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INFECTIOUS DISEASES

TYPHOID FEVER - CURRENT SCENARIO

*Surendranath M

Abstract: Typhoid fever is caused by a highly virulent organism Salmonella enterica serovar Typhi with a case fatality rate of 1% - 4%. In Indian subcontinent, incidence of typhoid fever is estimated to be more than 60 lakh cases per year. In many countries 27% of all cases occur in the age group of 0-4 years. Humans are the only known reservoir of S.typhi and transmission is through fecal-oral route. Though the blood culture done in the first week of illness is the gold standard for diagnosis, the sensitivity of blood culture is only 50%. Blood Widal test has poor positive predictive value but high negative preditive value. Multi drug resistant typhoid is reported in India while extremely drug resistant typhoid is reported in Pakistan since last few years. Recent reports in India suggest the susceptibility of S.typhi to first line of drugs and 100% to ceftriaxone. Improved sanitation, protected water supply, rational use of antibiotics and immunization with typhoid conjugate vaccine will reduce the disease burden.

Keywords: Salmonella enterica serovar Typhi, Enteric fever, Anti microbial resistance, Typhoid conjugate vaccine.

Typhoid fever is an acute generalized infection caused by highly virulent organism Salmonella enterica serovar Typhi. Salmonella Paratyphi A, Paratyphi B and Paratyphi C cause paratyphoid fever which is clinically indistinguishable from typhoid fever. Paratyphoid and typhoid are considered under enteric fever. It is a very important public health problem with disease burden between 11 and 21 million cases per year and resulting in approximately 128,000 to 161,000 deaths annually. Majority of cases occur in South and South East Asia and sub-Saharan Africa.

India has annual incidence of 493.5/100,000 persons per year with 340.1/100,000 cases per year occurring in children of 2-5 years. A systematic review of pooled estimates incidence typhoid in India was 377/100,000 person-years and the incidence was highest in 2-4 years age group. In Indian subcontinent, the total incidence of typhoid fever is estimated to be 63,45,776 cases per year. Surveillance data between 1998 and 2017 done from Africa, Asia and the Americas has shown 27% of all cases occurred in 0-4 years children, of which 30% occurred in <2 years age group and 10% in infants. Estimated case fatality rates are 1-4% who received adequate therapy and may be 10-20% in untreated cases or in cases who received inappropriate antibiotics. Case fatality rate in <4 years children is almost 10 times higher and may be highly under reported. Antibiotic resistance in salmonella has been reported to be 70% for fluoroquinolones and an ICMR study has shown that lower resistance rates for co-trimoxazole, chloramphenicol and third generation cephalosporins. Extremely drug resistant (XDR) typhoid outbreaks are reported in Pakistan and these are resistant to extended spectrum beta lactams (ESBL) such as third generation cephalosporins.

Humans are the only known reservoir of S.typhi. Transmission is by fecal-oral route by two main patterns either by short cycle, due to contamination of food and water by shedding of bacteria by temporary or chronic carriers, or by long cycle due to contamination of broader environment with pollution of water supplies by sewage and usage of untreated sewage as fertilizer for crops.

Case definitions (WHO): Suspected case of typhoid or para typhoid: (a) Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area or (b) fever at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever.

Suspected case of invasive non-typhoidal salmonellosis (iNTS): Case definition is not provided due to the nonspecific clinical presentation. iNTS should be considered as differential diagnosis in the presence of acute febrile illness in those at risk in endemic settings, including those immunocompromised or malnourished.

Confirmed cases

Typhoid fever: Laboratory confirmation by culture or molecular methods of S. typhi or detection of S.typhi DNA from a normally sterile site.
**Paratyphoid fever:** Laboratory confirmation by culture or molecular methods of S.paratyphi A, B or C or detection of DNA from a sterile site.

**Invasive non – typhoidal salmonellosis (iNTS):** Laboratory confirmation by culture or molecular methods of non-typhoidal Salmonella or detection of non-typhoidal Salmonella DNA from a normally sterile site.

**Relapse of typhoid or paratyphoid fever:** Laboratory confirmation of S.typhi or paratyphi from a normally sterile site within one month of completing an appropriate course of antimicrobial treatment and resolution of symptoms.

**Chronic carriers**

**Presumptive carrier:** Evidence of shedding of Salmonella spp (positive stool culture or PCR) of an unknown duration.

**Definitive carrier:** Evidence of shedding of Salmonella spp. (positive stool culture or PCR) at least 12 months after finishing appropriate course of antimicrobial treatment and resolution of symptoms following a laboratory-confirmed episode of acute disease or two positive stool samples 12 months apart.

**Convalescent carrier:** Evidence of shedding Salmonella spp. (positive stool culture or PCR) 1-2 months after finishing an appropriate course of antimicrobial treatment and resolution of symptoms following a laboratory-confirmed episode of acute disease.

**Case definition by national centre for disease control:**

**Acute non-complicated disease:** Prolonged fever is characterized by acute typhoid - altered bowel function (constipation in adults and diarrhea in children), headache, malaise and anorexia. Bronchitic cough and exanthem (rose spots on chest, abdomen and trunk) may be in the early disease.

**Confirmed case:** A patient with fever (38°C and above) that has lasted for at least 3 days with laboratory confirmed positive culture (blood, bone marrow, bowel fluid) of S. typhi.

**Complicated disease:** Severe disease can have abdominal pain, occult blood in the stools, malena, perforation, peritonitis, myocarditis, pneumonitis and enteric encephalopathy.

**Probable case:** A patient with fever (38°C and above) that has lasted for at least 3 days with a positive serology or antigen test but without isolation of S. typhi.

