INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

• **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**

• **Indexed in Excerpta Medica, CABI Publishing, Scopus**

Vol.17 No.4 **OCT.- DEC. 2015**

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TOPIC OF INTEREST - "INFECTIOUS DISEASES"

GENERAL ARTICLE

Journal Office and address for communications: Dr. P.Ramachandran, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

Published by Dr. P.Ramachandran, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai-14.

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INFECTIOUS DISEASES

PERINATALLY ACQUIRED HIV INFECTION IN CHILDREN IN INDIA

*Jagdish Chandra
**Puneet Sahi

Abstract: *India has the third largest HIV epidemic in the world. Children account for 7% of the HIV burden with an overwhelming 90% of it being acquired perinatally. Without any interventions the perinatal HIV transmission rate stands at 20%-45% in developing countries. Multiple risk factors exist, such as maternal advanced HIV disease, lack of anti-retroviral therapy (ART) and mixed feeding figuring amongst the most prominent ones. National AIDS Control Organization (NACO) aims to reduce the mother-to-child transmission by primary prevention of HIV and avoiding unintended pregnancies among women of child bearing age. Secondary prevention focuses on effective ART to all pregnant mothers and nevirapine prophylaxis to the baby. The latest NACO recommendations promote lifelong ART for all HIV positive pregnant mothers, insist on a vaginal delivery barring maternal indications for a Caesarean section, encourage exclusive breast feeds in first six months of life followed by complementary feeding with continuation of breast feeds up to one year of age and then gradual stoppage over the next one month. Effective institution of prevention of parent to child transmission (PPTCT) recommendations in India has brought down the mother to child transmission rate to 5.74%. HIV DNA PCR is used for early infant diagnosis followed by confirmation at 18 months with HIV ELISA. Common clinical features in HIV infected infants are low birth weight, preterm delivery, failure to thrive, oral thrush, hepatosplenomegaly, diarrhoea and chronic pulmonary infiltrates. Current recommendations support ART in all children less than 5 years of age irrespective of the clinical and immune status. Cotrimoxazole prophylaxis is recommended in all HIV exposed children till it is definitely excluded.*

Keywords: *Perinatal, HIV, Children, India.*

* Director, Professor and Head
* Senior Resident, Department of Pediatrics, Kalawati Saran Children's Hospital and Lady Hardinge Medical College, New Delhi.

In 1986, six years after the recognition of the first known human case of HIV/AIDS, the retrovirus found its way into the Indian subcontinent. The epidemic reached its peak in 2001, but with the institution of several robust programs at the global and national levels, the HIV trajectory has slowed. Despite these advances, India still continues to have the third highest number of estimated people living with HIV/AIDS, in the world.[1] Although, the prevalence of HIV in India is 0.27%, due to its large population, it equates to a staggering 2.1 million people.[2] The actual numbers may be much more as only 13% in India are aware of their HIV status.[3] Children less than 15 years account for 7% of HIV burden in India and an overwhelming 90% of it is acquired by perinatal transmission.[4] It is condemnable that every minute a child is born with HIV, despite perinatal transmission being highly preventable.[5]

The disease burden: Indian scene

In 2011, UNICEF set a global target to reduce the number of new HIV infections via prevention of mother-to-child transmission by 90% in 2015.[6] Thus, WHO identified 22 priority countries (including India in the top 10) which accounted for 90% of pregnant women living with HIV. More than 2,50,000 new infections can be prevented annually by scaling up of prevention of mother-to-child transmission services in these countries.[7] This is especially relevant to India where nearly 92%-100% of children who are infected with HIV, acquire so via the perinatal route.[8,9] In one of the high prevalent states in South India, a study enrolling 526 children showed that nearly 98% of them had acquired HIV via vertical transmission.[10] Another large study in North India, involving 454 children with HIV found 88.3% had perinatal transmission.[11] Unpublished data from the anti-retroviral therapy (ART) centre at our hospital collected from Nov 2006 to June 2015, shows that 77% of the enrolled 518 children had perinatally-acquired HIV. To combat this, India launched the prevention of parent-to-child transmission (PPTCT) of HIV program in 2002 which is being implemented by NACO. As of 2013-2014, the PPTCT services had a coverage of 74% in pregnant women with HIV.[12] Though it still falls short of the target of 90% coverage, it has given a hope that with acceleration of program expansion and implementation, the target will be achieved.

Risk factors for perinatal HIV transmission

HIV transmission from the mother to her baby can occur during pregnancy, labor, delivery or breastfeeding. Without any interventions perinatal HIV transmission rates stand at 15%-30% in developed countries and 20%-45% in the developing countries, the rise chiefly explainable by the different infant feeding practices.[13] Earlier studies in India, prior to the launch of the PPTCT program, showed a perinatal transmission rate of 24%-36%.[14,15] Lack of proper knowledge of mother-to-child transmission was an important reason.[15] Recent studies in India demonstrate mother-to-child transmission rates ranging from 3.3% to 9.7%, reflecting the impact of PPTCT services. Higher mother-to-child transmission rates seem to occur in the rural populations.[16-19]As per NACO 2012-13, the mother-to-child transmission rate in India is 5.74%. Multiple risk factors for perinatal HIV transmission have been identified:[20]

a) Viral: HIV-1, non-syncytium inducing phenotype.

b) Maternal: Infection acquired during pregnancy, advanced disease, high viral load, suboptimal/no ART, malnutrition, micronutrient deficiency, concomitant sexually transmitted infection (STI).

c) Perinatal: Rupture of membranes for more than 4 hours, mode of delivery, invasive procedures like episiotomy, fetal scalp electrodes, instrumental delivery, chorioamnionitis and placenta previa.

d) Infant: First of twins, prematurity, breast feeding infant with oral thrush at less than 6 months age.

e) Postnatal: Maternal seroconversion during breast feeding, breast feeding, mixed feeding, higher breast milk viral load and mastitis.

Clinical profile of HIV infected neonates and infants

Studies demonstrate that HIV infected neonates and infants have significant failure to thrive, persistent oral thrush, diarrhoea, chronic pulmonary infiltrates, hepatosplenomegaly and lymphadenopathy.[21] There is higher incidence of preterm delivery and low birth weight in HIV exposed neonates.[22] However, even when born as normal weight term babies, HIV positive newborns develop greater rates of stunting, wasting and underweight by as early as 4-6 weeks of age, compared to HIV negative newborns.[23] The existing Indian data suggests a rapid progression of HIV in the neonatal and infantile age group with high mortality unless ART is initiated early. A study from Chennai revealed that approximately 36% HIV positive newborns became symptomatic by 4-6 weeks of life, with bronchopneumonia as the leading infection. Other manifestations were diarrhea, skin lesions, cytomegalo virus (CMV) retinitis, oral thrush and hepatosplenomegaly. 77% of these newborns succumbed to their illness.[24]

Strategies to prevent perinatal HIV: Indian perspective

NACO has adopted four key strategies to prevent perinatal HIV transmission which include:[4]

a) Primary prevention of HIV, especially among women of child bearing age

b) Preventing unintended pregnancies among women living with HIV

c) Preventing HIV transmission from pregnant women with HIV to their infants

d) Providing care, support and treatment to women with HIV, their children and families.

The secondary prevention methods include antenatal, perinatal and postnatal interventions.

Antenatal interventions

The first step in prevention of perinatal HIV is knowledge to the pregnant mothers' HIV status. PPTCT offers HIV counselling and universal screening of all pregnant females with an 'opt out' option. Those who are initially negative but appear to be at high risk can be retested at 28 weeks of pregnancy.[25] All women who test positive during pregnancy should be started on anti-retroviral therapy irrespective of their clinical stage and CD4 counts. Women whose first contact with health authorities is at labor itself should be started on ARV prophylaxis based on a positive rapid HIV test, followed by confirmation later. WHO-recommended ARV regimens (Option A and B), if adequately implemented, could reduce perinatal HIV transmission from 35% to less than 5% in the breast feeding population and from 25 % to less than 2% in the non-breast feeding population.[26] For a long time, India used single dose nevirapine to the pregnant mother (not requiring ART for own health) during labor combined with single dose nevirapine to the newborn which best suited the countries with limited resources. A gradual shift to option B was made to further decrease mother to child transmission rates.[25]

In December 2013, NACO embraced the WHO guidelines propagating option B+ under which all pregnant women with HIV are to receive lifelong ART irrespective of the immune status and eligibility. Tenofovir, lamivudine and efavirenz combination is the first choice for HIV infected pregnant mothers and nevirapine for the baby till 6-12 weeks of life irrespective of the feeding practice. The advantages

of this approach include simplification of service delivery, early start of ART in immunocompromised pregnant women where CD4 testing is not easily available, delayed disease progression in mothers, protection against mother to child transmission in future pregnancies, prevention of sexual transmission to serodiscordant partners, and strong community acceptance.[27] Moreover, research highlights the problem of growing drug resistance due to use of regimens that do not fully suppress HIV replication, like use of single dose nevirapine during delivery and zidovudine monotherapy in pregnancy.[28-30] This may mean infection of newborns with drug resistant HIV and jeopardizing the efficacy of first line ART.

Perinatal interventions

NACO now recommends vaginal delivery in HIV positive pregnancy. Previously, an elective Caesarean section was recommended after 38 completed weeks of gestation prior to the onset of labor and rupture of membranes. However, recent evidence shows that the risk of maternal and infant morbidity and mortality, costs and recovery time overweigh the benefit of prevention of mother to child transmission. Thus, Caesarean section is to be conducted for obstetric indications only. In addition, the following practices reduce the risk of perinatal HIV transmission:[4]

a) Avoidance of artificial rupture of membranes.

b) Avoidance of instrumental delivery

c) Refrain from routine episiotomy

d) Minimal vaginal examinations

e) Avoidance of invasive procedures like fetal blood sampling

f) Avoid suctioning of newborn unless meconium stained

Postnatal interventions

Breast feeding is the predominant mode of feeding especially in the resource constrained countries. Its benefits go much beyond infant nutrition including immunity to pneumonia, diarrhoea and sepsis. However, it carries a 40% risk of mother to child transmission.[13] On the other hand, replacement feeding carries no risk of HIV transmission but fails to meet the acceptability, feasibility, affordability, sustainability and safety (AFASS) criteria in the developing nations. Replacement feeding did not improve HIV free survival in resource-poor nations. Thus, NACO recommends exclusive breast feeding for the first 6 months of life followed by complementary feeds. Breast feeding is to be continued till 1 year of age and thereafter gradually weaned over a period of 1 month once adequate complimentary feeding is ensured. Replacement feeding is an option only in the event of maternal death or terminal illness. Mixed feeding is to be avoided in the first 6 months of life.

To combat the mother-to-child transmission risk associated with breast feeding, the best bet is the use of ARV prophylaxis in the mother and the baby, which reduces PPTCT rates to less than2%.[31,32] The first dose of nevirapine should be given to the baby within an hour of delivery. Infants born to HIV positive mothers, should receive 6 weeks of daily nevirapine if mother has received more than 24 weeks of adequate ART during pregnancy, otherwise it is extended to12 weeks. In addition, care should be taken of mastitis, cracked nipples and oral thrush in infant.

Early infant diagnosis of HIV: NACO strategy

In children less than 18 months old, virological tests are used for diagnosis (HIV DNA PCR) as antibody testing is confounded by the presence of maternal antibodies. The first dry blood spot (DBS) method for HIV DNA PCR is conducted at 6 weeks of age. If the DBS test is positive, whole blood sample is tested for HIV confirmation as early as possible. If the initial PCR is negative, a repeat PCR is performed at 6 months or earlier if the infant becomes symptomatic. In a breast feeding child, a negative test needs to be documented 6-8 weeks after complete cessation of breast feeding. In an infant presenting after 6 months of age, an HIV serology is done as a screening test. Only if serology is positive, a PCR by DBS is done.

An infant with a positive PCR on DBS followed by positive PCR on whole blood is labelled as HIV positive and started on ART. An infant with negative PCR by DBS at 6 weeks and 6 months is labelled as HIV negative. Confirmation of HIV positive status is done at 18 months of age using 2 rapid tests for antibody testing, irrespective of previously determined status or ongoing ART.[4]

ART in children

Better survival of children with HIV warrants not only early diagnosis but also early initiation of treatment. As of December 2012, only 30.5% of HIV positive children in India were receiving free ART.[1] The latest NACO guidelines recommend (as recommended by WHO) initiation of ART in all HIV infected children less than 5 years irrespective of their clinical and immunological staging. This is based on research showing significantly decreased mortality and disease progression in children less than 5 years by early ART initiation.[33] This strategy has come up in India in a

phased manner: initially only infants were started on ART, subsequently this was extended to all under 2 years and now all under 5 years irrespective of the immune status.

Since 2006, pediatric fixed dose regimens became available reducing pill burden and drug toxicity. Stavudine has been phased out due to long term side effect of liposdystrophy. The more potent protease inhibitors have largely replaced the NNRTI. Efavirenz has been approved by FDA for use in children ≥ 3 months and weighing ≥ 3.5 kg which is now preferred over previously used nevirapine due to its better efficacy.[34] Thus currently, for non-anemic children less than 3 years of age, Zidovudine + Lamivudine + Lopinavir/ritonavir and for childen 3-12 years, Zidovudine + Lamivudine + Efavirenz is the first line ART.

Cotrimoxazole prophylaxis

This is to be given in all HIV exposed infants starting at 4-6 weeks of age and continued till 18 months of age when HIV is definitively excluded.[35] The infected children continue to receive the prophylaxis for upto 5 years or longer based on their immune status.

Immunisation

All standard vaccines as per the national schedule should be given to HIV exposed asymptomatic children. IPV should be preferred over OPV whenever affordable. HIV exposed symptomatic children should not receive BCG. Measles, MMR and Varicella can be given if CD4 count is more than15%.[36]

Conclusion

India has made significant progress in tackling its HIV burden in the past decade. However, the goal of an AIDS free generation still remains elusive. It will require a massive scale up of the existing PPTCT programmes and also an increased uptake of these services by the population. Elimination of HIV stigma and discrimination, dissemination of knowledge of existing services, overcoming cultural barriers and gender dynamics and effective counselling will go a long way in realizing this dream.

Points to Remember

- ***Lifelong ART is recommended for all HIV positive pregnant mothers.***
- ***Vaginal delivery is preferred barring maternal indications for a Caesarean section.***
- ***Exclusive breast feeding for first six months of life followed by complementary feeds with continuation of breast feeds up to one year of age and then gradual stoppage over the next one month is the current feeding recommendation***
- ***Infants of HIV positive mothers should receive 6 weeks of daily nevirapine. If the mother has not received adequate ART during pregnancy, it is extended to12 weeks.***
- ***Cotrimoxazole prophylaxis is for all HIV exposed children till infection is definitely excluded.***
- ***All children less than 5 years of age with proved HIV infection irrespective of the clinical and immune status should receive ART.***

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CLIPPINGS

Carnitine supplementation for preterm infants with recurrent apnea

More research is needed before the use of carnitine for the treatment of apnea of prematurity can be recommended in clinical practice. Apnea of prematurity is a common problem in preterm infants in the neonatal intensive care setting (NICU). Recurrent apnea episodes are correlated with adverse neurological development in this population. Carnitine deficiency has been shown to be associated with apnea and respiratory failure in infants and in adults. The reviewers investigated whether treatment of premature babies with carnitine will help in the reduction or resolution of apnea episodes, and the need for ventilation. No treatment trials were identified.

Authors' conclusions

Despite the plausible rationale for the treatment of apnea of prematurity with carnitine, there are insufficient data to support its use for this indication. Further studies are needed to determine the role of this treatment in clinical practice.

Kumar M, Kabra NS, Paes B. Carnitine supplementation for preterm infants with recurrent apnea. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004497. doi: 10.1002/14651858.CD004497.pub2. This version first published online: October 18. 2004

Evaluation of 563 children with chronic cough accompanied by a new clinical algorithm.

This study aims to evaluate the children with chronic cough and to analyze their etiological factors according to the age groups. Five hundred sixty-three children with chronic cough were included. Final diagnosis were established and were also emphasized according to the age groups. The mean age was 5.4 ± 3.8 years (2-months–17-years) and 52% of them were male. The most common final diagnosis from all the participants were: asthma (24.9%), asthma-like symptoms (19%), protracted bacterial bronchitis (PBB) (11.9%), and upper airway cough syndrome (9.1%). However, psychogenic cough was the second most common diagnosis in the subjects over 6 years of age.

Conclusion: Asthma and asthma-like symptoms were the most common diagnosis in children. Different age groups in children may have a different order of frequencies. Psychogenic cough should be thought of in the common causes especially in older children.

Ahmet Hakan Gedik, ErkanCcakir, Emel Torun, Aysegul Dogan Demir, Mehmet Kucukkoc, Ufuk Erenberk, et al. Evaluation of 563 children with chronic cough accompanied by a new clinical algorithm. I J Pediatr 2015;41:73.

INFECTIOUS DISEASES

RESISTANT INFECTIONS IN THE PEDIATRIC INTENSIVE CARE UNIT

*Gnanam R

Abstract: *In the critically ill child, antimicrobial resistance increases mortality, morbidity, length of hospital stay and health care costs. Resistant bacteria act by producing enzymes that inactivate/destroy antimicrobials or by altering/preventing access to the antimicrobial target sites. Apart from cross transmission and impaired host defence mechanisms, repeated exposure to antimicrobials plays an important role in the development of resistance. The surge in extended spectrum beta-lactamase (ESBL) and carbapenemase producing organisms leaves the intensivist with no other choice but to use more potent and toxic antimicrobials. Establishing institution specific treatment guidelines, optimizing the dose and duration of antimicrobial therapy, de-escalation as soon as cultures are obtained and implementation of an antimicrobial stewardship team are important steps towards containing antimicrobial resistance.*

Keywords: *Antimicrobial resistance, Optimal dosing, De-escalation, Antimicrobial stewardship*

Antimicrobial resistance has increased dramatically in the past 15 to 20 years and presents a safety concern in the pediatric intensive care unit (PICU). In the critically ill child, it increases mortality, morbidity, length of hospital stay and health care costs.

Genetics of resistance

Bacteria acquire antimicrobial resistance by way of a) chromosomal mutations, b) expression of latent resistant genes or c) acquisition of new genetic resistance. Resistant bacteria act by producing enzymes that inactivate/destroy the antimicrobial, by altering the antimicrobial target site or by preventing access of the antimicrobial to the access site. Multidrug resistance (MDR) is defined as resistance to more than one drug in 3 or more antimicrobial classes. Extensively drug resistant (XDR) organisms are those non susceptible to more than one agent in all but 2 categories. Pan drug resistance (PDR) is resistance to all antimicrobial classes.

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Factors promoting antimicrobial resistance

1. Cross-transmission: This can be minimized to a great extent by scrupulent hand washing and adherence to aseptic precautions.

2. Host defence: The critically ill child is especially vulnerable to hospital acquired infections (HAI) because of breakdown of normal host defence mechanisms. This may be due to the underlying illness, presence of invasive devices, suppressed immune system, malnutrition and previous hospitalizations/exposure to antimicrobials.

3. Antimicrobial use: Perhaps no other factor is more important in the development of antimicrobial resistance than antimicrobial use. The development of resistance to antimicrobials may even be considered an "Adverse drug event".[1] The genes that confer antibiotic resistance are predominantly found on transferable genetic elements called plasmids.

The profile of resistant bacteria in PICU

Gram positive pathogens: In general the Gram positive organisms (S. aureus, coagulase-negative staphylococci, enterococci) are associated with central line associated bloodstream or surgical site infections. The rates of oxacillin resistant S.aureus (ORSA/MRSA) has increased steadily over the past decade. The risk factors for MRSA is given in Box 1. With the increasing use of vancomycin for resistant S.aureus, there has been a dramatic rise in the percentage of vancomycin-resistant enterococci (VRE).

Box 1. Risk factors for MRSA

Exposure/Colonisation with MRSA
Immunosuppression
Dialysis
Presence of percutaneous catheters
Recent hospitalization (within 90 days)

Box 2. Risk factors for ESBL

- Prior antibiotic use (within 90 days)
- Recent hospitalization (within 90 days)
- Current hospitalization (>5 days)
- Immunosuppression
- Prolonged mechanical ventilation
- Presence of medical devices

Gram negative pathogens: They are associated with a variety of HAI, including ventilator associated pneumonia (VAP), catheter associated blood stream infections (CABSI) and catheter associated UTI. β-lactamase production appears to be the most important mechanism responsible for resistance. One group of β-lactamases - ESBL have the ability to hydrolyse and cause resistance to the third generation cephalosporins and aztreonam, but not to the carbapenems. Three subtypes of ESBL producing bacteria have been recognized- (a) CTX-M, (b) TEM and (c) SHV. The risk factors for ESBL is given in Box 2. Klebsiella and E.Coli are the most common ESBL producers. With increasing use of carbapenems, there has been a rise in the percentage of Gram negative bacteria producing carbapenamases. MDR pseudomonas and acinetobacter infections are associated with a two to six fold increased risk of mortality and 5-13 days of additional stay in the hospital.[2]

Managing and preventing antimicrobial resistance in PICU

Combating emerging resistance and optimizing antimicrobial coverage in critically ill children require integration of multiple and different strategies (Fig.1). These include:

1. Establishing institution specific treatment guidelines: Delivery of timely and appropriate antimicrobial therapy is crucial in critically ill children. Receipt of inadequate antimicrobial therapy has led to poor outcomes and increased mortality. When choosing an empirical antimicrobial regimen, the intensivist should account for the local bacterial ecology of the ICU and the individual patient's risk of having an antimicrobial resistant pathogen.

Table I. Antibiotic options for the treatment of MDR Gram negative pathogens[8]

Resistant Class	Site of infection	Preferred option	Alternatives
ESBL	Bacteremia/ Pneumonia UTI/low severity infections	Carbapenem	Piperacillin/tazobactam, 3rd/ 4thgeneration, cephalosporin (if MIC<1), aminoglycosides, fluoroquinolones
AmpC	Bacteremia/ Pneumonia UTI/low severity infections	Carbapenem/Cefepime	Piperacillin/tazobactam, fluoroquinolones 3rd/4th generation cephalosporins, aminoglycosides
CRE	Bacteremia/ Pneumonia	Colistin	Carbapenem (MIC<4) Tigecycline Only in combination- Rifampin, Fosfomycin
ACB	All sites	Carbapenem	Colistin/Tigecycline Sulbactam
CR ACB and PDR ACB	All sites		Sulbactam/Colistin Tigecycline

AmpC: AmpC producing β-lactamase, CRE: Carbapenemase resistant Enterobacteriacae, ACB-Acinetobacter baumanni, CR ACB: Carbapenemase resistant Acinetobacter baumanni,

PDR ACB:Pan drug resistant Acinetobacter baumanni

Monotherapy with a broad spectrum β-lactam antibiotic is an appropriate empirical regimen for most patients without risk factors for MDR pathogens. However in patients with severe sepsis and shock, late onset VAP or HAI and in those at risk for infection with MDR pathogens, empiric antibiotic therapy should be broadened further. The various options for treatment of Gram negative MDR pathogens are given in Table I. The intensivist should then deescalate to monotherapy once the report on pathogen and susceptibilities are available. Several studies have found reduced length of stay in the ICU, [3,4] shortened duration of mechanical ventilation,[5] of antimicrobial treatment[6] and reduction in hospital mortality[7] when clinical guidelines for pneumonia and other common infections were developed and implemented in the ICU.

2. Antibiograms-Looking at the local bacterial ecology of the PICU

Antibiograms can help identify local resistance patterns and assist in choosing empirical antimicrobial therapy. Combination antibiograms are a novel concept that accounts for cross resistance by identifying pairs of antimicrobials most likely to have activity.[9]

3. Effectively diagnosing infection by repeated cultures and rapid diagnostic tests when feasible

4. Importance of optimal dosing, duration and de-escalation of antimicrobial treatment

Antibiotic concentrations that are sub lethal, especially against the resistant subpopulation can promote the emergence of resistant pathogens. Antimicrobials either exhibit concentration dependent or time dependent kinetics. The duration of time that the serum drug concentration remains above the minimum inhibitory concentration (MIC) enhances bacterial eradication with β-lactams. Aminoglycosides, fluoroquinolones and polymyxins exhibit concentration dependent kinetics-maximal killing occurs when the antibiotic concentration is maintained equal to or greater than four times MIC. Either of these two is achieved by frequent dosing, prolonged infusion or continuous infusion.

