spread of infection results in cell fusion and the formation of multinuclear giant cells and/or non-caseating granulomas in affected organs.[18]

Epidemiology

Although known to be endemic to southeast Asia and northern Australia, the true incidence of melioidosis in India is unknown. *B.pseudomallei* has been identified from coastal soil and serosurveys have identified seropositivity in individuals involved in paddy cultivation in Tamil Nadu and Karnataka.[19-21] While melioidosis has been reported from various regions of India, these are mainly from large medical centers with facilities for identification.[22] The paucity of reports on melioidosis in children from India is due to poor ascertainment of cases as the disease mimics more common conditions such as tuberculosis.

Clinical manifestations

Most melioidosis presents, after an incubation period of 9 days (range 1-21 days) as either localized disease at the disease entry site with no systemic manifestations, or as an acute febrile bacteremic illness presenting as pneumonia or disseminated infection.[18]

Melioidosis in children is often significantly different from that in adults, as documented in a large prospective study of melioidosis in children and adults from Australia,[23] as follows:

- Children are less likely to have associated pre-disposing risk factors described in adults such as diabetes and are more likely to report an inoculating event.

- Localised melioidosis is more common in children at 60% compared to 13% in adults.

- Pneumonia is less commonly found in children at 20% compared to 54% of adults.

- Bacteremia is significantly lower in children at 16% vs. 59% in adults.

- Fewer children need intensive care compared to adults at 11% vs. 26%, and

- Mortality is lower in children (7% vs. 14% in adults), with mortality being highest in those with bacteremia, disseminated disease and/or septic shock and severe malnutrition.[24] High case fatality rates are also seen with neonatal melioidosis which is often bacteremic and neurological melioidosis.[25]

Most children with melioidosis have fever while other symptoms vary with mainly head and neck or body swellings in those with localized disease while poor appetite, cough and breathlessness, lethargy or irritability, headache, vomiting, diarrhea, abdominal pain, hepatosplenomegaly and abnormal lung findings are more common in children with disseminated disease.[25]

Most children with localized disease have head and neck involvement, with

- Cervical lymphadenitis (often unilateral),[25] which can mimic tuberculosis especially if granulomas are found on biopsy or FNAC.[26]

- Abscesses in lymph nodes, skin and soft tissue, and acute suppurative parotitis.

- Complications of acute suppurative parotitis include abscess formation, rupture into the auditory canal and lower motor neuron facial nerve palsy.[27]

The commonest manifestations in disseminated disease are bacteremia and concomitant pneumonia, with chest X ray findings of patchy consolidation in children and pneumatoceles in neonates.[25,28,29] Bacteremic children are also more likely to have leucopenia.[25,30]

In disseminated disease the spleen and liver are the commonest intra-abdominal organs involved, with multiple

occult abscesses < 1 cm often present on ultrasonogram examination even in the absence of hepatic or splenic enlargement, and mild to moderate hepatic enzyme elevation.[25,30]

Arthritis when present can involve multiple or single joints, with the knee and ankle being most commonly involved.[25]

CNS involvement (neuromelioidosis) is the least common manifestation of disseminated disease. In children it usually presents as meningitis or meningo-encephalitis with cranial nerve and/or bulbar palsy, but can also present as an acute demyelinating encephalo-myelitis (ADEM).[23,31]

Table II. Clinical manifestations of melioidosis in children[23-25,30,34-38]

Symptoms and signs of melioidosis	Findings in children from various studies, in percentages
Fever	83-100%
Localised disease	
Skin & soft tissue abscesses	18-49%
Cervical lymphadenitis	15-26%
Lymph node abscesses	8-18%
Pyomyositis	11%
Parotitis	3-38%
Mastoiditis	2-3%
Pharyngeal abscess	3%
Disseminated disease	
Septicemia	11-60%
Pneumonia	8-56%
Shock	31-38%
Multi-organ dysfunction / MODS	11-15%
Hepatomegaly/splenomegaly or both	27-36%
Liver / spleen abscesses	44%
Septic arthritis	4-10%
Osteomyelitis	2-11%
Psoas abscess	3%
Meningitis / meningoencephalitis	0.3-7%

CSF analysis is characterized by lymphocytic pleiocytosis with elevated protein and normal sugar.[32] MRI findings include leptomeningeal enhancement, white matter hyper intensities, ring-enhancing lesions and abscess or microabscess formation.[32,33]

Clinical manifestations of melioidosis in children, compiled from case series from India, Australia, Malaysia and Cambodia are given in Table II.[23-25,30,34-38] Some retrospective case series had a higher incidence of disseminated disease due to less aggressive case-finding, in places where empiric antibiotics such as co-trimoxazole were standard of care for skin and soft tissue infections without collecting samples from localized disease sites for culture.[36] However, most large retrospective case series showed a higher incidence of localized disease in children, similar to the large prospective study from Australia.[2, 24,30,38]

Laboratory investigations[39,40]

Culture is the mainstay of diagnosis in melioidosis, although its sensitivity is low and identification of the organism takes time. Specimens that can be cultured include blood, pus, tissue, sputum/BAL/ ET aspirate, CSF and joint fluid. *B.pseudomallei* can be cultured on routine culture media such as blood, MacConkey, or chocolate agar. Selective culture media such as Ashdown agar that contains gentamicin or Ashdown liquid broth that contains colistin allow selective growth of *B.pseudomallei,* especially for specimens from non-sterile sites such as throat or skin where normal flora may overgrow the organism. Automated blood culture systems allow for faster diagnosis but are less sensitive than conventional culture.

Serology is less sensitive than culture and is not recommended for diagnosis, although older tests such as the indirect hemagglutination assay (IHA) are still available and newer ELISAs are under evaluation.

PCR is also less sensitive than culture and PCR using specific primers is used mainly to identify *Burkholderia pseudomallei* from positive cultures, to differentiate it from other *Burkholderia* species.

As all tests for melioidosis have suboptimal sensitivity, the results of all available tests may be used to generate a pooled gold standard for laboratory diagnosis of melioidosis, as suggested by Australian and Brazilian investigators,[41] as follows.

Laboratory diagnosis of melioidosis may be made when the lab gives the following results:

Culture of a non-fermenting Gram-negative bacillus from blood or other sterile fluid that is oxidase positive and gentamicin resistant and colistin resistant.

PLUS one or more of:

B.pseudomallei agglutinating antibody positive

B.pseudomallei-specific PCR positive or

B.pseudomallei 16sDNA positive.

Optimizing laboratory diagnosis of melioidosis can be done by repeating blood cultures and culturing multiple specimens such as pus and CSF, as well as imaging the abdomen and other sites to look for sites of abscess formation, when there is a high index of suspicion for melioidosis.

Treatment [39,42,43]

Various treatment regimen are given in Box 2.

Prevention [18]

Avoiding exposure of bare skin to soil and surface water especially during the rainy season, and avoiding outdoor exposure to dust clouds when bacteria may be aerosolized from soil, are essential steps to prevent melioidosis in children. Chlorination of water has been shown to be effective in reducing exposure and boiling drinking water before ingestion is also recommended.

Box 2. Treatment regimens for Melioidosis

B. pseudomallei are intrinsically resistant to penicillin and ampicillin, first and second-generation cephalosporins, aminoglycosides and fluoroquinolones. Melioidosis is treated with ceftazidime, meropenem, trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline,

Treatment generally starts with intravenous antimicrobial therapy for a minimum of 2 weeks (up to 8 weeks depending on extent of infection), followed by 3-6 months of oral antimicrobial therapy.

1) Intensive phase

a) For non-critical illness without CNS infection

Ceftazidime IV 50 mg/kg/ dose (maximum 2 gm per dose) given every 6-8 hours for 2 weeks.

b) For critical illness needing ICU care and those with positive blood cultures or deep-seated infections, without CNS infection

Meropenem IV 25 mg/kg/ dose (maximum 1 gm per dose) given every 8 hours for 4 weeks.

Meropenem may be changed to ceftazidime once ICU care is no longer needed.

c) For osteomyelitis

Ceftazidime or meropenem, doses as above, for 6 weeks.

d) For CNS infection / meningitis

Meropenem IV 50 mg/kg/ dose (maximum 2 gms per dose) given every 8 hours for 8 weeks.

Adjunctive antibiotic in intensive phase

e) For non-pulmonary focal infection (neurologic, bone and joint, and skin and soft tissue melioidosis), add:

TMP-SMX 6 mg/kg of trimethoprim (maximum 240 mg/dose) IV or oral every 12 hours

PLUS

Folic acid 0.1 mg/kg (maximum dose 5 mg) once daily, for the entire duration of intensive phase.

2) Eradication phase (Duration 3 months, except for osteomyelitis or CNS infection: 6 months):

TMP-SMX PLUS folic acid, doses as above (preferred)

OR

Doxycycline 4 mg/kg/day (for children with adverse effects or contraindications to TMP-SMX)

OR

Amoxicillin-clavulanate at 20 mg/kg/dose of amoxycillin given three times daily (least preferred, more risk of relapse).

Lyme disease

Lyme disease is a zoonotic multi-system inflammatory disorder due to infection by the spirochete *Borrelia burgdorferii* transmitted to children though the bite of Ixodes ticks.

Etiology and pathogenesis

Three genospecies of the *Borrelia burgdorferiisensustricto* complex, namely *Borrelia burgdorferiisensustricto, Borrelia afzelii* and *Borrelia garinii* are associated with Lyme disease, named after the town of Lyme in Connecticut, USA where it was first described.[44] The vectors are *Ixodes* ticks such as *Ixodes scapularis* in America and *Ixodes persulcatus* in Asia. Ticks acquire the infection by feeding on wild and domestic animals that serve as reservoirs including deer, cattle, sheep, and small rodents such as mice and squirrels and can transmit the infection to incidental hosts including humans, dogs and cats. *Borrelia* is then disseminated via the blood and lymphatics to connective tissue, joints and other organs where it localizes in the extracellular matrix where it can evade the host's immune response and stay dormant for years, if the early manifestations are unrecognized and left untreated.[45]

Epidemiology

There are only a handful of case reports from India of Lyme disease from Haryana, Uttarakhand, Bihar, Himachal Pradesh, Karnataka and Kerala, mainly from rural communities and those living close to forested land. Although relatively high IgG antibody seropositivity to *B.burgdorferii* has been documented from several North-Eastern states including Arunachal Pradesh, Meghalaya, Nagaland, Manipur and Assam and Ixodes ticks have also been identified in buffaloes and cattle in the Himalayan regions and the Western Ghats, the animal reservoirs, specific tick vectors and life cycles of Lyme disease in India still need to be properly ascertained.[49,50,51]

Clinical manifestations

Common symptoms of Lyme disease include fever, fatigue, headache and arthralgia and less commonly nausea, abdominal pain, vomiting, diarrhea, myalgia, sore throat, cough and rhinorrhea.[52]

Based on clinical signs, Lyme disease in children may be classified as:

Early localized Lyme disease

Seen in 66% of children, occurs within 3 weeks of a tick bite, characterised by:

Fig.1. Red expanding rash of erythema migrans in Lyme disease.
(Source: CDC Public Health Library ID# 14470. Content provider: CDC).

A single erythema migrans lesion, usually at the site of the tick bite, over the trunk and extremities, with or without influenza-like illness. This can present as either a spreading erythematous lesion (Fig.1), or spread centrifugally with central clearing around the site of tick bite erythema, to give the appearance of a bull's eye lesion (Fig.2).

Early disseminated Lyme disease

Occurs in 28% of children, develops weeks to months after infection, characterised by:

Fig.2. Bull's-eye pattern of erythema migrans
(**Source:** CDC Public Health Library ID# 9874. Content provider: CDC/ James Gathany)

Multiple erythema migrans lesions in 23% of children, at sites distant from the site of the tick bite, over the face and extremities, sparing the palms and soles and / or borrelial lymphocytoma[53] that appears as a solitary bluish-red plaque or nodule, varying from one to few centimeters in diameter and occurring most frequently on the ear lobe in children,

OR

CNS disease (neuroborreliosis): Neurologic disease that presents as unilateral (more common) or bilateral seventh nerve palsy in 3% of children, aseptic meningitis in 1%, or transient or permanent visual loss due to optic neuritis or raised intracranial tension even without meningitis (pseudotumor cerebri), due to deposition of immune complexes in the arachnoid villi.[54] Ptosis and external ophthalmoplegia have also been described, as have cerebellar signs, status epilepticus and choreoathetosis in case reports of children with Lyme disease from India.[55]

OR

Carditis seen in 0.5%, which is the least common manifestation of early disseminated Lyme disease, manifesting as atrioventricular or other conduction disorders, myocarditis or pericarditis.[45]

Late Lyme disease

Occurs in 6% of children, months to years after primary infection, characterized by:

Arthritis, involving a single joint in 67% of cases and multiple joints in 37% of cases.

The knee is involved in 90% of all arthritis, with the hip, ankle wrist or elbow less commonly involved. Small joint involvement is rare. Recurrences are common, occurring in just under half of all arthritis,but chronic arthritis is unusual.[56]

Other manifestations of late Lyme disease such as acrodermatitis chronic atrophicans (the dermatological hallmark of late disease), peripheral neuropathy, cognitive and affective disorders, or eye involvement with uveitis, iridocyclitis, neuroretinitis, epicscleritis and keratitis[45] are not commonly described in children.

Laboratory investigations[57]

Erythema migrans (single or multiple): The diagnosis is made clinically, especially when the child with erythema migrans is likely to have come in contact with ticks. Serological testing is not recommended as the tests may be negative within the first 2 weeks.

Early disseminated and late Lyme disease: Serological (antibody) tests are the recommended first-line tests for the diagnosis of Lyme disease, as they are highly sensitive in those with extracutaneous manifestations of Lyme disease.

A two-tiered testing algorithm is recommended, with the first test being either a whole cell-based enzyme linked immunoassay (ELISA) or an indirect fluorescent antibody (IFA) test. If this is negative, the diagnosis is unlikely and no further testing is done.

If the ELISA or IFA is positive, a Western blot that tests for both IgM and IgG is done to confirm the diagnosis.

In early disseminated Lyme disease, both IgM and IgG should be positive on Western blot. If only IgM is positive and the child's symptoms are present for > 6-8 weeks, it is considered false-positive.

In late Lyme disease, a positive IgG alone on Western Blot is sufficient to make the diagnosis, as IgM may be negative by that time.

Alternatively, two different ELISAs with different targets such as a whole-cell ELISA followed by an ELISA that detects IgG and/or IgM may be performed to make the diagnosis of early disseminated Lyme disease as this is more sensitive and specific than the Western blot in early disease.

Biopsy, culture, PCR: Skin biopsies for histopathology are done only for borellial lymphocytoma and although PCRs on skin biopsy are sensitive and specific, biopsies are not usually performed for erythema migrans. Skin biopsies also have the best yield of 65% from culture compared to lesser yield from blood or CSF, but the need for selective media and the prolonged time taken for growth means that cultures are not practical for diagnostic confirmation of Lyme disease.[53]

Other lab tests

Blood counts and hemograms are often non-specific and acute phase reactants such as the ESR are elevated in just 50% of Lyme arthritis.[56]

Synovial fluid shows neutrophilic pleocytosis, but PCRs from synovial fluid may be negative.[45]

CSF shows evidence of aseptic meningitis with lymphocytic pleocytosis and normal CSF sugar and protein[45] and PCR on CSF is often negative.

MRIs of the brain may show meningeal or cranial nerve enhancement and non-specific edema of brain parenchyma.[58]

Treatment[57]

Preferred drug doses and duration by clinical manifestation are given in Box 3.

The prognosis for children with early Lyme disease is excellent[57] and even CNS disease responds to oral doxycyline with no sequelae in the majority on review at 6 months.[59] For the small minority of children with chronic arthritis, a rheumatological consultation prior to starting non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) or immunomodulation is warranted.[60]

Prevention[61]

Prevention of Lyme disease in children is achievable by minimizing tick exposure, checking for ticks and prompt removal if exposure has occurred and chemoprophylaxis if indicated (Fig.3 and Fig.4).

Minimizing exposure to ticks: Children playing outside the house should maintain a distance of at least 10 feet from any neighboring wooded area. If venturing into forested areas, children should wear long-sleeved shirts, trousers tucked into socks and closed shoes and use walking paths or trails to avoid contact with vegetation.

Checking for ticks: On returning from potentially tick-infected outdoor areas, parents should

- Check the child's clothing for ticks, then remove, wash in hot water and dry the clothes.

- Check the child's body for ticks in the following areas: in and around the hair and the ears, under the arms, inside the belly button, around the waist, between the legs and behind the knees.

Box 3. Treatment regimen for Lyme disease

1) Erythema migrans (single or multiple)

Doxycycline (oral) 4.4 mg/kg/day in 2 divided doses (maximum daily dose 200 mg), for 10 days.

OR

Amoxycillin (oral) 50 mg/kg/day in 3 divided doses (maximum 500 mg per dose) for 14 days

OR

Cefuroxime (oral) 30 mg/kg/day in 2 divided doses (maximum 500 mg per dose) orally for 14 days

2) Borellial lymphocytoma: Doxycycline, Amoxycillin or cefuroxime (oral, doses as above), for 14 days.

3) Cranial nerve palsy: Doxycycline (oral, dose as above), for 14-21 days,

4) Meningitis

Doxycycline (oral, dose as above), for 14-21 days,

OR

Ceftriaxone IV 50-75 mg/kg once daily, for 14-21 days.

5) Carditis

Doxycycline, amoxycillin or cefuroxime (oral, doses as above) for 14-21 days

OR

Ceftriaxone IV (dose as above) for 14-21 days.

6) Arthritis Initial treatment: Doxycycline, amoxycillin or cefuroxime (doses as above) for 28 days.

7) For recurrent or refractory arthritis

Repeat doxycycline, amoxycillin or cefuroxime (doses as above) for 28 days.

OR

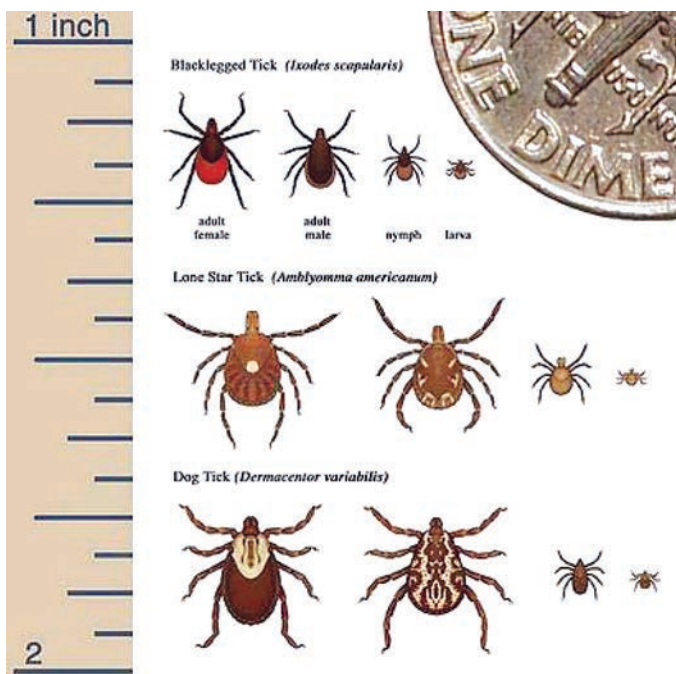give ceftriaxone IV (dose as above) for 14-21 days.

Fig.3 & 4. Different types of ticks

Source: Global Lyme Alliance to Host Free Education Program: "Lyme Disease: Your Child is at Risk. And So Are You" by Admin at Global Lyme Alliance Accessed on June 27 2022

- Ensure that the child has a bath immediately after return, to wash away any unattached ticks.

Removal of ticks: This should be done within 24 hours of attachment. Nymphal ticks that commonly transmit Lyme disease are only the size of the head of a pin and may be difficult to spot. Remove any tick by using tweezers or forceps to grasp the tick as close to the skin surface as possible, then pulling it straight upwards steadily to ensure that the mouth parts embedded in the skin come out. After removing the tick, disinfect the skin surface with spirit or a disinfectant. Removed ticks can be killed by putting them into containers containing spirit or alcohol-containing disinfectant. Watch for signs or symptoms of Lyme disease for 30 days from the date of a documented bite.

Chemoprophylaxis:[57] Chemoprophylaxis with doxycline is indicated in children only if an attached tick is identified as an *Ixodes* vector tick in a highly endemic area and the tick has been attached for ≥36 hours and prophylaxis can be started within 72 hours of tick removal.

If all the above conditions are satisfied, prophylaxis may be given as a single dose of doxycycline at 4.4 mg/kg/dose (maximum 200 mg). Doxycycline prophylaxis has been shown to reduce Lyme disease risk, albeit with wide confidence intervals, from clinical trials that included adults and children.[57]

Points to Remember

- *Brucellosis, melioidosis and Lyme disease are often unrecognized causes of acute febrile illness in children.*

- *A history of exposure to livestock or consumption of unboiled milk should lead the clinician to suspect brucellosis in the febrile child, and exposure to soil or surface water and living close to areas of paddy cultivation should raise the suspicion of melioidosis as a cause of fever without focus.*

- *Suspect Lyme disease in a child residing in a community at the edge of forested land who presents with fever and erythema migrans.*

- *Non-caseating granulomas may be seen on biopsy in both brucellosis and melioidosis and all three infections can present with fever and arthritis. Consider these infections as etiologic causes in children with prolonged fever, lymphadenitis or hepatosplenomegaly who fail to respond to empiric therapy for tuberculosis or enteric fever, and consider these as differential diagnoses in the child with suspected systemic-onset idiopathic juvenile arthritis.*

- *Children with brucellosis, melioidosis and Lyme disease tend to present with acute symptoms and*

pyrexia of unknown origin. Early diagnosis and appropriate therapy lead to good outcomes and complete recovery as children do not usually have the chronic or late manifestations seen in adults with these infections.

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CLIPPINGS

Follow-Up Duration of Echocardiography in Patients with Kawasaki Disease with No Initial Coronary Aneurysms.

The aim of this single-center, retrospective, observational study was to evaluate the optimal duration of echocardiographic follow-up in patients with Kawasaki disease without an initial coronary aneurysm.

The researchers reviewed the results of follow-up echocardiography in children with Kawasaki disease enrolled in the Prospective Observational Study on Stratified Treatment with Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease from a children's hospital. The main enrollment criterion was the absence of coronary aneurysms, defined as a maximum z-score (Zmax) ≥ 2.5, in the proximal right coronary artery and the proximal left anterior descending artery within 9 days from treatment initiation. The primary outcome was Zmax on follow-up echocardiography at up to 5 years.