**Clinical features**

Typhoid fever is an acute illness characterized by prolonged fever, headache, nausea, loss of appetite, and constipation or sometimes diarrhea. Symptoms are often non-specific and clinically non-distinguishable from other febrile illnesses.⁷

**Diagnosis**

**Blood culture:** Blood culture is the gold standard test for diagnosis of typhoid fever. Isolation of S.typhi from blood culture is challenging in India due to limited laboratory facilities.⁸,⁹,¹⁰,¹¹ Sensitivity is highest in the first week of illness. Overall sensitivity is about 50%. The yield of blood culture is affected by rampant use of antibiotics on clinical suspicion prior to blood culture, late presentation of patients to tertiary care hospitals and inadequate blood sample. Bone marrow culture is more sensitive but not feasible because of technical issues. It is important to ensure that optimum volume of blood (Table I) is drawn for culture as bacterial load in acute typhoid is low with an average of <1 cfu/ml.¹²,¹³

Urine culture, rose spot culture, clot culture and duodenal aspirate culture studies can also be done.¹¹,¹⁴ Stool culture is mainly used for detection of carrier state.

**PCR:** Its sensitivity is same as blood culture but is less specific. It has been found to be >90% sensitive. It is not the gold standard test as it picks up only the antigen 14, 15,

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Blood volume for culture bottles of 40ml of broth</th>
<th>Blood volume for culture bottles of 80ml broth</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months to 2 years</td>
<td>1-2ml</td>
<td></td>
</tr>
<tr>
<td>2 year to 5 years</td>
<td>2-3ml</td>
<td></td>
</tr>
<tr>
<td>5 to 15 years</td>
<td>5-10ml</td>
<td></td>
</tr>
<tr>
<td>&gt;15 years and adults</td>
<td></td>
<td>8-10ml</td>
</tr>
</tbody>
</table>
and 18. Its cost is high. Nested PCR is more sensitive and uses H1-d primers to amplify specific genes of S. typhi. The advantages are- higher case detection compared to blood culture, can be used as diagnostic test at any stage of the disease and not affected by prior antibiotic use.11,14

**Serology**

**Widal test:** Widal test has been used for over a century in developing countries for the diagnosis of enteric fever.15 Due to inaccessibility of laboratories for culture of S. typhi, blood Widal is the most widely used and misused test as it is cheap and easily available. It should not be done during the first week of fever. It has sensitivity of 47%-77% and specificity of 50%-92%; negative test has good predictive value (98.9%) while a positive test has low predictive value (5.7%).16 Widal can be negative in 30% of culture proven cases. Some of the Indian studies reported a baseline antibody titre of S. typhi for O antigen as 1:40 and H antigen as 1:80 at various geographical locations in healthy people.17,18,19,20 Titre of antibodies for O antigens ≥1:80 and for H antigen ≥1:160 may be considered suggestive of typhoid fever in a given clinical situation. False positive Widal test can occur in malaria, typhus, bacteremia, cirrhosis and infections with other salmonella species.21,22 One should be careful in interpreting the results as it may lead to antibiotic overuse, increasing the antibiotic antimicrobial resistance. However, negative test may rule out infection due to S. typhi. With all its shortcomings it still may be a useful test to diagnose typhoid fever in resource poor situations when it is interpreted properly.

**Typhidot:** Typhidot is a rapid enzyme immunoassay which detects IgG and IgM antibodies to a specific 50 kD outer membrane protein antigens of S. typhi. Detection of IgM signifies early phase of infection. IgG and IgM indicate middle phase of infection. It has a sensitivity of 95% and specificity of 75%. Limitation of the test is persistence of IgG of previous infection for more than two years which may give a false positive result. Typhidot M is a modified test obtained by inactivating total IgG in serum sample enabling access of antigen to IgM thereby enhancing the diagnostic accuracy.23

**Latex agglutination test:** It has a sensitivity of 100% and specificity of 97.6% and can be used as rapid diagnostic test.11,12

**IDL tubex test:** The O9 antigen is used. It is it extremely specific and can detect IgM antibodies within few minutes.11,12

**IgM dipstick test:** It is based on the detection of S. typhi – specific IgM antibodies in serum or whole blood.11,12

**Antibiotic resistance**

In 1948, chloramphenicol was introduced as treatment for typhoid. Though antimicrobial resistance was seen after 2 years, India has reported the first outbreak of chloramphenicol resistant strains in 1972 only.9,24,25 Since 1990, S. typhi became resistant to all first line drugs (chloramphenicol, cotrimoxazole and ampicillin) and multi drug resistance (MDR) typhoid fever emerged. Some strains of S. typhi have shown resistance to fluoroquinolones after the wide spread use of this antibiotic. With development of resistance to fluoroquinolones, third generation cephalosporins are being used in the treatment of MDR typhoid.9,24,25

S. Typhi H58 clad with H11 incompatibility type (IncH1) plasmids carrying MDR genes and mutation causing fluoroquinolones resistance, is responsible for much of the recent and current spread of resistant strains. This clad is believed to have emerged on Indian subcontinent around 30 years ago and subsequently spread to South-East Asia and most recently to sub-Saharan Africa. New resistant clads have also appeared in Nigeria and the Democratic Republic of the Congo.1

Recently S. typhi resistant to third generation cephalosporin has caused outbreaks of XDR typhoid in Pakistan. Since 2016, a total of 5274 cases of XDR typhoid have cases been reported from Pakistan. There were reports of international transmission of XDR typhoid through the persons who travelled to Pakistan. Six travel associated case of XDR typhoid were reported.26 The antimicrobial resistance (AMR) in typhoid and increased number of XDR cases will cause severe limitation of treatment options and the only option left would be azithromycin. Some of the molecular studies did not demonstrate extended spectrum beta lactamases in S. typhi in India. Only sporadic reports of typhoid resistant to third generation cephalosporins are reported in India. The classification of typhoid fever based on drug resistance is given in Table II.

In the recent past many Indian centers have reported susceptibility of S. typhi to first line of drug.25,27 The study conducted in one tertiary care hospital in North India has reported anti-microbial susceptibility for chloramphenicol, amoxicillin and co trimoxazole to be 87.9%, 75.5%, 87.3% for S. Typhi and 94.2%, 90.1% and 94.2% for Paratyphi A, respectively. Ciprofloxacin, ofloxacin and levofloxacin susceptibility were 71.3%, 70.8%, and 70.9% for S. Typhi and 58.1%, 57.4% and 57.1% for Paratyphi A respectively. Azithromycin susceptibility was 98.9% for S. Typhi. Although susceptibility to ceftriaxone and cefixime was 100%, there is a continuous increase in ceftriaxone
minimum inhibitory concentration (MIC) 50 and (MIC) 90 values over the time and is creeping towards resistance.28

**Treatment**

**National Treatment Guidelines for antimicrobial use in infectious diseases, NCDC (2016).**6 Outpatient treatment: Oral Cefixime 20 mg/kg/day for 14 days or Azithromycin 10-20mg/kg for 7-10 days.