5. Implementation of an antimicrobial stewardship team

The team comprises of the intensivist, ID specialist, infection control team, microbiologist and pharmacist. The goals of antimicrobial stewardship are to combat the emergence of resistance, to improve clinical outcomes and to control costs. It is important to have a restricted antibiotic use form for each patient, citing the justification for choosing broad spectrum antibiotics and also emphasizing the need to deescalate. Fig.1 shows the road map for management of antimicrobial resistance in ICU.

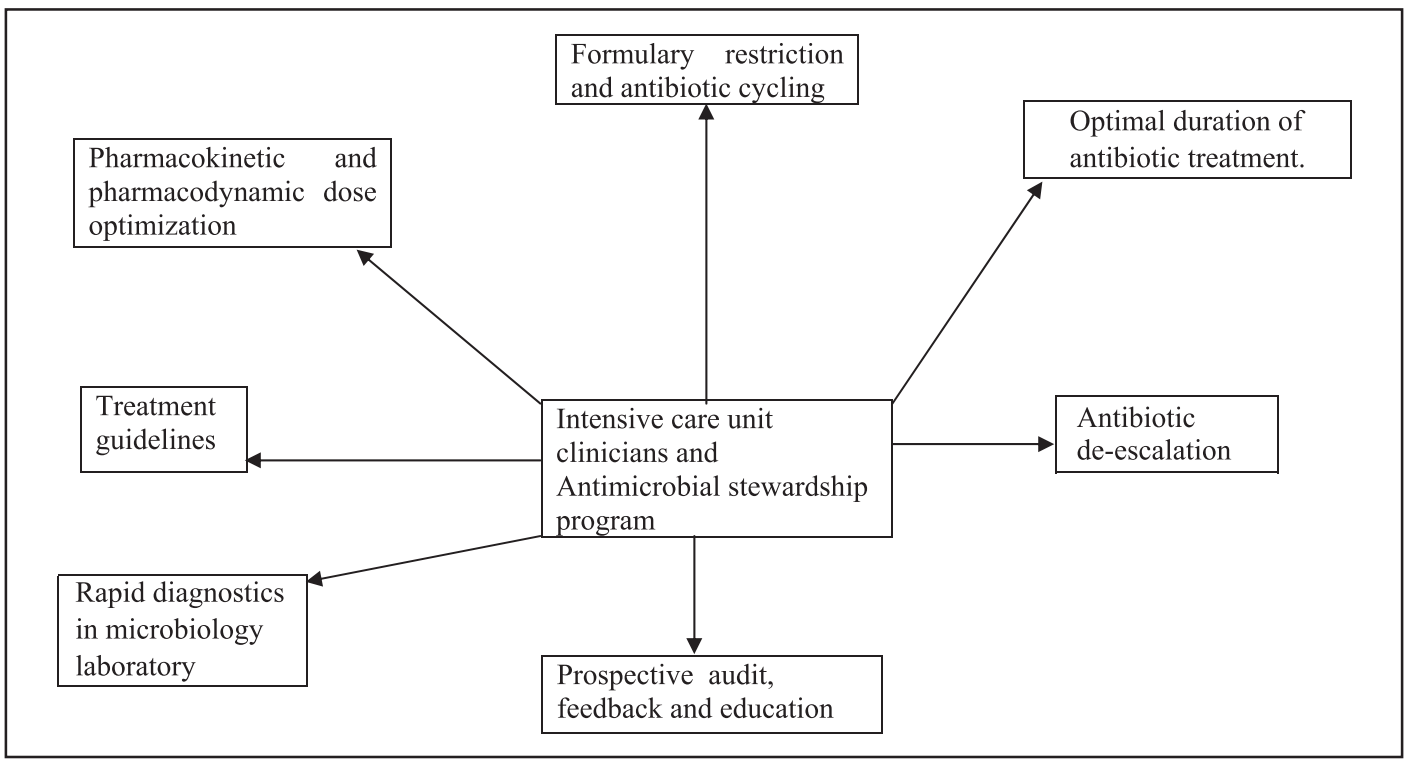

Fig.1. Strategies for prevention and management of antimicrobial resistance in the PICU

Points to Remember

- ***Resistant bacterial infections are on the rise in the PICU's. Resistance may be due to enzyme production or alteration of the antimicrobial target site.***
- ***Cross transmission and prior exposure to antimicrobials are the most important risk factors for resistance in the critically ill child.***
- ***Reviewing the local antimicrobial profile and establishing institution specific treatment guidelines will help contain antimicrobial resistance***
- ***Implementation of an antimicrobial stewardship team is important to combat the emergence of resistance and improve clinical outcomes.***

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CLIPPINGS

3% hypertonic saline versus normal saline in inpatient bronchiolitis: a randomized controlled trial.

Bronchiolitis, the most common reason for hospitalization in children younger than 1 year has no proven therapies effective beyond supportive care. The aim was to investigate the effect of nebulized 3% hypertonic saline (HS) compared with nebulized normal saline (NS) on length of stay (LOS) in infants hospitalized with bronchiolitis. 227 infants younger than 12 months old admitted with a diagnosis of bronchiolitis (190 completed the study) was enrolled in the study. 113 infants were randomized to HS (93 completed the study) and 114 to NS (97 completed the study).Subjects received 4 mL nebulized 3% HS or 4 mL 0.9% NS every 4 hours from enrollment until hospital discharge. The primary outcome was median LOS. Secondary outcomes were total adverse events, subdivided as clinical worsening and readmissions. In intention-to-treat analysis, median LOS (interquartile range) of HS and NS groups was 2.1 (1.2–4.6) vs 2.1 days (1.2–3.8), respectively, P = 0.73. We confirmed findings with per-protocol analysis, HS and NS groups with 2.0 (1.3–3.3) and 2.0 days (1.2–3.0), respectively, P =0 .96. Seven-day readmission rate for HS and NS groups were 4.3% and 3.1%, respectively, P = 0.77. Clinical worsening events were similar between groups (9% vs 8%, P = 0.97)..CONCLUSIONS: Among infants admitted to the hospital with bronchiolitis, treatment with nebulized 3% HS compared with NS had no difference in LOS or 7-day readmission rates.

Silver AH et al., 3% Hypertonic saline versus normal saline in inpatient bronchiolitis: a randomized controlled trial. Pediatrics 2015;136 (6): 1036-43

INFECTIOUS DISEASES

SKIN AND SOFT TISSUE INFECTIONS

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Abstract: *Skin and soft tissue infections in children are an important cause for hospital visits. The main pathogens involved in these infections are Staphylococcus aureus and group A beta-hemolytic streptococci, however, enteric organisms also play a role especially in nosocomial infections. Collection of specimen from lesions should be done prior to initiating antimicrobial therapy. Increasing incidence of methicillin-resistant S. aureus poses challenges for the future. Superficial infections such as folliculitis, pustules, erysipelas, cellulitis, impetigo and bite infections, are the commonest ones seen in day-to-day practice. Deeper infections such as orbital cellulitis, necrotizing fasciitis and pyomyositis require surgical intervention as well as parenteral antibacterial therapy. Hand hygiene is an important tool for the prevention and spread of skin and soft tissue infections.*

Keywords: *Skin and soft tissue infections, Necrotizing lesions, Staphylococci, Streptococci*

Skin and soft tissue infections

The skin is the largest organ of the body accounting for about 15% of the total adult body weight and, with the underlying soft tissue, which includes the fat layers, fascia and muscle, represents the majority of the tissue in the body. It acts as a tough, flexible, structural barrier to invasion. It performs many vital functions, including protection against external physical, chemical and biologic assailants, as well as prevention of excess water loss from the body and has a role in thermoregulation.[1]

Skin and soft tissue infections (SSTIs) are among the common infections encountered by all doctors. SSTIs reflect inflammatory microbial invasion of the epidermis, dermis and subcutaneous tissues. The skin is colonized with an indigenous microbial flora, which typically consists of a variety of species of staphylococci, corynebacteria, propionibacteria and yeasts, in numbers that may vary from a few hundred to many thousands per square centimeter in the moist areas such as the groin and axillae.[2] The normal flora may act as a competitive inhibitor for pathogenic microbes. Breaks in the skin, such as ulcers, burns and surgical or traumatic wounds, allow colonization with a broader range of bacteria.

Microbial disease of the skin may take place by one of the following routes.

- Direct invasion of the epidermis
- Hematogenous spread of organism (e.g. meningococcal rash or rickettsial macules in tick typhus) or viruses (measles or chickenpox for instance)
- Toxin-mediated damage from an infection elsewhere in the body (such as staphylococcal scalded skin syndrome or streptococcal scarlet fever).

Classification

SSTIs are best classified according to the anatomical site of infection (Table I).[3]

Etiology and epidemiology

The vast majority of SSTIs are caused by S. aureus and beta-hemolytic streptococci, usually Lancefield groups A, C and G, with group B occurring in diabetics and the elderly.[4,5] Localized pus-producing lesions such as boils, abscesses, carbuncles and localized wound sepsis are usually staphylococcal, while rapidly spreading infections such as erysipelas, lymphangitis or cellulitis are usually caused by beta-hemolytic streptococci.[3] In recent years, treatment of skin infection has become problematic as two most common bacteria S. aureus and S. pyogenes have started showing resistance to first line antibiotics like semisynthetic penicillin, erythromycin and first generation cephalosporins.[6] Methicillin resistance was first detected in S. aureus in 1961 shortly after the agent was introduced clinically, and over the last few decades there has been a global epidemic of methicillin resistant staphylococcus aureus (MRSA).[7] Skin and soft tissue infections account for 90% of infections by MRSA and contribute major burden of MRSA infection.[8] It is more common with community acquired methicillin resistant staphylococcus aureus

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Table I. Types of infection affecting skin and soft tissue structures

Anatomical structure	Infection	Microbial cause
Epithelium	Varicella, measles	Varicella zoster and measles virus
Keratin layer	Ringworm	Dermatophyte fungi (Microsporum, Trichophyton, Epidermophyton)
Epidermis	Impetigo	S pyogenes, S. aureus
Dermis	Erysipelas	S. pyogenes
Hair follicles	Folliculitis, boils, carbuncles	S. aureus
Sebum glands	A acne	Propionibacterium acnes
Subcutaneous fat	Cellulitis	β-hemolytic streptococci
Fascia	Necrotizing fasciitis	S. pyogenes or mixed anaerobic infection
Muscle	Myositis	Toxigenic strains of S. aureus
	Gangrene	C. perfringens

Table II. Risk factors for SSTIs caused by specific pathogens

Risk factor	Pathogens
Recurrent hospital admissions contact sports, recurrent boils and abscesses, H/o known contact	MRSA or MSSA producing Panton-Valentine leukocidin (PVL)
Diabetes	S aureus (MRSA and MSSA), Group β-hemolytic streptococci, anaerobes, Gram-negative bacilli
Neutropenia	Gram-negative bacilli, P aeruginosa, Fungus
Water exposure (sea, estuarine, rivers)	Vibrio spp. Aeromonas hydrophila Mycobacterium marinum P aeruginosa
Reptile contact	Salmonella spp
Drug addicts	MRSA

(CA MRSA) as compared to hospital acquired methicillin resistant staphylococcus aureus (HA MRSA).[9,10]

Gram-negative and anaerobic bacteria are more common in association with surgical site infections of the abdominal wall or infections of the soft tissue in the anal and perineal region. Polymicrobial infections involving both Gram-positive and Gram-negative organisms occur particularly where tissue vascular perfusion is compromised, such as diabetic foot infection or infection of ischemic or venous ulcers. Chronic infections, especially in patients previously treated with antibiotics, are likely to be polymicrobial with Gram-negative and obligate anaerobic pathogens found alongside Gram-positive organisms. Such infections with Gram-positive and Gram negative microbes clearly require broad-spectrum antibiotic treatment.

The predominant pathogens associated with SSTIs in hospitalized patients include S. aureus (ranked first in all geographical regions), Pseudomonas aeruginosa, Escherichia coli and Enterococcus spp.[8]

SSTIs accompanied by signs and symptoms of systemic toxicity such as fever, hypothermia, tachycardia

and hypotension can be classified as complicated.[4] They usually require hospitalization and surgical consultation. In many skin infections the presentation is usually mild where etiological diagnosis is not required. Etiological diagnosis is necessary if there is severe and necrotizing deep seated infection, disproportionate pain, violaceous bullae, skin anesthesia, hemorrhage and sloughing, gas with crepitus in the tissues and rapid progression.[4] Risk factors for specific pathogens are listed in Table II.

Common bacterial SSTIs

These are: a) impetigo, b) ecthyma, c) folliculitis furuncles and carbuncles, d) cellulitis and erysipelas, e) necrotising skin and soft tissue infection, f) paronychia and g) intertrigo

A. Impetigo and ecthyma

It is a common superficial skin infection characterized by inflammation and infection in the epidermis. This infection is primarily caused by S aureus and S pyogenes either alone or in combination.[9]

It exists in two major forms - Bullous impetigo and non-bullous impetigo. (impetigo contagiosa).

Non-bullous form can occur in any pediatric age group whereas bullous form is more common in infants and children. This infection is more common in overcrowded areas with poor hygiene during humid summer months. It is very important to recognize certain skin diseases that become secondarily 'impetiginized' thereby obscuring the primary skin disease.[9] The most common diseases include atopic and contact dermatitis, herpes simplex infection and tinia capitis.

Bullous impetigo is usually caused by S aureus, producing an exfoliating toxin. In fact it is a localized manifestation of staphylococcal scalded skin syndrome causing subgranular epidermolysis by the toxin. It may also occur in neonates. The initial red macule develops into larger vesicles or bullae, which are fragile and rupture leaving annular or circinate erythematous scaly areas. Bullous impetigo are commonly found on the face, limbs, hands and buttocks. Initially the bullae are filled with clear yellow fluid which later becomes darker, more turbid and sometimes purulent. Ruptured bullae show thin brown crust resembling lacquer.

Non-bullous impetigo (Impetigo contagiosa) is a crusted variety and may be caused by S aureus or S pyogenes or both. Minor scratch or skin trauma is the usual cause of skin breech which favours invasion by pathogenic organism. The anterior nares may be the reservoir for the infection, leading to recurrent episodes. Impetigo contagiosa starts with a small macule, which rapidly develops into vesicles or pustules or vesicopustule. Lesions rupture readily to form a crusted seropurulent oozing area of a typical honey colour. This honey coloured crust is highly characteristic. Individual lesions are usually 1-2 cm in diameter with satellite lesions usually seen nearby. They are commonly found on the face around the mouth and nares but may also spread to limbs including buttocks. Lesions are usually painless with mild discomfort and itching. Local lymphadenopathy can occur but are more common with streptococcal impetigo. Characteristics of the bullous and non-bullous impetigo are given in Table III.

Lesions with impetigo heal rapidly leaving behind no sequel, except mild post-inflammatory transient pigmentation. It may be widespread in conditions like atopic dermatitis, scabies and HIV. Patients with multiple and/or recurrent lesions are more likely to be contagious. Streptococcal impetigo may be followed by glomerulonephritis, scarlet fever, urticaria or erythema multiforme but not rheumatic fever.[9] Streptococcal antibodies are neither required for diagnosis nor for treatment of impetigo but they provide supporting evidence of recent streptococcal infection in patients with glomerulonephritis. ASO titre are low in patients with

Table III. Features of bullous and non-bullous impetigo

Non-bullous impetigo (impetigo contagiosa)	Bullous impetigo
Caused by S aureus or S pyogenes or both	Usually caused by S aureus
Site: Abdomen, flexural surfaces	Sites: Face and extremities
Systemic features: Absent	May be present
Lesions: Vesicles/ pustules/ dark gold or black crusts	Blisters/flaccid bullae which may rupture leaving golden yellow crusting

streptococcal impetigo as skin lipids suppress this response but anti DNAse B levels are consistently elevated.[10]

B. Ecthyma

Ecthyma is a deeper infection mainly caused by Group A Streptococci, but may be due to S. aureus or both. The typical feature is the formation of thick crust following small pustules on an erythematous base which may result in an area of ulceration. It is difficult to detach this crust from underlying skin. At any given point of time the lesions are multiple and new ones keep developing due to auto-inoculation.[9] They frequently occur over the lower legs and buttocks. It heals with scarring.[11] Healing takes several weeks. Treatment for ecthyma should be an oral antimicrobial with topical antibiotics.

Management of impetigo and ecthyma

1. In case of minor lesions which is often self-limiting, simple measures like debridement of the crust with warm soak along with cleaning several times daily with antibacterial soap is adequate
2. In limited lesion topical therapy with mupirocin application twice a day for 5 days is helpful.[12] Sodium fusidate is also efficacious but needs to be applied 4 times in a day.
3. Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify the causative organism, but treatment without these studies is reasonable in typical cases.[12]
4. Antibiotic therapy for ecthyma or impetigo should be a 7-day regimen with an agent active against S. aureus and streptococci Because S. aureus isolates from impetigo and ecthyma are usually methicillin susceptible, oral dicloxacillin or cephalexin is recommended.
5. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim (SMX-TMP) is recommended.[12]
6. Systemic antimicrobials should be used for infections during outbreaks of post-streptococcal glomerulonephritis to help eliminate nephritogenic strains of S. pyogenes from the community.
7. Antihistamines may be prescribed in case of severe pruritus.
8. Personal hygiene and good nutrition should be encouraged.

C. Folliculitis, furuncles and carbuncles

These pus forming lesions are common in tropical climates, poor hygiene and overcrowded living conditions.

Folliculitis is a superficial pustular infection involving the hair follicle and perifollicular structure. Folliculitis starts as a small pustule with a hair usually piercing it and a perifollicular erythema. Pustules rupture followed by crust formation. Systemic signs and symptoms are rare excepting mild itching. Lesions are typically located on the head, back, buttocks and extremities.

Furuncles are also single hair follicle associated infections extending through the dermis into the subcutaneous tissue where a small abscess forms. Furuncles which extend into the dermis and subcutaneus tissue are firm, tender and are seen over friction prone areas of the body like face, axilla, neck and buttocks. Multiple furunculosis are often seen in immunocompromised child with functional neutrophil disorder such as hyper immunoglobin E syndrome and Job syndrome.

If infection extends to involve several adjacent hair follicles forming a coalescent mass it is called carbuncle. Carbuncles are often located on the back of the neck, posterior trunk or thigh. They can be painful with systemic signs and symptoms like fever and malaise. The risk factors for this condition include obesity, diabetes mellitus, severe atopic dermatitis, impaired neutrophil function and prolonged corticosteroid use.

The most common causative microorganism is S aureus. At times P. aeruginosa may be the offending organism.

Management

1. In immunocompetent children folliculitis and small furuncles resolve spontaneously with use of warm compress and topical antibiotic therapy like mupirocin.
2. Incision and drainage is needed for carbuncles and larger furuncles.
3. Gram stain and culture of the pus or exudates from skin lesions are recommended to help identify the microbial agent.
4. Systemic antibiotics should be reserved for children who have systemic signs such as fever, tachypnea, tachycardia or if associated cellulitis is present.
5. Some children have repeated attacks of furunculosis. To eradicate staphylococcal carriage application of mupirocin ointment twice daily in the anterior nares

for the first five days of each month is recommended to reduce the recurrence by half. Whether such regimens are effective in the current era of community acquired MRSA is unclear.[13]

6. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
7. Majority of cases will respond to first generation cephalosporins.

D. Cellulitis and erysipelas

Cellulitis is a diffuse skin infection that involves the deep dermis and subcutaneous fat tissues. It should be distinguished from erysipelas which involves the upper dermis including the superficial lymphatics. Cellulitis most frequently occurs on the head and neck in children. It is also found on the scalp, perianal areas and sites of traumatic wound, bruises and bites. Erysipelas most commonly occurs on the face but also can involve scalp, extremities and genitalia. Predisposing factors include conditions which interfere with local host defense or make the skin more fragile. Lymphatic obstruction, venous stasis, trauma, pre-existing skin infection, eczema and obesity are few such conditions.[14] Both the conditions are associated with systemic signs like fever, regional lymphadenopathy and lymphangitis.

Streptococcus pyogenes is the most frequently responsible for cellulitis but S. aureus is also an important cause in children usually those associated with abscess or other primary lesion. H influnzae and S pneumoniae can also cause cellulitis in young children.

Cellulitis is characterized by spreading erythema with indistinct borders with an edematous infiltrated appearance and is warm to touch. This is in contrast to erysipelas which has a distinct elevated border and with a clear line of demarcation between involved and uninvolved tissue. The skin surface shows peau-de orange as superficial cutaneous edema surrounds the hair follicles which causes dimpling in the skin as they remain tethered to underlying dermis. Petechiae and ecchymoses, particularly if wide spread, developing in the inflamed skin may indicate deeper infections such as necrotising fascitis which need hospitalization and surgical consultation.[15] The condition should be distinguished from superficial thrombophlebitis which also presents as erythema with pain and warmth but the vein is palpable and may appear as a red line.

The diagnosis is clinical as isolation of the causative organism by culture of the tissue aspirate and skin biopsies is often negative. Blood cultures are generally positive in ≤5% of cases.[16] The yield of cultures of needle aspiration of the inflamed skin ranges from ≤5% to approximately 40%.[17]

Management

The treatment of cellulitis requires systemic antibiotics active against both streptococci and staphylococci. Suitable agents include cloxacillin, cephalexin, clindamycin or co-amoxiclav. In case of uncomplicated cellulitis five days antibiotic treatment is as effective as ten days course.[18] Most of the erysipelas cases can be treated with above mentioned antibiotic on an outpatient basis. Cefazolin or anti-staphylococcal penicillin is recommended for definitive therapy of lesions caused by MSSA.

For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS, vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. However it is to be noted that MRSA is an unusual cause of typical cellulitis.[19] Hospitalization is recommended if there is concern for a deeper necrotizing infection, for patients with poor adherence to therapy, for infection in a severely immunocompromised patient, or if outpatient treatment is failing. On symptomatic improvement one can switch over to oral antibiotic to complete ten days course.

Elevation of the affected area hastens recovery by aiding drainage of edema. Children should also receive appropriate therapy for the underlying condition that has predisposed to the infection.

Patients with a previous history of cellulitis have annual recurrences rates of about 8%–20%.[20] In case of recurrent cellulitis identify and treat predisposing conditions such as edema, obesity, eczema, venous insufficiency, and toe web abnormalities. Administration of prophylactic antibiotics, such as oral penicillin or erythromycin bid for 4–52 weeks, or intramuscular benzathine penicillin every 2–4 weeks, should be considered in patients who have 3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors.[12]

E. Necrotising skin and soft tissue infection

This medico-surgical emergency is a life-threatening, invasive, soft tissue infection caused by aggressive, usually gas-forming bacteria, which primarily involves the superficial fascia and extends rapidly along subcutaneous

tissue planes with relative sparing of skin and underlying muscle. Clinical presentation includes fever, signs of systemic toxicity and pain out of proportion to the clinical findings.[21] Paucity of cutaneous findings early in the course of the disease can make diagnosis challenging. Delay in diagnosis and/or treatment correlates with a poor outcome, leading to sepsis and/or multiple organ failure.

Necrotizing fasciitis

Necrotizing fasciitis is an aggressive subcutaneous infection that tracks along the superficial fascia, which comprises all the tissue between the skin and underlying muscles.[22] Most infection follow some abnormality leading to bacterial inoculation like minor trauma but a small proportion do not have a known predisposing cause.[23] At times it can arise from perianal abscess from which it spreads to the perineum through groin and abdomen. Necrotizing fasciitis is empirically divided into two categories based on number of organisms involved, monomicrobial and polymicrobial.