Among 386 patients, 106 (27.5%) received prednisolone with intravenous immunoglobulin for first-line therapy, and 57 (14.8%) showed a poor response. Echocardiography at 1 month detected 9 patients with a Zmax ≥ 2, including 3 (0.8%) with coronary aneurysms requiring additional antithrombotic treatment and observation. Of 7 patients (1.8%) with normal echocardiographic findings at 1 month but a Zmax ≥ 2 later, 2 were lost to follow-up and 5 experienced spontaneous resolution, but none of the 7 patients required any change in management.

The researchers conclude that the optimal duration of echocardiographic follow-up may be 1 month in patients with no initial coronary aneurysms and a Zmax < 2 at 1 month. Coronary artery abnormalities observed after 1 month are rare and mostly benign in this category of patients.

Wang Q, Morikawa Y, Akahoshi S, Miyata K, Sakakibara H, Matsushima T et al. Follow-Up Duration of Echocardiography in Patients with Kawasaki Disease with No Initial Coronary Aneurysms. J Pediatr 2022 May; 244:133-138.e1. doi: 10.1016/j.jpeds.2021.11.022.

TREATMENT OF DRUG RESISTANT PATHOGENS

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Abstract: *Drug resistant pathogens pose a huge threat to the community leading to many fatalities all over the world. The problem is much more exaggerated in the developing countries due to antibiotic misuse which further leads to longer hospitalization, higher cost of treatment, increased drug adverse effects, morbidity and mortality. However, these problems and can be controlled with good infection control policies and appropriate antimicrobial stewardship programs. Of the drug resistant pathogens, the commonly encountered organisms in clinical practice include Gram negative bacteria producing beta-lactamases, carbapenamases and methicillin resistant staphylococcus aureus. This article will review on the appropriate treatment of the above mentioned drug resistant organisms.*

Keywords: *Drug resistance, Extended spectrum betalactamases, Amp C betalactamases, Carbapenemases.*

Drug resistant pathogens are an important public health problem causing almost 700,000 deaths every year globally.[1] It is further estimated that drug resistant pathogens will cause 10 million deaths per year globally by 2050, more deaths than any other disease.[1] India is likely to bear the largest brunt of this problem of antimicrobial resistance. In clinical practice, drug resistant pathogens lead to increased cost of treatment and hospital stay, increased drug adverse effects, morbidity and mortality. The new drug pipeline is fast drying up.[2] Hence, it is very important that we prevent drug resistance by practicing good infection control and antimicrobial stewardship.

While drug resistance is a problem across all microbes including bacteria, mycobacteria, viruses, fungi and protozoa, this article focuses on management of drug resistant bacterial pathogens. In the Indian setting, drug resistance is a concern in Enterobacterales (*E.coli* and

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Klebsiella), non-fermenting gram negative bacilli (Pseudomonas and Acinetobacter), *Salmonella enterica*, *S. aureus*, *S. pneumoniae*, enterococci, and shigella in decreasing order of importance.[3] We shall restrict ourselves to definitive/ targeted treatment of drug resistant Gram negative bacilli and *staphylococcus aureus*.

Treatment of resistant Gram negative bacilli (GNB)

Resistance in GNB can occur by various mechanisms including production of drug inactivating enzymes, target modification, prevention of drug influx and active efflux of the drug outside the cell.[4] The most significant mechanism is by production of the beta lactamases enzymes that inactivate beta lactams (BL). The important beta lactamases are discussed in Table I. It is notable that a pathogen can produce multiple beta lactamases and harbor other mechanisms of resistance as well. This section will focus on pathogens resistant to third generation cephalosporins and carbapenems since these are the most relevant and challenging to treat.

Drug treatment of extended spectrum beta lactamase (ESBL) producing GNB

ESBL producing GNB are usually encountered in neonatal sepsis, infections in children with cancer and health care associated infections including catheter associated blood stream infections (CLABSI), health care associated pneumonia (HAP), catheter associated urinary tract infections (CAUTI) and surgical site infections (SSI). In addition, ESBL producing *E. coli* is being increasingly encountered in community acquired urinary tract and intra-abdominal infections in children.[6] Besides there are reports of emergence of resistance due to production of ESBL in *Salmonella enterica* as well.[7]

The options for treatment of ESBL producing pathogens including BL-BLI combinations (excluding amoxicillin clavulanic acid), carbapenems, cefepime, aminoglycosides, quinolones and cotrimoxazole.[8] The vast majority of ESBL producing pathogens are resistant to quinolones. Most ESBL producing strains in India have cefepime MIC's of > 1 which makes it unsuitable for therapy. Aminoglycosides and cotrimoxazole may be used to treat ESBL urinary tract infections if susceptible.[9] In all

Table I. Important betalactamases[5]

Beta lactamase	Source	Antibiotics inactivated	Drugs effective
First generation	*S. aureus, E coli*, H flu, Moraxella	Amoxicillin, penicillin	Cephalosporins Cloxacillin, Amoxiclav
Extended spectrum beta lactamases (ESBL)	Enterobacterales (*E. coli/ Klebsiella) Salmonella, Shigella*	Cephalosporins Penicillins Aztreonam	Cephamycins (cefoxitin) BL-BLI (beta lactamase inhibitors) (exception amoxiclav) Carbapenems
Amp C beta lactamases	Pseudomonas, Serratia, Proteus, Citrobacter, Enterobacter (SPICE)	BL-BLI, Cephamycins	Carbapenems New BLI (avibactam) Cefepime
Carbapenemases* (NDM/ KPC/ OXA-48)	Pseudomonas, Acinetobacter, Klebsiella*, E. coli*	Carbapenems	Polymyxins, Tigecycline, Fosfomycin, aztreonam, new BL- BLI

*NDM -New Delhi metallo-beta lactamase, KPC- K pneumonia carbapenemase, OXA-48 - oxacillinase 48

other cases, the choice is between BL-BLI combinations (piperacillin-tazobactam, cefoperazone-sulbactam, cefepime-tazobactam) and carbapenems. In most cases monotherapy with either of these agents is enough for targeted therapy and addition of aminoglycosides to the regime is not required. There are many systematic reviews and meta-analysis that have demonstrated equivalence of BL-BLI combinations and carbapenems in treatment of ESBL infections.[10] However the recent MERINO trial in adults with ESBL *E. coli/* Klebsiella bacteremia demonstrated significant mortality benefit with the carbapenems as compared to piperacillin tazobactam.[11] Hence carbapenems should be used in preference to BL-BLI in ESBL infections when the patient is seriously ill (severe sepsis/ septic shock when the inoculum is high), when adequate source control cannot be achieved, in neutropenic and immunocompromised hosts and when the MIC's to BL-BLI combinations are high.[12] The best results with piperacillin tazobactam are seen when the MIC is 4 or less (the susceptibility breakpoint being 8 mcg/ml).

BL-BLI combinations

Piperacillintazobactam (ratio of piperacillin to tazobactam as 8:1) is the BL-BLI combination for which the most evidence is available. Apart from its Gram negative spectrum it also covers MSSA (methicillin susceptible *S. aureus*), *Enterococcus fecalis* and anaerobes.[13] It is imperative that it be dosed correctly and given 6-8 hourly. The downside of piperacillin- tazobactam

is its need for frequent dosing and hence it is not suitable for outpatient parenteral antibiotic therapy (OPAT). It also needs modification in renal dysfunction.

Cefoperazone-sulbactam (ratio of cefoperazone to sulbactam as 2: 1) is another BL-BLI combination widely used in India, more in adults than in children and given twice daily. It does not need renal dose modification. It is better suited for OPAT as it is given twice daily. It can cause hypoprothombinemia and bleeding and hence prothrombin time should be monitored if therapy is prolonged.

Cefepime-tazobactam is an indigenous combination (ratio of cefepime - to tazobactam 8:1). It was formulated to combine the stability to Amp C property of cefepime and the ESBL inhibition activity of tazobactam.[14] While there is evidence of invitro susceptibility with this drug, clinical experience is limited. There is also the concern about the seizure potential of cefepime.

The new BL-BLI combination of ceftazidime-avibactam is primarily used for treatment of CR(carbapenem resistant) infections and is discussed later.

Finally the choice between the BL-BLI combinations rests between piperacillin- tazobactam and cefoperazone-sulbactam and practitioners can use either on case by case basis. However the maximum doses and recommended dosing interval should be followed.

Carbapenems

Carbapenems may be classified as group 1 carbapenems (ertapenem) and Group 2 carbapenems (imipenem and meropenem).[15] For initial therapy in an acutely sick patient with ESBL infections, imipenem/ meropenem is recommended. The spectrum of both imipenem and meropenem is nearly similar with the exception that imipenem has better Gram positive activity. Since the mechanisms of resistance to imipenem and meropenem (other than the common mechanism of production of carbapenemases) are slightly different, it is also possible to have differential susceptibility to meropenem and imipenem. Imipenem has increased tendency to cause seizures especially in patients with renal dysfunction and those with prior CNS disorders.[16] Meropenem is therefore the most commonly used carbapenem. Higher doses of carbapenems should be used in patients with CNS infections and severe infections; prolonged infusions over 3 hours are recommended in patients with infections with pathogens with relatively high MIC of 2 or above (susceptibility breakpoint is 1 and resistance breakpoint is 2).

Ertapenem is a group 1 carbapenem with no activity against Pseudomonas and Acinetobacter.[17] It is highly protein bound allowing for once daily dosing in adults; but in children below 12 years it is dosed twice daily. It is a suitable drug for de-escalation following initial therapy with meropenem/imipenem. Alternatively it can be started upfront in stable patients/ localized infections with ESBL pathogens.

Doripenem has a spectrum similar to imipenem/ meropenem (with slightly better activity against *Pseudomonas aeruginosa*) and offers no advantage over imipenem/ meropenem.[18]

Drug treatment of carbapenem resistant (CR) Gram negative infections

Carbapenem resistant infections have become one of the biggest challenges in recent times and are associated with mortality rates of greater than 50%.[19] CR is a concern in neonatal sepsis, health care associated infections and infections in the immunocompromised especially in neutropenic children. The drugs available for treatment of CR include polymyxins (polymyxin B/ colistin), high dose carbapenems, aminoglycosides, tigecycline, minocycline, rifampicin, cotrimoxazole and finally BL-BLI including ceftazidime-avibactam. Many of these drugs are not approved for use in children and used off label.

CR is generally mediated by production of the carbapenemases but also by porin and efflux mechanisms.

> **Box 1. Types of carbapenamases**
>
> 1. Metallo betalactamases: New Delhi metallo-β-lactamase (NDM), imipenemase (IMP) and Verona integron-mediated metallo-β-lactamase (VIM)
>
> 2. Serine carbapenemases: Klebsiella pneumoniae carbapenemase (KPC) and oxacillinase 48 (OXA-48 and others).

Most common carbapenemases and the carbapenemases common in the Indian setting are NDM and OXA (Box 1).[20,21]

Knowledge of the resistance mechanism and type of carbapenemase is important in clinical practice. The new BL-BLI, ceftazidime avibactam (CAZ-AVI) is effective against OXA-48 and OXA-48 like enzymes but not against NDM producing pathogens while a combination of CAZ-AVI and aztreonam may be used to treat NDM producing pathogens.[22,23] Commercial tests are available for detection of common type of catbapenamases; Xpert CARBA is a PCR test that detects the most prevalent carbapenemases gene families such as NDM, OXA-48, VIM, IMP and KPC.[24] The drawback of this test is that it does not detect other carbapenemases and also other mechanisms of resistance. Hence, direct testing for CAZ-AVI susceptibility and synergy between CAZ-AVI and aztreonam is now recommended instead of inferring susceptibility from the type of carbapenemases.[25] Treatment of CR infections also mandates knowledge of MIC's of the pathogen. High dose carbapenems cannot be used if the MIC is > 8.[26] Similarly while the current US FDA guidelines place the tigecycline susceptibility breakpoint as 2 and resistance breakpoint as 4, tigecycline MIC's of > 1 are difficult to treat even with double dose tigecycline.[27] The lab should also be equipped for determination of minocycline and fosfomycin susceptibility since these are important drugs for CR infections. Finally as colistin susceptibility testing by automated methods such as VITEK is not reliable, colistin testing should always be done by broth microdilution (BMD).[28] As per new guidelines, susceptibility tests pronounce a strain to be either intermediately sensitive (I) or resistant to the polymyxins (R).

Polymyxins[29,30]

Polymyxins are considered as the backbone of therapy for CR pathogens. The currently available polymyxins include colistin (polymyxin E) and polymyxin B. They are effective against the top four Gram negative pathogens

including Klebsiella, Acinetobacter, Pseudomonas and *E. coli*. However there are several limitations with their use. The penetration at many sites including the lung, bones, biliary tract and central nervous system is suboptimal. They have no activity against anaerobes, Gram positive bacteria and several GNB including Serratia, Proteus, Providencia, Burkholderia, etc. There are significant side effects including nephrotoxicity and neurotoxicity. Polymyxins can also be used for local therapy including inhalational and intrathecal administration, colistin being the preferred agent.

There are salient differences between colistin and polymyxin B. Colistin is available as a prodrug colistimethate sodium. After administration, 70% is excreted unchanged by the kidneys and the rest is slowly converted to colistin, Owing to this property a loading dose is needed and there is a lag time of 4-6 hours before the onset of therapeutic action. The drug accumulates in renal impairment and needs dose modification. Polymyxin B is the active drug itself and is not excreted by kidneys. This leads to quicker onset of action. It is not excreted in urine and hence does not need renal dose modification but is also not effective in urinary tract infections. It is less nephrotoxic than colistin but more neurotoxic. While polymyxin B is rapidly replacing colistin in adult CR infections, colistin is still the preferred drug in children as there is more data available for colistin.[31] It is crucial to dose the polymyxins correctly with doses higher than those listed in the product insert. The dose of colistin in neonates can be even higher and they need to be monitored carefully for hypokalemia and hypomagnesemia.

High dose carbapenems

High dose carbapenems especially meropenem given as prolonged infusion over 3 hours may be used when the MIC is ≤ 8.[26] However in the Indian setting most CR strains have carbapenem MIC's of > 16 which precludes their use. Similarly double carbapenem therapy using ertapenem with imipenem has been only demonstrated to be effective for KPC which is rare in India.[32]

Tigecycline[33]

This is a very broad spectrum drug with activity against most Gram negative bacteria (with the exception of Pseudomonas) and is also effective for enterococci, MSSA, MRSA and anaerobes. However, there is increasing resistance in CR GNB to tigecycline. Besides due to its high volume of distribution it achieves poor levels in blood, lung, urine and central nervous system. It has considerable side effects including nausea, anorexia, thrombocytopenia, hepatic dysfunction and coagulopathy. Hence it should only

be used if there is demonstrable susceptibility with MIC of ≤ 1 and in double doses for blood stream and respiratory infections. Though it is not approved in children, it is used if there are no other treatment options.

Minocycline[34]

This tetracycline has a narrower spectrum than tigecycline but enhanced activity against Acinetobacter. It achieves better levels in blood and brain. It has fewer side effects than tigecycline. It is thus preferred to tigecycline if the organism is sensitive on susceptibility tests. The drug is also useful for treatment of *Elizabethkingia meningoseptica*, an emerging nosocomial pathogen.

Aminoglycosides[35]

Aminoglycosides particularly amikacin are a valuable drug for treatment of CR infections as significant number of strains may be susceptible. It can be used as monotherapy for uncomplicated urinary tract infections but its use as combination with colistin is limited by the additive nephrotoxicity.

Fosfomycin[36]

Fosfomycin is available as both oral and IV formulations. Only the IV formulation should be used for systemic infections. Fosfomycin has activity against most strains of *E. coli*, some strains of Klebsiella and is also effective against MSSA and MRSA. It has limited activity against pseudomonas and no activity against Acinetobacter. It should be used as definitive therapy only if the organism is susceptible with MIC < 32. The side effects include diarrhea, hypernatremia and hypokalemia. Since there is rapid emergence of resistance, it should not be used as monotherapy.

Ceftriaxone-sulbactam-EDTA

Ceftriaxone-sulbactam-EDTA(disodium edetate) is another novel BL-BLI combination developed indigenously in India.[37] EDTA acts as an inhibitor of metallobetalactamases and also as an antibiotic resistance breaker. The combination has proved to be non-inferior to meropenem in a randomized controlled trial of urinary tract infections but information on the efficacy in treatment of carbapenem resistant (CR) infections is limited.[38] It may be used as a companion drug to polymyxins in treatment of CR infections or as monotherapy for non-severe CR infections.

Miscellaneous drugs

Some CR strains of *E. coli* are susceptible to TMP-SMX and here TMP-SMX may be used as

monotherapy for UTI or as combination with other drugs. Rifampicin has been tried as an adjunctive drug for CR infections especially for CR acinetobacter; however a recent randomized controlled trial did not show any benefit of rifampicin for resistant acinetobacter.[39] Sulbactam has inherent activity against acinetobacter and may be used in combination with other drugs for this pathogen if susceptible.

Ceftazidime-avibactam

This novel BL-BLI has avibactam a very effective BLI which inhibits amp C, ESBL, KPC, OXA-48 but not NDM.[22] It is effective against most Gram negative pathogens but not against Acinetobacter, *S. aureus* and anaerobes. Side effects are few. It is approved for blood stream, urinary tract and intraabdominal infections and also for pneumonia. Cohort studies have demonstrated superior efficacy of CAZ-AVI as compared to polymyxin based therapy for CR infections.[40] Therefore as per recent guidelines from the IDSA and ICMR it is the preferred therapy for CR Enterobacterales if the pathogen is susceptible.[41,42] It has also been used in children with good results (43, personal experience).

The drug combination of aztreonam-avibactam is effective against NDM producing strains but is still in clinical trials. In its absence, combination therapy of aztreonam with ceftazidime-avibactam has been used for CR Enterobacterales with excellent results.[23] Synergy should be demonstrated between aztreonam and CAZ AVI by E strip or disc elution methods before use for CAZ AVI resistant isolates.[43]

Choice of therapy[44,45]

The choice of therapy will be determined by the genus, susceptibility and MIC, site of infection, host comorbidities and severity of infection. Most of the recommendations for children are extrapolated from adult studies. While localized infections can be treated with monotherapy, patients with severe infections should be treated with combination therapy. The conventional approach has been to use polymyxin based therapy (polymyxin B/ colistin) combined with another drug. The choice of the companion drug depends again on the MIC: breakpoint ratio of the other drug (the drug with lower MIC: breakpoint ratio being preferred), site of infection and host comorbidities. The usual drugs combined with polymyxin include high dose tigecyline/minocycline/fosfomycin/aminoglycosides, etc. In some situations especially in acinetobacter and pseudomonas infection, there may be no other effective drug except for the polymyxins. Here, one may be forced to use monotherapy. For respiratory and CNS infections,

systemic therapy should be combined with inhalational and intrathecal/intraventricular colistin therapy respectively. As discussed earlier, there is a trend to move away from polymyxin based therapy to ceftazidime-avibactam with or without aztreonam for treatment of CR Enterobacterales in adults and the same may happen in neonates and children in future.

In the current day scenario, it is not unusual to find pan drug resistant pathogens such as providencia and colistin resistant klebsiella. Some of these infections may be untreatable.

Adjunctive therapy in Gram negative infections

Source control is extremely important in all infections but assumes even greater importance in resistant Gram negative infections to decrease the bacterial load. Source control may include drainage of pus, debridement of infected areas. Removal of central lines is not essential for Gram negative pathogens but should be considered in persistent bacteremia. The duration of therapy usually ranges from 7-14 days. Efforts should be made to limit the duration of therapy in these setting of CR infections to reduce cost and adverse drug effects and preserve future antimicrobial options.

MRSA

While MRSA is a less common pathogen than the drug resistant gram negative pathogens, it is equally challenging to treat. There are many anti MRSA drugs available, choice depends on many factors of which the most important is the site of infection. Table II compares the various anti MRSA drugs available in India.

MRSA bacteremia and endocarditis

The drug of choice is vancomycin if MIC is ≤1. In critically ill children a loading dose should be used. As per current recommendations, dose should be modified to achieve AUC/ MIC ratio of at least 400. Online calculators are available that calculate the required dose based on the trough and peak levels of vancomycin. However, drug levels are not always available in clinical practice. In patients with renal dysfunction an effort should be made to estimate the trough level and keep at 15-20 mcg/ml. Teicoplanin is another glycopeptide that has proven to be non-inferior to vancomycin in meta-analysis of observational studies though no head to head studies are available. If the vancomycin MIC is more than 1, then daptomycin may be used. However, strains with high vancomycin MIC may also be resistant to daptomycin. Recent trials have not demonstrated

Table II. Anti MRSA drugs available in India[46,47]

Vancomycin	Drug of choice in the treatment of MRSA. Loading dose needed in sick patients. Infusion related side effects, nephrotoxicity. Need for therapeutic drug monitoring in those with renal dysfunction. Rising MIC's may compromise efficacy. No oral switchover, not suitable for outpatient parenteral antibiotic therapy (OPAT)
Teicoplanin	Not FDA approved but widely used in Europe. Highly protein bound so once a day dosing possible. Suitable for OPAT. Good lung and bone/ joint penetration. Not suitable for critically ill patients, endocarditis and CNS infections
Linezolid	Bacteriostatic. Not suitable for bacteremia and endocarditis. Many adverse effects with prolonged therapy. Very crucial drug for MDR/ XDR TB
Clindamycin	Bacteriostatic. Protein synthesis inhibitor so has anti-toxin effect. Not all MRSA strains are susceptible. Not suitable for endocarditis, bacteremia and CNS infections.
Daptomycin	Limited pediatric data. Bactericidal and also has anti toxin effect. Suitable for endocarditis, bacteremia. Destroyed by lung surfactant so should not be given for respiratory infections. Not recommended for urinary tract and CNS infections either. Can cause myositis, so weekly CPK monitoring recommended
Cotrimoxazole	Not all strains are susceptible. Suitable for skin and soft tissue and bone and joint infections. Intravenous formulation may be used for bacteremia and CNS infections as salvage therapy.
Tigecycline	Very broad spectrum so not recommended unless no other option
Levonadifloxacin[48]	New quinolone with broad spectrum activity against non ESBL Gram negative pathogens, anerobes, atypical pathogens, MSSA and MRSA. Limited Pediatric data. Does not need dose adjustment in renal or hepatic dysfunction
Ceftaroline	Cephalosporin with anti MRSA activity. Limited pediatric data
Fosfomycin	Broad spectrum drug with anti MSSA and MRSA activity. Used in combination with beta lactams for salvage therapy

superiority of combination therapy of vancomycin with other drugs including cloxacillin/ rifampicin over vancomycin monotherapy for MRSA.[49]

Indwelling lines and catheters must be removed. In exceptional circumstances, catheter salvage may be attempted by antibiotic lock therapy. Blood cultures should be repeated every 48-72 hours until negative. The patient should be examined daily for metastatic sites of infections. Unlike adults where transthoracic ECHO is recommended in all with *S. aureus* bacteremia (SAB), in children it can be restricted to those with persistent positive cultures, congenital heart disease and clinical features of endocarditis. The duration of therapy in uncomplicated SAB is 2 weeks while in those with metastatic infections/ endocarditis is 4-6 weeks.