For in patients: Ceftriaxone 100mg/kg/day IV  and shift to oral cefixime once the child is afebrile, continuation of antibiotic therapy till one week post fever defervescence.

Alternate therapy: Ofloxacin 15 mg /kg/day in two divided doses for 10-14 days. Antibiotics should be continued till one week after fever defervescence or chloramphenicol 50-75mg/kg/day oral for 14 days or TMP-SMX 8 mg/kg/day of TMP oral for 14 days.

It will be interesting to see whether use of previous first line drugs (Chloramphenicol Ampicillin,TMP-SMX) will be helpful in combating the antimicrobial resistance which was prevalent in 1980 and 90s, as susceptibility of Salmonella typhi to these drugs has been reported recently. Lack of confidence on these drugs on treatment outcomes and unavailability of old formulations may be obstacles in changing the prescription behavior of treating physicians. Abuse of azithromycin for other conditions should be stopped because the threat of XDR typhoid is looming large on us. IAP guidelines for the treatment of typhoid fever is given in Table III.

**Prevention**

Improving sanitation, prevention of antibiotic resistance and vaccination are the main strategies in reducing the disease burden in India.

**Sanitation:** In India 128 million people lack safe water services and 840 million people don’t have sanitation services.29 Swachh Bharat Mission aims to achieve an “open-defecation free” India by 2nd October 2019 the 150th birth anniversary of Mahatma Gandhi by constructing 90 million toilets in rural India.30,31 This program may reduce the open air defecation practices of people and thereby reducing the contamination of environment.

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### Table II. Classification of typhoid fever cases based on drug resistance

<table>
<thead>
<tr>
<th>Classification</th>
<th>Case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non – resistant typhoid fever</td>
<td>Typhoid fever caused by Salmonella typhi and/or salmonella Paratyphi A, B or C strains which are sensitive to the first line of drugs and third generation cephalosporins, with or without resistance to second line of drugs</td>
</tr>
<tr>
<td>Multi drug resistant (MDR) typhoid fever</td>
<td>Typhoid fever caused by Salmonella typhi and/or Salmonella paratyphi A, B or C strains resistant to the first line of drugs with or without resistance to second line of drugs</td>
</tr>
<tr>
<td>Extensive drug resistant (XDR) typhoid fever</td>
<td>Typhoid fever caused by Salmonella typhi strains which are resistant to all the recommended antibiotics for typhoid fever.</td>
</tr>
</tbody>
</table>

### Table III. IAP guidelines for the treatment of typhoid (2006)9

<table>
<thead>
<tr>
<th>Typhoid fever</th>
<th>Susceptibility</th>
<th>First line oral drugs</th>
<th>Second line oral drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>Sensitive</td>
<td>Cefixime</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amoxicillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Multi drug resistant</td>
<td>Cefixime</td>
<td></td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Fever</td>
<td>Sensitive</td>
<td>Ceftriazone or cefotaxime</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Multi drug resistant</td>
<td>Ceftriazone orcefortaxime</td>
<td></td>
<td>Aztreonam</td>
</tr>
</tbody>
</table>
Success of program depends on changing the practices of people. Universal, affordable and sustainable access to water, sanitation and hygiene (WASH) is the key to prevent many public health issues and typhoid fever is one of them. Average rate of handwashing with soap after using toilet or being in contact with child’s excreta is estimated is India to be 15% in India. Annual net costs to India from not hand washing are estimated at US$ 23 billion and expected net returns of national behavior change hand washing programs would be US$ 5.6 billion. Teaching hygiene and hand washing in schools and communities will be rewarding in reducing infectious diseases.

### Antimicrobial resistance

Prevention of antimicrobial resistance by rational use of antibiotic and antibiotic stewardship is essential to prevent MDR and XDR typhoid. Controlling the sale of over the counter antibiotics, educating the health professionals in rational use of antibiotics and eminent danger of antibiotic resistance is the need of the hour. In 2011, the government of India launched a national policy for containment of antimicrobial resistance which aimed to review current use of antibiotics, create a national surveillance system for antibiotic resistance, enhance regulatory provisions for use of antibiotics and to recommend specific interventions to promote rational use of antibiotics. This was followed by Chennai declaration in 2012 and a 5 year plan to tackle antimicrobial resistance, which include restriction of over the counter antibiotic sale, hospital guidelines on infection control antibiotic stewardship and education of medical profession.

National Centre for Disease Control has published national Treatment Guidelines for Antimicrobial Use in Infectious Diseases in 2016 to tackle the antibiotic resistance. IAP also has prepared a module on Rational Antibiotic Practice as a presidential action plan in 2014 to educate the pediatricians.

### Vaccination

Vaccination is an important strategy to reduce the disease burden and reduce the antibiotic resistance and to protect the individual from resistant typhoid. Vaccines licensed for use are:

1. Typhoid conjugate vaccine (TCV) (for infant above 6 months to adults up to 45 years)
2. Typhoid polysaccharide vaccine (ViPS) (only for the children above 2 years)
3. Live attenuated Ty21a vaccine (oral vaccine for above 6 years, currently not available in India)

In infants aged 6-11 months and children aged 12-23 months, a single dose of typhoid conjugate vaccine containing 25microgram (TCV) elicited high titres of IgG anti-Vi antibody that persisted up to 5 years in approximately 84% of children. When evaluated in a human challenge study in a population of immunologically naïve adult volunteers aged 18-60 years of age (N-112) the efficacy of TCV was 87.1% at one month after vaccination compared with 52.3% for comparator Vi polysaccharide vaccine. Presently WHO and IAP ACVIP recommend a single dose of TCV at nine months. Catch up vaccination up to 15 years can be recommended when feasible and supported by evidence of epidemiological data. TCV can be co administered with measles containing vaccine. Present evidence shows that TCV immunogenicity and more sustained level of antibodies with one dose compared to Vi polysaccharide vaccine. The potential need for revaccination with TCV is currently unclear. Available evidence on TCV suggests protection may persist for 5 years or more after primary immunization and there is some evidence that natural boosting occurs. We may have to be cautious with one dose recommendation of TCV without booster in the scenario of XDR typhoid out breaks in the neighboring country as the inactivated vaccines may have waning immunity over a period of time. The WHO position paper in 2018 has remarked that the body of evidence for the 5 µg vaccine is very limited. TCV (25 microgram) is the only vaccine prequalified by WHO. For the first time typhoid conjugate vaccine is going to be used for outbreak response vaccine campaign in Zimbabwe with the goal of disrupting the transmission of S.typhi. GAVI funded vaccine campaign was scheduled in January-February 2019, targeting 350,000 persons.