Monomicrobial is more common; usually caused by S pyogenes or S aureus. Sometimes infection with staphylococci and hemolytic streptococci can occur simultaneously.[12] Other organisms like Vibrio vulnificus, anaerobic streptococci and Aeromonas hydrophila may also be responsible. Most of the infections involve the lower extremity and are community acquired. Fasciitis occurring after trivial injuries or chicken pox are almost always due to S pyogenes and very rarely due to CA-MRSA.[24]

Polymicrobial forms are less common and mainly caused by both aerobic and anaerobic bacteria. Common isolates include streptococcus other than group A, S. aureus, enterococcus, E coli, bacteroides, clostridia and peptostreptococcus to name a few. In the polymicrobial form, numerous different anaerobic and aerobic organisms can be cultured from the involved fascial plane, with an average of 5 pathogens in each wound.[12] Most of them originate from the bowel flora and follow surgical procedures involving the gut or penetrating abdominal trauma. It can also follow infection involving the perineal area which extends rapidly to the adjoining structures.

Clinical features: The clinical presentation of necrotizing fasciitis can be most non-specific and deceptively innocuous. Pain that is out of proportion to the clinical finding is an important symptom. Extension from a skin lesion is seen in most cases. The initial lesion can be trivial, such as a minor abrasion, insect bite, injection site (as in drug addicts), or boil and a small minority of patients have no visible skin lesion. The initial presentation is that of cellulitis, which can advance rapidly or slowly. As it progresses, there is systemic toxicity, often with high temperature, disorientation and lethargy. Examination of the local site typically reveals cutaneous inflammation, edema and discoloration or gangrene and anesthesia. A distinguishing clinical feature is the wooden-hard induration of the subcutaneous tissue. In cellulitis, the subcutaneous tissues are palpable and yielding; while in fasciitis the underlying tissues are firm, and the fascial planes and muscle groups cannot be discerned by palpation. A broad erythematous tract is sometimes evident along the route of the infection, as it advances proximally in an extremity.[21] If there is an open wound, probing the edges with a blunt instrument permits ready dissection of the superficial fascial planes well beyond the wound margins.[12]

Diagnosis: The diagnosis of fasciitis may not be apparent upon first seeing the patient. Overlying cutaneous inflammation may resemble cellulitis. However, features that suggest involvement of deeper tissues include (1) severe pain that seems disproportionate to the clinical findings, (2) failure to respond to initial antibiotic therapy, (3) the hard, wooden feel of the subcutaneous tissue, extending beyond the area of apparent skin involvement, (4) systemic toxicity, often with altered mental status, (5) edema or tenderness extending beyond the cutaneous erythema, (6) crepitus, indicating gas in the tissues, (7) bullous lesions and (8) skin necrosis or ecchymoses.

Systemic toxicity, with altered mental status, rigors, tachycardia and hypotension is suggestive of necrotizing fasciitis. The most important diagnostic criteria is the appearance of subcutaneous tissue at the operating table. The subcutaneous tissue is swollen, has dull grey appearance with dish water fluid like discharge from the affected area. Gram stain of the exudates gives a clue to the underlying pathogen. Culture should be obtained from deep tissues. Definitive bacteriological diagnosis is from tissue specimens or from blood culture results. Cultures of the superficial wound may be misleading because results may not reflect organisms in the deep tissue infection.

Radiographic imaging in the form of Computed tomography (CT) or MRI can be done. CT or magnetic resonance imaging (MRI) may show edema extending along the fascial plane, although the sensitivity and specificity of these imaging studies are ill defined. They reveal fluid and gas collection, muscle necrosis and fascial thickening.

Management

First and foremost in the treatment of necrotizing fasciitis is to identify the diseases and immediate institution

Table IV. Antimicrobial dosage for skin and soft issue infection[15]

Antibiotic	Dosage
Cloxacillin	50 – 100 mg/kg/day in 4 divided doses
Cephalexin	25-50 mg/kg/day in 4 divided doses
Cefazolin	50mg/kg in 3 divided doses
Clindamycin (if local strains susceptible)	10-20 mg/kg/day in 3 divided doses
Amoxycillin/Clavulunate	40mg/kg/day of the amoxicillin component in 2 divided doses

Table V. Drugs for MRSA[15]

Antibiotic	Dosage
Vancomycin	40-60 mg/kg/day IV 6-8 hourly (IV infusion over 1 hour or more)
Linezolid	30 mg/kg/day PO or IV q8 hourly
Clindamycin	10-20 mg/kg/day in 3 div. doses PO
Doxycycline (bacteriostatic, for children older than 7 years)	100 mg BD
TMP-SMX	8–12 mg/kg (based on trimethoprimcomponent) in either 4 divided doses IVor 2 divided doses PO
Daptomycin (No Pediatric data)	4 mg/kg/day OD X 7 days

of definitive treatment without any delay for investigations. Surgical debridement is the mainstay of therapy and at times repeated debridement by the surgical team is required. Antibiotic therapy should be aimed at the most likely pathogen(s) responsible and is required till there is obvious clinical improvement. Empiric treatment of polymicrobial necrotizing fasciitis should include agents effective against both aerobes, including MRSA, and anaerobes. Among the many choices is 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. Once the microbial etiology has been determined, the antibiotic coverage should be modified. For monomicrobial infection penicillin along with clindamycin should be used for streptococcal infection. Clindamycin suppresses toxin and cytokine production. There are some reports of streptococcus being resistant to penicillin. For methicillin sensitive S. aureus, cloxacillin or cefazolin may be used. For methicillin resistant S. aureus, vancomycin or linezolid is the drug of choice. Additional studies of the efficacy of IVIG are necessary before a recommendation can be made supporting its use.[12] Supportive measures like fluid resuscitation, adequate oxygen saturation and euglycemic control need emphasis. These wounds can discharge copious amounts of tissue fluid, and aggressive fluid administration is a necessary adjunct.

Antimicrobial dosage for skin and soft issue infections is given in Table IV and the drugs for MRSA are listed in Table V. Diagnosis and management for SSTIs are summarized in Fig.1

Paronychia

It is a superficial infection of periungual tissue of fingers and toes. Acute infection is usually caused by staphylococcus less commonly streptococcus and pseudomonas species. Chronic infection common in persons exposed to water, caused by candia albicans. A break in the epidermis due to minor trauma allows the offending organism to enter. In children it may be a result of finger sucking or nail biting. It may also follow cut hangnail and ingrown nail. Infections occur along the nail margin and may extend beneath the nail.

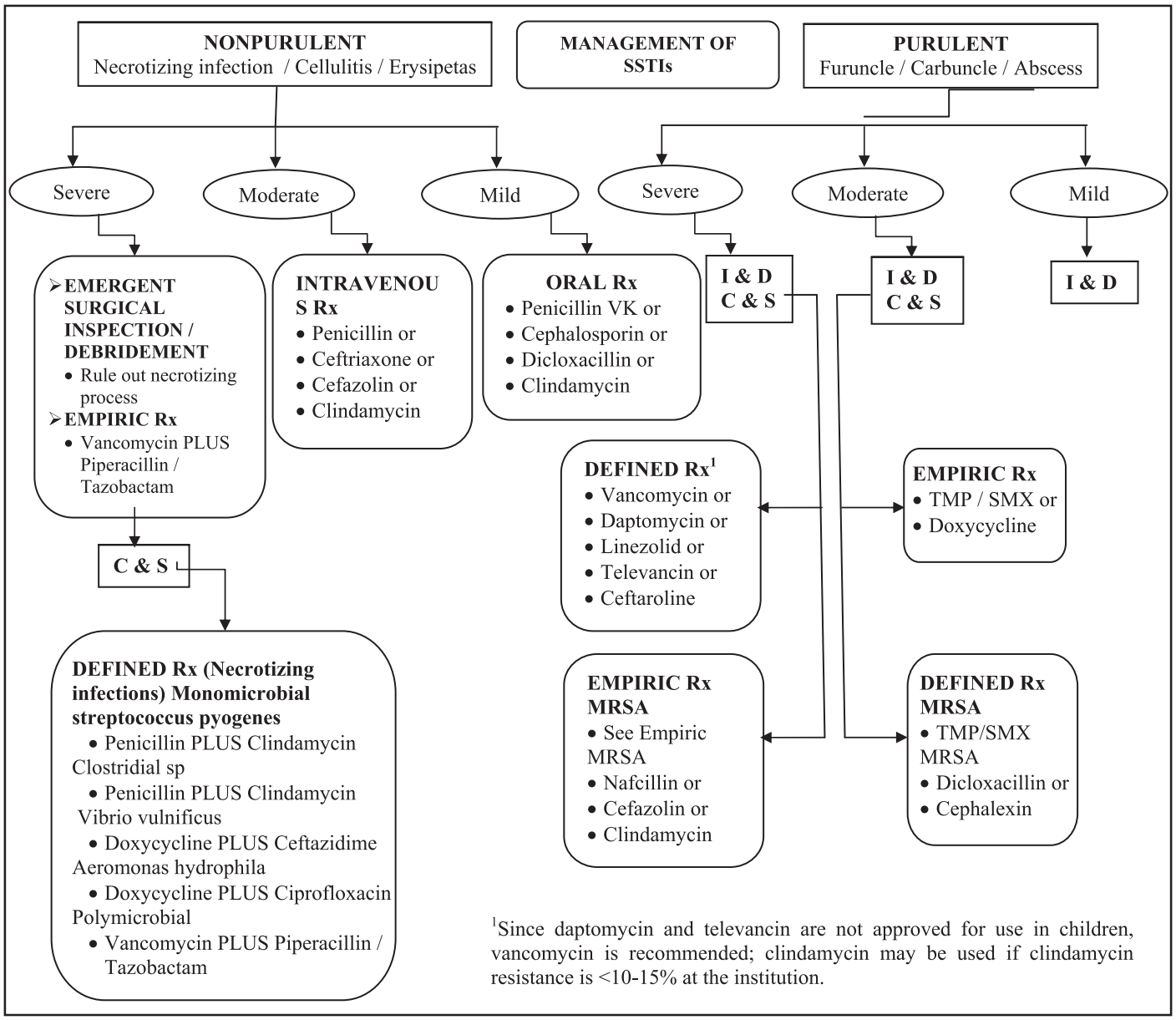

Fig.1. Management algorithm for SSTIs[15]

The affected digit shows acute inflammatory change of the nail fold with swelling, erythema, pain and pus formation. Greenish discoloration may be due to pseudomonas infection. In chronic infection the nail folds appears boggy. It should be distinguished from felon which is infection of the pulp of the finger tip not necessarily localized around the nail fold as in paronychia.

If possible, swab of the purulent discharge should be taken and gram stain done. Culture should also be done to identify the organism. Warm soak promotes drainage and provide symptomatic relief. It should be treated with oral antibiotics such as cephalaxin or cloxacillin. Patient allergic to penicillin should be treated with erythromycin or azithromycin. In selected cases incision and drainage of the abscess is required.

Intertrigo

It is an inflammatory process of the skin where there is friction as in groin, axilla, intergluteal cleft and neck folds in infants. Sweat, moisture and heat leads to maceration and skin erosion, which predispose to secondary infection with bacteria or Candida albicans. The condition should be distinguished from candidal napkin rash which shows somewhat scaly appearances with satellite lesion. Secondary infection with streptococcus or mixed infection with staphylococcus, pseudomonas species and proteus species result in foul smelling macerated erythema. They are resistant to topical antifungal medication but responds to antibiotics.

Table VI. Non-bacterial skin infections

Condition	Organism	Features	Treatment
Pediculosis	Pediculus human capitis (head louse)	Age:3-12 years More common in girls Site: ScalpIntense pruritis	Topical: 1% Permethrin to be applied over scalp as a cream rinse after shampoo and dried. Rinse it out after 10 minute with water. Second application after 1week. All close contacts need treatment Oral: Cotrimoxazole twice daily for 3 days
Scabies	Sarcoptes scabiei	Intense pruritis mainly at night and after hot shower Site: Multiple burrows at finger webs, wrist, elbow, margins of hands, belt line and genitals Face and neck are usually spared. Secondary bacterial infections and eczematization is quite common	Topical application of 5% permethrin lotion for 8 to 14 hours is highly effective. Reapplication after one week. Cure rate: nearly 90% Oral Ivermectin: 2doses of 200mcg/ Kg one week apart in scabies with HIV or immunosuppressed child Treat all family members and close contacts.
Tinea corporis	Dermatophyte	Site: exposed areas of the body Lesions: Circular, marginated with raised edges may be single or in plaques. Central resolution with post inflammatory pigmentation is common	Single lesion: Topical antifungals lie clotrimazole (1%), miconazole (2%), ketoconazole (2%) once or twice a day for 2 weeks. Extensive, persistent infections of scalp and nails is treated with griseofulvin 5 10mg/kg/day. Fluconazole is an alternative to it.

Perianal infectious dermatitis/Perianal streptococcal dermatitis

This infection of perianal skin and mucosa is often misdiagnosed as napkin dermatitis. The problem is more common in male child between the age of 3 to 4 years.[1] Group A beta haemolytic streptococcus remains the predominant pathogen hence also known as perianal streptococcal dermatitis.[12]

Lesion appears as moist erythema in a confluent perianal distribution extending 2-4 cm from the anal verge. Signs and symptoms include rectal tenderness, irritation, pruritus, painful defecation with encopresis. Constitutional symptoms like fever are usually absent. Differential diagnosis includes psoriasis, candidiasis, pinworms, sexual abuse and inflammatory bowel disease. Ten days course of oral penicillin is required. Table VI summarises non-bacterial skin infections

Points to Remember

- ***Skin and soft tissue infections in children are a common cause for hospital visit. Thorough history and physical examination can provide clues to the pathogens involved.***
- ***Systemic manifestation like septic shock, invasive diseases and toxic shock syndrome are potentially dreadful conditions associated with SSTIs.***

- ***Chronic and recurrent pyoderma are often associated with underlying chronic diseases like eczema and may be the first markers for underlying immunodeficiency states.***
- ***Scabies, tineasis and pediculosis are important common non-bacterial SSTIs.***

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INFECTIOUS DISEASES

PROPHYLACTIC ANTIMICROBIAL THERAPY

*Jaydeep Choudhury

Abstract: *The aim of prophylactic antimicrobials is to prevent infections. It is indicated only in certain selected situations. The antibiotic used should be of narrow spectrum, directed against specific pathogen, used for a short duration and standard protocols have to be followed. In neonates prophylactic antibiotics are used to prevent ophthalmia neonatorum and group B streptococcal infection. It is also indicated in certain diseases like rheumatic fever, infective endocarditis, urinary tract infection, recurrent otitis media and malaria. Post-exposure prophylaxis is used in tuberculosis, pertussis, meningococcal infection, diphtheria, varicella and influenza. Other indications are asplenia, human and animal bites and surgical prophylaxis.*

Keywords: *Prophylaxis, Antimicrobials, Infection prevention, Protocols.*

There are three indications of antimicrobial use: For treating confirmed or obvious infections, for empirical use and for prophylaxis. In ideal situation, antimicrobials should be used only in case of proven infections. Hence, proper diagnosis is the first step towards rational antimicrobial use. Empirical use is, by and large, subjective, where it is used mainly by personal experience and intuition. Though this is not the ideal way to use an antibiotic, it is the most common mode of antibiotic use. Prophylactic use is indicated only in certain selective situations where standard protocols need to be followed.

'Antibiotic prophylaxis' by definition is the use of antimicrobial drugs in the absence of suspected or documented infection with the intention of preventing an infection.[1] It is important to consider the risk of emergence of resistance and the possibility of adverse effect to the potential benefit of antibiotic prophylaxis. The following are the principles of antibiotic prophylaxis.[2]

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- The risk or potential severity of infection should be more than the risk of side effects of the concerned antibiotic.
- Narrow spectrum antibiotic, directed towards the specific pathogen, is to be used.
- The antibiotic should be given before the expected period of risk, such as surgical prophylaxis or soon after exposure to an infection, like meningococcal infection.
- It is to be used for as short a duration as possible to prevent the target infection.
- Least toxic and minimum adverse effects should be ensured.

Prophylaxis in neonates

Ophthalmia neonatorum

The main targets of prophylaxis are Neisseria gonorrheae and Chlamydia trachomatis where the drug should be administered soon after birth. Under ideal circumstances the prophylaxis should be initiated in neonates exposed to these pathogens but practically it is impossible to identify the exposed neonates. Routine prophylaxis is not mandatory in most countries.[2] The drugs used for prophylaxis are topical 0.5% erythromycin or 1% tetracycline single dose. Previously 1% topical silver nitrate solution was used.

Group B Streptococcal infections (GBS)

Neonatal GBS infection is not common in India and so routine screening of Indian women is not required.[3] In western countries vaginorectal GBS screening culture is done at 35-37 weeks. Maternal prophylaxis is started depending on the culture positivity.[1]

Drugs used for prophylaxis are penicillin G 5 x10^6 units every 6 hours or ampicillin 2g IV loading dose followed by 1-2g every 4-6 hourly. Erythromycin or clindamycin may be used in women allergic to penicillin. The prophylaxis is continued till delivery.

Disease specific prophylaxis

Rheumatic fever

Rheumatic fever is precipitated by group A

Table I. Drugs used for prevention of rheumatic fever

Drug	Dose	Route
Benzathine penicillin G	1,200,000 U every 21 days (> 27 kg) 600,000 U every 15 days (<27 kg)	IM
Penicillin V	250 mg 2 times daily	Oral
If allergic to penicillin, Erythromycin	20 mg/kg (max 500 mg) 2 times daily	Oral

β hemolytic streptococcus infection of pharynx. Appropriate antibiotic therapy of streptococcal pharyngitis prevents development of acute rheumatic fever. Most of the times acute rheumatic fever results from minor and inapparent streptococcal infection. An individual who has suffered an attack of acute rheumatic fever is at a higher risk of recurrence after a fresh group A streptococcal pharyngitis. Thus they need continuous chemoprophylaxis to prevent such recurrences.[1,3] The recommended drugs for prevention of acute rheumatic fever are listed in Table I.

The general recommendation is to continue prophylaxis till 5 years after the last attack of rheumatic fever or the age of 21 years, whichever is longer.

Infective endocarditis

American Heart Association has issued detailed recommendations on indications and antimicrobial regimens for prevention of bacterial endocarditis for people at increased risk.[2] Prophylaxis is indicated in the following cardiac conditions when dental procedures are to be carried out.[2]

(a) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair

(b) History of previous infective endocarditis

(c) Congenital heart disease

- Unrepaired congenital cyanotic heart disease
- Completely repaired congenital heart defects with prosthetic material or device inserted during the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of prosthetic device

(d) Cardiac transplant recipients who develop valvulopathy

All dental procedures that involve manipulation of gingival tissues, peri-apical region of teeth or perforation of oral mucosa are indications for administration of dental prophylaxis in children. Other procedures such as anesthetic injection through non-infected tissue, dental X-ray, placement or adjustment of orthodontic appliances or bleeding from trauma to the lips or oral mucosa do not require prophylaxis. Prophylactic antibiotics for dental procedures are listed in Table II and prophylaxis for patients at different grades of risk are listed in Table III.

In respiratory system, antibiotic prophylaxis is recommended for procedures that involve incision of the respiratory mucosa. Prophylaxis is not required for bronchoscopy. Incision of surgically scrubbed uninfected skin is unlikely to cause bacteremia, hence prophylaxis is not indicated. It is also not recommended for gastro intestinal or genitourinary procedures.

Urinary tract infection (UTI)

In spite of proper treatment of the first episode of UTI, recurrence is observed in 30% - 50% of children. Most often the patients have an underlying urinary tract anomaly, commonly VUR. Indications for antibiotic prophylaxis in UTI is given in Box 1[4,5] and drugs to be used is given in Table IV.

Box 1. Antibiotic prophylaxis in UTI[5,6]

- Infants with first episode of UTI until evaluation is complete
- Children with vesico-ureteric reflux
- UTI in infants on diapers
- Scarred kidneys with UTI
- Frequent febrile UTI (>3 episodes/year)
- Voiding dysfunction
- Following surgical correction of VUR for 6 months

The prophylactic drug should be given at bedtime to ensure good overnight concentration in the bladder urine. The duration of treatment varies according to the underlying condition.

Table II. Prophylactic antibiotics for dental procedures

Situation	Drugs	Dosage	Route	Timing with procedure
Oral	Amoxicillin	50 mg/kg, max 2g	Oral	1 hr before procedure
Unable to take oral medications	Ampicillin	50 mg/kg, max 2g	IM/IV	½ hr before procedure
Allergic to penicillin	Clindamycin or Cephalexin or Cefadroxil or Azithromycin or Clarithromycin	20 mg/kg, max 600 mg 50 mg/kg, max 2g 15 mg/kg, max 500 mg	Oral	1 hr before procedure
Allergic to penicillin and unable to take oral medications	Cefazolin or Clindamycin	50 mg/kg, max 1g 20 mg/kg, max 600 mg	IV/IM IV/IM	30 minutes before procedure

Table III. Prophylaxis for patients at risk[4]

Situations	Drugs	Regimens
High risk patient*	Ampicillin + Gentamycin	Ampicillin 50 mg/kg, max 2g IV/IM, Gentamycin 1.5 mg/kg, 30 min before procedure, 6 hours later ampicillin 25 mg/kg, IM/IV
High risk patient allergic to penicillin	Vancomycin + Gentamycin	Vancomycin 20 mg/kg, IV over 1-2 hrs + Gentamycin 1.5 mg/kg, 30 min before procedure
Moderate risk patient#	Amoxicillin / Ampicillin	Amoxicillin - 50 mg/kg orally, 1 hour before procedure, or ampicillin 50 mg/kg IV/IM, 30 min before procedure
Moderate risk patient allergic to penicillin	Vancomycin	20 mg/kg IV over 1-2 hours, 30 mins prior to procedure

*Prosthetic valves, previous episodes of endocarditis, complex cyanotic CHDs (TGA, TOF, single ventricle), surgically constructed systemic to pulmonary artery shunts, intravenous drug abuse, indwelling central venous catheters in ICU

#Uncorrected PDA, VSD, bicuspid aortic valves, atrial septal defect (Primum), mitral valve prolapse with regurgitation, rheumatic and aortic valve disease, hypertrophic cardiomyopathy.

Table IV. Drugs recommended for prophylaxis of UTI

Drug	Dosage (mg/kg/day)	Comments
Co-trimoxazole	1-2 of trimethoprim	Avoid in infants < 3 months, in G6PD deficiency
Nitrofurantoin	1-2	Avoid in infants < 3 months, contraindicated in G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in 3-6 months age

Recurrent otitis media

Antimicrobial prophylaxis is recommended for a child who has three or more episodes of acute otitis media in 6 months or four episodes in a year, with the last episode occurring during the past 6 months.[1] Prophylaxis is directed against the most common pathogens Streptococcus pneumoniae, Moraxella catarrhalis and non-typable Hemophilus influenzae.[3]

Amoxicillin 20 mg/kg is given orally in the evening every day for 3-6 months or during the winter months. Along with the prophylaxis other measures should also be taken such as, avoiding smoking in home, limiting day care for the child, discouraging pacifiers and administration of seasonal influenza and conjugate pneumococcal vaccines.

Malaria

The aim of chemoprophylaxis is to prevent the development of malaria in an individual. Prophylaxis for people living in malarious areas is not well established. Chemoprophylaxis with antimalarials for pregnant women is not advocated. Military and paramilitary forces especially on night duty in falciparum endemic areas in India need prophylaxis.[7,8]

Short term prophylaxis (for <6 weeks): Doxycycline 1.5 mg/kg once daily for children above 8 years and 100 mg once daily for adults. The drug should be started 2 days before entry and continued for 4 weeks after leaving the malarious area.

Long term prophylaxis (for longer stay more than 6 weeks): Mefloquine 5 mg/kg (Adults =250 mg) once in a week to be started 2 weeks before entry and continued for 4 weeks after leaving the malarious area. Mefloquine should be avoided in persons with neuro-psychiatric disorders, convulsion or cardiac problems.