MRSA skin and soft tissue infections

These may include minor infections such as furuncles/ abscesses or severe infections such as necrotizing fasciitis.

For severe infections parenteral vancomycin/ teicoplanin/ daptomycin may be used. Oral options include TMP-SMX, clindamycin, doxycycline and linezolid.

MRSA bone and joint infections

Here initial therapy should be with teicoplanin or vancomycin (teicoplanin preferred as better bone penetration as compared to vancomycin and suitable for OPAT). Oral switchover options include linezolid, clindamycin, TMP-SMX. Rifampicin may be added if there is prosthetic material. Duration of therapy for joint infections is 3-4 weeks and for osteomyelitis is 8 weeks.

MRSA pneumonia

Here the choice is between vancomycin, teicoplanin and linezolid. Teicoplanin is preferred to vancomycin owing to better penetration in alveolar epithelial cells. Linezolid should only be used for definitive therapy and

Table III. Drug doses in children* with normal renal function

Drug	Dose	Maximum daily dose
Piperacillin-tazobactam	200-300 mg/kg/day of piperacillin q 6-8 hourly	4.5 gm 6 hourly
Cefoperazone-sulbactam	100 mg/kg/day of cefoperazone q 12 hourly	4 gm of cefoperazone or 6 gm of cefoperazone sulbactam
Cefepime-tazobactam	100-150 mg/kg/day of cefepime q 8-12 hourly	2.25 gm 8 hourly
Ceftriaxone-sulbactam-EDTA	100 mg/kg/day of ceftriaxone q 12 hourly	6 gm of cefsul EDTA
Ceftazidime-avibactam	100 mg/kg/day of ceftazidime q 8 hourly	2.5 gm 8 hourly
Aztreonam	100-150 mg/kg/day of aztreonam q 8 hourly	2 gm 8 hourly
Meropenem	60-120 mg/kg/day q 8 hourly	2 gm 8 hourly
Imipenem- Cilastatin	60-100 mg/kg/day q 6-8 hourly	1 gm 8 hourly
Ertapenem	40 mg/kg/day q 12 hourly	1 gm
Colistin	Loading: 12 mg/kg/ 150,000 units/kg and then 12 mg/kg/day q 8-12 hourly1 mg= 12500 IU	9 million units
Polymyxin B	Loading: 20,000-25,000 units/kg and then 25,000-30,000 units/kg/day q 8-12 hourly	20 lakh units
Fosfomycin	200-300 mg/kg/day q 6-8 hrly	4 gm 6 hourly
Tigecycline	3 mg/kg loading and then 1.5 mg/kg/dose 12 hourly	200 mg loading and then 200 mg daily
Minocycline	3 mg/kg loading and then 1.5 mg/kg/dose 12 hourly	200 mg loading and then 200 mg daily
Cotrimoxazole	10 mg/kg/day of trimethoprim (TMP) q 12 hourly	TMP 640 mg daily
Amikacin	15-22.5 mg/kg/day q 24 hrly	1000 mg daily
Sulbactam	100-125 mg/kg/day q 6-8 hourly	2 gm 6 hourly
Vancomycin	Loading of 30 mg/kg and then 40-60 mg/kg/day q 6-8 hourly	Loading 2 gm and then 3 gm/day
Teicoplanin	6-12 mg/kg 12 hourly for 3 doses and then 6-12 mg/kg/day	1600 mg daily
Daptomycin	4-12 mg/kg/day q 24 hourly	700 mg daily
Clindamycin	20-40 mg/kg/day q 6-8 hourly	900 mg 8 hourly
Levo-nadifloxacin	30 mg/kg/day q 12 hourly	800 mg 12 hourly

*Please refer to standard formulary for neonatal dosing

not as empiric therapy as it may mask underlying tuberculosis which may sometimes present as community acquired pneumonia.[50] Duration of therapy ranges from 2-4 weeks. Empyema is common and will need drainage.

MRSA CNS infections

Here again the drugs recommended are vancomycin/linezolid and TMP-SMX. Foreign material such as shunts

should be removed and intrathecal/ intraventricular therapy with vancomycin may be needed.

MRSA urinary tract infections

Most MRSA pyelonephritis is descending infection from a bacteremia. Drugs which have good urinary penetration such as teicoplanin or linezolid are recommended. Drug dosing is shown in Table III.

Conclusions

AMR has emerged as an important cause of morbidity and mortality. Treatment of antimicrobial resistant pathogens includes sending appropriate cultures to standard laboratories before starting antibiotics, interpretation of culture results including the MIC, choice of the most appropriate agent in correct doses and through correct route, source control and treatment for the optimal duration. Equally important is good infection control and antimicrobial stewardship to prevent or slow he emergence of drug resistance.

Points to Remember

- *Drug resistant pathogens are an important public health problem causing almost 700,000 deaths every year globally which is more than any other single disease entity causing death.*

- *The carbapenemases are classified as metallo betalactamases - NDM, IMP and VIM, serine carbapenemases - KPC, OXA-48 and NDM. NDM and OXA are the most common carbapenemases in the Indian setting.*

- *Drugs used in carbapenem resistant (CR) Gram negative infections are polymixins, high dose carbopenams, tigecycline, minocycline, aminoglycosides, fosfomycin, ceftazidime-avibactam, ceftriaxone-sulbactam-EDTA and TMP-SMX.*

- *MRSA is a less common pathogen in India than the drug resistant Gram negative pathogens, but it is equally challenging to treat.*

- *Anti MRSA drugs available in India are vancomycin, clindamycin, teicoplanin, linezolid, daptomycin, cotrimoxazole, tigecycline, fosphomycin, ceftaroline and levonadifloxacin.*

- *Choice of the anti MRSA depends on many factors of which the most important is the site of infection; others are presence of critical illness, indwelling catheters, presence or absence of bacteremia and whether treated as outpatients or inpatients.*

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NEWS AND NOTES

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ANTIMICROBIALS - II

ANTIMICROBIAL STEWARDSHIP- GUIDELINES AND PRACTICE

*Divya Nandakumar
**Balasubramanian S

Abstract: *Along with the emergence of new infections in recent times and paucity of new antimicrobials in development, the future of successful antimicrobial therapy looks bleak. Antibiotics are becoming increasingly ineffective as drug resistance has spread globally, making it more difficult to treat even common infections. A multifaceted approach is necessary to prevent, detect and control the emergence of antimicrobial-resistant organisms. This includes ensuring the availability of adequate and appropriate therapeutic agents, the existence of diagnostic capacity to rapidly and reliably detect specific pathogens and their antimicrobial susceptibilities, promotion of robust infection control and antimicrobial stewardship programs. Antimicrobial stewardship optimises antimicrobial use to achieve the best clinical outcomes while minimizing adverse events and limiting selective pressures that drive the emergence of resistance and also reduce the cost of treatment. This article focuses on guidelines and practices relating to antimicrobial stewardship.*

Keywords: *Antibiotics, Antimicrobial resistance, Antimicrobial stewardship.*

Antimicrobial stewardship is defined as a coordinated intervention, 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.[1]

A more practical clinical definitionis-"the right antibiotic for the right patient, at the right time, with the right dose, route and duration,causing least harm to the patient and future patients".[2] Literal meaning of stewardship is supervising or taking care of a property.

The need for antimicrobial stewardship

Antibiotics have revolutionised the practice of modern medicine and improved outcomes among premature babies, critically ill patients with sepsis, transplant recipients and oncology patients. On the other hand, misuse of antibiotics has contributed to antibiotic resistance, posing a serious threat to public health.[3] Paradoxically, as global rates of antibiotic resistant infections increase, antibiotic research and development have been dwindling, resulting in a catastrophic lack of effective antimicrobials during public health crisis. In response to this challenge, healthcare workers have been forced to minimize unnecessary and inappropriate use of antibiotics in order to prevent development of drug resistance.[4] Antimicrobial stewardship programs can increase cure rates while reducing treatment failures, *Clostridium difficile* infections (results from disruption of normal, healthy bacteria in the colon, often as a result of antibiotics), adverse effects, antibiotic resistance, hospital costs and lengths of stay.[2]

Guidelines

Antibiotic stewardship programs can help to effectively treat infections, reduce unnecessary side effects and combat antibiotic resistance. Guidelines can use national recommendations but should incorporate local trends in antimicrobial resistance and hospital specific targets for increased effectiveness.

Active strategies

1. Prospective audit with feedback intervention

It is an external review of antibiotic therapy by an expert in antibiotic use, accompanied by suggestions to optimize use, at some point after the agent has been prescribed.[5] It maintains autonomy of prescribers and allows for de-escalation of antibiotics, once sensitivities are available. It has been shown to reduce inappropriate antimicrobial use in multiple settings, but is time and labour consuming.

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2. Preauthorisation

Preauthorisation requires prescribers to get approval prior to the use of certain antibiotics. This can help optimize initial empiric therapy because it allows for expert input on antibiotic selection and dosing, which can be lifesaving in serious infections like sepsis. It helps to reduce unnecessary initiation of antibiotics and decrease antibiotic costs.[6] However, it results in the loss of prescriber autonomy and can result in delay while initiating therapy.

3. Facility specific treatment guidelines

Facility-specific clinical practice guidelines and algorithms can be an effective way to standardize prescribing practices based on local epidemiology. It aids the clinician to make evidence-based antibiotic choices based on local antimicrobial resistance patterns, national guidelines and relevant clinical factors. Stewardship programs can prioritize the development of guidelines based on the infections most commonly encountered.

The most common infections for which antimicrobials are used frequently in the hospital setting include:

a) **Community-acquired pneumonia:** Interventions have focused on improving diagnostic accuracy, tailoring of therapy to culture results, optimizing the duration of treatment to ensure compliance with guidelines.

b) **Urinary tract infection (UTI):** The main area of focus is to avoid treatment of asymptomatic bacteriuria.[7]

c) **Skin and soft tissue infection:** Avoiding broad spectrum antibiotic for uncomplicated infections and prescribing the correct drug, route and dosage for appropriate duration remains the major area of intervention.[8]

4. Antibiotic timeouts

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 is available.[2] The spectrum of coverage may be narrowed or broadened as appropriate, the dose may be adjusted as needed and unnecessary components of the regimen can be eliminated. Antimicrobials may be discontinued altogether if it is apparent that the patient's clinical status is not due to bacterial infection.[9]

5. Antimicrobial cycling

Antimicrobial cycling refers to the scheduled removal and substitution of a specific antimicrobial or antimicrobial class to prevent or reverse the development of antimicrobial resistance. Cycling is an attempt at controlled heterogeneity of antimicrobial use to minimize antimicrobial selection pressures.[10]

6. Antimicrobial order forms

Antimicrobial order forms minimise antimicrobial consumption through the use of automatic stop orders and the requirement of physician justification. Defining the optimal timing and duration of perioperative antimicrobial prophylaxis and use of perioperative prophylactic order forms with automatic discontinuation at two days were shown to result in a decrease in the mean duration of antimicrobial prophylaxis.[10] Time-sensitive automatic stop orders for specified antibiotic prescriptions, especially for antibiotics administered for surgical prophylaxis helps to curtail the use of unnecessary antibiotics during surgeries.

7. Pharmacokinetic monitoring

It is defined as the use of pharmacokinetic and pharmacodynamic properties of antimicrobial agents to optimize drug efficacy based on organism, site of infection and patient characteristics.[11] It increases the likelihood of obtaining serum concentrations within the therapeutic range and reduces costs. Individual pharmacokinetic monitoring and adjustment programs should be implemented for patients receiving aminoglycosides or vancomycin.[12]

8. Dose and duration optimisation

Standard antimicrobial doses should be included in empirical therapy guidelines and optimised according to renal function, hepatic function, severity of infection and therapeutic drug monitoring.[4] While the optimization of duration helps to avoid automatic 10-14 day courses of therapy, it should be based on specific diagnosis.

9. IV to oral switch

Antimicrobial therapy for patients with serious infections requiring hospitalization is generally initiated with parenteral therapy. Enhanced bioavailability allows conversion to oral therapy once a patient meets a defined clinical criteria. This can decrease the length of hospital stay, health care costs and risk of hospital acquired infections. Important criteria for switching includes- afebrile period for 24 to 48 hours, oral antibiotic with good bioavailability, improving clinical status and intact, functioning gastrointestinal tract.

10. De-escalation

Antimicrobial prescriptions should be reviewed at 48-72 hours and de-escalated to a narrow-spectrum agent

or escalated in line with available microbiology culture and susceptibility results.[4] It helps to potentially reduce the use of broad-spectrum antibiotics and thereby reduce antimicrobial resistance.

11. Other strategies

a) Computer assisted decision support programs

Computer-based algorithm guides a practitioner and makes recommendations for antimicrobial regimens based on suspected infection, patient characteristics, local microbiology and optimal drug dosing.[11]

Computer physician order entry (CPOE) and electronic medical records (EMR) substantially improve patient safety.[13] Computer surveillance program presents epidemiological information with detailed recommendations and warnings regarding antimicrobial regimens and courses of therapy. Even if a physician overrides the recommendation for the antimicrobial and selects his or her own treatment plan, the computer still automatically reviews the patient's allergies and potential drug-drug interactions, recommending a dosage and interval based on the patient's renal and hepatic functions.[10]

b) Role of microbiological laboratory

The clinical microbiology laboratory plays an important role in the timely identification of microbial pathogens and the performance of susceptibility testing. The latter can aid in the prudent use of antimicrobials and direct appropriate therapy based on local guidelines. Novel diagnostic approaches like nucleic acid amplification tests (NAATs), mass spectrometry (MS) and peptide nucleic acid fluorescence in situ hybridization (PNA- FISH) have redefined the management approach. Rapid diagnostic tests for distinguishing between viral and bacterial infection greatly facilitate the decision of whether or not to prescribe antibiotics.[14] C-Reactive protein (CRP), an acute-phase reactant, is a useful aid in the diagnosis of bacterial infections. Procalcitonin (PCT) may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy.

c. Measuring antibiotic use

Antimicrobial use may be estimated in days of therapy (DOT) or defined daily dose (DDD).[15] 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. DOT refers to the number of days a patient receives an antimicrobial, regardless of the dose administered. Therefore, the calculation can be distorted if a patient receives more than one antimicrobial agent or if a patient receives antimicrobials administered every other day. DOT can be used for both pediatric and adult populations. DDD aggregates the total number of grams of each antimicrobial administered during a period of time divided by a standard DDD designated by the World Health Organization (WHO). Because the data needed are typically available from the pharmacy, it is relatively easy to calculate. However, DDD underestimates the antimicrobial exposure in patients with renal failure and does not account for weight-based dosing, making this metric inappropriate for pediatric populations.

d) Education

It is defined as the formal or informal teaching and training to engage prescribers and other health care workers in improving antibiotic prescribing, dispensing and administration practices.[16] It includes conference presentations, student and house staff teaching sessions, provision of written guidelines or e-mail alert. Passive educational activities such as lectures or informational pamphlets should also be used to complement stewardship activities. In a Cochrane review published in 2013, dissemination of educational materials via printed forms or meetings was associated with improved antibiotic use in 5 of 6 studies.[17]

Surgical prophylaxis guidelines

Surgical prophylaxis guidelines providing antibiotic choice, dose and duration should be formulated according to local needs. The use of pre and peri-operative antibiotics has become an essential component of the standard of care in virtually all surgical procedures and has resulted in a reduced risk of post-operative infection. But inappropriate and excessive use of antibiotics for this purpose leads to increase in hospital costs, ineffectiveness and/or a decline in susceptibility of pathogen. The need to prescribe single dose antibiotics for surgical prophylaxis in uncomplicated cases needs to be stressed.

f) Outpatient department

The core elements of outpatients antimicrobial stewardship recommended by CDC includes-accountability for optimising antibiotic prescription, use of evidence based diagnostic criteria and treatment recommendation, self-evaluation of antibiotic prescribing practices and use of effective communication strategy to educate patients.[2]

Current practices/ Irrational prescribing

Major driving forces for irrational use of antibiotics include lack of adequate knowledge on the behalf of the
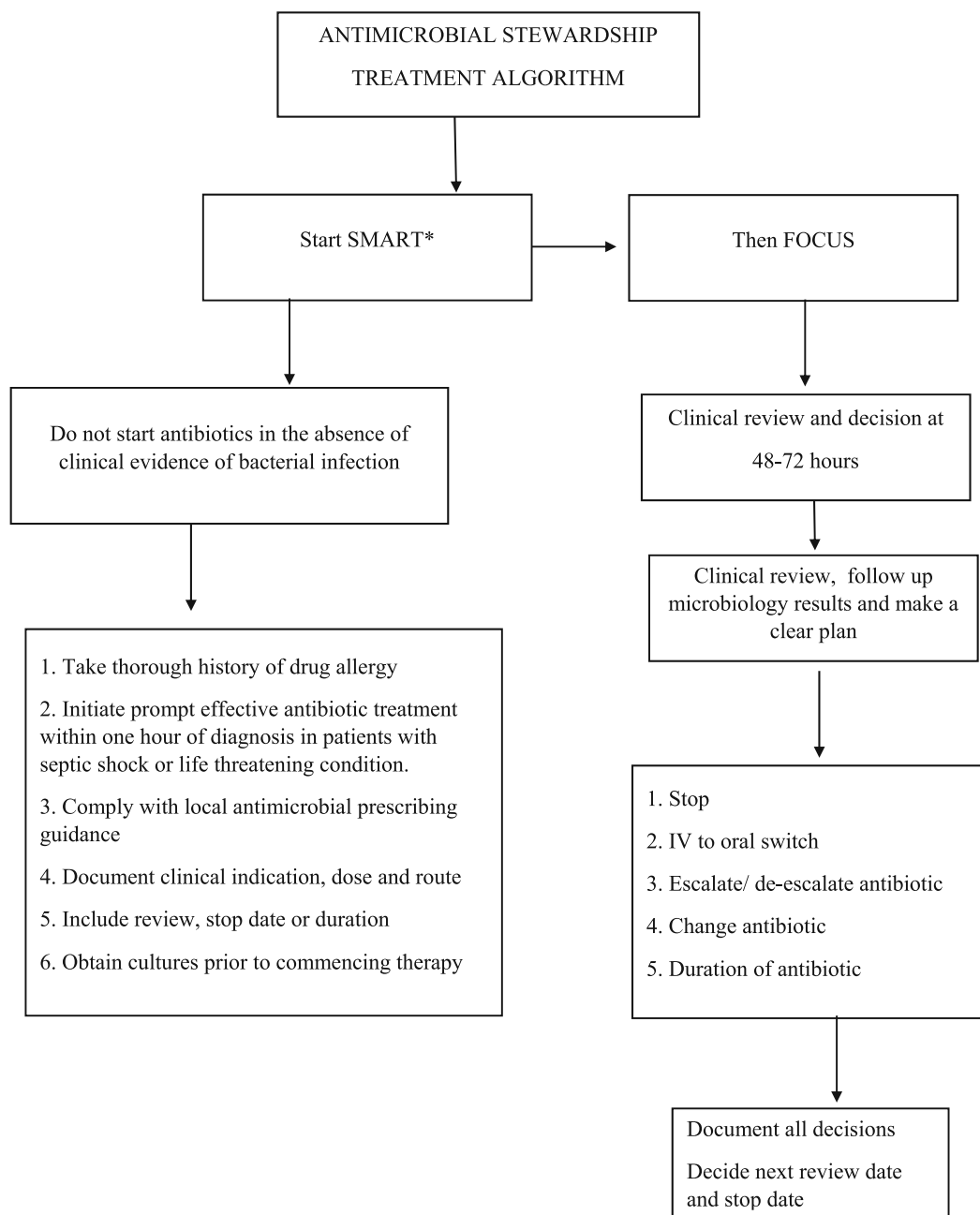
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┌─────────────────────────────────┐
│   ANTIMICROBIAL STEWARDSHIP      │
│     TREATMENT ALGORITHM          │
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Start SMART* → **Then FOCUS**

Do not start antibiotics in the absence of clinical evidence of bacterial infection

Clinical review and decision at 48-72 hours

Clinical review, follow up microbiology results and make a clear plan

1. Take thorough history of drug allergy

2. Initiate prompt effective antibiotic treatment within one hour of diagnosis in patients with septic shock or life threatening condition.

3. Comply with local antimicrobial prescribing guidance

4. Document clinical indication, dose and route

5. Include review, stop date or duration

6. Obtain cultures prior to commencing therapy

1. Stop

2. IV to oral switch

3. Escalate/ de-escalate antibiotic

4. Change antibiotic

5. Duration of antibiotic

Document all decisions
Decide next review date and stop date

Fig.1. Antimicrobial stewardship guideline in hospital settings

* Antibiotics SMART Use (ASU) was introduced in 2007 as an innovative model to promote the rational use of medicines and counteract antimicrobial resistance.

patients or prescriber, easy access to antimicrobials without prescriptions, pharmaceutical promotions, parental pressure on prescribers, lack of rapid microbial testing and poor communication among health professionals in the health system.[18]

Self-medication with antibiotics is a common practice where patients self-diagnose and purchase antibiotics without prescription. The recent COVID-19 pandemic has increased the inappropriate use of antibiotics, such as azithromycin, due to misinformation regarding the role of such antibiotics in treating COVID-19 infection.[19]

Antimicrobial prescribion facts: The 30% Rule[10]

- Out of the total hospitalised patients, 30% at any given time receive antibiotics

- Over 30% of antibiotics are prescribed inappropriately in the community

- Up to 30% of all surgical prophylaxis are inappropriate

- Out of total hospital pharmacy bills, 30% are due to antimicrobial use

- Antimicrobial stewardship programs save 10-30% of antimicrobial cost

Way forward

Appropriate antimicrobial therapy: Five 'D's are essential for optimal antimicrobial therapy which include right diagnosis/indication, right drug, right dose, right duration of therapy and de-escalation to pathogen-targeted therapy.[10] An important first step in building an antimicrobial stewardship program should be to identify current institutional resistance patterns and antimicrobial use. It should include multi-disciplinary approach involving the microbiology laboratory, infection control, pharmacy personnel and health care workers.