Field effectiveness trials of Vi Polysaccharide vaccine in Kolkata, India and Karachi, Pakistan showed moderate protection (56-59%) of older children while there was variable protection of preschool children 2-4 years of age but in India 80% effectiveness is reported. Indirect protection was shown in Kolkata but not in the Karachi trial. Polysaccharide vaccine needs to be given repeatedly every 3 year as the waning of immunity will be there, unlike conjugate vaccines.

Oral Ty21a vaccine is not routinely used in India. It is available as enteric coated capsule with capsule to be given on day 1, 3 and 5 and needs to be repeated every 3 years.

WHO recommends programmatic use of typhoid vaccines for control of typhoid fever and it should be implemented along with other control measures like health education, water, sanitation and hygiene improvement and training of health professionals in diagnosis and case management.
Conclusion

Enteric fever continues to be a major public health problem in India and other developing countries. Emergence of XDR typhoid organisms and spread may have devastating effect in health and economics of the country. Disease burden can be reduced by multi-pronged approach of government commitment, health care professional involvement and public awareness.

Points to Remember

- Typhoid fever continuous to be an important public health issue in India with many reports of incidence of MDR typhoid.
- Though the blood culture is the gold standard in the diagnosis of typhoid, positive blood culture rates are low.
- Blood Widal test has high negative predictive value.
- Improving sanitation, hygiene and vaccination with typhoid conjugate vaccine may reduce the disease burden.

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serovar Typhi, the etiological agent of typhoid.


27. Joshi S. Antibiogram of S. enterica serovar Typhi and S. enterica serovar paratyphi A: a multi-centre study from India. WHO South-East Asia J Public Health 2012; 1(2);182-188.


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**CLIPPINGS**

**Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial**

A double blind, parallel, stratified, randomised control trial was conducted in a tertiary neonatal unit in West Australia. Preterm infants (29⁰–33⁶ weeks’ gestational age, GA) less than 4 hours of age requiring 22%–30% supplemental oxygen, were studied. Infants were randomised within strata (29⁰–31⁶ and 32⁰–33⁶ weeks’ GA) to bubble nCPAP or bubble nCPAP and nebulised surfactant (200 mg/kg: poractant alfa) using a customised vibrating membrane nebuliser (eFlow neonatal). Surfactant nebulisation (100 mg/kg) was repeated after 12 hours for persistent supplemental oxygen requirement. The primary outcomes were requirement for intubation and duration of mechanical ventilation at 72 hours. Data analysis followed the intention-to-treat principle. 360 of 606 assessed infants were eligible; 64 of 360 infants were enrolled and randomised (n=32/group). Surfactant nebulisation reduced the requirement for intubation within 72 hours: 11 of 32 infants were intubated after continuous positive airway pressure (CPAP) and nebulised surfactant compared with 22 of 32 infants receiving CPAP alone (relative risk (95% CI) = 0.526 (0.292 to 0.950)). The reduced requirement for intubation was limited to the 32⁰–33⁶ weeks’ GA stratum. The median (range) duration of ventilation in the first 72 hours was not different between the intervention (0 (0–62) hours) and control (9 (0–64) hours; p=0.220) groups. There were no major adverse events. Early postnatal nebulised surfactant may reduce the need for intubation in the first 3 days of life compared with nCPAP alone in infants born at 29⁰–33⁶ weeks’ GA with mild respiratory distress syndrome.

Abstract: In children, upper respiratory infections are a leading cause of visit to pediatrician, mild morbidity and school absenteeism. Most of them are caused by viral infections and are self-limiting, while bacterial infections account for a small percentage but need appropriate treatment. Upper respiratory infection is one of the most common conditions where antibiotics are prescribed inappropriately. Hence, a prompt diagnosis of bacterial upper respiratory tract infections is important for institution of early and appropriate antimicrobial therapy, thereby preventing complications. Judicious use of antibiotics will also help to reduce the cost, adverse effects and antimicrobial resistance.

Keywords: Acute otitis media, Acute bacterial rhinosinusitis, Pharyngotonsillitis, Croup, Epiglottitis.

Common cold

It is also known as nasal catarrh / rhinitis / nasopharyngitis. Greater than 50% of URTI are caused by viruses from the rhinovirus family while coronavirus, respiratory syncytial virus (RSV), human metapneumovirus, influenza virus, parainfluenza virus, adenovirus and enterovirus are the other common viruses which causes cold. Young children less than 2 years of age have an average of 6-8 URTIs per year, but 10-15% of children have at least 12 infections per year. The incidence decreases with age, with 2-3 illnesses per year by adulthood. The usual complications are acute otitis media (AOM) and acute bacterial rhinosinusitis (ABRS).

Treatment: Non-prescription therapies (containing antihistamines, antitussives, decongestants) had no significant therapeutic benefits but may have serious side effects. Hence, they should be avoided in infants and children <6 years. Antibiotics have no role. Therapies which may not be effective in treating common cold is described in Table I.

Acute bacterial rhinosinusitis (ABRS)

A viral etiology associated with URI is the most frequent cause of acute rhino sinusitis. Secondary bacterial infection (ABRS) following viral URI occurs in about 5% of children.