Post-exposure prophylaxis

Tuberculosis

Neonates may be exposed to tuberculosis under the following circumstances.[9,10]

- Mother has active tuberculosis when the baby is born - pulmonary or extra-pulmonary.
- Mother has completed treatment but was having the disease while pregnant.
- Neonate exposed to a contact or health care worker with pulmonary tuberculosis.

These neonates should be examined and investigated for active infection. If the neonate is found to be suffering from tuberculosis then treatment should be started.[3] Prophylaxis should be started if active disease is ruled out. Isoniazid 10 mg/kg should be given for 6 months. BCG vaccine should be given. Breast feeding should be continued and isolation is required only if the mother is suffering from drug resistant tuberculosis.

Pertussis

Prophylaxis is indicated for close contacts of a pertussis case such as household members, attendees in childcare facilities and other individuals who are in contact with the index case for 4 hours or more a day.[1] Antibiotic prophylaxis should be given irrespective of age or vaccination status of the individual.[2] People coming in contact with an infected case should be monitored for 2 weeks for respiratory symptoms. Any of the following recommended antibiotics can be used (i) Erythromycin 40-50 mg/kg/day orally in 4 divided doses for 14 days, (ii) Clarithromycin 15 mg/kg/day orally in 2 divided doses for 7 days and (iii) Azithromycin 10 mg/kg on the first day, followed by 5 mg/kg orally from day 2 to 4.

Meningococcal infection

Secondary cases and outbreaks of meningococcal infection are common in close contacts of patients with invasive meningococcal disease. Chemoprophylaxis should be initiated at the earliest, preferably within 24 hours of identification of an index case.[11] Rifampicin 10 mg/kg every 12 hours for 2 days is the recommended regimen. During an outbreak, a single intramuscular injection of ceftriaxone is effective. It should be noted that treatment of meningococcal infection with penicillin, ampicillin or sulphonamides does not eradicate nasopharyngeal carriage.[1] Ceftriaxone and cefotaxime does eliminate carriage. Hence, appropriate prophylaxis must be administered prior to discharge if the patient has been treated with any of the former three drugs.

Diphtheria

Antibiotic prophylaxis is indicated in all household contacts, day care providers and those who had close respiratory and physical contact, irrespective of immunization status.[1] Erythromycin 40-50 mg/kg/day orally in 4 divided doses is recommended for 7 days.

Varicella

Prophylaxis is indicated in neonates whose mothers had chicken pox within 5 days before and 2 days after

delivery. Where varicella zoster immunoglobulin (VZIG) is not available or in neonates exposed to varicella whose mothers have no history of varicella, acyclovir 10-20 mg/kg/dose 4 times per day starting 7 days after exposure and continued for 7 days.[1,2]

Influenza

Immunization against influenza is an effective tool for prevention and antiviral therapy are important adjunct. Indications for chemoprophylaxis are shown in Box 2.[2]

Box 2. Influenza chemoprophylaxis - Indications

- Unimmunized high risk children or children who were immunized less than 2 weeks before influenza outbreak
- High risk children in whom vaccine is contraindicated
- Unimmunized close contacts of high risk children
- Immunocompromised children
- Influenza outbreak in closed setting
- High-risk children when vaccine strain poorly matches the circulating influenza strains

Antivirals do not interfere with the immune response of inactivated influenza vaccine. But antivirals cannot be given within 14 days of live attenuated vaccine. Oseltamivir may be used for prophylaxis, the dose in children and infants are shown in Table V.

Table V. Dose of oseltamivir

Children	
Body weight	**Dose/Frequency/Duration**
< 15 kg	30 mg 2 times daily for 5 days
15-23 kg	45 mg 2 times daily for 5 days
24-40 kg	60 mg 2 times daily for 5 days
>40 kg	75 mg 2 times daily for 5 days
Infants	
< 3 months	12 mg 2 times daily for 5 days
3-5 months	20 mg 2 times daily for 5 days
6-11 months	25 mg 2 times daily for 5 days

Other situations

Asplenia

Asplenia may be congenital or acquired. Overwhelming septicemia and meningitis occur with increased frequency in asplenic individuals. Most of the infections are due to infections caused by bacteria with capsular polysaccharides like Streptococcus pneumoniae and Hemophilus influenzae. Vaccination should be done against these infections at least 2 weeks prior to splenectomy.[2]

Penicillin is the drug of choice for prophylaxis. Penicillin V 125 mg twice daily for children below 5 years and 250 mg twice daily for older children. Erythromycin or co-trimoxazole are alternative options. Prophylaxis should be continued indefinitely.

Human and animal bites

Human and animal bites result in polymicrobial aerobic and anaerobic infections. The common organisms are Staphylococcus aureus, gamma-hemolytic streptococci, Bacteroides spp., Eikenella corrodens, Fusobacterium spp., Pasteurella multocida and anaerobic cocci.[1] Amoxicillin-clavulanic acid 30-50 mg/kg/day for 3-5 days is optimal. Clarithromycin and azithromycin are alternatives.

Surgical prophylaxis

Surgical procedures are classified as clean, clean-contaminated, contaminated and dirty as well as infected wounds.[2]

Clean wounds: Uninfected operative wounds where no inflammation is observed. Respiratory, alimentary, genitourinary tracts and oropharyngeal cavity are not entered. Risk of infection is low (1-2%). Antimicrobial prophylaxis is not justified.

Clean-contaminated wounds: Respiratory, alimentary and genitourinary tracts are entered under controlled conditions with no significant risk of contamination. Prophylaxis is indicated in procedures where a substantial amount of wound contamination is expected.

Contaminated wounds: Tissues are likely to be heavily contaminated in open, fresh accidental wounds, gross spillage from gastrointestinal tract, penetrating trauma of less than 4 hours duration and incision where acute non-purulent inflammation is encountered.

Dirty and infected wounds: Penetrating trauma of more than 4 hours duration, wounds with retained devitalized

Table VI. Recommendation for preoperative antimicrobial prophylaxis

Procedure	Likely pathogen	Recommended drugs and dose
Neonatal	Group B streptococci, Gram-negative bacilli, enterococci	Ampicillin (50 mg/kg) + gentamicin (3 mg/kg)
Cardiac	Staphylococcus epidermidis, Staphylococcus aureus, Coryne-bacterium spp, Gram-negative bacilli	Cefazolin ((25 mg/kg) or vancomycin (10 mg/kg) in suspected MRSA or MRSE
Gastrointestinal	Gram-negative bacilli, Gram-positive cocci, anaerobes, enterococci, clostridia	Cefazolin (25 mg/kg) additionally in high risk situations clindamycin (10 mg/kg) or gentamicin (3 mg/kg) or metronidazole (10 mg/kg)
Genitourinary	Gram-negative bacilli	Ampicillin (50 mg/kg) + gentamicin (3 mg/kg)
Head and neck surgery	Anaerobes, Gram-negative bacilli, Staphylococcus aureus	Gentamicin (3 mg/kg) + clindamycin (10 mg/kg) or cefazolin (25 mg/kg)
Neurosurgery	Staphylococcus epidermidis, Staphylococcus aureus	Cefazolin (25 mg/kg) or vancomycin (10 mg/kg) in suspected MRSA or MRSE
Ophthalmic	Staphylococcus epidermidis, Staphylococcus aureus, gram-negative bacilli, Pseudomonas spp.	Gentamicin, ciprofloxacin, ofloxacin, moxifloxacin, tobramycin multiple drops topically for 2-24 hours before procedure
Orthopedic	Staphylococcus epidermidis, Staphylococcus aureus	Cefazolin ((25 mg/kg) or vancomycin (10 mg/kg) in suspected MRSA or MRSE
Thoracic	Staphylococcus epidermidis, Staphylococcus aureus, gram-negative bacilli	Cefazolin ((25 mg/kg) or vancomycin (10 mg/kg) in suspected MRSA or MRSE
Traumatic wound	Staphylococcus aureus, group A streptococci, Clostridium spp.	Cefazolin 25 mg/kg

tissue and wounds involving existing clinical infection or perforated viscera.

Effective prophylaxis is achieved when adequate drug concentration is present in the tissue at the time of surgery. Accordingly administration is recommended at least 30 minutes before surgical incision.[1] A single dose of the antibiotic that provides adequate tissue concentration during the surgery is sufficient. Redosing every 1 to 2 half-lives of the drug is recommended when surgery is prolonged (more than 4 hours), major blood loss occurs or an antibiotic with short half-life is used The optimal period of prophylaxis should be restricted to less than 24 hours as the critical period for development of infection is short.[2] The antibiotic is chosen on the basis of the most likely bacterial pathogen as shown in Table VI. Routine use of extended spectrum cephalosporins or vancomycin for surgical prophylaxis generally is not recommended.[3]

Points to Remember

- ***Antibiotic prophylaxis is indicated only in certain situations where standard protocols have to be followed.***
- ***Antibiotic used should be narrow spectrum, directed against specific pathogen and used for a short duration.***
- ***In neonates prophylactic antibiotics are used to prevent ophthalmia neonatorum and group B streptococcal infection.***
- ***Prophylactic antibiotics are indicated in certain***

diseases like rheumatic fever, infective endocarditis, urinary tract infection, recurrent otitis media and malaria.

- ***Prophylaxis is also indicated in asplenia, human and animal bites and surgical prophylaxis.***
- ***Post-exposure prophylaxis is used in tuberculosis, pertussis, meningococcal infection, diphtheria, varicella and influenza.***

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CLIPPINGS

Caffeine versus theophylline for apnea in preterm infants

Some evidence that caffeine is as effective as theophylline in the short term for reducing apnea in premature babies is better tolerated and easier to give.

Apnea is a pause in breathing of greater than 20 seconds. It may occur repeatedly in preterm babies (born before 34 weeks). Apnea may be harmful to the developing brain or organs if it continues. Methylxanthines (such as theophylline and caffeine) are drugs that are believed to stimulate breathing efforts and have been used to reduce apnea. The review of trials found that caffeine has similar effects to theophylline but has a larger gap between levels that are therapeutic and those with toxic effects. Caffeine is more easily absorbed and has a longer half-life that allows once daily doses.

Authors' conclusions

Caffeine appears to have similar short term effects on apnea/bradycardia as does theophylline, although caffeine has certain therapeutic advantages over theophylline. The possibility that higher doses of caffeine might be more effective in extremely preterm infants needs further evaluation in randomized clinical trials.

Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD000273. DOI: 10.1002/14651858.CD000273. This version first published online: April 27. 1998.

INFECTIOUS DISEASES

MANAGEMENT OF FEBRILE NEUTROPENIA IN CHILDREN

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Abstract: *Febrile neutropenia in children is a medical emergency. Awareness on part of the caretakers and healthcare system is important. Repeated clinical assessments, radiological studies and cultures are needed to decide further care in these patients. Notable improvement in overall outcome has been reported after early introduction of broad-spectrum antibiotics covering pseudomonas. Coverage for resistant organisms and antifungal therapy is indicated if fever persists. Emergence of multidrug resistant organisms is a threat to survival of these patients. Risk stratification in children is still evolving. It seems possible to treat low risk children as outpatients thus reducing cost and burden on healthcare system while judiciously using antibiotics.*

Keywords: *Fever, Neutropenia, Children, Management*

Outcome of pediatric cancer has improved drastically in the last few decades due to advances in treatment protocols and supportive care. Infection due to chemotherapy-induced neutropenia is the biggest non-malignant cause of mortality in pediatric oncology. Febrile neutropenia occurs in a significant proportion of children receiving intensive chemotherapy and in those undergoing bone marrow transplant.[1] Notable improvement in overall outcome has been reported after early introduction of broad-spectrum antibiotics covering pseudomonas in the 1970s.[2] The spectrum of organisms and their antibiotic susceptibility pattern are taken into consideration while deciding empiric antibiotic therapy in patients with febrile neutropenia. Frequent use of broad-spectrum antibiotics in this patient population has resulted in emergence of infections with multidrug resistant organisms. Therefore, the current emphasis is to risk-stratify patients for optimal and judicious use of antibiotics.[3-5]

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Definitions[3,5]

- **Absolute neutrophil count (**ANC) includes both neutrophils and band cells. ANC is calculated by the formula:

  ANC = % of neutrophils and band cells × Total White Blood Cells Count/ 100

- For febrile neutropenia definition, **neutropenia** is defined as an ANC $<0.5x10^9$ cells/L or $<1 \times 10^9$ cells/L with a predicted decrease to $<0.5 \times 10^9$ cells/L within next 48 hours.

- **Fever** in a neutropenic patient is defined as a single measurement of oral temperature of ≥101°F (38.3°C) or a temperature of ≥100.4°F (38°C) for >1 hour.

Oral temperature is preferred but axillary temperature is acceptable and more practical in children. Axillary temperature is usually 0.5°C lower than oral temperature. Rectal temperature is not recommended in view of possible risk of rectal mucosal trauma and bacteremia.

Neutropenic patients with clinical evidence of infection without fever, also need to be treated like febrile neutropenia. Some children with sepsis may be hypothermic and some others may not have fever due to treatment with steroids as part of their chemotherapy regimen.

Etiology[3,5]

Host defenses against infection include innate and adaptive immunity. There is breach in the immunity among children with cancer due to the disease itself or the treatment.

- Mucocutaneous barriers are disrupted due to use of the central venous catheters, severe mucositis and the procedures needed to diagnose or treat cancer and its complications.

- Normal microflora serves as an extension of mucocutaneous barrier that undergo a change to aerobic Gram-negative organisms within 24 hours of

hospitalization. Approximately 50% of the pathogens causing infection are acquired after hospitalization. Prolonged use of antibiotics may lead to increased risk of fungal infections and antibiotic associated diarrhea.

- Phagocytic cells (neutrophils, monocytes and macrophages) are decreased in number or functionally impaired, due to the hematolymphoid malignancy itself or the chemotherapy, leading to high risk of infections.
- Humoral and cell-mediated immunity is impaired by hematolymphoid malignancy, chemotherapy, steroids, splenectomy and allogenic hematopoietic stem cell transplantation (HSCT).
- Neurological impairment, mechanical obstruction and malnourishment may lead to aspiration pneumonia, colonization of bacteria and impaired immune functions respectively.

Common microorganisms encountered in febrile neutropenic children are depicted in Box1. Extended-spectrum β-lactamase (ESBL) producing Gram-negative bacteria and carbapenemase producing carbapenem resistant organisms (CRO) are the real threats to febrile neutropenic children causing high mortality. Candida and aspergillus may cause fungemia, multiple hepatosplenic lesions, skin nodules and endocarditis. Mucor and aspergillus are common fungal organisms causing sino-nasal infection. Aspergillus may present with typical nodular lesions in lung fields on computerized tomography (CT) scan with ground glass halo sign and typical crescents or cavities. Pneumocystis jiroveci pneumonia (PJP) may show diffuse lung infiltrates on imaging.

Box 1. Common micro-organisms causing infection in febrile neutropenic children[3,5]

- Gram-negative bacilli: *P aeruginosa, E coli, Klebsiella pneumoniae* and *Acinetobacter sp.*
- Gram-positive bacteria: *Staphylococcus aureus*, coagulase negative staphylococci, methicillin resistant *Staphylococcus aureus*, viridans Streptococci, *pneumococcus*, vancomycin resistant enterococcus
- Fungi: *Candida, aspergillus, mucor.*
- *Pneumocystis jiroveci*
- Viral infections: Influenza, herpes, varicella, cytomegalovirus

Box 2. Rapid assessment as per PALS guidelines

Initial Impression

- Consciousness - unresponsive/ irritable/ alert
- Breathing - absent or decreased respiratory effort/ increased work of breathing/ abnormal sounds without auscultation
- Color of the skin- cyanosis/pallor/icterus

Primary assessment

- A rapid ABCDE approach to evaluate respiratory, cardiac and neurologic function
- Vital signs
- Pulse oximetry

Secondary assessment

- Focused medical history
- Focused physical examination

PALS- Pediatric Advanced Life Support; ABCDE- Airway, Breathing, Circulation, Disability, Exposure

Febrile neutropenia is a medical emergency

Parents must be strictly instructed not to treat the child on their own based on symptoms at home. They must have access to the health care facility as soon as possible (ideally within 2 hours) for any symptom especially fever.

Immediate assessment in emergency room[3,5]

In the emergency room, neutropenic children must get priority for immediate assessment and initiation of antimicrobial agent. Initial impression, primary and secondary assessment must be done as per pediatric advance life support (PALS) guidelines (Box 2). Additional information about type and status of the malignancy, date and intensity of the chemotherapy, prior prophylactic or outpatient antibiotics, and recent trends of blood counts in the patient should be obtained during secondary assessment. Secondary assessment should include search for a focus of infection including central line exit site and tunnel infections, mucositis and perianal infections. Fever may be absent in children with severe prolonged neutropenia and infection, but pain is not masked. Hence, any painful site must be examined and followed up closely.

Laboratory evaluation

1. **Complete blood count:** It is mandatory to have recent blood count (hemoglobin, white blood cells, differential count, platelet count) to define febrile neutropenia and risk stratification. The physician must look at the trends

in blood counts and expected recovery time (based on primary diagnosis, intensity and the time since chemotherapy, trends in blood counts, monocyte count,etc.)

2. **Biochemical tests:** Liver function, kidney function and electrolytes to assess seriousness of organ damage.
3. **Blood Culture:** Obtain blood culture from each lumen of an existing central line as any of the lumens might have been colonized. Consider peripheral blood culture concurrently with central line cultures to differentiate bacteremia from catheter colonization alone. Peripheral blood culture is mandatory if no central line is used. Consider 2 blood cultures from different peripheral venipuncture sites to differentiate bacteremia from skin contamination.[3] In all cases, strict aseptic precautions are necessary to avoid contamination of the sample. Pediatric specific blood culture bottles are recommended.
4. **Urine culture and urinalysis:** Consider obtaining urinalysis and culture if patient has urinary symptoms. Absence of pus cells in the urine of a neutropenic child does not rule out urine infection.
5. **Chest radiograph** is indicated only in symptomatic patients.
6. **Other culture samples** (e.g. pus, fluid, swab, scraping, tissue) can be considered as clinically indicated.
7. **Inflammatory markers** (C-reactive protein - CRP, interleukin-6, procalcitonin): Not routinely recommended but are used in febrile neutropenia to assess risk status by some groups.[6,7] A baseline low interleukin-6 may suggest low risk group and a rising CRP may suggest high risk of documented bacteremia or fungal infection.[8]

Risk stratification

Though there is no uniformly accepted validated criteria for risk assessment in children with febrile neutropenia, the physician should have an idea about risk group of the child based on the type of malignancy, intensity of chemotherapy, expected duration of neutropenia and comorbidities (Box3).[3,4] According to unpublished data presented in SIOP (International Society of Pediatric Oncology) meeting 2015 at Capetown, South Africa, PGIMER (Post Graduate Institute of Medical Education and Research) Chandigarh, is in process of prospective validation of scoring system in Indian children. They included 5 high risk features with total score of 13-undernutrition (2), time from last chemotherapy <7 days (2), Non-URI (upper respiratory infection) focus of infection (2), ANC <100/cmm (2), and CRP >60 mg/L (5). A score of <7 had robust performance in identification of low risk group.

Box 3. High risk features[4]

- Younger age (<5 years)
- Acute lymphoblastic leukemia on induction
- Acute myeloid leukemia
- Burkitt's lymphoma
- Bone marrow relapse in leukemia
- First 30 days of allogenic hematopoietic stem cell transplantation
- Non-URI focus of infection, vomiting, abdominal pain, severe mucositis
- Altered mental status, hypotension, hypoxia (SpO_2<94%), renal or hepatic insufficiency
- Presence of central venous catheter
- Anticipated duration of neutropenia more than 7 days
- Profound neutropenia (ANC<$0.1x10^9$ /L), absolute monocyte counts <$0.1x10^9$/L
- New chest X-ray findings
- CRP more than 50 mg/L

ANC- absolute neutrophil count; CRP- C-reactive protein; URI- upper respiratory infection

Initial management[3-5]

Recommendations for high-risk patients:

- Immediate initiation of antipseudomonal broad-spectrum antibiotic monotherapy is recommended (Fig.1).
- Aminoglycosides such as amikacin or gentamicin can be added as per sensitivity patterns of the blood culture isolates in the institution, in clinically unstable children or those likely to have infection with resistant gram-negative organism.
- Methicillin-resistant S. aureus (MRSA) coverage with glycopeptide antibiotic such as vancomycin is indicated in children with hypotension, severe mucositis, skin, subcutaneous or soft tissue infection, pneumonia, suspected central line related infection and previous history of documented MRSA infection.
- In our practice, we start piperacillin-tazobactum and amikacin as first line antibiotics for high-risk patients.

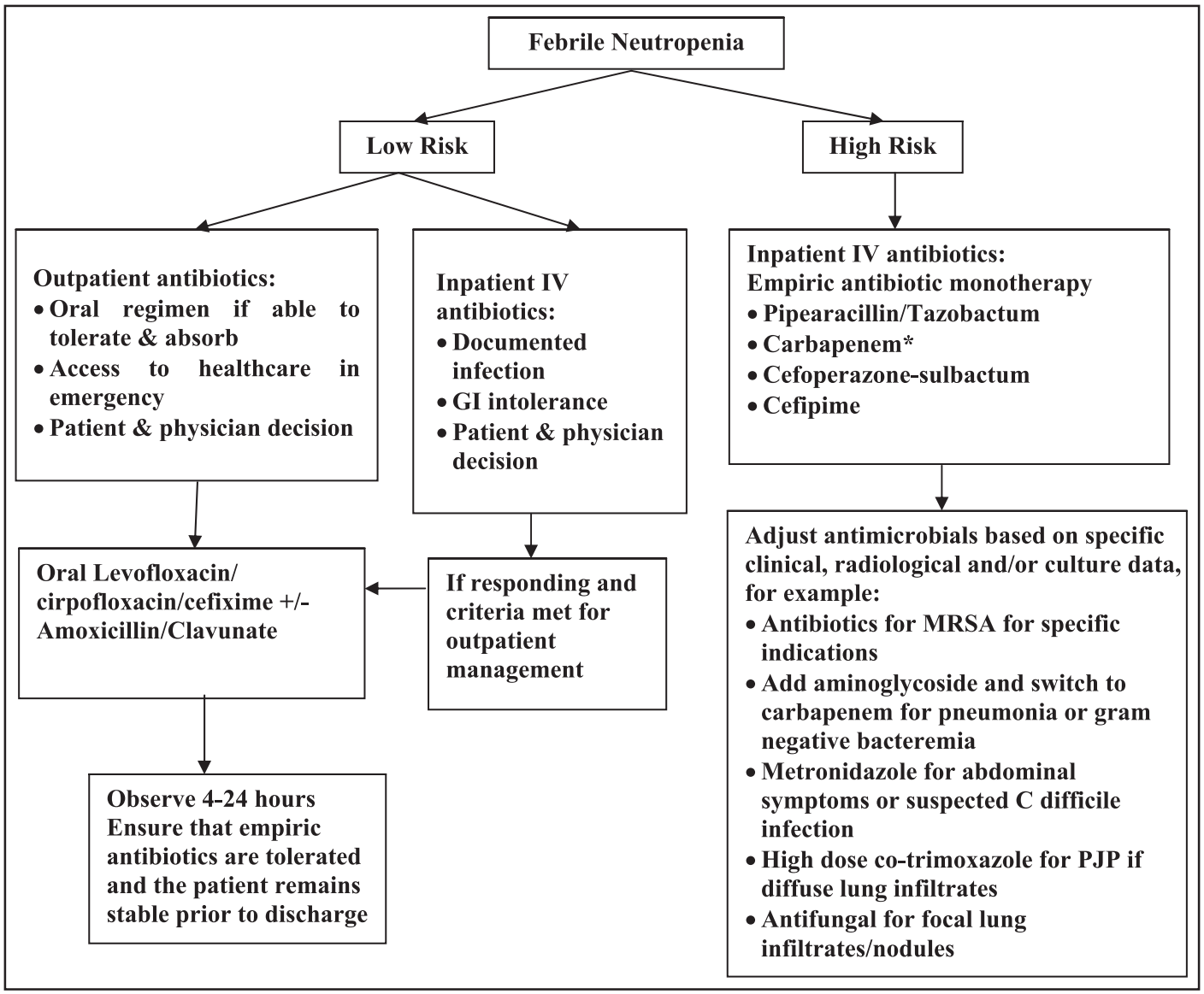

Fig.1. Initial management of febrile neutropenia.[3-5] IV=intravenous; GI=gastrointestinal; MRSA=Methicillin resistant Staphylococcus aureus; PJP=Pneumocystis jiroveci pneumonia. *Carbapenems are usually used as second line chemotherapy at most of the centers.