Efforts should be made to determine the most effective way of implementing change, for example - guidelines, order forms, guidebooks, electronic monitoring and educational detailing. Pharmacy purchasing systems usually track defined daily dose (DDD) or days of therapy (DOT), which are extremely useful measures for the success of the program.

Fig.1 gives an outline regarding the antimicrobial stewardship guideline in a hospital setting.

Points to Remember

- *Antimicrobial stewardship is defined as a coordinated intervention, designed to improve and measure the appropriate use of antimicrobial agents.*

- *Antimicrobial stewardship programs can use national guidelines but should incorporate local trends in antimicrobial resistance and hospital-specific targets for maximum benefits.*

- *The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use like toxicity, selection of pathogenic organisms such as Clostridium difficile, emergence of antimicrobial resistance, adverse effects, increased hospital costs and duration of stay.*

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CLIPPINGS

Duration of Shedding of Culturable Virus in SARS-CoV-2 Omicron (BA.1) Infection.

The B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a shorter incubation period and a higher transmission rate than previous variants. Recently, the Centers for Disease Control and Prevention recommended shortening the strict isolation period for infected persons in non-health care settings from 10 days to 5 days after symptom onset or after the initial positive test, followed by 5 days of masking. However, the viral decay kinetics of the omicron variant and the duration of shedding of culturable virus have not been well characterized.

At Brighams Hospital, Massachusetts, longitudinal sampling of nasal swabs was done for determination of viral load, sequencing, and viral culture in outpatients with newly diagnosed coronavirus disease 2019 (Covid-19). From July 2021 through January 2022, 66 participants were enrolled, including 32 with samples that were sequenced and identified as the B.1.617.2 (delta) variant and 34 with samples that were sequenced and identified as the omicron subvariant BA.1, inclusive of sublineages. Participants who received Covid-19-specific therapies were excluded; all but 1 participant had symptomatic infection.

The characteristics of the participants were similar in the two variant groups except that more participants with omicron infection had received a booster vaccine than had those with delta infection (35% vs. 3%). In this longitudinal cohort of participants, most of whom had symptomatic, nonsevere Covid-19 infection, the viral decay kinetics were similar with omicron infection and delta infection. Although vaccination has been shown to reduce the incidence of infection and the severity of disease, the researchers did not find large differences in the median duration of viral shedding among participants who were unvaccinated, those who were vaccinated but not boosted and those who were vaccinated and boosted.

Their results should be interpreted within the context of a small sample size, which limits precision and the possibility of residual confounding in comparisons according to variant, vaccination status, and the time period of infection. Although culture positivity has been proposed as a possible proxy for infectiousness, additional studies are needed to correlate viral-culture positivity with confirmed transmission in order to inform isolation periods. Their data suggest that some persons who are infected with the omicron and delta SARS-CoV-2 variants shed culturable virus more than 5 days after symptom onset or an initial positive test.

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MANAGEMENT OF ACUTE MYOCARDITIS IN PICU

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Abstract: *Acute myocarditis is a disease with protean manifestations and may present to the primary care pediatrician with symptoms ranging from minor flu like illness to severe cardiac failure, life threatening arrythmia or cardiogenic shock. Viruses are the major etiological agents. It is often missed in the initial visits and can easily be mistaken for a respiratory or gastrointestinal infection. Most children need admission in pediatric intensive care unit for monitoring, and supportive care, which remains the cornerstone of management. The prognosis is guarded, as there may be spontaneous complete recovery or irreversible chronic heart failure. In the fulminant variety with cardiogenic shock, efforts should be directed towards carefully optimizing systemic oxygen delivery and reducing oxygen consumption and some may need mechanical circulatory support as a bridge to recovery/cardiac transplantation. There is little evidence to support the routine use of immunomodulation in acute myocarditis.*

Keywords: *Myocarditis, Fulminant, Management, PICU.*

Myocarditis is an inflammatory disease of the myocardium due to various infectious and non-infectious etiologies, with the majority resulting from infections.[1,2] The manifestations of myocarditis can be protean ranging from minor flu like illness to severe heart failure, refractory arrythmias, fulminant myocarditis with cardiogenic shock and sudden cardiac arrest.[3,4] Data from western registries indicate that myocarditis could be the possible inciting cause of dilated cardiomyopathy (DCM) in close to one-third of children.[5] The heterogenicity in presentation makes diagnosis difficult, in the hands of the primary care pediatrician. The variability in outcome spanning from spontaneous complete recovery to irreversible chronic heart

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failure and lack of robust evidence regarding antiviral, immunosuppressive and immunomodulatory therapy add to the complexity of the conundrum.[1-3]

Etiology

Viral infections remain the most common cause of acute myocarditis, though bacteria, fungi and protozoa are also implicated. The recognised non-infectious causes of myocarditis include autoimmunity, hypersensitivity, medications and toxins.[1,2] Viruses which are implicated in the causation of myocarditis are discuseed in Box.1.

Though adenoviruses and enteroviruses had long been the primary culprits, recent epidemiological data from past two decades identify PVB19 and HHV-6 as the commonest.[6]

Similar data has been replicated from the recent German myocardial registry for children and adolescents (MYKKE) registry in which, of 207 children with endomyocardial biopsy (EMB) proven viral lymphocytic myocarditis, viral DNA could be identified in 50%, of which PVB19 DNA was the commonest (57%), followed by HHV-6 DNA(19%), mixed PBV-19/HHV-6 (9.5%) and enterovirus only in 6.6%.[7]

Box 1. Viruses implicated in the causation of myocarditis

1. Cardiotropic viruses: Adeno and entero viruses (Coxsackieviruses A, B, echoviruses)

2. Vaculotropic viruses: Parvovirus B19(PVB19),

3. Lymphotropic viruses (human herpes virus 6 (HHV-6)

4. Cardiotoxic viruses like human immunodeficiency virus (HIV), hepatitis C virus (HCV) and influenza viruses

Viruses that directly infiltrate heart: cardiotropic viruses like adeno and entero and vasculotropic viruses like parvovirus B19.

Viruses that indirectly induce cardiac injury: Lymphotropic viruses (HHV-6) and cardiotoxic viruses like HIV, Hep C and Influenza.

Though significant myocardial involvement as part of post COVID-19 multisystem inflammatory syndrome in children (MIS-C) is well known and myocardial injury due to various mechanisms have been described in acute SARS-COV2 infection, classic lymphocytic myocarditis is relatively uncommon with COVID-19 as described in autopsy series.[6]

Diphtheria continues to be one of the important causes of bacterial toxin mediated myocarditis in developing countries and parts of the developed world where immunization coverage has fallen.[1,5] Scorpion sting is also an important cause of acute severe myocarditis, in the Indian setting, which however has excellent prognosis if the associated autonomic storm is appropriately managed early in the course along with good supportive therapy.

Giant cell myocarditis is almost never seen in children, while eosinophilic myocarditis is a rare entity caused by eosinophilic syndromes, allergies to drugs or parasitic infections.[1]

Pathogenesis

The pathogenesis of myocarditis can be broken down into 3 separate phases, based on murine models infected with coxsackie virus. Phase 1 (1-7 days) is characterized by myocellular invasion of virus and rapid replication resulting in myocellular necrosis and apoptosis and activation of innate immune responses. Phase 2 (1-4 weeks) involves transition to adaptive immunity, with infiltration of T cells, and presence of cardiac autoantibodies. Phase 3 (months to years) is associated with clearance of virus and recovery or ineffective viral clearance and disease progression.

Clinical presentation

US and German multicentric studies reveal a bimodal distribution of age at presentation (<2 years, >12-13 years) with a median age of around 13 years.[7-9] While the classical myocarditis patient may present with a viral prodrome followed by features of acute heart failure, the vast majority have heterogenous presentation which may range from just flu like symptoms, mild chest pain to refractory arrhythmia, cardiogenic shock and sudden cardiac arrest.

Acute fulminant myocarditis typically presents with a short viral prodrome, with distinct onset of symptoms (<14 days), followed by progression to severe heart failure, hypotension and cardiogenic shock requiring inotropic support or mechanical circulatory support (MCS) to maintain cardiac output. In a Japanese series, the fulminant form comprised of 38% of pediatric myocarditis.[10] It is often difficult to distinguish from severe sepsis with shock and hence antibiotic coverage is warranted when in doubt.

The acute non-fulminant myocarditis, has a longer prodrome, with a less distinct onset of illness, and often presents with non-specific complaints. Gastrointestinal (GI) complaints, including abdominal pain, nausea, poor appetite, vomiting and diarrhea predominate over cardiorespiratory complaints as the initial symptoms, in various series. This likely represents the poor GI perfusion and has been found to co-relate with the severity of ventricular function.[8,10] Respiratory symptoms of cough and coryza may also predominate, and in young children, myocarditis can be easily mistaken for a gastroenteritis or upper respiratory tract infection.[11] Older children and adolescents may present with chest pain, fatiguability, palpitations and syncope. Infants may present with poor feeding, lethargy, listlessness, respiratory distress mimicking bronchiolitis or sepsis. It is worthwhile noting that close to 85% of children in a series with myocarditis, required a second hospital visit before myocarditis was diagnosed, reiterating the fact that a high index of suspicion is required.[1]

Diagnosis

The physical signs of heart failure in the form of pulmonary congestion, elevated JVP, cardiomegaly, S3 gallop and hepatomegaly may be present.[4] Hepatomegaly may be the most reliable sign; edema is uncommon especially in infants. Persistent tachycardia without a clearly defined cause is one of the most important pointers towards myocarditis. Chest X-ray may show cardiomegaly except in fulminant acute myocarditis. The presence of severe cardiomegaly (and correspondingly dilated ventricles on ECHO) in the setting of significant hemodynamic compromise suggests the diagnosis of DCM rather than acute myocarditis.[11,12]

Electrocardiogram (ECG) is abnormal in majority of cases with most common findings being sinus tachycardia, low voltage QRS complexes, low amplitude q waves in lateral precordial leads and ST-T changes (flattening, T inversion and sometimes ST elevation mimicking acute myocardial infarction may occur.). Atrial and ventricular arrythmias and varying degrees of AV blocks can also be seen.[5]

Echocardiogram is the mainstay of diagnosis in our setting and reveals LV dysfunction. When LV enlargement is present, it will be much less compared to DCM. Children with the fulminant variety have marked LV dysfunction, normal dimensions (LVEDV Z score <3)

and thickened interventricular septum and LV wall due to edema.[1,11,12] It is also useful in ruling out anomalous origin of left coronary artery from pulmonary artery (ALCAPA), undiagnosed coarctation of aorta, and other structural heart diseases.

Cardiac biomarkers including CK-MB and troponin T, and I are likely to be elevated, but specificity is low. Nonspecific markers of inflammation - including leukocytosis, elevated ESR, CRP may or may not be present.[2]

Cardiac magnetic resonance (CMR) has been evolving as one of the major non-invasive diagnostic modalities in acute myocarditis. MRI can evaluate the function of ventricles and delineate edema (T2 enhancement), hyperemia or capillary leak (early gadolinium enhancement on T1) and fibrosis (late gadolinium enhancement), which could differentiate myocarditis from DCM, when performed in the first 14 days.[1,13] According to the 2009 Lake Louise Criteria (LLC), adult myocarditis was deemed likely if two out of the above three features were present, though operational performance has been variable. Recent data from adults show that newer T1, T2 and extracellular volume (ECV) mapping techniques, backed by normal values from healthy controls are better at characterizing the injured myocardium of myocarditis. Though pediatric experience is limited, in a small study of 23 children with clinically suspected myocarditis, increased T1, T2 and ECV values on CMR mapping demonstrated sensitivities between 86% and 91% and specificities between 74% and 89%. The advancements in CMR have led to the American Heart Association (AHA) recognising CMR as a confirmatory test for pediatric myocarditis in its recent 2021 statement.[2,14]

However, these may not be readily translatable to our setting, especially with the risks associated with sedation and need for endotracheal intubation in the pediatric patient with significantly impaired LV function.

Endomyocardial biopsy (EMB) has been considered the gold standard in the diagnosis of myocarditis since the proposal of the Dallas histological criteria in 1987. The criteria required are presence of inflammatory infiltrate and associated myocyte necrosis not characteristic of an ischemic event. However, it had poor sensitivity, high inter-observer variability and required multiple sampling. It has been complemented by the WHO criteria, where inflammation is detected by the immunohistochemical (IHC) detection of focal or diffuse mononuclear infiltrates (>14 T cells / macrophages/ mm^2), in addition to enhanced expression of HLA class II molecules. Considering the invasiveness and risks involved (myocardial perforation and tamponade), routine use for diagnosis is not supported by guidelines.[1,5] Complications are higher in children (1-10%);even higher in infants.[7] The current recommendations suggest that EMB be limited to patients with fulminant myocarditis, severe ventricular arrhythmias, advanced heart block or unexplained cardiomyopathy.[15] It is most useful in the differentiation of lymphocytic myocarditis from giant cell myocarditis and eosinophilic myocarditis, as the latter two require immunosuppression. Obtaining a biopsy also helps in isolation of viral DNA/ RNA, which may add to diagnosis or suggest treatment options.[13]

Treatment

The treatment of acute myocarditis is predominantly supportive. All cases of heart failure should be managed

		Congestion	
		No	**Yes**
Hypoperfusion	No	Warm and dry A	Warm and wet B
	Yes	Cold and dry L	Cold and wet C

Fig.1. Profile of hemodynamics[4]

Profile "L" refers to severely low cardiac output, with limited options for therapy. The letter L was chosen rather than D to avoid the implication that it may not necessarily follow C

in the Pediatric Intensive Care Unit (PICU), for continuous monitoring.

All patients should have continuous ECG monitoring (to look for arrhythmias) and frequent assessment of respiratory status, perfusion, sensorium and urine output. In patients with cardiogenic shock on vasoactive drugs, central venous access has to be obtained preferably (taking into consideration the associated risks) though drugs can be started peripherally. In such patients an arterial line is necessary for continuous accurate invasive BP measurement and to titrate vasoactive medications.

The management of decompensated heart failure starts with systematic clinical assessment of hemodynamic status. A rapid assessment algorithm borrowed from the adult world, classifies the child with cardiac failure into four possible states based on the presence of elevated filling pressures/ congestion (wet or dry) and adequacy of perfusion (warm or cold) (Fig.1).[4]

Symptoms and signs of poor perfusion include poor feeding, irritability, decreased level of consciousness, tachycardia, narrow pulse pressure, cool extremities and eventually hypotension. Congestive signs include tachypnea, orthopnea, elevated JVP, hepatomegaly, basal crackles and edema.[16] "Warm and dry" represents optimal systolic (adequate prefusion) and diastolic (acceptable filling pressures) functions and is the eventual goal of heart failure therapy.

Shock is a state of supply demand mismatch where there is final inadequate delivery of oxygen and nutrients to the tissues. Oxygen delivery is determined by the cardiac output and the oxygen content of the blood. In normal case, the cardiac output is 3 times the requirement at tissue level

and hence the normal oxygen extraction ratio (OER) (arteriovenous saturation difference) is 25% (Table I).

As the DO_2 falls, OER increases to maintain VO_2 till a critical DO_2 is reached, below which VO_2 falls, shock ensues and anaerobic metabolism begins. In the setting of low CO, the goals are to increase systemic oxygen delivery and decrease oxygen consumption.[17]

This is achieved by optimizing ventilation and gas exchange (by supplemental oxygen therapy, institution of positive pressure ventilation), optimizing the cardiac output by means of manipulating preload, afterload and administration of inotropes, discontinuation of deleterious medications and treating correctable causes (fever, electrolyte imbalance, arrhythmia)

In the PICU, point of care ultrasound (POCUS) is used to assess contractility (Visual ejection fractions on parasternal long short axis views) and volume status (B lines, IVC fullness, IVC collapsibility/distensibility in spontaneously breathing/muscle relaxed ventilated patients respectively)

In the 'Warm and wet" type, perfusion is maintained and diuretics are the first line agents of choice to address congestion. Furosemide 1-2 mg/kg is given as a bolus over 15-20 minutes and rapid improvement usually ensues.

Children in the "Cold and Wet" phase are sicker and the initial therapy depends on the extent of circulatory compromise. The failing heart operates on the flat portion of 'Frank-Starling's curve'. Therefore reducing the afterload is the most effective way of increasing stroke volume (and hence cardiac output) rather than whipping it with inotropic agents.[18]

Table I. Equations describing oxygen delivery

1	$DO_2 = CO \times CaO_2$	$CO = SV \times HR$	
		$CaO_2 = (1.34 \times Hb \times SaO_2) + (PaO_2 \times 0.003)$	
2	$VO_2 = CO (CaO_2 - CvO_2)$		
3	$OER = \dfrac{SaO_2 - SmvO_2}{SaO_2}$	25 % Normal 30% - 50% Elevated 50% -60% Impending shock >60% Shock, lactic acidosis	

DO_2-Oxygen delivery, VO_2-Oxygen Consumption CO-Cardiac output, CaO2-Arterial oxygen content, CvO_2-venous oxygen content, OER-Oxygen extraction ratio, SaO2-arterial oxygen saturation, $SmvO_2$-mixed venous oxygen saturation. ScvO2 or SmvO2 can be measured by drawing blood from the distal line of central venous catheter for blood gas analysis. SV-Stroke volume, HR- Heart rate.

However, inotropes are required in the setting of significantly impaired perfusion and hypotension. Inodilators (dobutamine and milrinone), which have inotropy as well as afterload reduction, usually cause a further drop in BP that may significantly compromise the coronary perfusion, in very unstable patients and may precipitate cardiac arrest.

Adrenaline in a dose of 0.05 to 0.1 mcg /kg/min has predominant β activity and is an excellent inotrope. At doses >0.2-0.3 mcg /kg/min α activity and hence peripheral vasoconstriction takes over.[13,17] The vasoconstrictor doses of adrenaline or noradrenaline may sometimes be required in the acutely hypotensive patient to tide over crisis and may be lifesaving.[17] However, long term use of the same is not advisable, as it causes tachycardia and increased myocardial oxygen demand. Once an acceptable BP is achieved, inodilators are added.

Dobutamine in a dose of 2-20 mcg /kg/min increases CO by virtue of its modest inotropic activity (β1) and reduction in SVR (β2). It is safe to be used in the normotensive patient with low cardiac output, however increased myocardial O_2 demand, tachycardia and arrhythmogenicity are the problems.

Milrinone, a phosphodiesterase III inhibitor, reduces the degradation of cAMP and via increased intracellular Ca 2+, produces modest inotropy, peripheral vasodilation and has lusitropic properties helping in diastolic dysfunction. Milrinone is the preferred drug in cardiogenic shock in children, primarily based on studies extrapolated from post cardiac surgery setting. A loading dose is never given in the PICU setting, for fear of hypotension and the usual infusion doses are 0.25-0.75 mcg/kg/min. A long half life (<1 hour in children and >3 hours in infants) makes titration to effect in the acute setting difficult, especially as hypotension can occur. As it is renally eliminated dose adjustment is warranted in renal dysfunction.[17,18]

The decision to start inotropes should be based on the clinical assessment of perfusion and not echocardiographic findings, as many children may be adequately compensated and inotropes could actually be harmful.[11]

The "Cold and dry" category represents an ominous stage of low cardiac output with limited scope for medical therapy, require a combination of inotropes, vasopressors (to maintain a diastolic BP of >25-30 mm) and may require mechanical circulatory support (see below), as prolonged high doses of vasoactives cause myocyte death and decrease chances of recovery.[18]

Mechanical ventilation is one of the main stays of management of acute LV failure. In the failing LV, the institution of positive intra thoracic pressure reduces the trans mural stress on the LV and hence significantly reduces the afterload. Positive end expiratory pressure (PEEP) clears the pulmonary edema and improves oxygenation and ventilation. By taking over the work of the breathing in the cardiac failure patient with severe pulmonary congestion, mechanical ventilation helps redistribute the already compromised CO away from the respiratory muscles to the vital organs. Though non-invasive ventilation can be tried in the relatively stable patient, intubation is preferred, for all the aforementioned benefits.[16-18]

However, the process of intubating a child with poor cardiac function is a high-risk procedure and needs to be meticulously done in the PICU environment, with the team adequately prepared to manage a precipitous cardiac arrest. Low dose adrenaline infusion is started, if not already done so. Resuscitation doses of adrenaline (1/10000) should be loaded and kept. The child should be adequately preoxygenated and drugs with the least myocardial depression and vasodilatory effects are used. In general, a very low dose of sedative along with a good dose of muscle relaxant is used. We generally use ketamine (though in the catecholamine depleted end-stage heart failure, ketamine can cause myocardial depression and hypotension) and vecuronium for induction. Poor circulation may mean longer time for the drugs to reach full effect. Care must be taken to match the pre intubation minute ventilation in the peri-intubation period, as significant respiratory acidosis coupled with existing metabolic acidosis in the setting of existing myocardial dysfunction can be deleterious. Preload may have to be optimized with careful fluid boluses.[16-18] In the event of significant hypotension, careful administration of adrenaline mini-boluses (<10 mcg /kg) could help avert a cardiac arrest.

Mechanical circulatory support (MCS) may be necessary in children with the fulminant form of myocarditis, refractory to conventional therapy as a bridge to recovery / transplantation. Veno-arterial extracorporeal membrane oxygenation (VA- ECMO) remains the main mode of the MCS in India, though some specialised centres have performed implantation of ventricular assist devices (VADs). ECMO can be deployed emergently, provides biventricular and respiratory support and may be especially useful in the fulminant myocarditis where chance of recovery is high compared to cardiomyopathy. Western data show that survival to discharge rate with ECMO support is 69 to 76 %.[2] Initiation of MCS, before significant MODS

sets in, is essential.[5] The primary VAD used in children, in the centres with expertise is the pulsatile Berlin Heart EXCOR (EXCOR® is a ventricular assist device), which comes in various sizes, allowing support for infants as small as 3.5kg. Others include HeartMate and HeartWare. VADs are primarily used as long-term support as a bridge to transplant.[5,11]

Other supportive therapies

In the patient with cardiogenic shock, IV fluids are restricted to 60%. The patient may require fluid boluses to optimize preload and trends in CVP may guide the same. Frequent glucose monitoring is needed and hypoglycemia has to be treated aggressively. Potassium has to be kept around 4 mEq/L. Ionized calcium has to be preferably kept around 1.2 mmol/L. Care has to be taken to ensure that heparin has been completely flushed out before wrongly interpreting falsely low values. Packed red blood cell transfusion may be considered, to maintain a Hb of 9-10g/dL and improve oxygen delivery, if the $ScvO_2$ is persistently less than 60-70%, despite other supportive therapy.[16]

Aggressive control of fever (and sometimes cooling) and muscle relaxing the patient are strategies to decrease the metabolic demand and oxygen extraction.