Etiology: Common organisms implicated are Streptococcus pneumoniae (30%), non-typable H.influenzae (20%), Moraxella catarrhalis (20%) and Staphylococcus aureus. Streptococcus pyogenes and anaerobes are uncommon in children. Nearly 50% of H. influenzae isolates and almost all isolates of M. catarrhalis are β-lactamase positive.

Symptoms in ABRS

Persistent URI symptoms for 10 days (nasal congestion, rhinorrhea of any quality, day time cough without any evidence of clinical improvement) (or) severe acute symptoms of URI (temperature of >102°F with purulent nasal discharge for at least 3 consecutive days at the beginning of illness) or worsening of symptoms (either by recurrence of symptoms after an initial improvement or new symptoms of fever, nasal discharge and daytime cough).

Investigation: ABRS is essentially a clinical diagnosis based on history and physical examination. Sinus aspirate culture is the only accurate method of diagnosis but is not practical for routine use. Radiological investigation is not required in uncomplicated cases.
Treatment: For uncomplicated mild to moderate sinusitis

1st line: Amoxicillin (45-50 mg/kg/day) orally in two or three divided doses.\textsuperscript{9,10}

2nd line: If there are risk factors like preceding antibiotics in the last 1-3 months, day care attendance, children <2 years of age, those with severe infection (systemic toxicity with fever of 102° F or higher and threat of supplicative complications), recent hospitalization, those who live in regions of >10% penicillin -nonsusceptible Streptococcus pneumoniae, immunocompromised children, persistent vomiting and no response after 3 days of amoxicillin, - change to high dose amoxicillin-clavulanate (80-90 mg/kg/day of amoxicillin oral/IV) or ceftriaxone (50 mg/kg IM/ IV).\textsuperscript{9,10} The duration of treatment is a minimum of 10 days or for 7 days after resolution of symptoms. If allergic to penicillin, a respiratory flouroquinolone (levofloxacin) for type I penicillin allergy and third generation oral cephalosporin (cef肟oxime or cefdinir) plus clindamycin for non-type I penicillin allergy.\textsuperscript{9,10} Macrolides (azithromycin and clarithromycin) and trimethoprim-sulfamethoxazole are no longer indicated because of a high degree of antibiotic resistance.

Complications: Periorbital cellulitis and orbital cellulitis can occur most often secondary to acute bacterial ethmoiditis. Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema and brain abscess. Appropriate imaging and treatment with broad-spectrum intravenous antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin) should be initiated immediately. Surgical drainage may be required in select situations.

Acute otitis media (AOM)

Etiology: AOM can be caused both by bacteria and virus.

Bacterial: S pneumoniae, nontypable H. influenzae, Moraxella catarrhalis, rarely group A Streptococci, Staphylococci and Gram negative organisms.\textsuperscript{11} are the common bacteria.

Viral: Respiratory viruses may be identified in children with AOM either alone or along with bacteria. Respiratory syncytial virus (RSV), influenza, adenovirus, parainfluenza and rhinoviruses are commonly implicated.\textsuperscript{11}

Diagnosis: \textsuperscript{12} Children who present with moderate bulging of the tympanic membrane (TM) or new-onset otorrhea

Table I. Therapies not effective for the common cold in children

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Evidence</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Cochrane review of four studies\textsuperscript{5}(Level of evidence A)\textsuperscript{2}</td>
<td>No difference in persistence of symptoms for the common cold or acute purulent rhinitis compared with placebo</td>
</tr>
<tr>
<td>Over the counter antihistamines and antitussives</td>
<td>Cochrane review of two studies\textsuperscript{6}(Level of evidence B)\textsuperscript{2}</td>
<td>No more effective than placebo for cough</td>
</tr>
<tr>
<td>Dextromethorphan and Diphenhydramine</td>
<td>Cohort study\textsuperscript{7}(Level of evidence B)\textsuperscript{2}</td>
<td>Not superior to placebo in nocturnal cough or sleep quality in the child or parents</td>
</tr>
</tbody>
</table>

\textsuperscript{A} = consistent, good-quality patient-oriented evidence; \textsuperscript{B} = inconsistent or limited-quality patient-oriented evidence; \textsuperscript{C} = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.
not caused by otitis externa, mild bulging of the TM and recent (<48 hr) onset of ear pain or intense TM erythema (Fig.2) are suggestive of AOM.

Treatment: Oral paracetamol or ibuprofen gives relief from the pain in the initial 24 hours. Topical lidocaine or benzocaine is not much useful. As most episodes will spontaneously resolve and considering the burden of antimicrobial resistance, clinicians can adopt “watchful waiting” or observation prior to treating non-severe AOM with antibiotics provided the compliance for follow up is ensured.

Decision to start antibiotics or observation without antibiotics should be made on the basis of severity of the disease and age of the child (Table II) wherein non severe disease is one which has mild otalgia, fever < 39 ° C in the preceding 24 hours while moderate to severe otalgia or high grade fever is indicative of severe disease.

The treatment based on severity is given in Table III. The important reasons favouring antimicrobial treatment for AOM are that most of the episodes being caused by pathogenic bacteria, symptomatic improvement and resolution of symptoms occur much faster after starting antimicrobial and acute supplicative complications like mastoiditis can be prevented.

The antibiotic concentration in middle ear fluid exceeds the minimum inhibitory concentrations (MIC) of all pneumococcal isolates including the penicillin intermediate and highly resistant serotypes when high dose amoxicillin (80 mg/kg/day) is given. Amoxicillin – clavulanate may be considered in patients who have received amoxicillin in the previous 30 days or who have otitis–conjunctivitis syndrome (Possibility of H influenzae which may be beta-lactamase producer). The duration of treatment is 10 days.

For type I penicillin allergy azithromycin (efficacy is variable because of increasing rate of resistance) / respiratory quinolones (levofloxacin though not approved in children) and for non-type I penicillin allergy - Cefdinir, cefuroxime, cefpodoxime and ceftriaxone can be used since they are highly unlikely to be associated with cross reactivity on the basis of their distinct chemical structures.

Complications: Infratemporal complications can be TM perforation, chronic suppurative OM (CSOM), mastoiditis, hearing loss, facial nerve paralysis, cholesteatoma and labyrinthitis. Intracranial complications include meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess and sigmoid sinus thrombosis.