Meropenem is used as second line agent or in cases of hypotension or suspected meningitis. Colistin is reserved for use in infections with proven or suspected CRO after discussion with pediatric infectious disease team.

Recommendations for low risk patients

- Consider initial outpatient management with oral antibiotics like amoxicillin-clavulanic acid, ciprofloxacin/ levofloxacin/ofloxacin or cefixime provided oral intake is reliable and the child has immediate access to the healthcare in case of deterioration. At least 4-24 hour of observation is recommended. This approach reduces cost of treatment and burden on busy health care systems in developing countries.[9]
- Those who are unable to take oral antibiotics or where accessibility to medical care is doubtful, intravenous antibiotic therapy is recommended. There are studies showing effectiveness and safety of 24 hourly ceftriaxone and amikacin combination and 12 hourly cefipime on an outpatient basis.[10,11] Early step down of antibiotics and change to oral medication after 24 hours can be considered provided patient is stable.
- Further prospective studies are required to find optimum management strategy for low risk children.

Twenty four to seventy two hours after initiation of empiric therapy[3,4]

A) For patients responding to the initial empiric therapy:

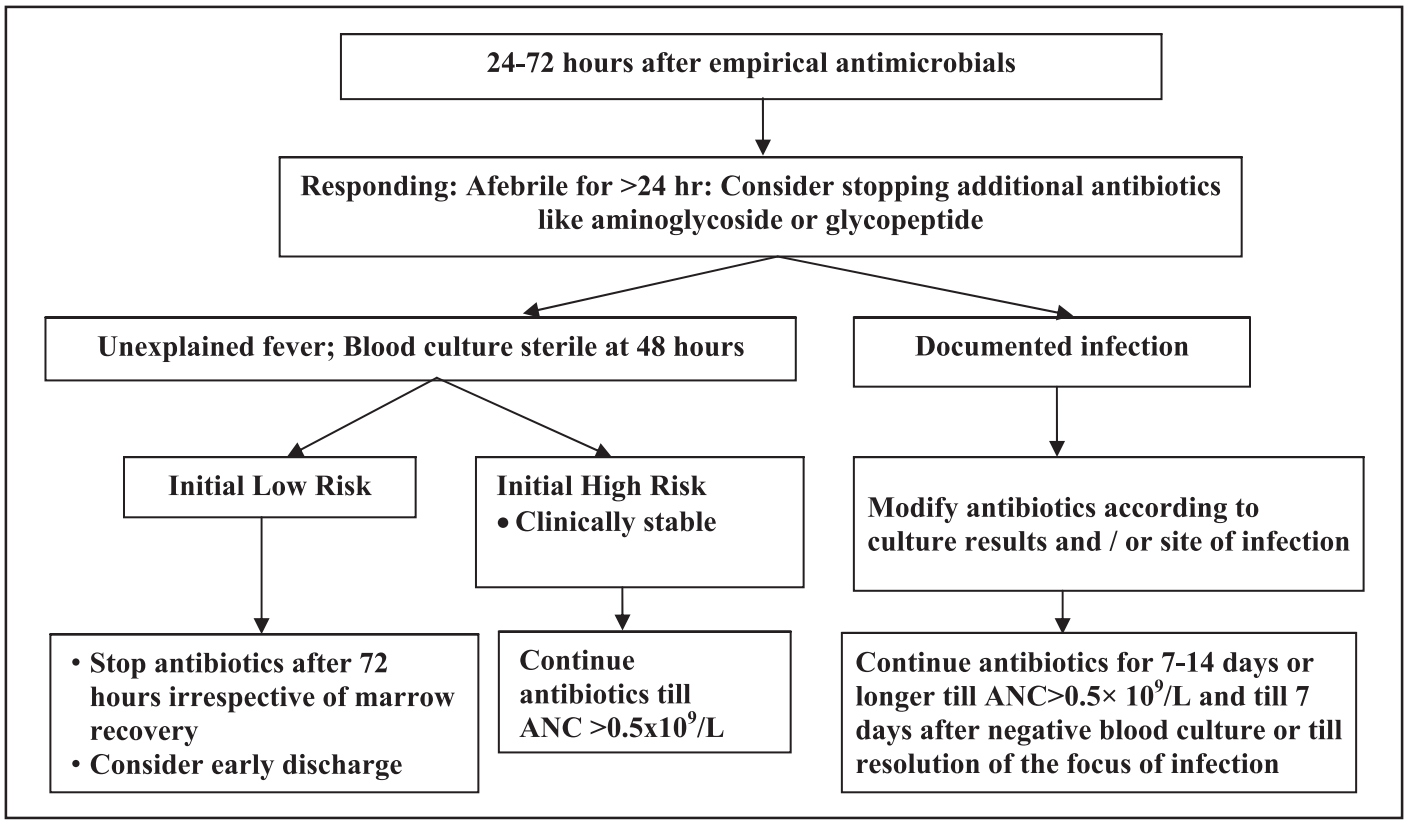

Fig.2. Management of febrile neutropenia if responded within 24-72 hours of empirical antimicrobials.[3-5] ANC= absolute neutrophil count.

- Consider stopping aminoglycoside or glycopeptide antibiotic if there is no microbiological indication to continue the same.
- In general, physician needs to decide duration of antibiotics based on initial risk status, response to treatment, marrow recovery, focus of infection and culture results as per algorithm depicted in Fig.2.
- Physicians must assess the patient thoroughly before making step-down decisions.

B) For patients not responding to the initial therapy:

- For documented infections, modify antibiotics according to clinical scenario, focus of infection and culture results (Fig.3).
- In cases of unexplained fever in a **clinically stable child**, aggressive escalation of antibiotics is not recommended. A continuous watch on clinical scenario along with repeated search for focus of infection clinically, radiologically and by repeated cultures may help further decisions.
- In case of unexplained fever in a **clinically unstable child**, escalate or add antibiotics to cover resistant Gram-negative organisms such as ESBL+ organisms,CRO and resistant Gram-positive infections (Table-I).[12-15]
- Examine thoroughly for new foci of infections at least twice daily, repeat bacteriological cultures, imaging such as ultrasound abdomen, chest X-ray/CT and ECHO cardiogram as clinically warranted.
- Consider empirical administration of high dose co-trimoxazole for diffuse lung infiltrates (for *Pneumocystis jiroveci*) and amphotericin-B for focal lung infiltrates (for fungal pneumonia).[5]
- Treat antibiotic associated diarrhea (C. difficile infection) with metronidazole or vancomycin.[3]
- Consider addition of antibiotics for atypical organisms such as chlamydia and mycoplasma.
- Consider epidemiologically prevalent infections like dengue or influenza during outbreaks.
- Appropriate supportive care is mandatory to maintain oxygen saturation, perfusion, fluid and electrolyte balance. Blood components must be transfused as needed.

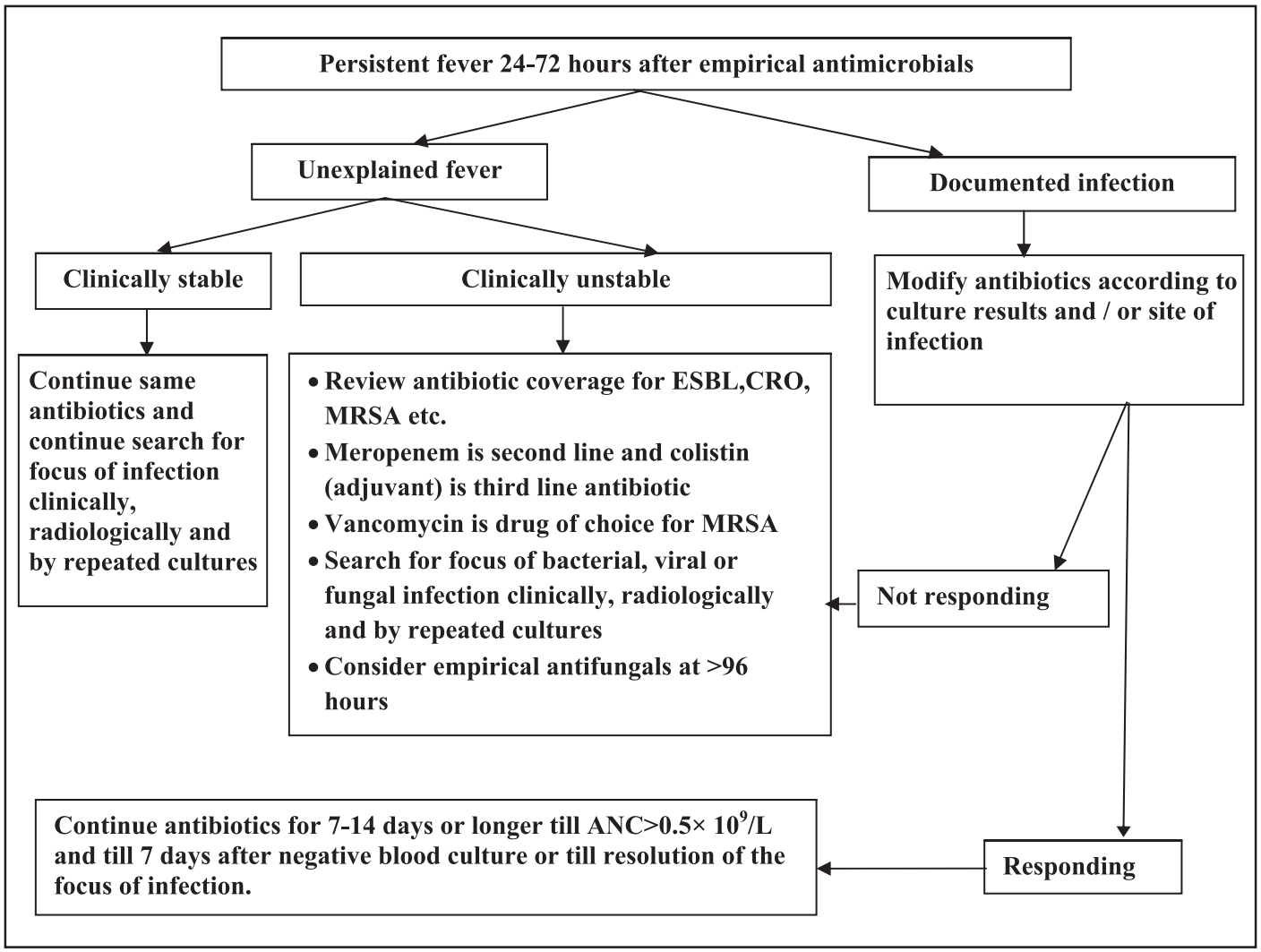

Fig.3. Management of febrile neutropenia if not responded within 24-72 hours of empirical antimicrobials.[3-5] ANC= absolute neutrophil count.

Table I. Choice of antimicrobials against specific resistant organisms

Type of infection	1st choice	Alternative choice(s)
ESBL[12]	Meropenem	Ceftolozane-tazobactam, Ceftazidime-avibactam, nitrofurantoin, fosfomycin, tigecycline, cefipime at higher doses, ciprofloxacin
CRO[13-15]	Colistin with meropenem or tigecycline	Aztreonam, aminoglycosides (Gentamicin for Klebsiella- pneumoniae and amikacin for others), ciprofloxacin, fosfomycin, nitrofurantoin
MRSA[3,5]	Vancomycin	Teicoplanin, linezolid, daptomycin
VRE*[3,5]	Linezolid	Daptomycin

*Vancomycin-resistant enterococci

Persistent fever beyond 96 hours of empirical therapy

- In general, continuous search for focus of infection (by history, examination, chest X-ray/CT, ultrasound abdomen, 2D-echoand repeated blood cultures) is important in children having persistent fever spikes irrespective of neutropenia status.
- In case of persistent fever, assess risk factors for invasive fungal disease (IFD).
- Empiric antifungal therapy is recommended for IFD high risk and needs consideration in IFD low risk children.[3,4]

High risk for IFD

- Febrile neutropenic children with AML, relapse ALL, solid tumours, patients receiving highly myelosuppressive chemotherapy, allogenic bone marrow transplant patients
- Fever persistent more than96 hours on empirical antibiotics
- Expected duration of neutropenia more than10 days. Diagnosis of IFD is given in Box.4

Box 4. Diagnosis of IFD

- Blood, broncho-alveolar lavage (BAL), scraping, swabor tissue microscopy/culture
- CT of thorax and other suspected regions (CT of the sinuses can be considered in children more than 2 years of age. Role of routine CT scan of sinuses and abdomen in an asymptomatic child is uncertain)[4]
- Ultrasound screening of liver and spleen
- 2D-echo for vegetations
- Galactomannan in serum, BAL and cerebrospinal fluid to support diagnosis of aspergillosis (may give false positive results due to use of piperacillin-tazobactam)

Empiric treatment of IFD

- Caspofungin or liposomal amphotericin-B are the empiric antifungals of choice in febrile neutropenia.
- In resource-restricted setting, conventional amphotericin-B is still commonly used. Infusion reaction, nephrotoxicity and hypokalemia are more common side effects encountered with the use of conventional amphotericin-B.
- A less expensive form of liposomal amphotericin-B (fungisome) is marketed in India.This preparation needs a 45 minutes procedure called 'sonication' which leads to conversion of large multilamellar vesicles to small unilamellar vesicles thus leading to higher number of particles per mg of amphotericin-B, better drug delivery to target site and lesser nephrotoxicity.
- Other lipid formulation of amphotericin-B includes amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion, the latter causes more infusion reactions than conventional preparation resulting in cessation of at least one clinical trial.[16] More experience of use of ABLC is needed in febrile neutropenia setting.

Other antifungal agents

- Voriconazole is the drug of choice for aspergillus infection. It is relatively well tolerated and available in both intravenous and oral formulation. It has no activity against mucormycosis. Hence, it should not be used for empirical treatment.
- Fluconazole is inherently resistant to some candida species (C. krusei and C. glabrata) and it has no activity against aspergillus or mucor. Hence, it is also not a good choice as empirical agent.

Doses of commonly used antimicrobial agents are presented in Box 5.

Central line associated blood stream infection (CLABSI)

- CLABSIs are suspected if there are signs of inflammation at exit site, tunnel infections or if patient develops fever with or without rigors when line is accessed.
- Blood cultures should be sent from each of the lumen of the existing central venous access device as well as a peripheral blood sample.
- Empiric antibiotic therapy should be initiated to cover both Gram negative and Gram-positive infections including MRSA.
- Infected central line must be removed as soon as possible in following situations[3,5]
  - *S. aureus*, *P. aeruginosa*, fungal or mycobacterial infection
  - Tunnel infection or port pocket site infection
  - Septic thrombosis, endocarditis
  - Sepsis with hemodynamic instability
  - Blood stream infection that persists for more than 72 hours despite therapy with appropriate antibiotics

Box 5. Dosage of antimicrobials commonly used in febrile neutropenia[3,4,5]

- Piperacillin-tazobactam 300mg/kg/day q8h
- Cefipime 100 mg/kg/day q8h
- Cefoperazone-sulbactam 100mg/kg/day q8h
- Meropenem 60-120 mg/kg/day q8h (high doses for CNS infection or severe infection)
- Amikacin 15-20 mg/kg/day
- Gentamicin 6 mg/kg/day
- Vancomycin 25-40 mg/kg/day q6-12h (60 mg/kg/day divided in 3 doses in meningitis or severe infection)
- Teicoplanin 10-12 mg/kg/day q12h for 3 doses, then q24h
- Linezolid 20 mg/kg/day q12h
- Colistin 50000-75000 IU/kg/day q8h
- Fluconazole 3-12 mg/kg/day (higher doses for life threatening infection)
- Amphotericin-B 0.5 mg/kg/day empirical; 1-1.5 mg/kg/day for documented infection
- Liposomal Amphotericin-B 3-5 mg/kg/day (Fungisome 1-3 mg/kg/day)
- Voriconazole 3mg/kg/dose 12 hourly empirical; 4 mg/kg/dose for documented infection 12 hourly (higher doses of oral formulations are necessary in children to achieve comparable adult drug exposures; ideal to monitor drug levels)
- Caspofungin 75 mg/M^2 loading followed by 50 mg/ M^2/day
- Acyclovir 750 mg/ M^2/day for HSV; 1500 mg/ M^2/day for VZV divided in 3 doses
- Ganciclovir 5mg/kg 12 hourly for 14 days followed by 5 mg/kg/day maintenance
- Trimethoprim-sulfamethoxazole 5 mg/kg/day divided in 2 doses 2-3 times a week for PJP prophylaxis; 20 mg/kg/day in 2 divided doses for treatment
- Dapsone 2mg/kg/day (max 100mg) for PJP prophylaxis

- The patient should receive a minimum of two weeks of appropriate antibiotics after removal of central line. More prolonged antibiotics are needed for complicated CLABSI (deep tissue infection, endocarditis, or septic thrombosis) or persistent blood stream infection after appropriate antimicrobial therapy.[3]

Antiviral prophylaxis and treatment: Respiratory virus testing and chest X-ray are indicated for the patients with upper respiratory tract infection. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive empirical treatment with oseltamivir. Infectious diseases society of America (IDSA) recommends flu vaccine every year even during chemotherapy (preferably 7 days after and 2 weeks before chemotherapy). IDSA also recommends antiviral prophylaxis with acyclovir in herpes simplex virus (HSV) seropositive patients undergoing allogenic HSCT or leukemia induction chemotherapy.[3] HSV and Varicella zoster virus needs treatment with acyclovir in case of active disease. Any ocular symptom must be evaluated for possible cytomegalovirus chorioretinitis as immediate treatment with ganciclovir may save vision in the eye.

Role of prophylactic antimicrobials: *Pneumocystis-jiroveci* prophylaxis with trimethoprim-sulfamethoxazoleis recommended in all cases. If allergic/ intolerant to trimethoprim, dapsone, atovaquone and aerosolized pentamidine can be used. Prophylaxis against candida with fluconazole or other azoles is recommended by IDSA in patients with acute leukemia on induction chemotherapy or in patients undergoing HSCT.[3] Prophylaxis against aspergillus with voriconazole or posaconazole is indicated in patients more than 13 years of age with acute myeloid leukemia on intensive chemotherapy. Use of other prophylactic antibiotics is controversial due to risk of emergence of resistance. Hence, its use must be guided by institutional guidelines and protocols.[5]

Use of granulocyte colony stimulating factor (GCSF): Prophylactic use of GCSF is recommended for the patients in whom anticipated risk of febrile neutropenia is more than 20%. It has been shown to reduce infection related mortality and is cost effective if given prophylactically. Though used frequently, therapeutic use of GCSF in established febrile neutropenia has not shown any survival benefit.[3]

Environmental prophylaxis: Hand hygiene, barrier precautions and cutaneous asepsis are key measures for prevention of CLABSI and other infections in neutropenic cases. Room ventilation with more than 12 air exchanges/hour and HEPA filtration and use of neutropenic diet further help to reduce risk of infection.[3]

Points to Remember

- ***Febrile neutropenia is a medical emergency.***
- ***Early administration of broad-spectrum intravenous antibiotics is required to improve outcome.***

- ***Reassess the patient regularly to look for foci of infection.***
- ***Periodic review of spectrum of bacteremia and antibiotic susceptibility pattern in each institution will guide clinicians in choosing appropriate empiric antibiotics.***

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CLIPPINGS

Neuroimaging and neurodevelopmental outcome in extremely preterm infants.

The authors prospectively evaluated MRI white matter abnormality (WMA) and cerebellar lesions, and serial cranial ultrasound (CUS) adverse findings as predictors of outcomes at 18 to 22 months' corrected age. Outcomes included neurodevelopmental impairment (NDI) or death, with NDI defined as cognitive composite score <70, significant gross motor impairment, and severe hearing or visual impairment.They concluded that both late CUS and near–term MRI abnormalities were associated with adverse outcomes (NDI or death), independent of early CUS and other factors, underscoring the relative prognostic value of near-term neuroimaging.

Hintz SR, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. Pediatrics 2015;135(1):e32-42. doi.10.1542/peds 2014-0898.

INFECTIOUS DISEASES

BONE AND JOINT INFECTIONS IN CHILDREN

***Sankar R**

Abstract: *Though there is no change in the incidence of bone and joint infections in India, there is a change in the epidemiology and clinical manifestations of these conditions due to the emergence of community acquired methicillin-resistant Staphylococcus aureus infections. The primary aim is to diagnose the condition early by imaging, appropriately use antibiotics and perform meticulous surgical intervention when necessary. Isolating the pathogen and obtaining a culture sensitivity report is critical for choosing appropriate antibiotic therapy. The effects of infection in children may last well beyond the acute episode and long term follow up is needed to identify joint deformity or limb length discrepancy.*

Keywords: *Osteomyelitis, Staphylococcus aureus, MRSA, Septic arthritis*

Osteomyelitis and septic arthritis are the commonest causes of a child presenting with a limp to a pediatrician. A high index of suspicion and careful clinical assessment are essential if one is to avoid the numerous problems that can accompany these conditions. Incidence of bone and joint infections in children has not changed in India over the last 20 years. During this period, changes in the epidemiology due to emergence of community acquired MRSA infection, newer imaging modalities and molecular diagnostic facilities have impacted the clinical manifestations, diagnosis and management of bone and joint infections. Before the antibiotic era, morbidity and mortality were more common. Since the advent of antibiotics, emphasis has shifted from survival to limb preservation. With recent advances in management, normal function and growth of affected limb should be maintained even after bone and joint infections. This is possible only if the diagnosis is made early and appropriate treatment is begun promptly. Late presentation cannot be controlled, but delay in diagnosis will affect child's ability to function normally.

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Acute hematogenous osteomyelitis (AHO) has been defined as an inflammation of bone caused by pyogenic organisms settling from the blood stream, their presence being proven by culture or their effect on bone, being demonstrated radiographically.[1] Acute septic arthritis is the inflammation of a joint caused by pus forming organisms.

Acute hematogenous osteomyelitis

The estimated annual incidence of AHO in children younger than 13 years is 1 in 5000, with the majority of cases occurring in children younger than 5 years (Fig.1). Staphylococcus aureus is the most commonly identified pathogen in all age groups, accounting for 70% to 90% of culture-positive cases of AHO. Children with underlying disease such as sickle cell disease or injury may also be predisposed to infection with specific organisms (Salmonella sp., Staphylococcus aureus in sickle cell disease or Pseudomonas auroginosa in foot puncture wounds). Infection with obscure or multidrug resistant organisms may occur under unusual circumstances, including immune-deficient states, prolonged hospitalization with multiple invasive procedures and residing in endemic environments. Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) has recently emerged as a major factor in the changing epidemiology of musculoskeletal infection in many parts of the world.

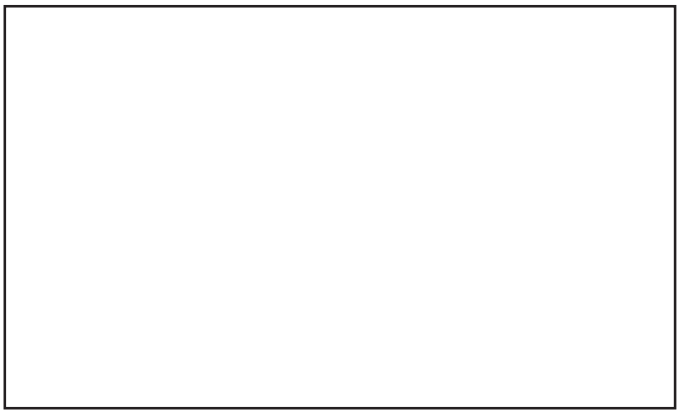

Fig.1. Frequency of Osteomyelitis and Septic arthritis according to age

The commonest site of involvement in AHO is the metaphyseal ends of the long bones, especially distal femur and upper tibia. Bacteria can be introduced into bone by hematogenous spread from bacteremia, local invasion from

a nearby infection or direct inoculation from a penetrating trauma, such as an open fracture or foot puncture wound. The reason for the increased incidence of metaphyseal end involvement is the sluggish blood flow in the capillaries. Typically, acute hematogenous osteomyelitis in children begins in the metaphyseal venous sinus, where there are vascular loops and terminal branches with low oxygen tension and inhibited phagocytosis that is conducive to bacterial growth. Trauma may play a role in up to 30% of the cases of acute hematogenous osteomyelitis.