Arrythmias are difficult to treat as most antiarrhythmic agents could cause decompensation in view of the negative inotropy. Temporary transvenous pacing should be considered in the setting of bradyarrhythmia and heart block. Refractory arrhythmia with low cardiac output will need MCS.[2,5,16]

In patients who are out of the cardiogenic shock phase, ACE inhibitors, beta blockers and aldosterone antagonists are carefully added.[16]

Immunomodulation and antiviral therapy

There's a huge dearth in the availability of quality evidence on the use of immunomodulation in myocarditis. Understanding the pathophysiology of myocarditis may be of particular importance in planning specific therapies.

Much of the immunomodulatory therapy target Phase 2. IVIG has been long used in acute myocarditis because of its familiarity among pediatricians and relative safety compounded by the fear of terminal outcomes and the long term sequelae. However, ventricular function improves or recovers fully in many children spontaneously, making it difficult to assess treatment effect in uncontrolled trials.[2]

IVIG is not thought to be immunosuppressive, but has anti-inflammatory, antiviral and immunomodulatory properties. A possible survival benefit with IVIG in pediatric myocarditis was first proposed by Drucker, et al in 1994, where improved LV function was noted at 1 year in 21 children, when compared to historical controls. The two groups were not comparable and the mortality benefit was not statistically significant either.[19] Similar findings have not been subsequently reproduced. A 2015 Cochrane review and its subsequent update in 2020 (including 2 RCTs in adults and 1 RCT in children) have not been able to determine a beneficial effect for IVIG in adult and pediatric acute myocarditis, though the evidence is of low certainty.[20] A 2019 meta-analysis including 12 retrospective studies and one non-randomized control study, showed significant heterogenicity and publication biases and concluded that IVIG treatment was not beneficial in myocarditis in children.[21] The non-randomized pediatric study from India, which was included in the 2015 Cochrane review (subsequently removed from 2020 update) and 2019 meta-analysis, show improvement in LV function and overall survival, with IVIG, in children with myocarditis, in the setting of acute encephalitis, however has significant bias and cannot be generalized.[22] IVIG has also been reported to be useful in neonatal enteroviral sepsis with myocarditis based on retrospective data.[23] IVIG is indicated in myocardial dysfunction of Kawasaki shock syndrome and most cases of MIS-C.

Corticosteroids are considered immunosuppressants with potent anti-inflammatory effects. Adult studies have shown improvement in LV function with prednisolone and azathioprine in the particular subset of the patients with biopsy proven myocarditis, absence of active viral infection and presence of chronic inflammation. Similar results have not been consistently reproduced in children.[2,5,6] Decision for immunosuppression should be individualized based on clinical, EMB findings.

Immunosuppression is warranted in autoimmune, giant cell and eosinophilic myocarditis, though the latter two are rare in children.

Antivirals have not been rigorously studied in acute myocarditis. Plecoranil has been shown to have survival benefit in neonates with enteroviral sepsis, but not specifically in myocarditis.[24] The 2021 AHA scientific statement on the management of myocarditis in children advocates that it may be reasonable to treat with antiviral agents if an active infection is diagnosed, even without proof of infection in the myocardium, given their benefit in noncardiac infections.[2] Antiviral therapy may be

particularly useful in inflammatory cardiomyopathies where active viral replication and inflammation are demonstrated on EMB.[6] It is also useful in HIV, HBV and HCV associated myocarditis.[2,6]

Conclusion

Acute myocarditis in children is a heterogeneous condition, the most common etiology being viral infections. The diagnosis is often delayed due to the relative rarity of the condition and nonspecific clinical features early in the course. Once diagnosed, management is predominantly supportive, with very little evidence for specific modalities like antivirals and/or immunomodulation. Significant knowledge gap exists in management options including reliable and safe diagnostic tests.

Points to Remember

- *Viruses are the major cause of acute myocarditis and recent data suggest that parvovirus B19(PVB19) and human herpesvirus 6 predominate over entero and adenoviruses.*

- *The initial manifestations of acute myocarditis may be nonspecific and gastrointestinal symptoms may be commoner than cardiorespiratory symptoms and a high index of suspicion is needed for diagnosis.*

- *Presentations range between minor flu like symptoms, mild chest pain, acute heart failure, refractory arrhythmia, cardiogenic shock and sudden cardiac death.*

- *Persistent tachycardia without a clearly identified cause should prompt evaluation for myocarditis.*

- *Cardiac MRI is an evolving tool in the diagnosis of acute myocarditis.*

- *PICU admission is needed in most patients for monitoring and early identification of decompensation.*

- *Supportive care remains the cornerstone in the management of acute myocarditis.*

- *In patients with acute decompensated heart failure and cardiogenic shock, the management should focus on optimizing systemic oxygen delivery and decreasing oxygen consumption.*

- *The routine use of IVIG, steroids and antivirals in acute myocarditis is unfounded.*

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CLIPPINGS

Neurodevelopmental Outcomes at 1 Year in Infants of Mothers Who Tested Positive for SARS-CoV-2 During Pregnancy.

Epidemiologic studies suggest maternal immune activation during pregnancy may be associated with neurodevelopmental effects in offspring. This retrospective cohort study aimed to evaluate whether in utero exposure to SARS-CoV-2 is associated with risk for neurodevelopmental disorders in the first 12 months after birth. Live offspring of all mothers who delivered between March and September 2020 at any of 6 Massachusetts hospitals across 2 health systems were examined. All infants born to mothers with SARS-CoV-2 infection confirmed by a polymerase chain reaction test during pregnancy were followed up for neurodevelopmental disorders in the first year of life (ICD-10). Statistical analysis was performed from October to December 2021.

The cohort included 7772 live births (7466 pregnancies, 96% singleton, 222 births to SARS-CoV-2 positive mothers). Preterm delivery was more likely among exposed mothers: 14.4% vs 8.7%. (P = .003). Maternal SARS-CoV-2 positivity during pregnancy was associated with greater rate of neurodevelopmental diagnoses in unadjusted models as well as those adjusted for race, ethnicity, insurance status, offspring sex, maternal age, and preterm status. Third-trimester infection was associated with effects of larger magnitude.

This cohort study of SARS-CoV-2 exposure in utero found preliminary evidence that maternal SARS-CoV-2 may be associated with neurodevelopmental sequelae in some offspring. Prospective studies with longer follow-up duration will be required to exclude confounding and confirm these associations.

Edlow AG, Castro VM, Shook LL, Kaimal AJ, Perlis RH. Neurodevelopmental Outcomes at 1 Year in Infants of Mothers Who Tested Positive for SARS-CoV-2 During Pregnancy. JAMA Network Open 2022; 5(6):e2215787. doi:10.1001/jamanetworkopen.2022.15787.

<div style="text-align:center">**DRUG PROFILE**</div>

PAIN MANAGEMENT IN PALLIATIVE CARE

Jeeson C. Unni

Abstract : *Most children on the point of death due to life-limiting diseases often experience distressing pain, which is not adequately addressed or relieved. Multidisciplinary approach to pain management in these terminally ill children comprises rehabilitation, psychological modalities, integrative therapies (all more effective with minimal side effects) and lastly, pharmacotherapy. All modalities act synergistically for pain control. This article focuses on pharmacotherapeutic options which comprise use of opioids, such as morphine, fentanyl, hydromorphone, oxycodone, tramadol, methadone and diamorphine.*

Keywords: *Pain management, Palliative care, Children, Opioids.*

Palliative care is the active and comprehensive approach to the care of children and young adults with life-limiting and life-threatening conditions, inclusive of their physical, emotional, social, and spiritual wellbeing.[1] It focuses on bettering the quality of life for the patient and support for their family and includes not only management of disturbing symptoms, but also provides psychological support, relieves fears and anxieties, helps achieve inner peace and care during bereavement.

Effective palliative care imbibes a multidisciplinary mode that involves the whole family, and ideally is activated as soon as a life-threatening condition is diagnosed.[2]

Pain is a common and often under recognized and under treated symptom in children with cancer, chronic illnesses and progressive neurodegenerative and chromosomal conditions with CNS impairment.[3] This article attempts to discuss pharmacotherapeutic interventions that could be considered in these children.

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General principles of pain relief

It is important to prescribe as few medications for pain relief as possible. It is preferable to use oral medications. Parenteral and other routes of administration are employed only if these children have severe nausea and vomiting, dysphagia, weakness or coma.

Pharmacological interventions to relieve pain are best when used in combination with non-pharmacological measures.[4] Each child needs to be administered the right drug in the right dose at the right time for the condition at hand.

Analgesics can be divided into three broad classes:

- Non-opioids (paracetamol, NSAID)
- Opioids (e.g. weak opioid - codeine phosphate, strong opioid - morphine)
- Adjuvants (e.g. antidepressants, antiepileptics).

Choice of analgesics

Drugs from the different classes are used alone or in combination, according to the type of pain and response to treatment. The WHO analgesic ladder is a validated system for ensuring judicious decision making regarding choice of medications (Fig.1).[5,6]

Analgesics are more effective as pain preventers than as relievers of established pain and they need to be given on a regular basis and not SOS. Paracetamol or a non steroidal antiinflammatory drug (NSAID) given round-the-clock will often suffice for mild pain.

If non-opioid analgesics alone are not sufficient, then an opioid analgesic alone or in combination with a non-opioid analgesic at an adequate dosage may be helpful

Step 1	Step 2	Step 3
Simple analgesic $\pm$ Simple adjunct	Weak opicid $\pm$ Simple analgesic $\pm$ Simple adjunct	Strong opicid $\pm$ Simple analgesic $\pm$ Simple adjunct
e.g. paracetamol + NSAID	e.g. codeine + paracetamol + NSAID	e.g. morphine + paracetamol + NSAID

Fig.1. WHO analgesic ladder

in the control of moderate pain. Codeine phosphate or tramadol hydrochloride can be considered for this purpose.

If these preparations do not control the pain adequately, the most powerful opioid analgesic such as morphine, needs to be considered. Alternatives to morphine, include transdermal buprenorphine, transdermal fentanyl, hydromorphone hydrochloride, methadone hydrochloride or oxycodone hydrochloride. These agents may be initiated by those with experience in palliative care.

Fear of psychological dependence should not be a reason for delay in starting an opioid analgesic.

Specific situations

Bone metastases - In addition to the above approach, radiotherapy and bisphosphonates may be useful for pain due to bone metastases.[7]

Radiation therapy is often used to manage pain for palliative treatment of children with bone, brain, liver, lung, abdomino-pelvic and head-and-neck metastases, spinal cord compression and superior vena cava syndrome.[8]

Neuropathic pain is one scenario in pediatric palliative care wherein adjuvant medications are useful. The three drugs worth a trial when neuropathic pain responds poorly to opioid analgesics, are tricyclic antidepressants (most used being amitriptyline hydrochloride),[9] carbamazepine and ketamine.[4] Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone, which reduces oedema around the tumour.[4,10] Nerve blocks can be considered when pain is localised to a specific area. Transcutaneous electrical nerve stimulation (TENS) may also help.[11]

Pain management with opioids

Sixty to ninety percent of chronically ill children in palliative care are prescribed opioids only when they are terminally ill.[12] The choice of first-line opioid for pain relief in these children depends on the etiopathogenesis of pain and the mode of administration appropriate for the given child.

Oral administration of opioids

Morphine

Morphine, the gold standard for pain management in palliation[12], often needs to be administered at a higher dose in proportion to their body-weight in children compared to adults.[13] Treatment with morphine is given by mouth as immediate-release or modified-release preparations. During the titration phase the initial dose is based on the previous medication used, the severity of the pain and other factors such as presence of renal impairment or frailty. The dose is given either as an immediate-release preparation 4th hourly, or as a 12-hourly modified-release preparation, in addition to rescue doses.[14] Rescue dose of immediate-release morphine at 1/10th to 1/6th of the regular 24 hr dose, is given for breakthrough pain and 30 minutes before an activity that causes pain, such as wound dressing. This dose may be repeated 2nd to 4th hourly and even hourly for severe pain or in the last few days of life. However, it is advisable to review medication for pain if rescue doses are required more than twice daily. Each child should be assessed on an individual basis.

When adjusting the dose of morphine, the number of rescue doses required and the response to them should be taken into account increments of morphine should not exceed one-third to one-half of the total daily dose every 24 hours. Thereafter, the dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics should also be considered. Increments should be made to the dose, not to the frequency of administration. Upward titration of the dose of morphine stops when either the pain is relieved or unacceptable adverse effects occur, after which it is necessary to consider alternative measures.

Once pain is controlled, children started on 4-hourly immediate-release morphine can be changed to modified-release preparation; the total dose given is either 12-hourly or 24-hourly. The first dose of the modified-release preparation is given within 4 hours of the last dose of the immediate-release preparation.

The child must be monitored closely for efficacy and side-effects, particularly constipation (may require regular use of laxatives), nausea and vomiting, urinary retention (which can be eased by bethanechol chloride) and opioid-induced pruritus.

Morphine is alternated with slow-release hydromorphone as and when morphine toxicity develops.[11] When replacing a weaker opioid analgesic such as codeine phosphate, starting doses are usually higher.

Fentanyl

Fentanyl transdermal therapeutic system (TTS) with a drug-release rate of 12.5 microgram/hour matches the lower dose requirements of pediatric cancer pain control. The approximate conversion factor of this dose of fentanyl to oral morphine is 45 mg/day and may be used for initial therapy in children receiving long-term morphine therapy.[15] This dose of fentanyl is not associated with respiratory depression. Daily oral morphine equivalent dose should

be at least 30 mg/day before fentanyl TTS therapy is started with 12.5 mcg/hr. Its use may be associated with less constipation compared with morphine use. Though oral transmucosal fentanyl citrate has reduced bioavailability (25%), it is useful for breakthrough pain management.[12] Formulations of fentanyl that are administered nasally, buccally or sublingually are not licensed for use in children; their usefulness in children is also limited by dose availability.

Buprenorphine

Buprenorphine can be administered through different routes. It has a long duration of action and its metabolism being largely independent of renal function and is effective for neuropathic pain due to antihyperalgesic effect achieved through antagonism at the kappa-receptor.[12]

Methadone

Methadone[16] may have a role in the management of pain in children with life-limiting illness. Its complex pharmacokinetic profile and lack of studies in children limits its use. Methadone acts mainly at the mu opioid receptors [a class of receptors that neuromodulate different physiological functions, nociception, stress, temperature, respiration, endocrine activity, gastrointestinal activity, memory, mood and motivation. Because they bind to opioids, they are also called as mu-opioid receptors (MORs) and also at serotonin, noradrenaline and N-methyl-D-aspartic acid (NMDA) receptors resulting in less sedation and development of tolerance]. All routes of administration are possible. Half-life is shorter in children but variable such that steady state is achieved anytime between 4 to 10 days resulting in danger of accumulation and deaths due to overdose within the first 4 to 6 days of commencing treatment.

Oxycodone

Oxycodone is a possible alternative to morphine with a Cochrane systematic review indicating efficacy and tolerability similar (but NOT superior) to morphine.[17] Oxycodone does not appear to offer any advantage over morphine as a first-choice opioid analgesic but may be considered in a child who does not tolerate morphine and for breakthrough pain at appropriate equivalent dose (Table I).

Routes of administration

Diamorphine hydrochloride is preferred for injection because, being more soluble, it can be given in a smaller volume.[6,18] The equivalent subcutaneous dose is

Table I. Equivalent doses of opioid analgesics

An approximate guide - children should be carefully monitored after any change in medication and dose titration may be required.		
Analgesic	**Route**	**Dose**
Codeine	Oral	100mg
Diamorphine	IM, IV, SC	3mg
Dihydrocodeine	Oral	2mg
Morphine	Oral	10mg
Morphine	IM, IV, SC	5mg
Oxycodone	Oral	6.6mg
Tramadol	Oral	100mg

PO = by mouth; IM = intramuscular; IV = intravenous; SC = subcutaneous

(Modified from: Dose equivalents and changing opioids - Faculty of Pain Medicine of the Royal College of Anaesthetics. https://fpm.ac.uk › dose-equivalents-and-changing-opioids. Accessed on 04 June 2022).

approximately a third of the oral dose of morphine (Table I). Subcutaneous infusion of diamorphine hydrochloride via a continuous infusion device can be useful. If the child can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of diamorphine hydrochloride. Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours are given in Table II.

Rectal route - Suppositories are useful alternative to injections, particularly at home. The oral to rectal potency ratio is 1:1; i.e. the oral and rectal doses are the same.[19] Unfortunately, morphine suppositories are not available in India and many palliative care units use the tablets rectally. If administration every 4 hours proves difficult, it is possible to give slow-release morphine tablets per rectum every 12 hours. Pharmacokinetic studies have demonstrated that they are equally well absorbed by this route.

Transdermal route - Transdermal preparations of fentanyl and buprenorphine [not licensed for use in children] are available; they are not suitable for acute pain or in those children whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations because inappropriate use has caused fatalities.[20] The 24-hour oral

Table II. Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours[14]

These equivalences are approximate only and should be adjusted according to response		
Oral morphine	**Parenteral morphine**	**Parenteral diamorphine**
Oral morphine sulfate over 24 hours	Subcutaneous infusion of morphine sulfate over 24 hours	Subcutaneous infusion of diamorphine hydrochloride over 24 hours
30 mg	15 mg	10 mg
60 mg	30 mg	20 mg
90 mg	45 mg	30 mg
120 mg	60 mg	40 mg
180 mg	90 mg	60 mg
240 mg	120 mg	80 mg
360 mg	180 mg	120 mg
480 mg	240 mg	160 mg
600 mg	300 mg	200 mg
780 mg	390 mg	260 mg
960 mg	480 mg	320 mg
1200 mg	600 mg	400 mg
If breakthrough pain occurs, give a subcutaneous injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. With an intermittent subcutaneous injection absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle). No individual subcutaneous infusion solution should be used for longer than 24 hours because of concern over risk of infection.		

doses of morphine are considered to be approximately equivalent to the buprenorphine as in Table III and fentanyl patches as in Table IV, however when switching due to possible opioid-induced hyperalgesia, it is prudent to reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

Transdermal patch: Formulations of transdermal patches are available as 72-hourly, 96-hourly and 7-day patches. Conversion ratios vary and these figures are a guide only.

BuTrans 5 microgram/hour is a square, beige coloured patch with rounded corners marked BuTrans 5 mcg/h.

BuTrans 10 microgram/hour is a rectangular, beige coloured patch with rounded corners marked BuTrans 10 mcg/h.

BuTrans 20 microgram/hour is a square, beige coloured patch with rounded corners marked BuTrans 20 mcg/h.

Table III. Buprenorphine patches are approximately equivalent to the following 24-hour doses of oral morphine[14]

Morphine salt 12 mg daily	Buprenorphine '5' patch
Morphine salt 24 mg daily	Buprenorphine '10' patch
Morphine salt 36 mg daily	Buprenorphine '15' patch
Morphine salt 48 mg daily	Buprenorphine '20' patch
Morphine salt 84 mg daily	Buprenorphine '35' patch
Morphine salt 126 mg daily	Buprenorphine '52.5' patch
Morphine salt 168 mg daily	Buprenorphine '70' patch
Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.	

Table IV. 72-hour fentanyl patches are approximately equivalent to the following 24-hour doses of oral morphine[14]

Morphine salt 30 mg daily	Fentanyl '12' patch
Morphine salt 60 mg daily	Fentanyl '25' patch
Morphine salt 120 mg daily	Fentanyl '50' patch
Morphine salt 180 mg daily	Fentanyl '75' patch
Morphine salt 240 mg daily	Fentanyl '100' patch

Fentanyl equivalences in this table are for children on well tolerated opioid therapy for long periods; fentanyl patches should not be used in opioid naive children. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

Each 5 microgram/hour transdermal patch contains 5 mg of buprenorphine in a 6.25 cm2 area releasing a nominal 5 micrograms of buprenorphine per hour over a period of 7 days.

Note: Both the health care providers and the family should understand that patients using fentanyl transdermal system needs careful monitoring There is a risk of opioid addiction, abuse, and misuse, and overdose which can lead to life threatening situations and death.

Tramadol is a medication that is typically viewed as an opioid, albeit a "weak" mu-agonist. It is perceived to have the same potency as codeine and is often prescribed to avoid "stronger" opioids such as morphine, oxycodone, or hydromorphone. Though FDA warns against its use in children, prescribing tramadol for children 12-17-year age, admitted with nociceptive pain at the minimal effective dose, in a child-appropriate dose and after clear instructions to the parents, remains a reasonable option based on current data. In all other situations, morphine should be preferred for moderate to severe nociceptive pain conditions.

Conclusion

The pharmacological management of pain in pediatric palliative care is an often ill-understood and neglected area. There have been many developments in this field in adult palliative care and most of what is practiced in children currently is extrapolation of these developments. There is a compelling need to generate more data in this area by controlled trials wherever possible.

Points to Remember

- *Pharmacological interventions to relieve pain in palliative care of children are best achieved used in conjunction with other measures.*

- *Opioid, non-opioid and adjuvants drugs are used alone or in combination according to the type of pain and response to treatment.*

- *Treatment can be initiated with non-opioid analgesic like paracetamol or NSAIDs. If non-opioid analgesics alone are not sufficient for moderate pain, they can be combined with opioid analgesics like codeine phosphate or tramadol hydrochloride at an adequate dosage.*

- *Morphine, the opioid is considered the gold standard for initiating therapy for pain in palliation. Alternatives to morphine include transdermal buprenorphine, transdermal fentanyl, hydromorphone hydrochloride, methadone hydrochloride, or oxycodone hydrochloride.*

- *Though oral route is the preferred mode of administration, other parenteral routes like rectal, transdermal etc. are used only if there is severe nausea, vomiting, dysphagia, weakness or coma.*

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CLIPPINGS

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability.

Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

This cohort study was done to determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders. The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway and Sweden (1996-2017); analysis performed February 2022. A total of 4 494 926 children were included. Children from a multiple pregnancy or with chromosomal disorders or uncertain pregnancy length were excluded. Prenatal exposure to ASM determined from maternal prescription fills between last menstrual period and birth.

Cumulative incidence was estimated at age 8 years in exposed and unexposed children. Among 21/634 unexposed children of mothers with epilepsy, 1.5% had a diagnosis of ASD (autistic spectrum disorder) and 0.8% of ID (intellectual disability) by age 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD, and 3.1% and 2.4% had ID.

The duotherapies levetiracetam with carbamazepine and lamotrigine with topiramate were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy. No increased risk was associated with levetiracetam with lamotrigine.

No consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital.

Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269.