Acute pharyngitis / pharyngotonsillitis

Pharyngitis refers to inflammation of the pharynx, where there can be erythema, edema, exudates or an enanthem (ulcers, vesicles).

Box 1. Infectious etiology of acute pharyngitis in children

Viral: Rhinovirus, adenovirus, enterovirus, influenza virus, parainfluenza virus, corona virus, respiratory syncytial virus, Ebstein-Barr virus, Herpes simplex virus, human metapneumovirus.

Bacterial: Group A beta hemolytic streptococcus, group C and G streptococci, Arcanobacterium haemolyticum, N.gonorrhoea, Fusobacterium necrophorum, Corynebacterium diphtheriae, Chlamydomphila pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae.
Etiology: It can be viral or bacterial; the common etiological agents are described in Box 1.

Group A streptococcus: It is common between 5-15 years of age and decreases in frequency in late adolescent period. The pharynx will be erythematous, tonsils enlarged and often covered with exudates. There may be petechiae on the soft palate and posterior pharynx and the uvula may be red and swollen. When the papillae are inflamed, it gives the appearance of strawberry tongue. Tender anterior cervical lymphnodes, headache, abdominal pain and vomiting are frequently associated.

However, it is very difficult to differentiate viral and bacterial pharyngotonsillitis by history and clinical examination. McIssac score (Table IV) can be of help to differentiate both.\textsuperscript{15,16}

Table IV. Centor Score (Modified/McIsaac) for Streptococcal pharyngitis\textsuperscript{15,16}

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature &gt; 38°C (100.4°F)</td>
<td>1</td>
</tr>
<tr>
<td>No cough</td>
<td>1</td>
</tr>
<tr>
<td>Tender anterior cervical adenopathy</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillar swelling or exudates</td>
<td>1</td>
</tr>
<tr>
<td>Age 3-14 years</td>
<td>1</td>
</tr>
<tr>
<td>Age 15-44 years</td>
<td>0</td>
</tr>
<tr>
<td>Age ≥ 45 years</td>
<td>-1</td>
</tr>
</tbody>
</table>

If score 0 & 1: do not test for strep and do not treat.

Score 2: Treat - if rapid strep test is positive

Score 3: Two options - treat if rapid strep test is positive or treat empirically

Score 4: Treat empirically

Diagnosis: It can be confirmed by rapid antigen detection test (RADT) or throat swab culture. RADT is a point of care test. Recent study done on the utility of RADT in children observed that it has a high specificity of 98.4% and sensitivity of 89.7% with positive predictive value of 94.6% and negative predictive value of 96.9% and a diagnostic accuracy of 96.4%.\textsuperscript{17}

Table V. Treatment of pharyngotonsillitis\textsuperscript{18,19}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V, oral (children: 250 mg two or three times daily)</td>
<td>10 days</td>
<td>1st line</td>
</tr>
<tr>
<td>Amoxicillin (50 mg/kg/day) Max dose -1 gram/day</td>
<td>10 days</td>
<td>1st line</td>
</tr>
<tr>
<td>Azithromycin (12 mg/kg/day ) Max dose – 500 mg once daily Or Cephalexin (20 mg/kg/dose) twice daily. Max dose – 1 gram/day</td>
<td>5 days</td>
<td>If allergic to penicillin</td>
</tr>
<tr>
<td>Clindamycin (20 mg/kg/day) in 3 divided doses. Max dose – 1.8 gram/day.</td>
<td>10 days</td>
<td>Eradication of carrier state</td>
</tr>
</tbody>
</table>
Since it has an excellent specificity, if the test is positive throat swab culture is not necessary. If RADT is negative, but still if there is a strong clinical suspicion of Group A streptococcal pharyngitis, then throat swab culture should be done.

The main limitation of the test is that it is not freely available. An approach to the management of pharyngotonsillitis is shown in Fig.3.

**Treatment (Table V)**

The main aim of treatment is the prevention of acute rheumatic fever (ARF) and it is highly effective when started within 9 days of onset of illness. Antibiotics will not prevent acute post-streptococcal glomerulonephritis (APSGN). It is usually not necessary to attempt to eradicate the chronic carriage state. However, it may be attempted in circumstances like a community outbreak of ARF or APSGN; personal or family history of ARF; an outbreak of GAS pharyngitis in a closed community, repeated episodes of symptomatic GAS pharyngitis in a family with spread among family members despite adequate therapy or recurrent streptococcal pharyngitis.

**Complications:** The complications of GAS pharyngitis include i) Local supplicative complications such as parapharyngeal abscess and ii) Non-suppurative illnesses such as ARF, APSGN, post-streptococcal reactive arthritis and possible Pediatric autoimmune neuropsychiatric disorders associated with S.pyogenes (PANDAS) or Childhood acute neuropsychiatric symptoms (CANS).

**Other bacterial causes of pharyngitis:** Group C and Group G streptococcus and Arcanobacterium haemolyticum can cause pharyngitis in adolescents and

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Assigned score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Normal, including sleep = 0</td>
</tr>
<tr>
<td></td>
<td>Disoriented =5</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>None = 0</td>
</tr>
<tr>
<td></td>
<td>With agitation =4</td>
</tr>
<tr>
<td></td>
<td>At rest = 5</td>
</tr>
<tr>
<td>Stridor</td>
<td>None = 0</td>
</tr>
<tr>
<td></td>
<td>With agitation =1</td>
</tr>
<tr>
<td></td>
<td>At rest = 2</td>
</tr>
<tr>
<td>Air entry</td>
<td>Normal = 0</td>
</tr>
<tr>
<td></td>
<td>Decreased =1</td>
</tr>
<tr>
<td></td>
<td>Markedly decreased =2</td>
</tr>
<tr>
<td>Retractions</td>
<td>None=0</td>
</tr>
<tr>
<td></td>
<td>Mild =1</td>
</tr>
<tr>
<td></td>
<td>Moderate =2</td>
</tr>
<tr>
<td></td>
<td>Severe=3</td>
</tr>
</tbody>
</table>
### Table VII. Westley croup severity score - Interpretation