Diagnosis

Diagnosis of acute osteomyelitis is mostly clinical. In any child presenting to a clinician with fever and pain in the end of long bones, osteomyelitis should be considered as one of the most important differential diagnosis. Other conditions that may present with clinical symptoms and signs mimicking this disorder, include extraosseous infection, trauma and neoplasia.

The onset of acute hematogenous osteomyelitis is usually sudden and up to 50% of patients have had a recent or have a concurrent non-muscular infection.[1] Children are usually ill and show the cardinal signs of inflammation, swelling, redness, warmth and pain. The main clinical symptoms and signs in acute hematogenous osteomyelitis (AHO) are pain and tenderness over the affected bone especially in the metaphyseal region. They might even present with pseudoparalysis or adjacent sympathetic joint effusion. However, in a neonate the clinical presentation may be subtle and misleading.

Neonatal osteomyelitis

Neonatal osteomyelitis presents in two distinct varieties. The first is seen in neonates and infants of 2 weeks to 8 weeks of age presenting with restriction of movement or visible swelling of an extremity. Diagnosis and treatment may be delayed in this age group because fever and irritability are usually not present.[2] Laboratory studies and their radiographic evaluation may be equivocal as well. Because of these issues, a high index of suspicion must be maintained. Staphylococcus aureus is the most commonly identified organism in this age group. Other common organisms include those encountered during the childbirth process, such as Streptococcus agalactiae (group B streptococcus), enterococci and enterobacteriaceae (Escherichia coli, Proteus species, Klebsiella species). The second type of neonatal osteomyelitis is encountered in the neonatal intensive care unit, typically in low-birth-weight neonates requiring endotracheal intubation, positive-pressure ventilation, intra-arterial or intravenous lines or umbilical artery or vein cannulation.[3]

Investigations

Routine screening laboratory tests remain useful in the initial assessment of a child with suspected bone infection. The white blood cell count, erythrocyte sedimentation rate and the C-reactive protein (CRP) are all usually elevated. In some studies, osteomyelitis caused by community acquired methicillin resistant Staphylococcus aureus (CA-MRSA) is associated with higher ESR values and CRP concentrations compared to community acquired methicillin sensitive Staphylococcus aureus (CA-MSSA) osteomyelitis. CRP is a very useful marker not only for the diagnosis but also for monitoring the response. Blood cultures should be performed in all suspected cases and are positive in about 30% to 50% of patients. The availability of PCR has increased the recognition of Kingella kingae (K kingae) as a cause of bone and joint infections. Plain radiography continues to be an essential first step in the evaluation of suspected osteomyelitis and may on occasion be the only imaging study required for diagnosis and treatment.[4] It may not reveal any abnormality if done at early stage of osteomyelitis. Ultrasound is often used in the diagnosis and its usefulness stretches to guided aspiration of deep space fluid.[5,6] CT scan shows non-specific changes early and proves more useful for detecting extra-osseous deep soft tissue swelling or abscesses as well as the sub-acute or chronic forms of infection that may be confused with a neoplasm. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) should be considered as a useful diagnostic tool in children with suspected AHO, if conventional diagnostic imaging techniques have failed to yield positive results.[7]

Another imaging study that may be helpful is the technetium-99m-diphosphonate bone scan, a three-phase scan that usually demonstrates increased uptake as a result of alteration in physiology of involved bone. An abnormal technetium bone scan is non-specific and may yield false positive results associated with trauma or tumours. There is a possibility of false negative results especially when there is osteonecrosis or in very early OM. A bone scan is best used to identify AHO in multiple or difficult locations like spine and pelvis.[8]

Magnetic resonance imaging is now considered the optimal imaging technique for assessing osteomyelitis. MRI is more sensitive than radionuclide bone scan or plain films in detecting osteomyelitis. It can also detect extraosseous manifestations or complications of acute osteomyelitis such as the presence of a sub-periosteal abscess and contiguous septic arthritis much more readily than conventional imaging studies. It is also the most useful

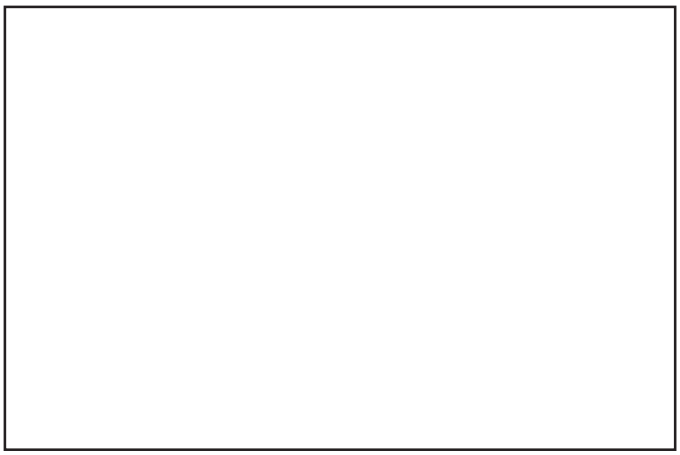

Fig.2. CT scan shows evidence of osteomyelitis of shaft of right femur, whereas MRI shows multifocal involvement at femoral shaft and acetabulum on right side

imaging modality for AHO especially if involving the axial skeleton[8] (Fig.2).

Management

Management of AHO begins with the intravenous administration of an antibiotic to cover the most likely causative organism until a more specific antibiotic can be chosen based on culture and sensitivity results[9] (Table.I).

Staphylococcus aureus is still the predominant organism in all age groups. MRSA accounts for significant percentage of such infections which is a testament of excessive and inappropriate use of antibiotics in the community.[10] Gram negative organisms form a very small fraction of these infections. In children with allergy to penicillin group of antibiotics, clindamycin is recommended because of its superior intraosseous concentration compared to vancomycin. Because of lack of availability of cloxacillin, cefazolin (100mg/kg/day divided q8h) may be the preferred initial therapy for MSSA with changeover to oral cephalexin later. Neonatal osteomyelitis requires the addition of an aminoglycoside or the use of a third-generation cephalosporin to cover gram-negative organisms. Culture-negative osteomyelitis can be managed the same way as for methicillin-susceptible S. aureus (MSSA).

De-escalation: Traditionally 3-4 weeks of intravenous antibiotics were used prior to switching to oral antibiotics. A case can be made for earlier transition to oral antibiotics if the child's condition clearly has improved and is afebrile for 48 to 72 hours[9] (Table II). CRP is a useful investigation to monitor progress of the disease; it rises faster and returns to normal more quickly than ESR and is the laboratory investigation of choice when following infants and children being treated for AHO.[11]

Duration: The total duration of antibiotics for treatment of MRSA osteomyelitis is usually 4-6 weeks while for others it is approximately 3 weeks.[12]

If a child does not respond to antibiotics within 36 hours, then surgical debridement should be considered. The surgical technique for patients with established osteomyelitis includes periosteal incision and removal of all exudates and necrotic bone. Placement of long term intravenous access like a percutaneous long line or portacath should be considered under the same anesthetic procedure.

Table I. Antibiotics used in osteomyelitis and septic arthritis

Situation	Likely Causative Organism	Initial Treatment
Neonates	S.aureus (MSSA) Group B Strep E. Coli	Nafcillin 50-100mg/kg/day in two to three divided doses* + Broad spectrum cephalosporin eg. Cefatoxime 150-225mg/Kg/day divided q8h. Vancomycin instead of nafcillin (If MRSA suspected)
Older children	S. aureus Grp A strep	Vancomycin (If MRSA suspected/critically ill child) 60mg/Kg/day divided q6h (or) Clindamycin (child not severely ill, no bacteremia and blood culture negative) 40mg/Kg/day divided sq8h + Ceftriaxone (Gram neg. cover)
Open injury	S. aureus Anaerobes	Clindamycin 40mg/Kg/day divided q8h

*If nafcillin not available cloxacillin 100-200mg/kg/day q6h IV or Cefazolin 100mg/kg/day q8h IV

Table II. Antibiotics used for de-escalation in osteomyelitis and septic arthritis

For susceptible staphylococci and streptococci	Cephalexin 80 -100mg/kg/day divided q8h
For clindamycin susceptible CAMRSA or penicillin allergy	Clindamycin 30 -40mg/kg/day divided q8h
For clindamycin resistant CAMRSA	Linezolid 20 – 30mg/kg/day divided q12h

Septic arthritis

Septic arthritis (SA) in children can occur in any joint, but the most common and devastating location is the hip. Incidence is estimated to be between 5.5 and 12 cases per 100,000 children with a peak incidence in the early years of the first decade.[13] Most cases of septic arthritis occur in children younger than 3 years of age. Boys are affected twice as much as girls as they are probably more likely to be involved in activities leading to repetitive minor trauma.

The hip and knee are the most common sites of septic arthritis with symptoms of acute onset of joint pain, fever, irritability and limp.[14] Septic arthritis can occur from primary seeding of the synovial membrane, secondarily from infection in the adjacent metaphyseal bone or directly from infection in the adjoining epiphysis. In the hip, vessels cross the epiphysis until the age of approximately 18 months and this provides a direct route for infection to spread from the metaphysis to the hip joint. Destruction of the articular cartilage begins quickly and is secondary to proteolytic enzymes released from synovial cells. Interleukin-1 triggers the release of proteases from chondrocytes and synoviocytes in response to polymorphonuclear leukocytes and bacteria. Degradation results in the loss of proteoglycans at five days and of collagen by nine days. Impairment of the intra-capsular vascular supply also plays a role in the articular destruction, with elevation of the intra-capsular pressure, thrombosis and progressive displacement of the femoral head from the acetabulum (Fig.3&4).[1]

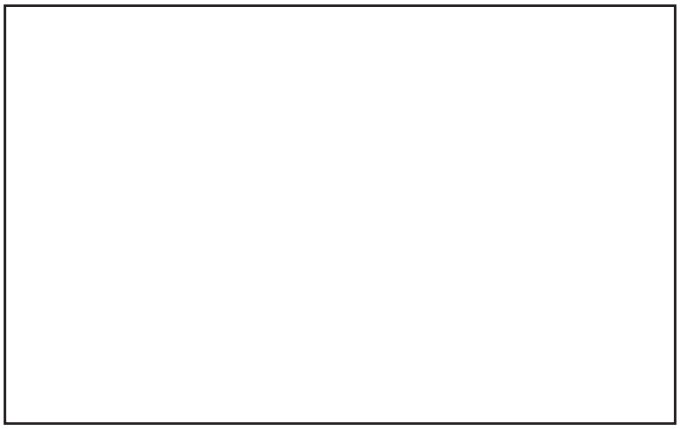

Fig.3. One month old child with right hip septic arthritis

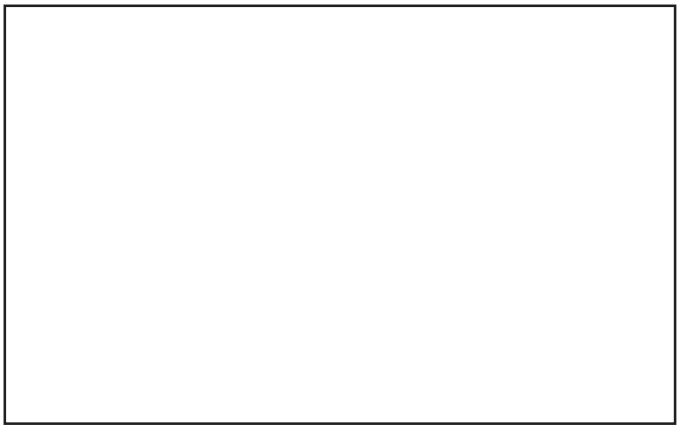

Fig.4. Septic arthritis, with dislocation of right hip

Staph aureus is again the commonest organism with MRSA seen sometimes. Due to excellent immunization, H influenzae type b has almost ceased to be a causative organism in children. K kingae is relatively a common cause of osteoarticular infection, primarily septic arthritis in children under 5 years of age. The exact frequency of K kingae bone and joint infections is difficult to determine because the organism is somewhat difficult to isolate using routine techniques. When polymerase chain reaction (PCR) techniques are applied to culture negative specimens from patients with presumed septic arthritis or acute osteomyelitis, K kingae has been identified in a high percentage of cases for younger children. In one study from France, K kingae was the most common cause of osteoarticular infection (OAI) in young children; the most frequent site of K kingae septic arthritis was the knee and sternum was the most common site for osteomyelitis. A model to allow the differentiation of *K kingae OAI* from those due to typical pathogens in children aged less than 4 years, has been described and consists of the following four parameters: Temperature at admission below 38°C ; C-reactive protein less than 55 mg/L; WBC less than 14,000 /mm^3 and band forms <150 /mm^3.[15]

Diagnosis

As it is with AHO, a high degree of suspicion is necessary in children presenting with acute onset of joint pain, irritability, fever and anorexia. In septic arthritis involving the lower limb, there will be a limp or refusal to

Table III. Differences between transient synovitis and septic arthritis

Features	Transient synovitis	Septic arthritis
General condition	Normal	Irritable
Local Examination	Painful passive range of movement of joint	Painful range of movement, warmth and tenderness
Fever	No	Present
WBC count	<12000	>12000
ESR/ CRP	Normal	Elevated
X-ray	Normal	Displaced periarticular fat pad
Ultrasound	Minimal effusion	Large effusion
Management	Rest and analgesia	Drainage and antibiotics
Sequelae	Self-limiting	Destruction of joint and growth plate

bear weight. When the hip is affected the child typically holds the joint in a position of flexion, abduction and external rotation (FABER), as the intra-capsular pressure increases. Swelling of the anterior aspect of the thigh is a late sign.[16] Neonates may display anorexia, irritability and lethargy and may not move the affected limb (pseudoparalysis). Transient synovitis can mimic septic arthritis and is difficult to distinguish clinically. The former requires bed rest and pain relief, while the latter requires aggressive antibiotic and surgical treatment in many cases (Table III).

Kocher et al, developed four clinical criteria to aid in the assessment of a child with a painful hip. A history of fever, difficulty in weight bearing, along with an erythrocyte sedimentation rate greater than 40 mm/h and a peripheral white blood cell (WBC) count of more than 12,000 cells/µL were independent variables that best distinguished SA from transient synovitis.[17] The probability of SA was 99.6% for children with all 4 factors and 93.1% for those with any 3 factors. Recently CRP has been used instead of ESR. In another series, none of the children with transient synovitis had fever and fever was found to be the most influential predictor in distinguishing between these two conditions.[18]

Investigations

Laboratory tests including CRP, total white cell count and ESR are typically raised. Blood cultures can help in some of these cases. CRP is probably the most useful marker both at the time of diagnosis and for follow up.

Imaging studies are important as a diagnostic tool and this includes a plain radiography, ultrasound and MRI scan. Ultrasonography is quick and painless and presence of hip effusion points to the suspicion of septic arthritis. It is difficult to assess presence of pus or simple effusion in ultrasound, but absence of an effusion makes septic arthritis less likely. Ultrasonography is also a useful tool for guiding aspiration and confirming needle location.

Osteomyelitis and septic arthritis clinically present at any age with overlapping signs and symptoms. Monsalve, et al in their study noted that in children who underwent MRI for suspected musculoskeletal infection, septic arthritis was more prevalent in children less than 2 years of age. However, both septic arthritis and osteomyelitis were found frequently in older children. Musculoskeletal infection imaging workup guidelines for children of all ages should address the frequent association of osteomyelitis and septic arthritis. It is recommended that MRI should be used in the evaluation of suspected musculoskeletal infections in children and the nearest joint should always be included to evaluate the extent of articular disease.[19]

Treatment

To ensure a good prognosis, treatment of septic arthritis not only requires prompt recognition and rapid and aggressive antimicrobial therapy, but primarily surgical irrigation of the joint in order to clear the factors responsible for the potent activation of the immune response. The cornerstone of treatment is surgical drainage and irrigation of the involved joint with appropriate constitutional support, including hydration and antibiotics. The antibiotic regimen should be started immediately after aspiration. It should initially be based on the suspected organism and

later tailored to the sensitivity reports. Intravenous antibiotics should be continued until the symptoms resolve. Recent reports suggest that children with septic arthritis treated early with a short course of adjuvant dexamethasone show earlier improvement in clinical and laboratory parameters than children treated with antibiotics alone.[20] If there is a co-existent osteomyelitis, that should dictate the duration of antibiotics, both IV and oral.

Acute septic arthritis of childhood is a potentially devastating disease that causes permanent disability and can result in death. Traditional treatment consisted of a prolonged course of intravenous antibiotics combined with aggressive surgery. However, this approach is challenged by trials showing satisfactory outcomes with shorter treatment and less invasive surgery. Diagnostic arthrocentesis alone and antibiotics for a fortnight, including initial intravenous administration for 2-4 days, suffice in most children beyond neonatal period. A good penetrating agent, such as clindamycin or a first-generation cephalosporin, in exceptionally high doses, administered four times a day are probably key factors. If the symptoms and signs subside within a few days and the serum C-reactive protein level drops below 20 mg/L, the antibiotic can usually be safely discontinued.[20]

It must be remembered that the effects of infection in children may last well beyond the acute episode and long term follow up is needed for deformities of joints and limb length discrepancy.

Points to Remember

- ***Staph. aureus, CA-MRSA and K kingae are common pathogens for osteomyelitis and septic arthritis.***
- ***MRI is the diagnostic imaging modality of choice for osteoarticular infections.***
- ***Early diagnosis and management will result in better outcome.***
- ***Identifying the causative pathogen by blood or tissue culture is important for selecting the more appropriate antibiotic therapy.***
- ***Switching to oral antibiotics when there is evidence of clinical improvement along with falling CRP is an accepted mode of therapy in older children.***
- ***Long term follow up is needed for any deformities of joints and limb length discrepancy.***

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CLIPPINGS

Abdominal radiography is not necessary in children with intussusception

The aim of this study was to investigate the benefit of Abdominal Radiography (AR) in intussusception by determining diagnostic accuracy and analysing correlation of AR findings with outcome. In this study AR is not recommended for the diagnosis of intussusception in children, for the prediction of the outcome of pneumatic reduction of intestine (PRI) or for the detection of occult pneumoperitoneum. AR should always be performed when there are features of clinical peritonitis but is not otherwise necessary in children with suspected or confirmed intussusception.

Tareen F, Mc Laughlin D, Cianci F, Hoare SM, Sweeney B, Mortell A, Puri P.Abdominal radiography is not necessary in children with intussusception. Pediatr Surg Int. 2015 Nov 6. [Epub ahead of print].

NEWS AND NOTES

International Conference on Paediatric Gastroenterology, Hepatobiliary, Transplant and Nutrition: Controversies and Consensus – New Dimensions to Expore, Jaipur, India.

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INFECTIOUS DISEASES

INFECTIVE ENDOCARDITIS

*Anita Khalil

Abstract: *Infective endocarditis is a serious infection, associated with significant morbidity and mortality and it is increasingly being recognised in children and adolescents. Infective endocarditis is defined as an endovascular infection of cardiovascular structures. However, due to the occult nature of the disease, the treating physician should have a high index of suspicion to make an early diagnosis, so as to institute prompt and appropriate antibiotic therapy for optimal outcome and prevent disease related complications.*

Keywords: *Infective endocarditis, Children.*

Infective endocarditis (IE) is one of the most dreaded complications of structural heart disease and is associated with considerable morbidity and mortality.

It is defined as an 'endovascular microbial infection of cardiovascular structures'.[1] William Osler was the first to describe infective endocarditis in 1885 and then on, many advances have been made in the diagnosis and therapy. Native or prosthetic heart valves are the most frequently involved sites but the infection can also involve septal defects, mural endocardium or intravascular devices such as intra-cardiac patches, surgically constructed shunts and intravenous catheters. Because of the occult nature of the disease, the treating physician should have a high index of suspicion so that treatment can be started at the earliest.

Epidemiology

At least 70% of IE cases occur in children with congenital heart disease (CHD). But in the last two decades, a number of cases of neonatal IE have been reported in structurally normal heart with vegetations being right sided.[2] This is because of increased use of prosthetic indwelling intravascular catheters in NICU. Children with underlying cardiovascular disease may develop endocarditis at any age and mortality due to IE ranges from 16% to 25%[3,4] and almost 20% require emergency surgery.[5]

Incidence of endocarditis may be increasing in recent years because of increased use of indwelling catheters, valves and prosthetic tubes during any surgery. Pressure gradients pose a particularly high risk for IE, e.g., VSD, PDA, MR, tetralogy of Fallot and bicuspid aortic valve (Box 1). In a review of studies between 1986-1995, estimated incidence of IE in children was 0.3/ 1,00,000 children per year with a mortality of 11.66%.[6]

Box 1. Risk factors for infective endocarditis

High Risk

- Prosthetic valves
- Previous episodes of endocarditis
- Complex cyanotic CHDs (TGA, TOF, single ventricle)
- Surgically constructed systemic to pulmonary artery shunts
- Intravenous drug abuse
- Indwelling central venous catheters in ICU

Moderate risk

- Uncorrected PDA, VSD
- Bicuspid aortic valves
- Atrial septal defect (Primum)
- Mitral valve prolapse with regurgitation
- Rheumatic and aortic valve disease
- Hypertrophic cardiomyopathy

Pathogenesis

A complex interaction between host, vascular endothelium, hemostatic response and circulating bacteria results in IE as described below.

1. The important factors in the pathogenesis of infective endocarditis are presence of structural abnormality of heart and great vessels with a significant turbulence (resulting in endothelial damage and platelet fibrin thrombus formation) and bacteremia, even if it is transient.

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2. Presence of underlying heart disease (e.g.) bicuspid aortic valve / mitral valve prolapse or HOCM, which is usually asymptomatic, may be a precipitating factor.
3. Those with prosthetic valves or prosthetic material in the heart are particularly at high risk for IE (Box 1).
4. Any localized infection, abscess, osteomyelitis and tissue manipulations like dental, cardiac, gastro intestinal, genital urinary procedures predispose to bacteremia and subsequent IE.
5. The greater the turbulence of flow around a cardiac lesion, e.g., VSD, TOF, higher is the risk of IE. The high turbulence damages the endothelium predisposing to platelet and fibrin deposition. This subsequently becomes infected to form vegetations (Fig.1).

Microbiology

The bacteria most frequently responsible for endocarditis such as Streptococcus viridans have a propensity for adherence to human or canine valves.[7] Gram positive cocci have a predilection for subendocardial connective tissue, i.e., fibronectin that gets exposed when endocardium is damaged to which Gram negative organisms adhere rather poorly. Systemic gram positive cocci account for 90% of IE with hemolytic streptococci being the commonest causative organism and staphylococci (S. aureus and coagulase negative staphylococci) form the second largest group.[8] Prevalence of definite IE due to S.aureus was approximately 12% and possible IE was 20% (Table I).[9] This is probably due to infected intra ventricular device.

Gram negative organisms (esp. Hemophilus species) predispose to endocarditis in neonates, immune compromised patients and drug addicts. Fungal endocarditis (Candida, histoplasma, cryptococcus) is resistant to treatment and may occur in neonates, where it may be a complication following intensive care interventions (Table I). Mortality due to fungal endocarditis is high, even with intensive medical or surgical therapy.[10]

Clinical manifestations

Fever is the most common finding in all children having endocarditis with the exception of neonates. When the causative organism is hemolytic streptococcus, the fever is low grade (subacute) but when the organism is Staphylococcus aureus, the fever is high grade (acute) with toxic manifestations.