RADIOLOGY

CONGENITAL LUNG MALFORMATIONS - I

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Congenital lung malformations comprise a spectrum of anomalies involving the lung parenchyma and its bronchovascular structures. They account for 5-18% of all congenital anomalies, with a cumulative incidence of 30-42 cases per 100,000 population. These are likely to be underestimates, as significant proportion could be undetected / asymptomatic.Clinically occult lesions identified incidentally in patients examined for other clinical indications,using advanced diagnostic imaging including sonography, multi-detector computer tomography, magnetic resonance imaging and angiography have contributed to increased detection of lesions, both antenatally and in later life. Given the wide variability in clinical presentations, accurate diagnosis is critical for counselling, with sweeping implications for viability of pregnancies and planning of surgery. In this article, the common lung malformations will be discussed which may give clues to early diagnosis.

Classification of lung malformations according to the site of involvement is shown in Box 1.

In the malformations of lungs and tracheobronchial tree, pulmonary agenesis means complete absence of a lung or lobe and its bronchi. Aplasia refers to absence of lung tissue, in which rudimentary lobar bronchi are present. Hypoplasia refers to an underdeveloped lobe that contains both alveoli and bronchi.

Lung and tracheobronchial tree malformation

Congenital pulmonary airway malformations

Congenital pulmonary airway malformations (CPAM) are multicystic masses of segmental lung tissue with abnormal bronchial proliferation. CPAMs are considered part of the spectrum of bronchopulmonary foregut malformations. Subtypes are outlined in Table I.

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Box 1. Classification of lung malformations

Lungs and tracheobronchial tree

- Congenital pulmonary airway malformation
- Bronchial atresia
- Bronchogenic cyst
- Congenital lobar overinflation
- Pulmonary sequestration
- Pulmonary hypoplasia
- Pulmonary agenesis
- Pulmonary aplasia
- Azygous lobe

Vascular abnormalities

- Pulmonary arteriovenous malformations
- Anomalous pulmonary venous return
- Pulmonary artery sling
- Pulmonary varix
- Pulmonary lymphangiectasia

Radiological features

The appearance of CPAM will vary depending on the type. They can be diagnosed prenatally and are the most common prenatally diagnosed lung malformation. The diagnostic modality used is fetal ultrasound which can help to further classify as either microcystic or macrocystic based on the size of the cysts. If further differentiation of the lesion is needed, MRI is used, especially to distinguish between bronchopulmonary sequestration and congenital diaphragmatic hernia. If there is a prenatal diagnosis of CPAM, a chest radiograph should be done after birth. (Fig.1a & b), which may or may not show the abnormality, CT chest will be able to delineate CPAM better (Fig. 2a & b).

Bronchial atresia

Bronchial atresia is a developmental anomaly characterised by focal obliteration of the proximal segment

Table I. Subtypes of Congenital pulmonary airway malformations

Types	Characteristics
Type I	Most common: 70% of cases; large cysts; one or more dominant cysts: 2-10 cm in size; may be surrounded by smaller cysts
Type II	15-20% of cases; cysts are <2 cm in diameter; associated with other abnormalities (renal agenesis or dysgenesis, pulmonary sequestration, congenital cardiac anomalies)
Type III	~10% of cases; microcysts: <5 mm in diameter; typically involves an entire lobe; has a poorer prognosis
Type IV	Unlined cyst; typically affects a single lobe; indistinguishable from type I on imaging
Type 0	Very rare, lethal postnatally; acinar dysgenesis or dysplasia; represents global arrest of lung development
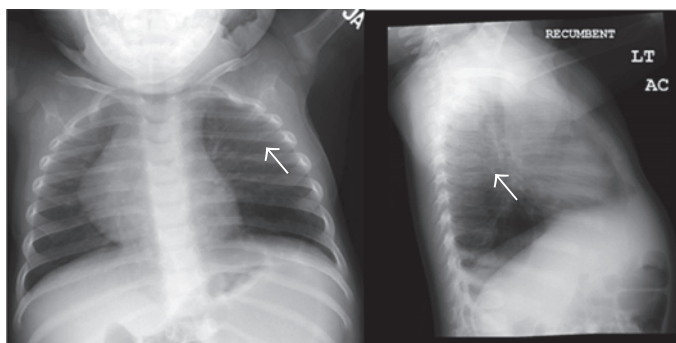
Fig.1a & b. Chest X-ray AP and lateral -left lower lobe CPAM
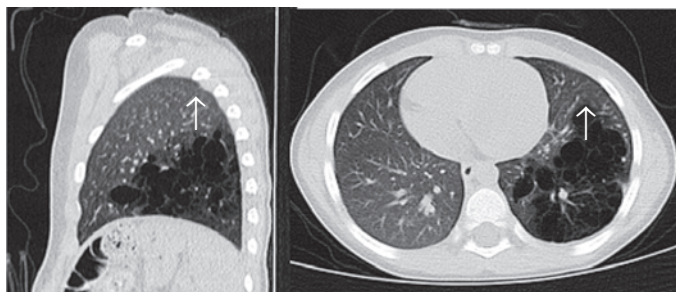
Fig.2a. CT chest (sagittal view) - CPAM left lower lobe
Fig.2b. CT coronal view - CPAM left lower lobe

Fig.3a. X-ray chest PA - Left bronchial atresia (arrow head) bronchocele as small ovoid parahilar mass.
Fig.3b.CT Chest (coronal view): Left bronchial atresia finger-in-glove appearance (stump plugged with mucus)

of a bronchus associated with hyperinflation of the distal lung.On imaging, it commonly presents as a proximal focal tubular-shaped opacity radiating from the hilum; distal lung parenchyma supplied by the atretic segment can be hyperlucent due to oligemia and air trapping due to air entering through pores of Kohn (Fig.3a & Fig.3b).

Bronchogenic cysts

Bronchogenic cysts are congenital malformations of the bronchial tree (a type of bronchopulmonary foregut malformation). They can present as a mediastinal mass that may enlarge and cause local compression. It is also considered the commonest of the foregut duplication cysts.They can be intrapulmonary or mediastinal. The most

common location is the middle mediastinum (65-90%) but the distribution of locations can be quite varied

Radiological features

Although bronchogenic cysts are usually fluid-filled, occasionally a communication may develop following infection or intervention, resulting in an air-filled cystic structure with or without an air-fluid level.

Chest X-ray:The cysts usually appear as rounded soft-tissue density sometimes with compression of surrounding structures. Occasionally such compression can

Box 2. Distribution of bronchogenic cysts

Mediastinal (~70%)

Usually does not communicate with the tracheobronchial tree.

Subcarinal, right paratracheal and hilar areas are the most common locations

Approximate incidence includes - carinal area: ~50%, paratracheal

area: ~20%, oropharyngeal wall: ~15%, retrocardiac area: ~10%

Parenchymal (intrapulmonary)

Typically perihilar; predilection for lower lobes

Other uncommon locations

Neck, cutaneous, pericardium, extending across the diaphragm and appearing dumb-bell shaped; retroperitoneal - tend to be in a subdiaphragmatic or peripancreatic distribution, usually to the left of the midline.

Fig.5a. Barium esophagogram (AP view) laterally displaced esophagus (arrow)

Fig.5b. Barium esophagogram (lateral view) mass compressing and displacing trachea anteriorly and esophagus posteriorly (arrow)
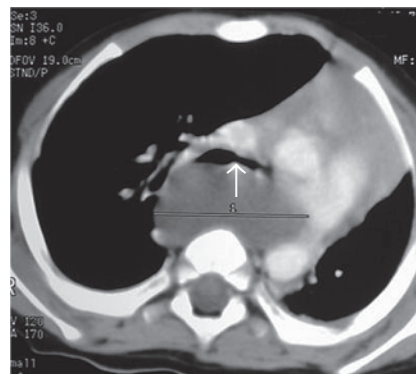
Fig.6. Bronchogenic cyst posterior to trachea causing compression of carina and narrowing of left main bronchus

lead to air-trapping and a hyperlucent hemithorax (Fig.4a & b). As the cysts may contain calcium oxalate, dependent layering of calcific density material (milk of calcium) may be seen occasionally.

Barium study (Fig.5a and b): this can show displacement or compression of trachea, main bronchi and esophagus if the cyst is in mediastinum. Before the advent of CT scan, this modality of investigation was useful to make a reasonable diagnosis.

CT chest (Fig.6): appear typically as well-circumscribed spherical or ovoid masses of variable attenuation, with variable fluid composition explaining the different CT attenuations observed. Approximately 50% are of fluid density (0-20 HU), however, a significant proportion is of soft tissue density (>30 HU) or even hyperattenuating to surrounding mediastinal soft tissues. The degree of CT attenuation often depends on the amount of internal proteinaceous content. CT is able to detect calcium oxalate (milk of calcium) layering. There is no solid contrast enhancement.

Magnetic resonance imaging (MRI): Sometimes performed for confirmation, especially with atypical cases. Cysts are mostly homogeneous. **T1 films show** variable signal intensity, from low (similar to fluid) to high (due to protein content). Fluid-fluid level has also been reported, attributed to the layering of variable fluid content. **T2 -films** usually show high signal intensity due to fluid content.

Fig.4a. Chest X-ray AP: Left lung hyperlucent with decreased pulmonary vascularity.

Fig.4b. Chest X-ray lateral arrowhead shows mass compressing lower trachea posteriorly
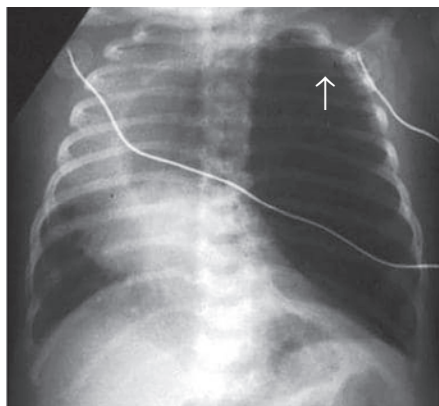
Fig.7a. Chest X-ray: Left upper lobe CLE
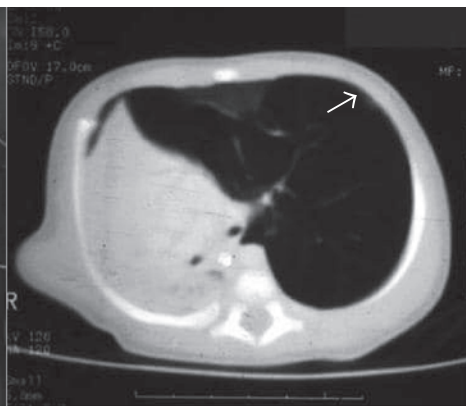
Fig.7b. CT chest: Left upper lobe CLE showing mediastinal shift to right

Congenital lobar Emphysema (CLE)

Congenital lobar emphysema also called congenital lobar overinflation (CLO), a congenital lung abnormality that results in progressive overinflation of one or more lobes of a neonate's lung.

Radiological features

Interestingly, there is a pronounced predilection for certain lobes - left upper lobe, most common, accounting for 40-45%, right middle lobe- 30%, right upper lobe- 20%, involving more than a single lobe- 5%. It is much rarer in the lower lobes. Although the left upper lobe is most commonly affected, the right hemithorax is more commonly affected than the left.

Chest X-ray

Immediate postpartum period - the affected lobe tends to appear opaque and homogeneous because of fetal lung fluid or it may show a diffuse reticular pattern that represents distended lymphatic channels filled with fetal lung fluid. Later findings are shown in Fig.7a. CLE appears as an area of hyperlucency in the lung with oligemia (i.e. paucity of vessels),mass effect with mediastinal shift and hemidiaphragmatic depression. There is also compression of underlying/overlying lobe with shift of mediastinum to the opposite side. Lateral decubitus film with the patient lying on the affected side will show little or no change in lung volume. Lateral film may show posterior displacement of the heart.

CT chest - CT is usually performed to confirm the diagnosis, evaluate the mediastinal vascular structures, and to rule out other abnormalities (Fig.7b). Features seen in chest X-ray are seen in greater detail with attenuation of vascular structures in the affected lobe. Compressive atelectasis of adjacent lobes may also be seen.

Pulmonary sequestration

Pulmonary sequestration, also called accessory lung, refers to the aberrant formation of segmental lung tissue that has no connection with the bronchial tree or pulmonary arteries. It is a bronchopulmonary foregut malformation (BPFM).There are two types - intralobar sequestration (ILS) and extralobar sequestration (ELS). In extralobar pulmonary sequestration, it can be intrathoracic or subdiaphragmatic.

Radiological features

Chest X-ray often shows a triangular opacity in the affected segment. Cystic space may be seen if infected. Both ILS and ELS can rarely have air bronchograms as they may acquire a connection to the bronchial tree due to an infective process or, rarely, they can have foregut communication (oesophagus or stomach) as part of a hybrid lesion.

Ultrasound-the sequestrated portion of the lung is usually more echogenic than the rest of the lung. On antenatal ultrasound, an extralobar sequestration may be seen as early
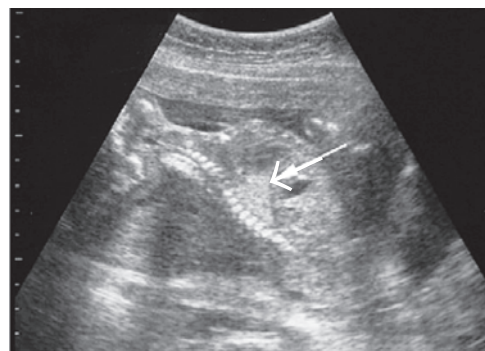
Fig.8. Antenatal ultrasound-intralobar pulmonary sequestration - seen as a triangular echogenic mass astride the leftdiaphragm (arrow)
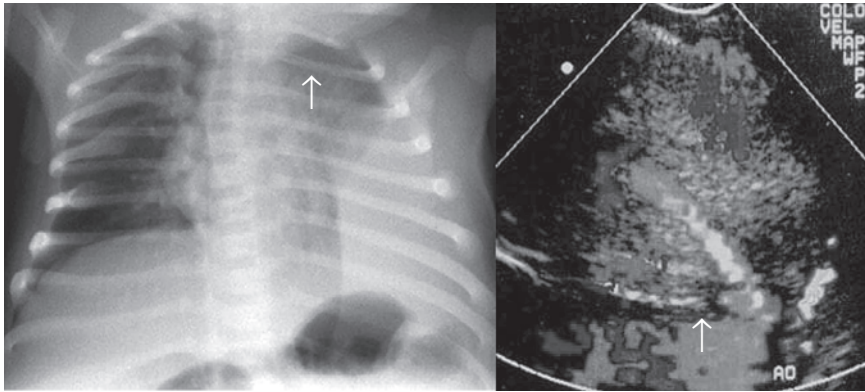
Fig.9a and b. Figure 9a shows opacification in left lower hemithorax. 9b shows infradiaphragmatic artery arising from aorta (arrow)
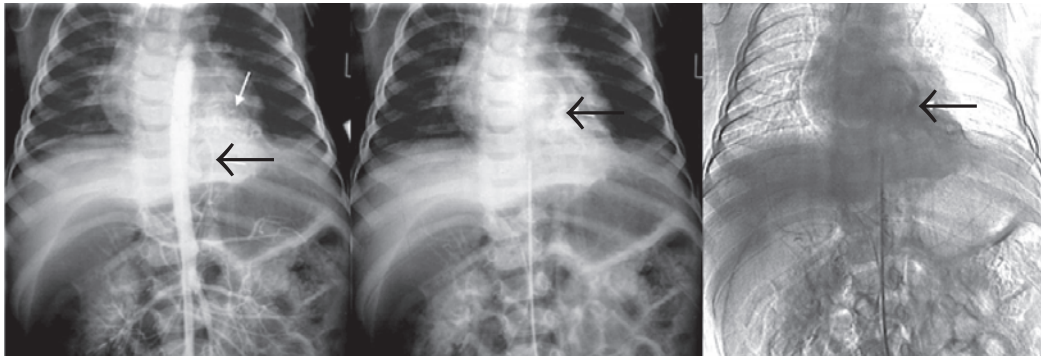

Fig.10a and b. Aortogram- Intralobar pulmonary sequestration; an anomalous artery arising from infradiaphragmatic portion of aorta (bottom arrow) supplying supradiaphragmatic mass in left lower lobe (top, longer arrow).

Fig.10c. Venous phase of aortogram - pulmonary venous drainage into left atrium (arrow).

Intralobar pulmonary sequestration (same patient as in the previous 2 images). Radiographic subtraction of the image directly, previous to this one shows pulmonary venous drainage (arrow).

as 16 weeks gestation and typically appears as a solid well-defined triangular echogenic mass (Fig.8), but CPAM can be a close mimic of this condition. Postnatally, colour doppler may identify a feeding vessel (diagnosed in utero) from the aorta (Fig.9). If the sequestration is subdiaphragmatic, it may appear as an echogenic intra-abdominal mass.

Digital subtraction angiography (DSA): This is not part of the routine investigations but is the gold standard in determining arterial supply (Fig.10a, b and c).

CT chest: Cross-sectional imaging frequently demonstrates the arterial supply from the descending aorta. They may arise below the diaphragm in 20% of patients. Usually does not contain air unless infected. 3D reconstructions can be particularly helpful in detecting anomalous arterial vessels, concurrent anomalous veins and in differentiating between intralobar and extralobar sequestrations (Fig.11).

MRI - **T1-** the sequestrated segment tends to have comparatively higher signal to that of normal lung tissue. **T2-** also tends to show comparatively high signal. **MRA** can be helpful in demonstrating anomalous arterial supply.

Pulmonary hypoplasia

Pulmonary hypoplasia (PH) refers to deficient or incomplete development of parts of the lung and is defined by the presence of a bronchus and rudimentary lung parenchyma with a reduction in number and size of airways, alveoli and pulmonary vasculature.It can develop as a result of a number of other in-utero anomalies.

Radiological features

Chest X-ray (Fig.12a) shows decreased lung volume on the side of pulmonary hypoplasia with shift of mediastinum to the same side of hypoplasia. CT chest (Fig.12b) also shows the same in finer details.
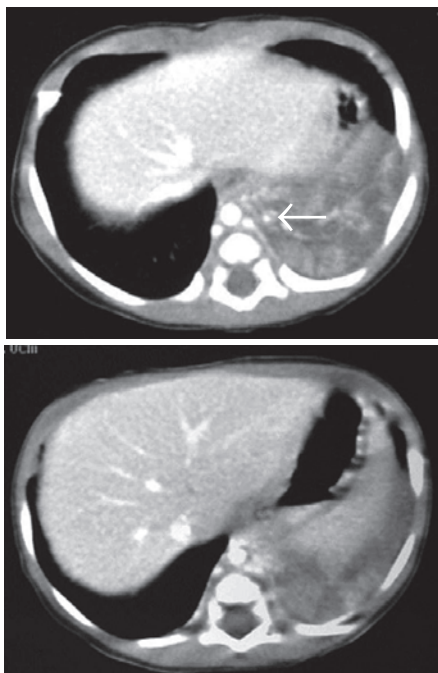
Fig.11. Extralobar sequestration - contrast-enhanced portal venous phase shows a large mass of mixed attenuation with an arterial supply from the aorta and an enlarged hemiazygos vein from venous return.

Ultrasound - Antenatal ultrasound may show ancillary features such as the presence of oligohydramnios and/or also show any of the causative anomalies. Several sonographic parameters may give indirect clues as to the presence and extent of pulmonary hypoplasia Box 3.

Doppler-peripheral pulmonary arterial resistance is often increased with pulmonary hypoplasia

Pulmonary agenesis

Pulmonary agenesis is the complete absence of the lung parenchyma, bronchus and lung vasculature. Agenesis is a primary defect in organogenesis.CXR and CT findings shown in Fig.13 and Fig.14 a,b,c,d respectively.

Box 3. US parameters suggesting pulmonary hypoplasia

- Fetal lung: head ratio: reduced (ratios <1 usually indicate a poor prognosis)
- Fetal chest circumference or thoracic circumference (TC): reduced
- Thoracic:abdominal circumference ratio <0.6
- Femur length:abdominal circumference ratio <0.16

Fig.12a & b. a) X-ray chest: Left pulmonary hypoplasia. b) CT chest: pulmonary hypoplasia (left).

Pulmonary aplasia

Pulmonary aplasia is a rare congenital pathology in which there is unilateral or bilateral absence of lung tissue. It is different from pulmonary agenesis, in that there is a short-blind ending bronchus in aplasia.It is usually unilateral, as bilateral pulmonary aplasia is not viable. It is frequently associated with other congenital abnormalities, mainly cardiovascular and has been reported to occur with the VACTERL syndrome.
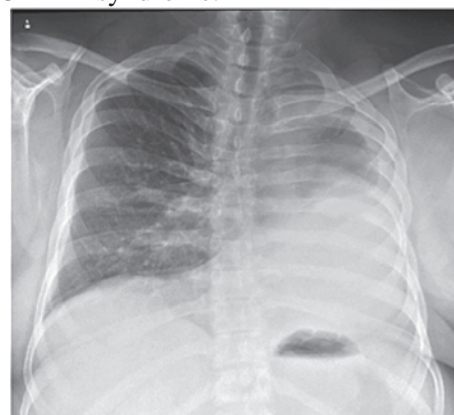
Fig.13. Chest X-ray: Left lung agenesis - Homogenous opacity of left hemithorax with mediastinal shift and contralateral herniation of right lung into left upper hemithorax
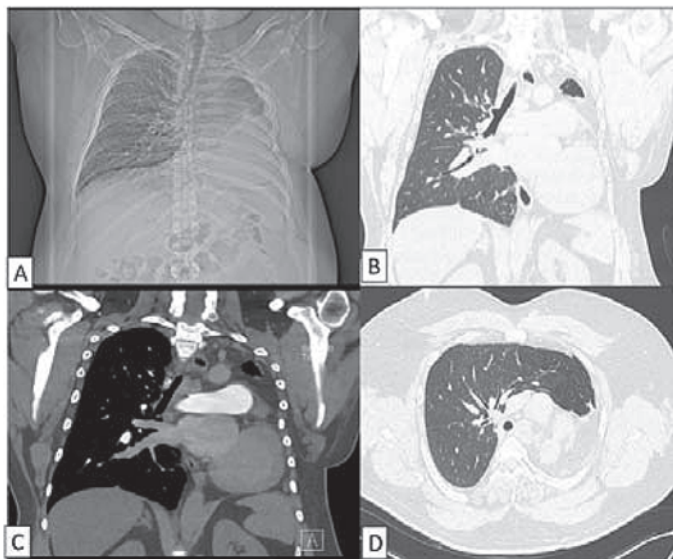
Fig.14.CT topogram (a) showing homogenous opacity of left hemithorax with non-bifurcation of trachea with mediastinal shift and contralateral herniation of right lung. (b) CT coronal lung window (c) showing absent left lung with shift of mediastinal structures into left hemithorax (d) axial lung window settings

Radiological features

Chest X-ray: It can present as a white-out hemithorax or ipsilateral lung volume loss with ipsilateral shift of mediastinal structures (Fig.15a). Contralateral compensatory lung hyperinflation is usual with herniation of the normal lung into the contralateral hemithorax. A main ipsilateral bronchus is rarely seen, although CT can demonstrate a rudimentary main bronchus.