<table>
<thead>
<tr>
<th>Score</th>
<th>Severity</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>Mild</td>
<td>Occasional barky cough, no stridor at rest, mild or no retractions</td>
<td>Home treatment: Symptomatic care including antipyretics, mist and oral fluids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outpatient treatment: single dose of oral dexamethasone 0.15 to 0.6 mg/kg (maximum 16 mg)*</td>
</tr>
<tr>
<td>3 to 7</td>
<td>Moderate</td>
<td>Frequent barky cough, stridor at rest and mild to moderate retractions, but no or little distress or agitation</td>
<td>Single dose of oral dexamethasone 0.6mg/kg (maximum 16 mg)* Nebulized epinephrine¶ Hospitalization is generally not needed, but may be warranted for persistent or worsening symptoms after treatment with glucocorticoid and nebulized epinephrine</td>
</tr>
<tr>
<td>8 to 11</td>
<td>Severe</td>
<td>Frequent barky cough, stridor at rest, marked retractions, significant distress and agitation</td>
<td>Single dose of oral/IM/IV dexamethasone 0.6mg/kg (maximum 16 mg)* Repeated doses of nebulized epinephrine¶ may be needed Inpatient admission is generally required unless marked Improvement occurs after treatment with glucocorticoid and nebulized epinephrine</td>
</tr>
<tr>
<td>≥12</td>
<td>Impending</td>
<td>Depressed level of consciousness, stridor at rest, severe retractions, poor air entry, cyanosis or pallor</td>
<td>Single dose of Im/IV dexamethasone 0.6 mg/kg (maximumum 16 mg) Repeated doses of nebulized epinephrine¶ may be needed Intensive care unit admission is generally required Consultation with anesthesiologist or ENT surgeon may be warranted to arrange for intubation in a controlled setting</td>
</tr>
</tbody>
</table>

*IV: Intravenous; IM: Intramuscular; ENT: ear, nose, throat

*The intravenous preparation of dexamethasone (4 mg per mL) can be given orally; mix with flavored syrup.

†Nebulized epinephrine has an onset of effect within 10 minutes. Nebulized racemic epinephrine is administered as 0.05 mL/kg per dose (maximum of 0.5 mL) of a 2.25% solution diluted to 3mL total volume with normal saline. Racemic epinephrine is commercially available in the United States and some other countries as a nebulized preparation (i.e single-use preservative free bullets [ampoules]). Nebulized L-epinephrine is administered as 0.5 mL/kg per dose (maximum of 5 mL) of a 1mg/mL (1:1000) preservative-free solution. L-epinephrine is the same type of epinephrine used in other medical indications (eg, IM injection for anaphylaxis) and is widely available as a parenteral preparation. Use of either product by nebulization is acceptable and may be determined by availability and institutional protocol. Refer to topic for detail.


**Infectious upper airway obstruction**

Most of the infections in the upper airway are caused by viruses except diphtheria, acute epiglottitis and bacterial tracheitis.

**Croup:** The term croup refers to a heterogeneous group of mainly acute and infectious processes that are characterized by a bark like or brassy cough and may be associated with...
Table VIII. Difference between croup and epiglottitis

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Croup</th>
<th>Epiglottitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidity of onset</td>
<td>Progress over 12-48 hours</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>Preceding URI</td>
<td>Present</td>
<td>No</td>
</tr>
<tr>
<td>Cough</td>
<td>Barking cough</td>
<td>Minimal</td>
</tr>
<tr>
<td>Posture</td>
<td>Unremarkable</td>
<td>Tripod posture</td>
</tr>
<tr>
<td>Drooling of saliva</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>Temperature</td>
<td>Fever &lt; 38°C</td>
<td>High grade &gt;38°C</td>
</tr>
<tr>
<td>Stridor</td>
<td>Loud inspiratory</td>
<td>Soft</td>
</tr>
<tr>
<td>Cry</td>
<td>Hoarse</td>
<td>Muffled</td>
</tr>
</tbody>
</table>

hoarseness, inspiratory stridor and respiratory distress. It affects the larynx, trachea and bronchi. Common causative organisms are parainfluenza viruses (75%) followed by influenza A and B, adenovirus, respiratory syncytial virus and measles. It is common between the ages of 3 months and 5 years with a peak in the 2nd year of life. Croup is a clinical diagnosis and does not require a radiograph of the neck. It is diagnosed clinically and the severity is assessed by Westley Croup score (Table VI and VII). Radiographic confirmation of acute croup is not required in the vast majority of children with croup. Sometimes, severe laryngotracheobronchitis is difficult to differentiate from epiglottitis, despite more acute onset and rapid course of the latter.

Treatment: Oral steroids (single dose dexamethasone 0.15 mg/kg to 0.6 mg/kg) with or without nebulised epinephrine administered as 0.5 mL/kg per dose (maximum of 5 mL) of 1:1000 solution given over 15 minutes.

Epi glottitis

It is characterized by an acute rapidly progressive and fulminating course of high fever, sore throat, dyspnea and rapidly progressing respiratory obstruction.

Etiology: H.influenzae type B (unimmunized children), Streptococcus pyogenes, Streptococcus pneumoniae, nontypeable H. influenzae and Staphylococcus aureus are the common agents causing epiglottitis.

Epiglottitis is suspected in any child with 3D’s – distress, dysphagia and drooling. The child with sore throat and fever, typically becomes toxic within few hours and develops dysphagia and laboured breathing. Drooling is usually present and the neck is hyper extended to maintain the airway. The child may assume the tripod position, sitting upright and leaning forward with the chin up and mouth open while bracing on the arms.

Diagnosis: If epiglottitis is suspected, laryngoscopy should be done only in a controlled environment such as an operating room or intensive care unit. Anxiety-provoking interventions such as phlebotomy, intravenous line placement, placing the child supine or direct inspection of the oral cavity should be avoided. Radiograph of lateral neck is not necessary if index of suspicion is low (characteristic brassy cough and immunization with HiB) or high (impending airway obstruction).