Acute presentation: Acute infective endocarditis has a fulminant course with high spiking fever, rapidly deteriorating cardiac function with cardiogenic shock necessitating urgent and appropriate therapy. It causes rapid destruction of heart valves, abscess formation and hence is associated with significant morbidity and high mortality. Staphylococcus aureus is the usual causative agent.

Subacute presentation: Clinical features seen are prolonged low grade fever, headache, weight loss, fatigue, arthralgia, myalgia**,** exercise intolerance, diaphoresis and often microscopic hematuria (a feature of immunologically mediated glomerulonephritis). Petechiae are present over the skin of the extremities or mucous membrane of palate and hemorrhages may also be seen on the palpebral conjunctiva. Other rare manifestations include Roth spots in the retina, Janeway lesions over palms and soles and Oslers nodes in the pulp of fingers or toes.[11]

In neonatal endocarditis, signs and symptoms are non-specific and they include feeding intolerance, tachycardia and respiratory distress, hypotension and changing murmurs. Fever is usually absent and persistent positive blood culture may be the only clue to the diagnosis. Fungal endocarditis is common in newborns and may present as septicemia and heart failure.

Fig.1. Evolution of infected vegetation on a traumatized valve

Table I. Etiologic agents with specific predisposing factors

Common organism	Predisposing factors
Staphylococcus aureus	Native valves (acute fulminant process with high mortality)
Streptococcal viridans Group D enterococci Coagulase negative staphylococcus	Dental procedures Lower bowel or genitourinary manipulation Indwelling central venous catheter and use of high glucose concentrations, parenteral nutrition especially in premature infants
Pseudomonas aeruginosa Fungi	Intravenous drug users Open heart surgery

Fig.2. Vegetations attached to aortic and mitral valves : (A) Trans-esophageal echocardiographic (TEE) images demonstrating a vegetation attached to the non-coronary cusp of the aortic valve in systole. (B) Apical four-chamber view demonstrating a large vegetation attached to the anterior mitral leaflet in a patient with mitral stenosis

Diagnosis

Diagnosis of IE is straight forward in patients with classical manifestations: bacteremia, active valvulitis, peripheral emboli and immunologic vascular phenomenon. A diagnostic strategy has been developed (Duke criteria - Box.2) that uses a combination of clinical, pathologic, microbiologic and echocardiographic findings (Fig.2). A rapid diagnosis is of critical importance for the survival of the affected child.[12]

Management

Management includes: 1. Antimicrobial therapy, 2. Surgery if indicated and 3. Monitoring for complications.

Antimicrobial therapy

In acutely ill children: Three to four blood cultures have to be taken at one hourly interval in the first 24 hours preferably during the febrile period. After the blood culture has been sent, bactericidal antibiotics must be started intravenously to reduce the possibility of treatment failure or relapse. It is generally directed to the most common pathogens namely streptococci, staphylococci and enterococci. Duration of therapy in native valve endocarditis ranges from 2 to 6 weeks. Infection of prosthetic valves and tissue and infection with highly virulent or more resistant pathogens may require antibiotics for 6-8 weeks.[14]

Guidelines recommended by American heart association (AHA) are summarized as follows:

1. Penicillin susceptible streptococcal endocarditis (PSSE) on native cardiac valve
   - Penicillin for 4 weeks or
   - Penicillin or ceftriaxone combined with gentamicin for 2 weeks

Box 2. Modified Duke criteria for diagnosis of infective endocarditis[13]

Definite Infective Endocarditis

1. Pathologic criteria

a. Micro-organism: Demonstrated by culture or histologic examination of a vegetation/embolized vegetation/ abscess.

Or

b. Pathologic lesions: Vegetation or intracardiac abscess.

Confirmed by histology showing active endocarditis.

2. Clinical criteria

a. 2 major criteria or

b. 1 major and three minor criteria

c. 5 minor criteria

Possible

1. 1 major and 1 minor criterion or
2. 3 minor criteria

Rejected

1. Firm alternate diagnosis for manifestations of endocarditis.
2. Resolution of manifestations of endocarditis with antibiotic therapy in <4 days.
3. No pathologic evidence of infective endocarditis at surgery or autopsy, etc with antibiotic therapy for <4 days
4. Does not merit criteria for possible IE as above.

2. Penicillin resistant streptococcal endocarditis (PRSE) on native cardiac valve
   - Penicillin or ampicillin or ceftriaxone for 4 weeks combined with gentamicin for first 2 weeks
3. PSSE on a prosthetic valve or other prosthetic material:
   - Penicillin or ampicillin or ceftriaxone for 6 weeks combined with gentamicin for first 2 weeks
4. PRSE on a prosthetic valve or other prosthetic material:
   - Penicillin or ampicillin or ceftriaxone for 6 weeks combined with gentamicin for first 2 weeks; vancomycin can be used in patients who do not tolerate penicillin or ceftriaxone
5. Susceptible enterococcal infection on native valves: Penicillin or ampicillin combined with gentamicin for 4-6 weeks
6. Susceptible enterococcal on prosthetic material: Should be treated for at least 6 weeks
7. Methicillin susceptible S. aureus (MSSA) infection on native valves: Nafcillin or oxacillin for at least 6 weeks with optional gentamicin for 3-5 days
8. Methicillin resistant S.aureus (MRSA) infection on native valves: Vancomycin for at least 6 weeks with 3-5 days of gentamicin
9. MSSA infection on prosthetic tissue - Naficillin or oxacillin plus rifampin for 6 weeks in combination of gentamicin for 2 weeks
10. MRSA- Infection on prosthetic tissue - Vancomycin plus rifampin for at least 6 weeks in combination with gentamicin for 2 weeks
11. Gram negative endocarditis caused by HACEK organisms – Ceftriaxone or ampicillin plus gentamicin for 4 weeks

Linezolid or daptomycin are options for patients with intolerance to vancomycin or resistant organisms. Substitution of linezolid for vancomycin should be considered in patients with unstable renal function, because of difficulty of achieving therapeutic levels. Repeat blood cultures and ESR are necessary tools for monitoring progress, though clinical response is often sufficient. Use of recombinant tissue plasminogen activator to lyse intracardiac vegetations in severely ill patients has been mentioned in literature. Rest of the therapy includes (e.g.) digitalis, diuretics, ACE inhibitors, potassium supplementation and salt restricted diet as indicated.[15]

Fungal endocarditis

Fungal endocarditis is a complication with high morbidity and it occurs mostly in those patients with immune compromised status, on prolonged antibiotic therapy and also in those with cardiac devices, e.g., prosthetic valves or central venous catheters. Treatment with anti-fungal drugs is almost always unsuccessful and surgical excision of valve and infected tissue is required along with anti fungal treatment. Amphotericin B remains the most effective antifungal agent though it is severely nephrotoxic and renal function and potassium levels should be monitored carefully. Maintenance dose of 1mg/kg for 6-8 weeks should be given followed by oral anti-fungal agents like fluconazole. The total duration of therapy may be 1 year or more if surgical intervention is to be done.

Surgery

About one fifth of patients require surgery in acute phase. Indications for surgery are as follows:

1. Valvular dysfunction: Leading to resistant congestive heart failure, paravalvular necrosis and abscess, aortic dissection or valvular orifice obstruction because of large vegetation (>10mm)
2. Persistent bacteremia despite adequate antimicrobial therapy for 10-14 days
3. Fungal endocarditis
4. Repeated systemic embolization
   - Single major embolus, systemic, coronary, pulmonary or cerebral
   - Echocardiographic demonstration of large vegetation
   - Extension of infection to an annular or myocardial abscess
5. Pathogens which are difficult to eradicate with medical therapy alone (e.g.) Pseudomonas aeruginosa, brucella, etc
6. Leaflet perforation or sinus of Valsalva aneurysm
7. Prosthetic valve dysfunction like valve dehiscence

Post-operatively, a full course of antimicrobial therapy starting from the time of surgery is indicated depending on the culture sensitivity of the operated valve / tissue cultures. An approach to the management of native and prosthetic valve andocarditid is given in Fig.3.

Prophylaxis

Because of high rates of morbidity and mortality, endocarditis can often be prevented by repairing the underlying cardiac defect and successful surgical repair of certain cardiac conditions will reduce or eliminate the risk of endocarditis.

The American Heart Association has put forward new preventive guidelines in 2007. It has been concluded that bacteremia resulting from daily activities is more likely to cause IE than bacteremia associated with dental procedures. Prophylaxis is suggested only for patients with underlying cardiac conditions associated with highest risk for developing IE (Box 3).

Maintenance of optimal dental care and oral hygiene is important for prevention of endocarditis in children with underlying cardiac disease. Patients in whom prosthetic valves or other devices are to be placed should undergo needed dental procedure to establish optimal oral hygiene before cardiac surgery.

Antibiotic prophylaxis is also recommended for procedures on respiratory tract or infected skin, skin structures or musculoskeletal tissue, but not genito-urinary (GU) or gastrointestinal (GI) procedures for those patients with underlying cardiac conditions associated with the highest risk of IE (Table II).

Prophylaxis is most effective when given peri-procedurally, starting shortly before a procedure. Streptococcus viridians remains the most common cause of endocarditis following dental, oral or upper respiratory tract procedures.

Box 3. Cardiac conditions for prophylaxis

I. Cardiac conditions associated with the highest risk for developing endocarditis following dental procedure.
   - Prosthetic cardiac valve
   - Previous IE
   - Congenital heart disease
- Unrepaired cyanotic CHD including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or devices, whether placed by surgery / catheter intervention during first 6 months of the procedure.
- Repaired CHD with residual defect at the site of a prosthetic patch / device
- Cardiac transplant recipients with cardiac valvulopathy.
   - Rheumatic heart disease - prosthetic valve / material used in valve repair.

II. Prophylaxis not needed
   - ASD, VSD, PDA
   - Mitral valve prolapse
   - Previous Kawasaki disease
   - Hypertrophic cardiomyopathy
   - Previous coronary artery bypass graft (CABG), cardiac pacemakers / implanted defibrillators, bicuspid aortic valve, coarctation of aorta, calcified aortic stenosis, pulmonic stenosis

Table II. Prophylactic regimens for dental, oral or respiratory tract procedures

	Agent	Regimen (single dose 30-60min before procedure)
Standard oral prophylaxis	Amoxicillin	50mg/kg po (max 2gm)
Unable to take oral medication	Ampicillin or Cefazolin or Ceftriaxone	50mg/kg IM or IV (max 2gm) or 50mg/kg IM or IV (max 1gm)
Allergic to penicillin or ampicillin (Oral)	Cephalexin or Clindamycin or Azithromycin / Clarithromycin	50mg/kg (max 2gm) 20mg/kg (600gm) 15mg/kg (500gm)
Allergic to penicillin or ampicillin and unable to take orally	Cefazolin or Ceftriaxone or Clindamycin Phosphate	50mg/kg IM or IV (1gm) 20mg/kg IM or IV

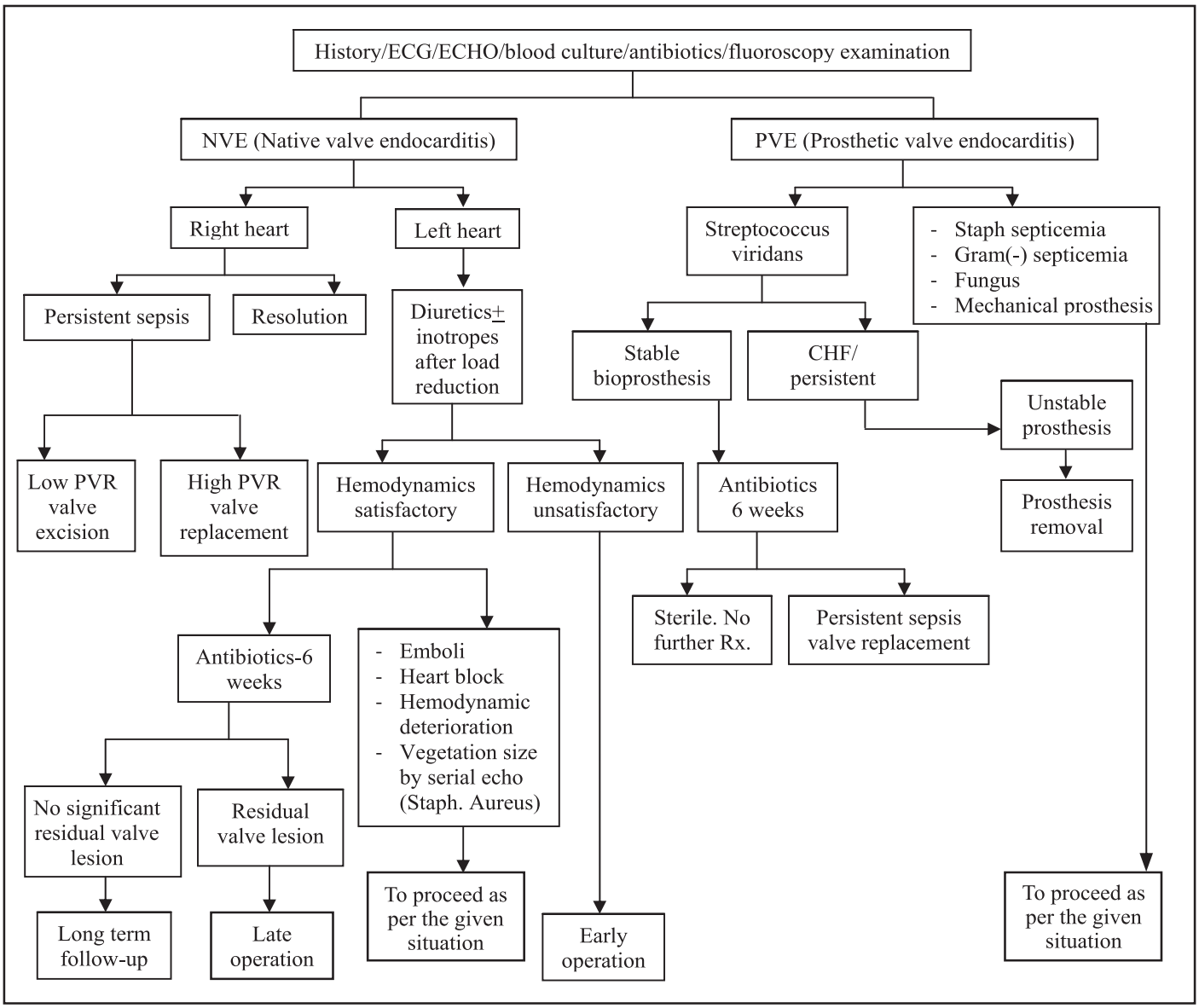

Fig.3. Presentation and management of native and prosthetic valve endocarditis

Children who are receiving penicillin prophylaxis for recurrence of rheumatic fever, may have hemolytic streptococci in the oral cavities which are resistant to penicillins. In such cases, a macrolide or clindamycin should be selected for IE prophylaxis. In addition, prophylaxis should also be used against Staph aureus and coagulase negative staphylococci.

Finally, new AHA recommendations note the importance of good oral hygiene as an important factor in preventing IE in susceptible patients and urge clinicians to educate their patients in this regard.

Complications

Complications arise either due to embolization of vegetation, local extension of infection or rupture / perforation of local structure.

Complications are common in following conditions:

1. Children <2 years of age
2. Cyanotic congenital heart disease
3. Prosthetic cardiac valves
4. Endocarditis due to Staph aureus or fungus
5. Prolonged clinical symptoms >3 months
6. Left sided endocarditis
7. Patients with systemic to pulmonary shunts

Points to Remember

- ***Most children with infective endocarditis (IE) have an identifiable risk factor for the disease. It should be part of a differential diagnosis of a persistent febrile or inflammatory illness, particularly if there are pre- existing cardiac lesions.***
- ***Diagnosis of IE is based on clinical findings, positive blood cultures, laboratory results and an echocardiogram.***
- ***The modified Duke's criteria is the most commonly used among several available diagnostic criteria for IE.***
- ***Principles of management of IE in children are adequate antibiotic therapy, timely surgical intervention in selected cases and monitoring for complications.***
- ***Despite the use of potent antibiotics, serious morbidity occurs in 50%-60% and mortality in 20%-25%.***

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INFECTIOUS DISEASES

SYSTEMIC FUNGAL INFECTIONS AND THEIR MANAGEMENT

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Abstract: *Despite recent advances in medicine, advent of newer antifungal drugs and widespread use of prophylaxis in high risk groups, invasive fungal infections continue to remain a significant health problem. One of the most difficult challenges in treating fungal infections is the early identification of invasive infections and initiation of effective antifungal therapy since clinical manifestations can be highly variable and related to host immunity. Since fungi are ubiquitous and opportunistic, fungal infections in immunocompromised can be fatal, and investigations may have to be repeated to confirm the diagnosis.*

Keywords: *Systemic fungal infections, Children, Immunocompromised*

Advances in medical practice have resulted in increase in the number of severely ill, immunocompromised and hospitalized patients, thereby leading to increasing incidence of local and systemic fungal infections. The HIV epidemic, improved survival rates of children with immunodeficiency, malignancies and transplantation have also added to this growing at-risk population. The clinical manifestations being non-specific, a high degree of suspicion is required for early diagnosis and management.

General characteristics of fungi

Fungi are ubiquitous organisms living as environmental saprophytes or commensals in humans and animals. Isolation of the organism from clinical samples may indicate colonization, infection or disease, making the interpretation of results challenging. Morphologically they are distinguished into yeasts (unicellular) and moulds (multicellular). Some species known as dimorphic fungi can be found as yeasts or moulds depending on the temperature and substrate on which they develop.

Based on their pathogenic role, they can be divided into (a) Primary pathogens: Dimorphic fungi such as histoplasma and coccidioides, which can infect immune competent hosts and (b) Opportunistic pathogens: Yeasts and moulds such as candida, cryptococcus, aspergillus, zygomycetes and fusarium which cause morbidity in immunocompromised hosts. Based on the route of acquisition, infecting fungi may be exogenous or endogenous. Moulds have their natural habitat in the environment and hence cause exogenous infections by the inhalation of air spread conidia. Yeasts can be endogenous as well exogenous. Endogenous yeasts colonize mucosa, causing invasion and disease in post-chemotherapy induced mucositis and in immunocompromised hosts. Exogenous yeasts are commensals of skin and invade via contaminated catheters. The common species causing deep fungal infections are given in Table I.

According to the site and degree of tissue involvement, these fungi are classified as cutaneous, subcutaneous, superficial and deep mycosis - a) Superficial mycoses: Limited to stratum corneum, caused by the fungi dermatophytes, eliciting no inflammatory response (b) Cutaneous mycoses: Involve the integument and its appendage (c) Subcutaneous mycoses: Affect subcutaneous tissues usually at the point of traumatic inoculation of the etiological agent (d) Deep mycoses: involve multiple systems and organs.

According to the European Organization for Research and Treatment of Cancer/Mycoses study group (EORTC/MSG), the diagnosis of invasive fungal infection can be classified as proven, probable and possible.[1] (a) Proven: When there is histopathological proof of infection and positive culture of a specimen from a normally sterile site (b) Probable: When there are existing host factors, clinical manifestations and radiological features with microbiological evidence (c) Possible: When there are only existing host factors and clinical manifestation.

Role of immunity against fungal infections

Th1 mediated immunity clears the fungal infection,

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Table I. Common species causing deep fungal infections

Dimorphic fungi	Blastomycosis	Blastomyces dermatitidis
	Coccidioidomycosis	Coccidioides immitis
	Histoplasmosis	Histoplasma capsulatum
	Paracoccidioidomycosis	Paracoccidioides brasiliensis
Opportunistic fungi	Aspergillosis	Aspergillus spp
	Systemic candidiasis	Candida spp
	Cryptococcosis	Cryptococcus neoformans/gattii
	Mucormycosis (Zygomycosis)	Rhizopus, Absidia, Mucor

Th2 mediated immunity is responsible for the susceptibility to infections.[2] Functional defects of phagocytosis predispose to invasive fungal infections by the opportunistic candida and aspergillus and alterations in T lymphocytes cause mucocutaneous candidiasis and invasive infections by Cryptococcus neoformans[3]. Many of the neoplastic diseases like Hodgkins lymphoma, hairy cell leukemia and chronic lymphocytic leukemia are associated with malfunctioning of the cell mediated immunity. Corticosteroids, a main component of chemotherapy result in further impairment of cellular immunity. Immunological defects constitute a major risk factor for pulmonary involvement in children. Severe combined immunodeficiency and Wiskott Aldrich syndrome cause high mortality when they develop pulmonary fungal infection.[4] The populations at risk for invasive fungal infections are listed in Box 1.

In children with cancer, the important risk factors for fungal infections are indwelling catheters, chemotherapy induced mucositis, broad spectrum antibiotic usage and therapeutic use of steroids. Candida and aspergillus are the most common etiological agents in these population. The risk factors and various clinical presentation of various fungal infections are given in Table II.

Common diagnostic methods of fungal infections

Despite the scientific progress and newer diagnostic tools, diagnosis of fungal infections are still complex.

Culture: Though the microscopic identification and cultures are the gold standard, it is difficult to obtain appropriate specimens and cultures have a long turnaround time. The need for invasive techniques to obtain appropriate specimens in sick patients and the high likelihood of negative yield make diagnosis by cultures even more difficult.

Box 1. Populations at risk for invasive fungal infections (IFI)

- Preterm neonates with prolonged ICU stay
- Extremely low birth weight babies
- Children with :
  - Congenital immune deficiencies and acquired immune deficiencies
  - HIV infection
  - Cancer
  - Chemotherapy
  - Chronic lung diseases
  - Chronic kidney disease
  - Severe burns
  - Diabetes mellitus
  - Long term indwelling central line catheters
  - Long term parenteral nutrition
  - Long term broad spectrum antibiotics
  - Long term corticosteroids
  - Bone marrow and solid organ transplantation
  - Malnutrition

Galactomannan test: Galactomannan is a polysaccharide found within the cell wall of aspergillus and is released into the extracellular fluid during hyphal growth and cell wall turnover. Its sensitivity is high in neutropenics (93%). The sensitivity of bronchoalveolar lavage (BAL) galactomannan is up to 100% in neutropenics and 90% in non-neutropenics.[5] However, usage of certain antibiotics like piperacillin-tazobactum and amoxicillin with clavulanic acid may lead to false positive results.

Table II. Risk factors and clinical presentation of individual fungal infections

Fungal agents	Risk factors	Clinical presentation
Candida : Candida parapsilosis Candida albicans Candida glabrata Candida krusei Candida tropicalis	Febrile neutropenia Non-neutropenic critically ill ICU patients Long term indwelling catheters Mucosal or skin colonization	Sepsis
Aspergillus : Aspergillus fumigatus Aspergillus flavus Aspergillus niger Aspergillus terreus Aspergillus nidulans	Prolonged neutropenia, long term steroids, solid organ transplants, hematopoietic stem cell transplants, liver cirrhosis	Pulmonary and sinus involvement
Cryptococcus	HIV	Meningitis, pulmonary and skin involvement
Mucorales : Rhizopus Mucor Absidia	Uncontrolled diabetes, chronic kidney disease,solid organ transplant, hematopoietic stem cell transplant	Paranasal/nose with blackish discharge, eschar with orbital and cerebral involvement

1,3 beta D glucan (BDG): It is a component of the cell wall of a wide variety of fungi except zygomycetes and cryptococcus, and has relevance in preterms and pediatric hematological malignancies especially for invasive candidiasis.[6] But being ubiquitous in the environment, glucan can cause false positive results due to contamination of specimens.[7]

Candida mannan antigen: It is an antigen found in the membrane of candida spp, and has high specificity (94.4%) and sensitivity (94.2 %) especially in neonatal population but the transient nature of the antigen and very low sensitivity in C.parapsilosis infection are its disadvantages.[8]

Polymerase chain reaction: Though it helps in identification of the species and has high specificity, it is still not commercially available and not standardized.

Antifungal therapy

The four major categories of antifungal agents available are: Polyenes, azoles, fluropyrimidines and echinocandins (Table III).