CT will confirm the absence of lung parenchyma (Fig.15b & 15c) and mediastinal ipsilateral shift. Contralateral lung hyperinflation is usual with herniation of the normal lung into the contralateral hemithorax. Also, there is an ipsilateral absence of pulmonary artery. It may also show other congenital cardiac malformations and ipsilateral bronchus remnant.

Azygos lobe

This is found as an anatomic variant in about 1% of people. The azygos lobe forms when the posterior cardinal vein, instead of remaining along the apex of the lung, penetrates the upper medial portion of the apical segment of the right upper lobe.Its demarcating fissure contains both visceral and parietal pleural layers. It has no bronchus and
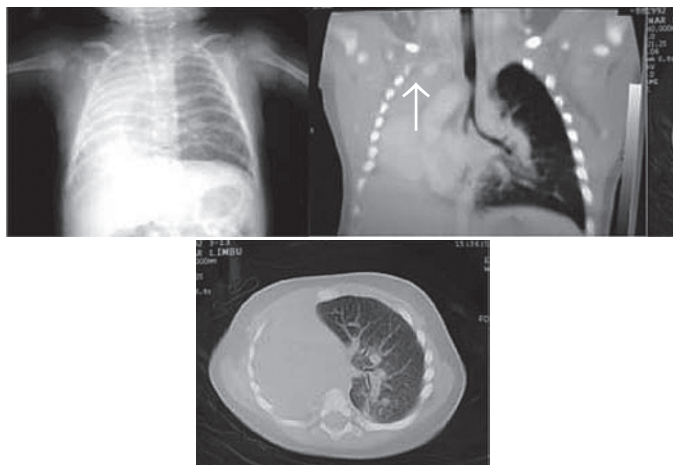
Fig.15a. Chest X-ray Right sided pulmonary aplasia. Fig.15b.CT Chest (coronal section) presence of ipsilateral bronchus with absence of lung, pulmonary artery and veins on right side. Fig.15c.CT Chest (transverse section) absence of lung, pulmonary artery and veins on right side.
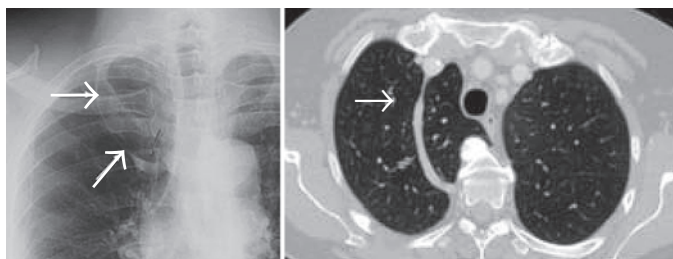

Fig.16a. Chest X-ray: Azygos fissure (white arrows) demarcates lateral boundary of azygos lobe. Tear-shaped azygos vein at base of fissure (double arrow).b)azygos lobe in axial CT (Arrow on azygos vein).

hence is not a true accessory lobe. The size of the lobe is variable.

Radiological features

CXR (Fig.16a) shows a curvilinear lobe of opaque line in the right upper zone.

CT- typical findings are shown in Fig.16b. A thin, curvilinear density is seen in the right upper lobe of lungwith convexity towards the chest wall. At its base is the azygos vein which can be seen as a teardrop-shaped structure. In those with an azygos fissure, the azygos vein will no longer be visible at its normal position at the junction of the trachea and right main bronchus. It should not be mistaken for an abnormality.

CASE REPORT

GASTRIC LACTOBEZOAR IN A NEONATE

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***Divia Nath
***Vishnumohan PT
***Anand MR

Abstract: *Lacto-bezoar is an aggregation of mucus and undigested milk and can obstruct any part of the digestive tract. Its presentation can be varied. The diagnosis of this entity theoretically is very straight forward. However, a high index of suspicion is essential for timely diagnosis and this reduces severe complications and mortality in vulnerable kids. In the following report we are presenting a case of neonatal gastric lactobezoar in a preterm with incidental detection.*

Keywords: *Lactobezoar, Gastric.*

Lactobezoars are undigested milk concretions, usually located in the stomach, resulting in varying degrees of gastric outlet obstruction.[1] Gastric lacto bezoar (GLB) can present with a myriad of nonspecific symptoms making the diagnosis challenging. The diagnosis can be made by carefully inspecting an abdominal radiograph, which entitles a high index of suspicion and the radiologic skills of an experienced neonatologist. A delay in the diagnosis can lead to gastric perforation in rare cases. In addition, the management of GLB remains controversial with the mainstay of therapy consisting of bowel rest and parenteral nutrition.

The index case was a premature new born girl baby born at 28 weeks of gestation, born to a primi mother who had severe Covid pneumonia and ARDS by emergency LSCS. Baby needed cardiopulmonary resuscitation at birth. Her birth weight was 990 g. She required invasive ventilation for 3days and was weaned to blended oxygen by 6 days. She was started on total parenteral nutrition

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within 24 hours of life, in view of extreme low birth weight. Minimal enteral nutrition was initiated on second day of life with human milk substitute by an orogastric tube. As it was tolerated, she was advanced to full feeds (150ml/kg/day) by day 15 of life after changing to age suitable premature formula milk by day 12 of life. Regular meconium passage was noted and child was well till day 18 of life, when desaturations and apnea were noted which got corrected spontaneously. There was no hemodynamic instability. X-ray of chest and abdomen showed with a radio-opaque mass in the stomach lumen (Fig.1). An ultrasound scan confirmed a large heterogenous hyperechoic mass with multiple entrapped air foci in the stomach measuring 2 cm x 3 cm, suggestive of lactobezoar (Fig.2).
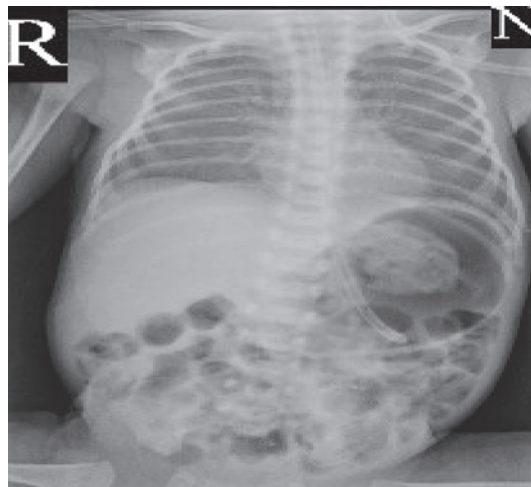

Fig.1. Markedly distended stomach with a radio-opaque mass in the lumen.

Fig.2. Intraluminal isoechoic lesion in stomach with multiple air foci

Patient underwent conservative management. Baby was kept nil per oral under observation. After 3 days repeat X-ray was taken which showed full resolution of Lactobezoar. Feeding was restarted with partially hydrolysed formula and reached full feeds within 4 days. Subsequently the baby was changed over to preterm formula and expressed breast milk. Baby remained clinically stable & there was no radiological evidence of recurrence.

Discussion

Gastric lactobezoars (GLBs) are compact aggregations of undigested milk constituents that develop within the gastric lumen in infants.[2] They were first described in 1959.[3] Fewer than 100 cases have been reported. The pathophysiology of lactobezoars is unclear though likely to be multifactorial. Intrinsic risk factors, such as gestational age, immature gastrointestinal motility and age-related changes in protein digestion, in addition to extrinsic factors, such as formula composition, may all contribute to their formation.

Up to 77% of reported lactobezoar cases occur in premature babies.[4] This has been attributed to slower gastric emptying due to immature gastrointestinal development. Premature formulas may also increase risk because these formulas are higher in caloric density, which is known to slow gastric emptying. Premature formulas are also higher in medium-chain triglycerides.[5] Medium-chain triglycerides are thought to pass rapidly into the duodenum, triggering neural and hormonal mechanisms to slow gastric emptying, although this has not been conclusively established.[6] These mechanisms may allow more time for increased accumulations of protein and mucus. In our case a diagnosis of GLB was made six days after initiating preterm formula feeds.

GLB can present with a variety of clinical symptoms. Frequently, they manifest with abdominal distention, vomiting, diarrhoea, or a palpable mass. Occasionally, respiratory or cardiovascular symptoms are observed.[4] GLB are underdiagnosed and often not included in the differential diagnosis for the above mentioned, non-specific symptoms. Apnea was the predominant manifestation in our baby. Baby did not have any abdominal signs or symptoms. The diagnosis of a gastric lactobezoar is confirmed by an abdominal radiograph.[7] And in cases of doubt, an abdominal ultrasound and an upper gastrointestinal water-soluble contrast series should be considered.[7,8] Plain X-ray shows intra-gastric rounded mass only visible when surrounded by sufficient air or fluid, calcifications may be visible. Ultrasound shows free-floating intra-gastric mass, moves with patient positioning and intra-bezoaric echogenic air trapping. Air-/fluid contrast opaque contrast medium shows intra-gastric rounded mass large circular filling defect with mottled surface. X-ray video-imaging reveals that the mass moves with patient positioning.

There is no consensus on treatment but conservative treatment is the usual option. Conservative treatment involves bowel rest, intravenous hydration and/or parenteral nutrition with or without gastric lavage. Severe cases may be treated aggressively with gastric lavages of N-acetylcysteine to decrease the viscosity of the lactobezoar.[9] Endoscopic or surgical removal is required infrequently. Surgical treatment is only warranted when 1) a pneumoperitoneum is diagnosed, 2) the cause for an acute abdomen remains unidentified, or 3) an already diagnosed GLB cannot be dissolved by conservative management within 72 hours. In this case baby showed an improvement after three days of conservative treatment.

GLB has an excellent outcome provided diagnosis and treatment occur on due time. Lactobezoars can cause abdominal distension, respiratory distress, apnoea, cardiovascular instability, gastric outlet obstruction and rarely gastric perforation. An improved index of suspicion leads to timely diagnosis and reduces severe complications and mortality in vulnerable kids.

It is unclear whether lactobezoars can be prevented. The role of acid suppression is inconclusive. Increased gastric pH may decrease casein coagulation and improve digestion. Conversely, a higher pH could decrease pepsin activation, decreasing proteolysis and facilitating protein accumulation. Hydrolyzed formulas may help to improve protein digestibility, theoretically reducing the risk of conglomeration. However, extensively hydrolyzed formulas are solely casein based and hence may slow gastric emptying. We initiated feeds in this baby with hydrolyzed formula subsequently changing over to preterm formula and expressed breast milk. Subsequent X-rays were normal. Neonatal gastric lactobezoar is a rare benign disease only if diagnosed early. It is important to be aware of the possibility of gastric lactobezoars even if there are no features of acute abdomen.

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CLIPPINGS

SARS-CoV-2 Infection in Patients with a History of VITT.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a prothrombotic adverse effect of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an important measure in the prevention of severe coronavirus disease 2019 (Covid-19). VITT is caused by platelet-activating antiplatelet factor 4 (PF4) antibodies of immunoglobulin G class that have been rarely induced by two adenovirus vector–based Covid-19 vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen).

All available Covid-19 vaccines generate an immune response against the SARS-CoV-2 spike protein, which arouses concern that VITT may be triggered by cross-reactivity between PF4 and spike protein, a view that has been reinforced by the detection of antibodies against PF4 in some patients with Covid-19. Despite encouraging in vitro studies that provided no evidence of a link between anti–SARS-CoV-2 and anti-PF4 immune responses, investigators could not provide in vivo evidence to exclude such a link due to the lack of an animal model. However, if both immune responses are indeed linked, VITT survivors who subsequently contract Covid-19 should have an increase in anti–PF4 antibodies, potentially even retriggering thrombocytopenia or thrombosis.

We performed periodic evaluation of VITT antibody status in a cohort of 69 patients with a history of VITT who had received an adenovirus vector Covid-19 vaccine. Of these patients, 24 did not receive any subsequent doses of a Covid-19 vaccine; the remaining 45 patients received subsequent doses of a messenger RNA (mRNA) vaccine (either Pfizer–BioNTech or the Moderna vaccine). Of these patients, 31 received a second dose and 14 received a third dose.

Of the 69 patients, Covid-19 developed in 11 (16%), all of whom had mild symptoms. Covid-19 occurred more frequently in the patients who had received only the adenovirus vector vaccine than in those who had subsequently received one or two doses of an mRNA vaccine (7 of 24 patients [29%] vs. 4 of 45 patients [9%]; P=0.04 by Fisher's exact test). This lower frequency of symptomatic Covid-19 supports the concept of offering patients with a history of VITT subsequent vaccination with an mRNA-based SARS-CoV-2 vaccine.

In all the patients who had contracted Covid-19, a follow-up blood sample that was obtained after their recovery was available at a median of 2 weeks after the onset of infection. No major increases in PF4-antibody levels developed after recovery from Covid-19. In most of the patients, repeat optical density readings were lower than those in the last sample obtained before the onset of Covid-19, a finding that was consistent with the inherent natural decline in anti–PF4 antibodies. No patient had recurrent thrombocytopenia, new or recurrent thrombosis, or reversion to a positive platelet-activation assay. Our observations provide in vivo evidence that corroborate our previous in vitro findings that the immune responses against the SARS-CoV-2 spike protein (induced by Covid-19 or any of the Covid-19 vaccines) and against PF4 (induced in association with VITT) are independent. Our finding that Covid-19 does not restimulate anti–PF4 antibodies in patients with a history of VITT provides further insights into the pathogenesis of this disorder and may be helpful in counseling patients regarding further Covid-19 vaccination with an mRNA vaccine.

Schönborn L, Seck SE, Thiele T, Warkentin TE, Greinacher A. SARS-CoV-2 Infection in Patients with a History of VITT. N Engl J Med 2022; 387:88-90. DOI: 10.1056/NEJMc2206601.

CASE REPORT

COVID-19 INFECTION ASSOCIATED ACUTE MOTOR SENSORY AXONAL NEUROPATHY

*Mohd Izhar Jaweed
**Aniket Chandrakant Pande
***Rupa Sudhakerrao Karewar

Abstract: *Post Covid-19 MISC as an immune mediated complication of Covid-19 infection. Recently, interesting reports of transverse myelitis in children with Covid-19 and uncommonly Covid-19 associated Guillain-Barre Syndrome have been documented in children.*

Keywords: *COVID-19, Guillain barre syndrome.*

Guillain-Barre syndrome (GBS) is a progressive, near symmetrical weakness occurring in more than one limb with areflexia. Common subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), Miller Fisher syndrome and polyneuritis cranialis. Preceding infections associated with GBS includes *Campylobacter jejuni*, cytomegalovirus, Ebstein Barr virus, mycoplasma and HIV.

We report a 7-year-old boy who presented with acute onset weakness of all four extremities with nasal twang and breathing difficulty over 24 hours. On examination, he had poor respiratory drive with single breath count of 3/10 and tachycardia. Power was of grade 2/5 in all the four limbs, with areflexia in lower limbs and depressed upper limb reflexes, poor gag, pooling of secretion, bifacial palsy. He was brought to us at 24 hours of illness. In view of respiratory muscle fatigue and pco2 of 60 mm Hg, emergency intubation was done and mechanical ventilation started. He required invasive and noninvasive ventilation for next 3 weeks with nasogastric tube feeds, bowel and bladder care. There was a history of Covid-19 infection in grandmother as well as the child 3 weeks back with RTPCR

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positivity for Covid-19. The child was asymptomatic and was kept in isolation with other infected family members.

Investigation showed normal creatinine phosphokinase, electrolytes and liver function tests. Cerebrospinal fluid (CSF) analysis was done on day 7 of admission which suggested albumino cytological dissociation with protein of 70mg, sugar of 68mg and cytology showing 2 lymphocytes. CSF / stool virology was negative for enterovirus. Nerve conduction velocity (NCV) done on day 3 of illness was expectedly normal apart from absent f waves (Fig.1). However, on follow up, NCV after 2 weeks suggested compound motor action potential amplitude reduction from sensory and motor nerves of both upper and lower limb confirming motor sensory axonal neuropathy in upper and lower limbs. Covid-19 RTPCR at present admission was negative but Covid-19 antibody titre IgG spike protein was 21.03 au/mL. Post extubation, on day 15 of illness child went through MRI brain and spine with contrast which was normal. Clinical diagnosis of Gullian-Barre syndrome (GBS) was made on admission and the child received a total of 2 gm/kg intravenous immunoglobulin on admission over next 5 days. However, in view of no improvement in respiratory and neurological parameters 2nd dose of immunoglobulin in the dose of 400 mg/kg/day over next 5 days given in next week of admission. Plasmapheresis was not given in view of resource limitations in our settings. Child started showing improvement from day 12 of admission in respiratory parameters; child was extubated, required short phase of noninvasive ventilation with high flow nasal cannula and was subsequently off oxygen. The child had improvement in muscle power as well as pain and was discharged on day 21 on tube feeds with proper explanation of basic care and physiotherapy. Child was followed up after 1month post discharge, was on complete oral feeds and able to sit without support and stand with support. There is a role of physiotherapy in recovery phase of GBS as increases muscle through strengthening and mobilization.

Discussion

Neurological immune mediated complication following Covid-19 infection is known and GBS is one of them, though rare.[1-6] As per systematic review of 73 cases, mean duration of onset of illness after covid19 infection is
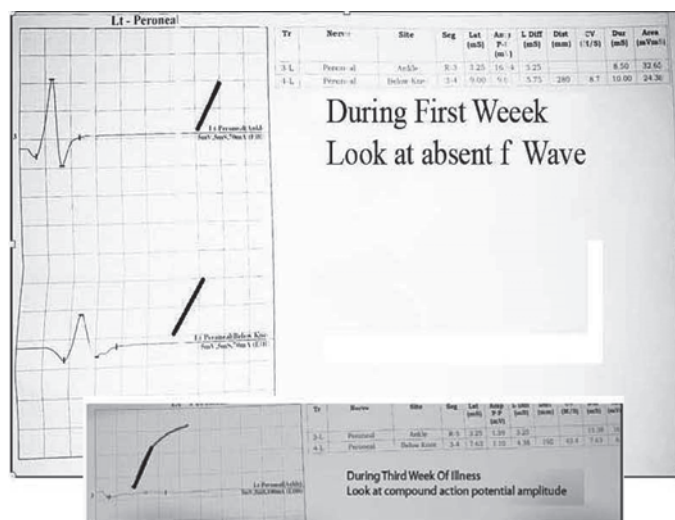
Fig.1. Nerve conduction velocity

13 to 22 days.[7] In our patient absence of viral isolation from CSF and preceding infection with Covid-19 virus with presence of IgG spike protein antibody shows causal relationship. Child had acute onset progressive weakness with areflexia, symmetrical involvement, significant pain and paresthesia, retention of urine, absent fever, CSF suggesting albuminocytological dissociation and nerve conduction confirming acute motor sensory axonal neuropathy (AMSAN). It appears AMSAN is potential Covid-19 related complication and needs further case reporting. Amongst post covid 19 GBS reported cases 70 % are classical AIDP, rest are other subtypes.[8] There is no significant difference in clinical presentation compared to other post infective causes of GBS. There is no correlation in severity of initial covid infection and severity of GBS and its complications.[5] Acute motor sensory axonal neuropathy has rapid progression and course of illness is prolonged. There is always a need to rule out transverse myelitis and ADEM by clinical progression, CSF, NCV and neuroimaging in child suspected to be having post covid GBS.

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CLIPPINGS

Diagnosis of tuberculosis based on the two specific antigens ESAT-6 and CFP10.

Tests based on tuberculin purified protein derivative (PPD) cannot distinguish between tuberculosis infection, Mycobacterium bovis BCG vaccination, or exposure to environmental mycobacteria. The present study investigated the diagnostic potential of two Mycobacterium tuberculosis-specific antigens (ESAT-6 and CFP10) in experimental animals as well as during natural infection in humans and cattle. Both antigens were frequently recognized in vivo and in vitro based on the induction of delayed-type hypersensitivity responses and the ability to induce gamma interferon production by lymphocytes, respectively. The combination of ESAT-6 and CFP10 was found to be highly sensitive and specific for both in vivo and in vitro diagnosis. In humans, the combination had a high sensitivity (73%) and a much higher specificity (93%) than PPD (7%).

van Pinxteren LA, Ravn P, Agger EM, Pollock J, Andersen P. Diagnosis of tuberculosis based on the two specific antigens ESAT-6 and CFP10. Clin Diagn Lab Immunol 2000; 7(2):155-60. doi: 10.1128/CDLI.7.2.155-160.2000. PMID: 10702486; PMCID: PMC95842.

<div style="text-align:center">**CASE VIGNETTE**</div>

A CHILD WITH HEMIHYPERTROPHY

Aravinth S
Anu MS
Dheepane K
***Raghupathy NS**

A seven-year-old boy was brought with asymmetrical growth and hyperpigmentation of skin of left side of body since birth. Examination showed hemi-hypertrophy (Fig.1),

Fig.1. Hemihypertrophy, Skull asymmetry and finger hypertrophy

hyper pigmentation of face and limbs with dilated veins on left side, macroglossia, limb length discrepancy, gait instability and mild splenomegaly with a body mass index of 17.6 (overweight). Investigations showed platelet count of 2.20 lakhs/cu.mm, serum electrolytes and liver function tests were within normal limits and serum calcium was 9.1 mg/dL. 25-hydroxy vitamin D level was 20.4 ng/mL. X-ray pelvis showed right ilium smaller than left and left lower limb larger than right (Fig.2). Abdominal ultrasound showed mild splenomegaly. Doppler showed few dilated tortuous veins seen with bulky muscle in left lower limb and superficial veins mildly increased in diameter in left upper limb. A diagnosis of Klippel Trenauny syndrome was made and the patient was counselled on skin care and is on periodic follow-up.