Specific fungal infections

Candidiasis: Candidiasis can cause focal invasive infections like endopthalmitis, osteomyelitis, septic arthritis, endocarditis, urinary tract infection or candidemia and disseminated candidiasis. The principal clinical manifestations of candidiasis are fever that does not respond to broad spectrum antibiotics, especially in cases of prolonged catheter use or other major risk factors like multiple organ involvement, macronodular skin lesions and septic shock.[4]

Neonates: Twenty percentage of the babies weighing less than 1 kg develop invasive fungal infections and the overall mortality rate for disseminated fungal infections in this subset of population is 50%.[9] In critically ill neonates, candida is the third common agent of late onset infections with an incidence of 2.6%-10% among very low birth weight and 5.5%-20% among extremely low birth weight babies.[10] The preterm infants are commonly infected by C.albicans and C.parapsilosis. Children aged less than 1 year are infected by C.parapsilosis, while in adolescents C.glabrata incidence exceeds that of C.parapsilosis.[11] C.parapsilosis and C.albicans form a biofilm on the plastic surface of the catheter, thus becoming a continuous source of infection.[3]

Disseminated candidiasis presents with non-specific symptoms simulating sepsis-like features such as temperature instability, apnea, bradycardia, respiratory distress, refusal of feeds, abdominal distention and lethargy.[12] Leon score[13] (Table IV) is used to predict the risk of candidemia, with good negative predictive value.

Table III. Common fungal agents used in systemic fungal infections and their adverse effects

Fungal Agents	Individual drugs	Dose	Usage	Adverse effects/Precautions
Polyenes	**Amphotericin B** Available in 4 forms: conventional, liposomal, colloidal and lipid complex	Conventional : 0.5- 1mg/kg/day Liposomal : 3-5 mg/kg/day Colloidal: Initial dose 1mg/kg/day, can be increased to 3-4mg/kg/day Lipid complex: 5mg/kg/day	Invasive aspergillosis, invasive candidiasis, zygomycosis	Adverse effects : Chills, fever, vomiting, flushing, muscle and joint pains, progressive normochromic anemia is indicative of bone marrow supression. Precautions: Do not reconstitute with saline to avoid precipitation. Monitor renal function tests and serum potassium closely; potassium supplements might be required; monitor blood counts once a week. Corticosteroids may worsen hypokalemia.
Azoles	**Fluconazole**	Mucosal candidiasis – 3mg/kg/day Systemic candidiasis and cryptococcosis – 6-12 mg/kg/day Prophylaxis: 3-12 mg/kg/day	Mucosal and cutaneous candidiasis Acute cryptococcal meningitis in AIDS Ineffective against aspergillosis Prophylaxis against candidiasis	Adverse effect: Nausea, vomiting, abdominal distention, elevation of hepatic enzymes, Stevens Johnson syndrome. Precautions: Hepatic function should be monitored
	Voriconazole	8mg/kg/dose bd dose	First line drug for invasive aspergillosis Alternate drug in fluconazole resistant invasive candidiasis	Adverse effects: Transient visual disturbances, gastrointestinal upset, Stevens Johnson syndrome, hepatitis, cholestasis, fulminant hepatic failure Precautions: Avoid strong direct sunlight
	Itraconazole	2.5mg/kg/dose bd	Alternate drug to amphotericin B in invasive aspergillosis Maintenance to prevent relapse in AIDS patients with histoplasmosis and cryptococcosis	Adverse effects: Abdominal discomfort, epigastric pain, dizziness, pruritus, allergic rashes, vomiting, constipation Precautions: Monitor hepatic function,watch for hypokalemia and hypertension at higher doses

			Allergic broncho pulmonary aspergillosis	Should not be used in those who have heart failure
	Posaconazole	Not much data in pediatric age group	Invasive aspergillosis in neutropenic patients with hematological malignancies; also active against zygomycetes	
Fluropyrimidines	**5 Flucytosine**	150mg/kg/day q 6hrly	Seldom used as a single drug; used used in combination with amphotericin B for cryptococcosis and systemic candidiasis	Adverse effects: Transient rashes, nausea , vomiting, diarrhea, mild changes in liver function tests, rarely leukopenia and fatal thrombocytopenia Precautions: Monitor serum creatinine levels twice weekly, blood counts and hepatic function tests regularly When administered with amphotericin B, clearance of flucytosine is reduced
Echinocandins	**Caspofungin**	50mg/kg/day IV over 1 hour	As an alternate drug in invasive aspergillosis, when there is resistance or intolerance to other antifungal agents Invasive candidiasis – peritonitis, pleural space infections intra peritoneal abscesses	Well tolerated, can cause fever, rash, nausea and vomiting, transient elevation of liver enzymes, causes histamine release
	Anidulafungin	1.5 mg/kg/day ; iv	In neonatal candidiasis, in case of resistance or toxicity to amphotericin B or fluconazole	Facial rash, erythema, elevation of blood urea nitrogen, fever, hypotension

Table IV. Leon score for predicting risk of candidemia

Clinical features	Score*
Sepsis	2
Surgery	1
Total parenteral nutrition	1
Multifocal colonization	1

*A score of > 2.5 is associated with 7 fold increase in candidemia.

All indwelling catheter aspirates, blood and urine must be examined for hyphae or budding yeast. Prompt and aggressive use of antifungal treatment is justified in a clinically septic neonate, with a raised serum concentration of C reactive protein and not responding to antibiotics. The treatment of disseminated candidiasis is to remove the catheters and treatment with fluconazole for 14 days after the disappearance of signs and symptoms of infection. For unstable patients, or with persistent candidemia >5 days, caspofungin with fluconazole or amphotericin B should be considered.

Aspergillus

Aspergillus can cause invasive, saprophytic (non-invasive) or allergic diseases (hypersensitivity) depending upon the host characteristics. The saprophytic infections include otomycosis and pulmonary aspergilloma. Allergic conditions include allergic sinusitis and allergic bronchopulmonary aspergillosis. Invasive aspergillosis is an important cause of morbidity and mortality in children with hematological malignancies and bone marrow transplant (BMT) recipients, chronic granulomatous disease and cystic fibrosis. As per recent studies, invasive aspergillosis affects 10-15 % of BMT recipients. In most cases, aspergillosis affects lungs. The most common symptoms are fever, cough and dyspnea. The X-ray findings are single/multiple nodules, segmental or subsegmental consolidation. The characteristic feature seen in CT in initial phase is the 'halo sign', an area of low attenuation that surrounds the nodule and represents edema or hemorrhage. Halo sign is seen in >90% of neutropenic patients with aspergillosis. At later stages, imaging studies show areas of necrosis and sequestration of lung tissue that detaches from the surrounding parenchyma - causing 'air crescent sign'.

Amphotericin B is the standard treatment for invasive pulmonary aspergillosis. But the most important determinant of survival is resolution of neutropenia as bone marrow recovery is central to fight the infection and prevent development of fatal complications. Because of the ubiquitous nature of aspergillus, environmental control measures recommended during the construction work in hospitals to prevent the incidence of aspergillosis are high efficiency filters, horizontal laminar flow systems and rooms with positive pressure.[14]

Cryptococcus

It is a monomorphic, encapsulated yeast and causes the most predominant fungal infection, cryptococcosis in patients infected with HIV. It is the third most common invasive fungal infection after candidiasis and aspergillosis in solid organ transplant patients. Lungs and CNS are the common organs involved. Progressive pulmonary disease presents with fever, cough, pleuritic chest pain and constitutional symptoms. Chest radiographs reveal a poorly localized bronchopneumonia, nodular changes or lobar consolidations. Cavitation and pleural effusions are rare.

Meningitis is the most common clinical manifestation of disseminated cryptococcal infection. The clinical presentation is prognostic and associated with good outcomes when presenting with headache as the initial symptom, with normal mental status, no predisposing condition, normal CSF opening pressure and glucose, negative India ink stain, no extra neural infection and when cryptococcal antigen titres in CSF and serum is <1:32. Post infectious sequelae such as hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures and ataxia are common.[15]

Diagnosis: A latex agglutination test which detects cryptococcal antigen in serum and CSF is the most useful diagnostic test. Titres of >1:4 in body fluids strongly suggest infection and titres of >1: 1024 reflect high burden of yeast, poor host immune response and high likelihood of therapeutic failure.[5] CSF tap is therapeutic as well as diagnostic. CSF reveals lymphocytic pleocytosis with high protein and low sugar.

Treatment: Induction is done with amphotericin B 0.7mg/kg and 5-flucytosine 100mg/kg for 2 weeks, followed by consolidation phase with fluconazole 400 mg daily for 8 weeks and maintenance phase 200-400 mg for 6 months.[16]

Mucormycosis

Mucarales causing mucormycosis primarily colonize the sinus and nasopharynx and causes primary infection in upper and lower respiratory tract. It causes invasive disease in diabetics, chronic kidney disease patients, solid organ and bone marrow transplant patients. Diabetics may present with invasive sinusitis with nasal or orbital involvement

causing blackish discharge or eschar. Its angio-invasive property resulting in thrombosis and tissue necrosis makes its early identification very important as extensive involvement and intracranial spread is associated with high mortality. Scrapings and biopsy with histopathological examination using Periodic acid-Schiff (PAS) or Gomori Methenamine Silver (GMS) stains are required for identification and diagnosis.

Treatment: The principles of successful management are early diagnosis, reversal of the underlying predisposing factors, early and wide surgical debridement of infected tissue and rapid initiation of effective systemic antifungal therapy.[17] Amphotericin B is the drug of choice. Chelating agents such as deferiprone and deferasirox exert anti-mucor activity by iron deprivation and can be used along with amphotericin.

Histoplasmosis

Children with primary congenital immune defects such as interferon gamma R1 deficiency, interleukin-12R beta1 deficiency, STAT1 gain of function mutations, idiopathic CD4 lymphopenia, DOCK 8 deficiency, X- linked CD4OL deficiency are at increased risk of histoplasmosis. Symptomatic disease occurs more often in young children. The prodrome is non-specific and consists of flu like symptoms, headache, fever, cough and myalgia. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress, hypoxia and require intubation and steroid therapy. In 10% of patients, infection has sarcoid like presentation - arthritis, arthralgia, erythema nodosum. In patients with suspected progressive and disseminated histoplasmosis, the commonest diagnostic test is detection of fungal polysaccharide antigen by radioimmunoassay. Antigenuria correlates with the severity of the disease, levels >19ng/mL is associated with hospitalization and intensive care. Antigenuria is present in 83% of patients with acute disease and 30% patients with subacute pulmonary disease.

Amphotericin B is the drug of choice in progressive disseminated histoplasmosis. Oral itraconazole or fluconazole is used in acute pulmonary infections.[18]

Conclusion

Clinicians should have a strong suspicion of fungal infection in a sick child, when septicemia is not found to be responding to antibiotics. It is necessary to differentiate colonization from disease states and analyze antifungal susceptibility for appropriate and timely management of life threatening fungal infections.

Points to Remember

- ***High index of suspicion for fungal infections should be maintained among the high risk population.***
- ***Whenever possible clinical material should be obtained for culture and histopathological diagnosis and if not possible, molecular methods should be tried.***
- ***Availability of serum galactomannan has revolutionized the diagnosis of invasive pulmonary aspergillosis in neutropenics.***
- ***Successful antifungal treatment depends upon the accurate identification of the etiological agent and initiation of appropriate antifungal drugs.***
- ***Early and wide surgical debridement of infected tissue is essential in mucormycosis.***

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CLIPPINGS

Eosinopenia in children following traumatic intracranial hemorrhage is associated with poor prognosis and prolonged hospital admission.

Neutrophilia is associated with brain injury and is frequently accompanied by eosinopenia. Although eosinopenia is a poor prognostic indicator for various diseases, its significance in intracranial events has not been investigated. The authors retrospectively included 22 pediatric patients (≤18 years old) who experienced traumatic intracranial hemorrhage between 2002 and 2015. Patients were divided into two groups based on the presence or absence of eosinopenia on admission. The mean Glasgow Coma Scale score was marginally lower in the eosinopenia group The mean Glasgow Outcome Scale-Extended (GOSE) score was significantly lower in the eosinopenia group and the mean length of hospital stay tended to be longer in patients with eosinopenia. Eosinopenia was the only significant risk factor for poor outcome and prolonged hospital stay These results demonstrate the significance of eosinopenia as a novel prognostic factor in traumatic intracranial hemorrhage in children.

Hori YS, et al. Eosinopenia in children following traumatic intracranial hemorrhage is associated with poor prognosis and prolonged hospital admission. Pediatr Neurosurg doi:10.1159/000441390.

Anticonvulsants for neonates with seizures

Authors' conclusions

At present there is little evidence from randomised controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period. In the literature, there remains a body of opinion that seizures should be treated because of the concern that seizures in themselves may be harmful, although this is only supported by relatively low grade evidence (Levene 2002; Massingale 1993). Development of safe and effective treatment strategies relies on future studies of high quality (randomised controlled trials with methodology that assures validity) and of sufficient size to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability in addition to any short term reduction in seizure burden.

Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004218. DOI: 10.1002/14651858.CD004218.pub2. This version first published online: October 18. 2004

INFECTIOUS DISEASES

ESCALATION AND DE-ESCALATION OF ANTIBIOTICS

Suhas V Prabhu

Abstract: *Drug resistance has reached proportions alarming enough to threaten the occurrence of a post-antibiotic era when all antibiotics will be useless because of multi-drug resistance by most bacteria. Antibiotic resistance is on the rise partly because of misuse and overuse of antibiotics by clinicians. Rational use of antibiotics requires not just the correct initial choice (whether empiric or definitive) but a continuing re-appraisal of the choice of antibiotic and the route and duration of the therapy. So the antibiotic initially started may have to be changed to higher (escalation) or lower one (de-escalation) to optimize therapy. This decision has to be based on clinical as well as laboratory criteria. The methods of escalation and de-escalation, the correct indications for doing so and for making a rational choice of the new antibiotic are detailed. Similarly, the switch from parenteral to oral therapy has to be timed correctly and the right choice of oral antibiotic has to be used. The strategy to make these changes rationally in actual clinical settings is discussed. We need to quickly and vigorously adopt these methods of escalation and de-escalation of antibiotics to ensure that whatever antibiotics are available to use now are used wisely and their potency preserved for the future.*

Keywords: *Antibiotics, Escalation, De-escalation, Drug resistance*

Antibiotic resistance is a looming threat to the 20th century success story of the fight against infectious diseases. Drug resistance is reaching alarming proportions and multi-drug resistant infections are the bane of clinicians and intensivists.[1] One of the reasons for this state of affairs is misuse and abuse of antibiotics by clinicians, not only in India but world-wide.[2,3] This happens when broad spectrum antibiotics are used haphazardly, i.e., inappropriately or for prolonged periods. Unfortunately, due to a variety of reasons, the discovery of new antibiotic molecules is declining. So, it is time we clinicians learn to shepherd the antibiotics that are currently available and use them wisely in order to preserve their efficacy in future. The initial choice of antibiotic, whether empirical or based on culture sensitivity report, is only the first step of antibiotic therapy. But whether the patient responds to this initial choice or not, the treating physician needs to remember to review the continued need for using the antibiotics with regards to their appropriateness and duration. The antibiotic chosen may have to be changed but this should be done after proper rational thought. Appropriate use of antibiotics requires us to make not only good initial choices of antibiotics tailored to each individual infection but also to escalate or de-escalate them correctly for optimum benefit.

Escalation

Escalation means changing over from the current (one or more) antibiotic(s) to another one (or more) which is more potent and has a broader spectrum. It is applicable only when we have started a less potent antibiotic. If the antibiotic choice is definitive (i.e., based on a positive culture and sensitivity), then the patient will respond and there will be no need for escalation. The question of escalation arises more commonly when the earlier choice of antibiotic has been empirical. In such cases, if prior cultures have been sent, escalation may be required once the sensitivity report arrives, as it may show that the organism is not sensitive to the antibiotic chosen empirically. Escalation is not possible beyond a certain limit. If the patient is already receiving one or more broad spectrum antibiotic(s), (e.g. meropenem and vancomycin with colistin), the question of escalation does not arise. Therefore, starting broad spectrum antibiotics empirically for every patient is counter-productive as it leaves no room for escalation if the patient does not respond to them.

Method of escalation

It can be done in a variety of ways:

a) Adding an enzyme inhibitor to the currently used antibiotic, e.g., changing from amoxicillin to co-amoxiclav in a patient with acute otitis media.

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b) Changing to a more potent molecule, e.g., from cefazolin (1st generation cephalosporin) to ceftriaxone (3rd generation cephalosporin)

c) Adding another antibiotic of a different class: e.g., adding clarithromycin to amoxicillin in a school age child with pneumonia.

In this last example, escalation is achieved by adding a new antibiotic while continuing the old one. This is because the macrolide added is required to cover atypical organisms like mycoplasma which are not attacked by the betalactam antibiotic amoxicillin. This is justified in community acquired pneumonia as the causative organism is hardly ever identified by culture or other means, i.e., the treatment is empirical. But generally speaking, especially when backed by a positive culture, escalation calls for replacement of the old drug with the new one.

Time of escalation

Escalation should be done when the patient has not responded. Objective proof of non-response is obtained by a repeat positive culture showing an organism demonstrating resistance to the anti-microbial in use. (The earlier culture if positive would have showed either another organism or the same organism but sensitive to the drug used). If one has such a report in hand, escalation is justified.

However, such a situation is rare. More often, the non-response has to be judged on clinical grounds. In that case, it is important to decide the parameters for judging clinical non-response. This can be done rationally only with a thorough knowledge of the clinical course expected even when the patient is on the correct antibiotic treatment. For example, in a case of enteric fever, one should be aware that defervescence may take upto one week and need not escalate the antibiotic just because the patient is febrile 4 or 5 days after administration of a correctly chosen drug. Similarly, non-resolution of a pulmonary consolidation on X-ray in a patient who is otherwise improving, is not a good reason for escalation as the radiographic shadows after an acute pneumonia may take weeks to resolve. Another example is a case of pulmonary tuberculosis which would be labelled as resistant only if the sputum (or gastric aspirate) remains positive after 8 weeks of therapy.[4]

On the other hand, a toddler with acute otitis media who is still febrile and in pain on 3rd day of an empirically chosen antibiotic calls for escalation. Similarly, a child with bacillary dysentery, who is still febrile and has visible blood in the stool with or without fever and tenesmus after two days of antibiotic therapy, requires a change in his treatment.[5] So, also a neonate with bacterial sepsis whose parameters have shown no improvement after 48 hours of a chosen course of antibiotics requires escalation. But it is important to allow sufficient time for the antibiotics chosen to act (generally at least 48 hours), before giving up and deciding to change them.

When not to escalate?

Escalation generally is not justified before 48 hours completion of the current antibiotic regimen. The exception is only if the patient becomes seriously ill, i.e., he or she develops septic shock. Changing antibiotics very frequently, without any objective data of resistance is irrational and must be deplored.

Escalation is also not justified if the repeat culture shows the same organism with the same sensitivity. In these cases, escalation of the antibiotic may not be the answer. The non-response may be due to pharmacological reasons like non-adherence, inadequate dosage or drug-drug interaction (such as giving an oral fluoroquinolone with an antacid that hinders its absorption form the gut); or there may be some other reasons for failure: e.g., collection of pus (abscess or empyema), presence of dead tissue (like a sequestrum) or a foreign body like an indwelling catheter. Attention to these problems and continuation of the same antibiotic in the correct dose will suffice to effect a cure.

Principles of escalation

While changing antibiotics to a more potent one, it is still important to make a rational choice rather than just starting any broad spectrum drug. This requires one to think of the possible organisms causing the infection in that particular case and which of these would have failed to respond to the antibiotic used.[3] For example, if a child with acute otitis media has not responded to amoxicillin, one should think that there is possibly infection with a beta lactamase producing organism like H. influenzae and step up to a drug (like co-amoxiclav or cefpodoxime) that will specifically cover such organisms and not just any broad spectrum antibiotic like vancomycin or meropenem.

De-escalation

De-escalation is a method of narrowing empiric therapy.[6] This has to be based both on culture reports and clinical improvement. The decisive factor for definite success of de-escalation is a positive identification of the causative organism. Only then it is safe to de-escalate without jeopardizing the patient's safety and risking a relapse of the infection.

Reasons for de-escalation

It is a human tendency to not 'rock the boat'. The usual refrain is "My patient is doing so well on the current combination of broad-spectrum antibiotics. Why take a chance and try to reduce or change the antibiotics being given?" But while it is tempting to continue and complete a course of antibiotics on which the patient has shown good improvement, it is noteworthy to remember that de-escalation of antibiotic therapy has multiple benefits.[7] De-escalation, properly done, results in treatment outcomes that are non-inferior to continuing the previous therapy.

Some of the benefits of de-escalation are:

a) Decrease in antibiotic related adverse events and super infection: By stepping down to a narrower spectrum antibiotic, you can prevent secondary infection with a 'super-bug' that would be resistant to the broad spectrum drug that the patient would be on.

b) Cost savings: The narrower spectrum, more specific antibiotic is likely to be cheaper than the broad spectrum combinations.

c) Reduction in multidrug resistant organisms: Multi-drug resistant (MDR) bugs in the hospital environment are reduced by reduction of environmental exposure to broad-spectrum antibiotics. We need to remember that whenever an antibiotic is administered to even one patient, because of spillage at the time of preparation, or administration and release into the environment via excreta of the patient, the hospital flora gets repeatedly exposed to these powerful antibiotics and they become resistant to them over a period of time. Also the patient's normal gut organisms also get exposed to these antibiotics and can become resistant. When these environmental or gut organisms cause a nosocomial infection in the patient (or in the next patient), treatment becomes difficult as these will be resistant to the broad spectrum antibiotics.

Time of de-escalation

While de-escalation is desirable, it has to be timed correctly. If done too early, the patient's infection may worsen and if done too late, the benefit will only be marginal. The timing of de-escalation has to be based both on clinical as well as some laboratory criteria.[8] One point at which this can be easily done is when the result of the culture arrives. Take the example of a young infant admitted with septic shock and started (correctly so) on broad spectrum combination of meropenem and amikacin. If after 2 days of this therapy, his blood culture report shows S. pneumoniae sensitive to all beta-lactam antibiotics, it is easy to confidently de-escalate to ampicillin or even penicillin G. All of us are also familiar with the 'de-escalation' of anti-tubercular therapy from 4 drugs to 2 (or 3) after two months of therapy is over.

Method of de-escalation

De-escalation can be done in a variety of ways. One simple example is by dropping one of the two (or more) antibiotics started. If one has started ceftriaxone and gentamycin in a 7 week old child with pyogenic meningitis and the culture report shows S. pneumoniae, gentamycin can be safely omitted. Or take the example of a school age group child with a severe community acquired pneumonia started on ceftriaxone and a macrolide. If evidence for mycoplasma is obtained (such as IgM ELISA or cold agglutinins positive) then ceftriaxone can and should be omitted. At other times, de-escalation is done by shifting to another antibiotic of narrower spectrum of the same or other class. One example of this is stepping down from a combination of cefoperazone-sulbactam and amikacin to cloxacillin if the culture throws up methicillin sensitive Staphylococcus aureus (MSSA).

Switch over therapy

Some infections such as those of bone and joints and deep tissue abscesses require prolonged antibiotic therapy for several weeks. The financial costs, social problems and medical risks of prolonged hospitalization are well known. Persisting with intravenous administration of antibiotics necessitates prolongation of hospital stay with all these associated problems and risks. Hence, the treating clinician must consider discharging the child on oral medication as soon as it is safely possible, unless there are special situations like an immunocompromised state.

For common infections such as enteric fever, an oral switch (and discharge) can be done as soon as the patient is afebrile.[9,10] For other infections like osteomyelitis, specific guidelines exist to decide the timing of the switch over, which can be as early as 4 to 7 days in milder cases.[11] This would include absence of fever, normal CRP, near normal counts and a declining ESR.[12] In the presence of retained sequestrum, an abscess or a foreign body, oral switch will have to delayed till the resolution of these issues.

Parenteral to oral switch

Th