Incidence of hemihypertrophy is 1 out of 86000 live births. Hemihypertrophy is often associated with overgrowth syndromes such as Klippel Trenaunay
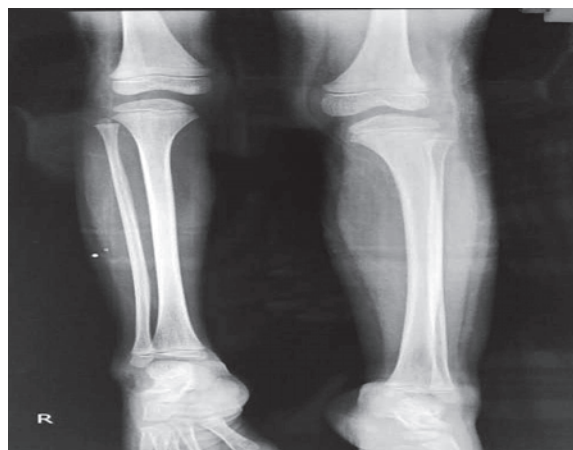

Fig.2.Left lower limb is larger than right-side

syndrome, Beckwith-Wiedemann syndrome, proteus syndrome. Klippel-Trenaunay syndrome (KTS) is a complex mixed vascular malformation with overgrowth of bone and soft tissue.[1,2] KTS is a nonheritable triad of port-wine nevus, bony and soft tissue hypertrophy and congenital venous varicosities.[3] Incidence is 2-5/100,000 male predominance.[4] Two third of patients had triad while one third of them had 2 clinical features.[3] Hypertrophy is related to soft tissue and fat overgrowth, although bony hypertrophy may be present. Legs are more often affected than arms.[4] PIK3CA gene mutation is often noted.[5] In these children, antithrombotic prophylaxis is indicated two weeks prior to elective surgery.

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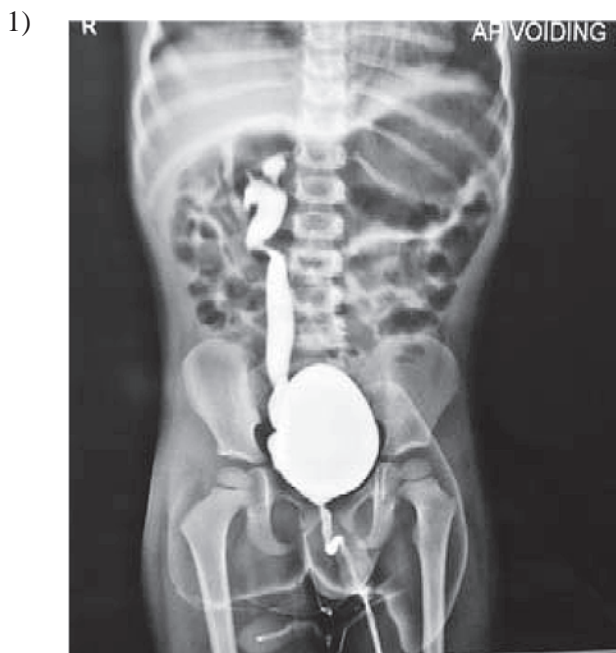
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LEARNING TOGETHER

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OSCE - IMAGING IN PEDIATRIC NEPHROLOGY

*** Arpitha KR**
*** Pooja GN**
**** Sudha E**
**** Sukanya Govindan**
*** Sunil K Reddy**

1)

a) Identify the test showed here.

b) What is the interpretation of the test ?

c) How will you assess the severity of the condition?

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2)

a) What is the finding in the ultrasound?

b) Give at least 3 causes for this finding

3)

a) Identify this condition shown in lower urinary tract imaging

b) What is this test used to confirm this condition?

c) What are the antenatal ultrasound findings associated with this condition?

4) 3-month-old female infant is referred for further evaluation for antenatally diagnosed left sided hydronephrosis. The postnatal ultrasound shows left sided hydronephrosis with normal ureter.

    a) What is the investigation shown below? Name any one pharmaceutical agent used in this test

    b) Interpret the findings?

    c) The differential function of the left kidney is 20% and right kidney is 80%. What intervention is required?

    d) Parents want to wait for a month. What is the advice given during the waiting period?

    e) What is the other investigation required for antenatally diagnosed hydronephrosis?
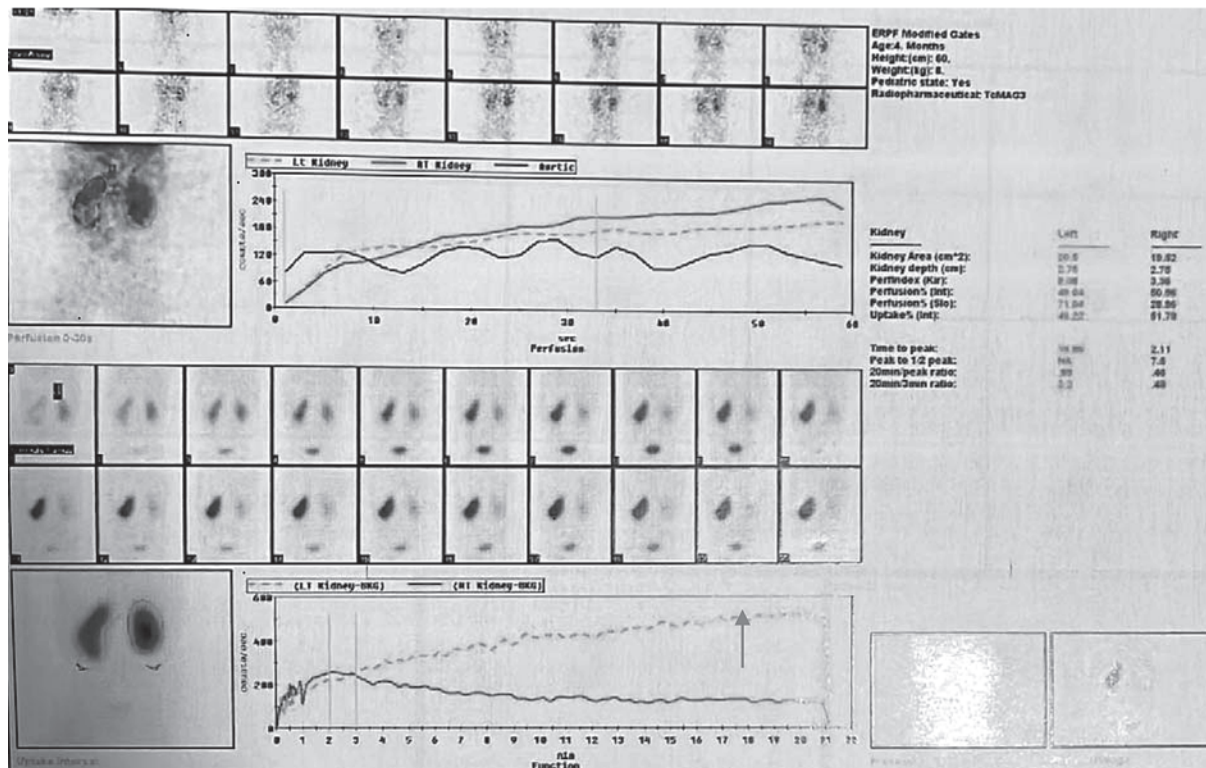
5)   a) Identify the test

    b) What are the indications for performing this test?

    c) What are the other renal anomalies that can be identified?
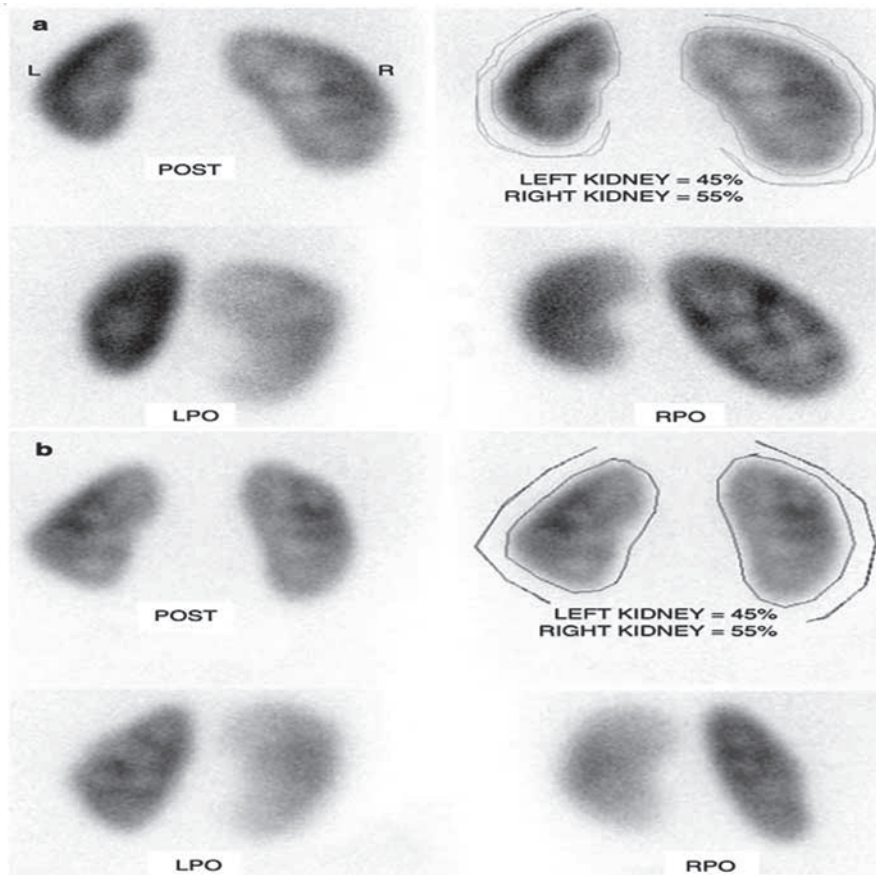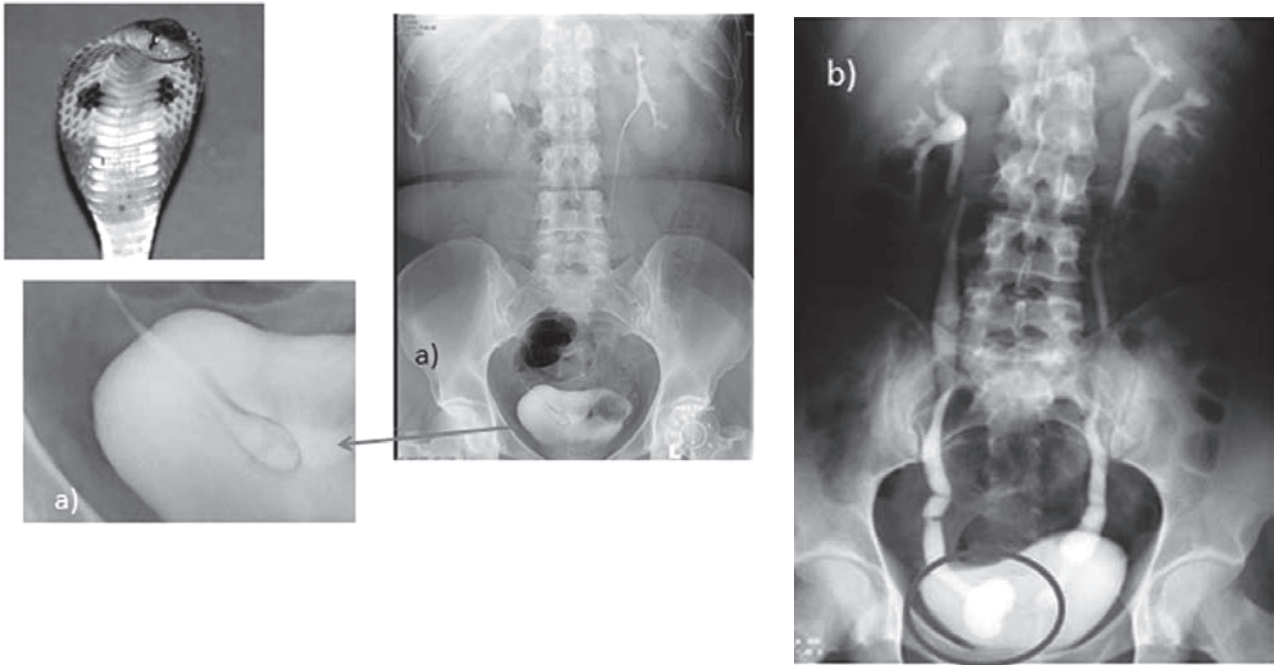
    d) Identify the following images.
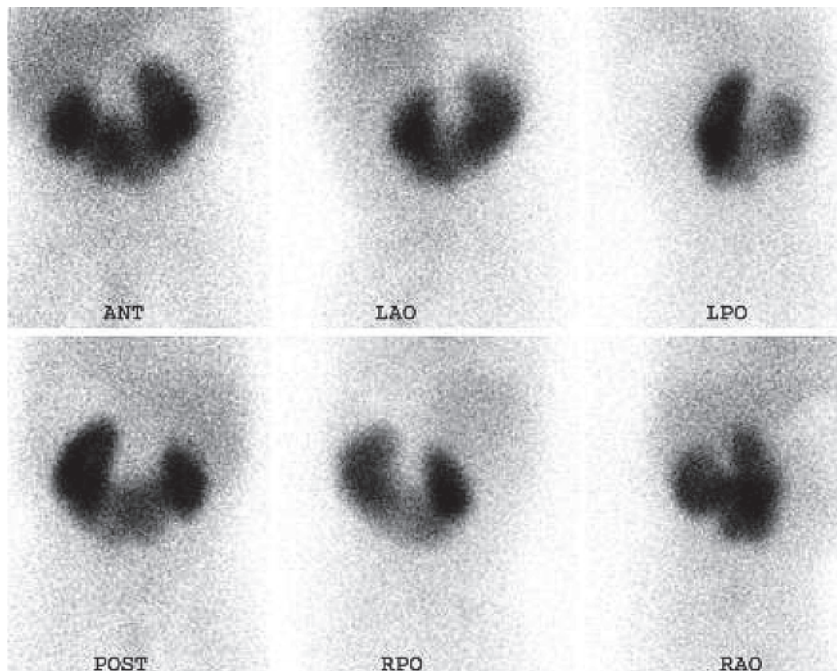
FIGURE (A)

FIGURE (B)

References : Sisters of Charity University Hospital - Zagreb/HR

6)   a) Identify the anomaly in the above picture

b) What is Meyer Wiegert rule?

7) 5 years old boy weighing 20 kg and with a height of 110cm was admitted to PICU with shock. He had loose stools and vomiting with improper management. At admission Urea - 60, Cr 1.0 mg/dL, S. Sodium - 148 mEq/L, S.Potassium 3.9 mEq/L, Bicarbonate - 17 mEqL and urine sodium 20 mEq/L and urine spot creatinine 30 mg/dL. He had reduced urine output over the last 12 hours. His creatinine done 1 week back was 0.5 mg/dl.

a) What is the formula used for calculating eGFR

b) Calculate e GFR

c) Stage of AKI according to KDIGO guideline

d) Calculate FENA (Fractional Excretion Of Sodium) for this child

8) A 12 year old girl presents with recurrent abdominal pain. Evaluation shows blood pressure 140/90 mm Hg. Her facial appearance showed reddish nodular lesions in the face, both cheeks (Panel A). Creatinine 1 mg/dL, normal electrolytes and microscopic hematuria. Panel B shows ultrasonographic findings.

I. Describe findings in panels A and B.

II. What is your diagnosis?

III. List two investigations that are required for confirmation or management?

9) Ultrasound done in a 10 yrs old child with recurrent abdominal pain and hematuria. The same features of ultrasound is present on both the kidneys. There is a family history of similar disease, renal failure, hypertension, hematuria and transplantation done for his father

a) What is the possible diagnosis in ultrasound?

b) Name two differential diagnosis for this condition.

c) What is the genetic defect in this condition?

d) What are the extra renal manifestations (name 2 conditions) in this disease?

e) What is the plan of follow-up in this child?

Answers

1) a) Micturating cystourethrogram

   b) Grade IV VUR Right kidney

   c) As per International Reflux study(IRS), VUR severity is graded into

Grade I: VUR into a non-dilated ureter

Grade II: VUR into the upper collecting system without dilation

Grade III: VUR into a dilated ureter and/ or blunting of calyceal fornices

Grade IV: VUR into a grossly dilated ureter

Grade V: Massive VUR with significant dilation, tortuosity and loss of papillary impression.

2) a) Medullary nephrocalcinosis

   b) causes:

   • Type 1 or distal RTA

   • Dent's disease (proximal RTA)

   • Hyperoxaluria (primary and secondary)

   • Hypercalcemia with Hypercalciuria

   • (familial) hypercalciuria, hypomagnesemic hypercalciuria

   • Primary hyperparathyroidism

   • Sarcoidosis

   • Hypervitaminosis D

   • Medullary sponge kidney

   • Bartter's syndrome

3) a) Dilated posterior urethra

   b) Micturating cystourethrogram

   c) Bilateral hydroureteronephrosis, distended bladder, oligohydramnios, hypoplastic lungs

4) a) DTPA renogram. Diethylenetriaminepentaacetate (DTPA), Technetium 99 - ethylene dicysteine (EC), mercapto acetyl triglycine (MAG3) are used for DTPA.

b) Obstruction to drainage in the left kidney. The arrow points to the excretory phase of the dye of left kidney depicted in a graphical manner. It shows obstruction to the excretion/clearance of the dye from the collecting system. The excretory curve of the dye in right kidney touches the baseline indicating no obstruction to the clearance.

c) Left dismembered pyeloplasty

d) Start on uroprophylaxis

e) Micturating cystourethrogram (MCU)

5) a) DMSA renal scan (dimercapto succinic acid)

b) To identify cortical defects/scars, to diagnose acute pyelonephritis, identify ectopic kidney, absent or multicystic dysplastic kidney

c) FIGURE (A)- DMSA image showing horse shoe kidney with fused lower poles.

FIGURE (B)- The image shows Right ureterocele. The sign is called "cobra head" sign which is seen on IVP (Intra venous Pyelogram)

6) a) Double moiety kidney with ureteric duplication

b) Meyer Wiegert rule: With duplex kidney and complete ureteral duplication, the upper renal and lower renal moieties are drained by separate ureters, each having its own ureteral orifice in the bladder.

- upper renal moiety ureter has ectopic insertion medial and inferior to the lower renal moiety ureter
- lower renal moiety ureter has orthotopic insertion lateral and superior to the upper renal moiety ureter(radiopedia.org-2020)

7) a) Modified Schwartz formula (0.41 x Ht in cm/ serum creatinine in mg/dl)

b) 45 ml/min/1.73m^2

c) S creatinine 2-2.9 times baseline (creatinine increased by 2 times), stage 2 by KDIGO.

d) FENA = [(urine sodium × serum creatinine) / (serum sodium × urine creatinine)] × 100 = [(20 × 1)/ (148 × 30)] × 100 = 0.45.

8) I. a)Adenoma sebaceum, appearing as tiny red nodules over the nose and cheeks.

b) Ultrasonography shows (i) grossly disorganized architecture of the kidney; (ii) multiple irregular shaped cysts and (iii) foci of calcification.

II. Tuberous sclerosis with autosomal dominant polycystic kidney disease.

III. Any two of the following: Computed tomography of the brain, echocardiography, CT chest and abdomen, genetic testing for *TSC2* mutation.

9) a) Cystic disease of the kidney, ADPKD.

b) Other cystic diseases include ARPKD, MCDK, glomerular cystic disease and rarely acquired cystic disease of the kidney.

c) Autosomal dominant inheritance with PKD1 (85%) and PKD2 (15%) mutations. PKD3 is being considered. New mutations when ADPKD occurs without family history to be considered. Gene that is mutated for PKD1 is localized to chromosome 16p13.3 which encodes for polycystin 1. The gene that is mutated for PKD2 is located in chromosome 4q13-q23 and encodes the polycystin 2.

9) Extra renal manifestations include MVPs, cerebral aneurysms, hepatic/pancreatic/ovarian/seminal vesicle cysts and GI diverticuli.

10) Most of the pediatric ADPKD maintain normal renal function during the childhood and about 50% progress to ESRD in adulthood. Control of hypertension, attention to electrolyte disturbances and growth and development, use of ACE inhibitors/ARBs, identification and treatment of infection and dietary modulation are the steps in follow-up in children.

NEWS AND NOTES

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Day 3: 16th Oct 2022 (Sunday)	CME and 14th Dr BR Nammalwar Oration - Venue: Rain Tree Hotel, Chennai.
For any queries Contact: Mrs. Leena and Mrs. Aruna through WhatsApp - 9791866771; 9962102204 or mail us at info@nephkids.in	

PICTURE QUIZ

This child presented with severe pallor. CBC showed pancytopenia

Questions

1. What is the findings and diagnosis?

2. Describe the expected peripheral smear findings?

3. Name two biochemical tests which may aid in the diagnosis.

Answers

1. Hyperpigmented knuckles

2. Aniso, poikilocytosis, macroovalocytes, hypersegmented polymorphs

3. B 12, Folic acid levels

CLIPPINGS

Positioning for acute respiratory distress in hospitalised infants and children.

Positioning and mechanical ventilation have been regularly used to reduce respiratory distress and improve oxygenation in hospitalised patients. Due to the association of prone positioning (lying on the abdomen) with sudden infant death syndrome (SIDS) within the first six months, it is recommended that young infants be placed on their back (supine). However, prone positioning may be a noninvasive way of increasing oxygenation in individuals with acute respiratory distress, and offers a more significant survival advantage in those who are mechanically ventilated. However, there is a reduced risk of SIDS during artificial ventilation in hospitalised infants.This is an update of a review published in 2005, 2009 and 2012. To compare the effects of different body positions in hospitalised infants and children with acute respiratory distress syndrome aged between four weeks and 16 years. Randomised controlled trials (RCTs) or quasiRCTs comparing two or more positions for the management of infants and children hospitalised with ARDS.

Although included studies suggest that prone positioning may offer some advantage, there was little evidence to make definitive recommendations. There appears to be low certainty evidence that positioning improves oxygenation in mechanically ventilated children with ARDS. Due to the increased risk of SIDS with prone positioning and lung injury with artificial ventilation, it is recommended that hospitalised infants and children should only be placed in this position while under continuous cardiorespiratory monitoring.

Bhandari AP, Nnate DN, Vasanthan L, Konstantinidis M, Thompson J. Positioning for acute respiratory distress in hospitalised infants and children. 06 June 2022, https://doi.org/10.1002/14651858.CD003645.pub4. Cochrane Database Syst Rev 2022 Jun 6; 6(6):CD003645. doi: 10.1002/14651858.CD003645.pub4

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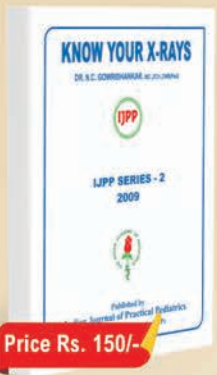
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Indian Journal of Practical Pediatrics,

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