Management: Airway management along with antibiotics. 1st line: Ceftriaxone or Cefotaxime for 7 to 10 days plus. Vancomycin if staphylococcus is suspected. There is no role for steroids or bronchodilators.

The major clinical differences between croup and epiglottitis is described in Table VIII.

Points to Remember

- Most of the upper respiratory tract infections are caused by viruses.
- Centor / McIssac score can be of help to differentiate viral and bacterial pharyngitis.
- Amoxicillin is the first line drug for acute otitis media, acute bacterial rhinosinusitis and Group A beta hemolytic streptococcus.
- Macrolides should be avoided for bacterial upper respiratory tract infections since there is a high degree of resistance.
- Avoid antibiotics for common cold, otitis media with effusion and croup.

References


**INFECTIONIOUS DISEASES**

**MISSED INFECTIONS – BRUCELLOSIS, MELIOIDOSIS**

*Jaydeep Choudhury*

Abstract: With changing epidemiology, widespread travel of human population and better diagnostic modality, the hitherto rare infections are being detected more frequently. The missed infections are gaining more importance. Brucellosis and melioidosis are two such infections which are not commonly seen but should be suspected as they have overlapping clinical presentation with many other infectious diseases and are liable to be missed if not suspected.

Keywords: Zoonoses, PUO, Rare infections.

**Brucellosis**

In the 19th century, brucellosis was known as Mediterranean fever, Malta fever, Crimean fever, Bang’s disease and later in 1913 as undulant fever following various outbreaks of this hitherto unknown fever. Transmission by fresh goat’s milk to humans was identified in the early 20th century. Subsequently it has been established that brucellosis is primarily a disease of the animals (zoonotic disease) and humans may acquire it by chance. It is also the most frequently encountered zoonotic disease worldwide. Humans acquire the disease from direct contact with an infected animal or consumption of products of an infected animal. Brucellosis in children is mainly food borne. It is usually associated with consumption of unpasteurized milk products. Human-to-human transmission of brucellosis is rare. Brucellosis affects people of all ages. Over the years many children suffering from brucellosis has been reported. Brucellosis is classified as category B biological weapon by CDC owing to the ease of facilitated transmission.

**Etiology**

Brucella are fastidious, nonmotile, non-spore forming gram-negative coccobacilli. Though it grows in various culture media, including blood and chocolate agar, in vitro growth is characteristically slow. The usual organisms responsible for human disease are Brucella abortus (cattle), Brucella melitensis (goat and sheep), Brucella suis (pig) and Brucella canis (dog). Lipopolysaccharide (LPS) antigen of the cell wall is the principal mediator in the pathogenesis of brucellosis. Organisms that escape phagocytosis get localized within the reticuloendothelial system and reside within liver, spleen, lymph nodes and bone marrow and result in granuloma formation.

**Pathogenesis**

The dynamics of transmission of brucella from animals to human varies in different places. Children frequently come in contact with animals if it is reared at home. Food borne infection can occur to anybody even without any direct contact. Incubation period is usually around 2-3 weeks. History of travel to brucella endemic regions, consumption of exotic food or unpasteurized dairy products may be an important clue to the diagnosis of brucellosis. Brucella can survive in various dairy products for up to 100 days. Other routes of transmission of brucella include inoculation through cuts or abrasions in the skin, inhalation of aerosols, inoculation of conjunctival sac or ingestion.

**Clinical features**

There is a wide spectrum of disease ranging from subclinical, mild to moderate disease in children, but the chronic form is rare. There may be various nonspecific clinical manifestations like anorexia, nausea, fatigue, sweats, weight loss and depression. Brucellosis can involve any organ or system of the body, but occasionally it can be localized. The classical triad of fever, arthralgia or arthritis and hepatosplenomegaly is seen in most patients and the constellation of these features should raise the suspicion of brucellosis. Sometimes children may present with lassitude, refusal to eat, refusal to bear weight and failure to thrive.

The following are the various localized involvements of brucellosis.

---

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  Institute of Child Health, Kolkata
  email: drjaydeep_choudhury@yahoo.co.in
**Osteoarticular:** Osteoarticular manifestations are the most frequent localized manifestation of brucellosis and are seen in up to half of brucellosis cases. In children usually the hips, knees, ankles or sacroiliac joints are involved and manifest as monoarticular arthritis. Spondylitis, osteomyelitis or inflammatory arthropathies are rare in children.

**Neurobrucellosis:** Headache and weakness is a frequent complaint in children suffering from brucellosis. But direct invasion of central nervous system is rare. Neurobrucellosis comprises of meningitis, encephalitis, myelitis, neuropathies and demyelinating syndromes. Vasculitis is a common feature of neurobrucellosis.

**Gastrointestinal:** Anorexia, nausea, vomiting, abdominal discomfort and weight loss are common in uncomplicated brucellosis. Ileitis, colitis, peritonitis and hepatitis are rare complications.

**Genitourinary:** Orchitis or epididymo-orchitis are the manifestations. Glomerulonephritis may be seen rarely.

**Respiratory:** Brucellosis may cause hilar adenopathy, lobar pneumonia, pleural effusion or empyema.

**Cardiovascular:** Endocarditis, myocarditis, pericarditis and aneurysm of aorta or cerebral vessels are rare but serious manifestations.

**Ocular:** Uveitis is the most frequent ocular lesion of brucellosis. Endophthalmitis, optic neuritis, keratitis and chorioretinitis are other rare complications.

**Cutaneous:** Rashes, abscess and vasculitis are usual manifestations.

**Hematological:** Anemia, leucopenia and thrombocytopenia are common manifestations in brucellosis which are generally mild but occasionally thrombocytopenia may be severe.

**Neonatal brucellosis:** Neonatal or congenital infections due to transmission from breast milk or blood transfusion has been described.

Relapse in brucellosis is defined by reappearance of signs and symptoms with or without positive culture. It usually occurs within 6 months and is milder. Relapse is frequently due to poor compliance. Sometimes it is due to inappropriate antibiotic, microbial virulence factors or focal infections.

**Differential diagnosis**

Various causes of fever of unknown origin including different causes for hepatosplenomegaly like typhoid, malaria, tuberculosis, leptospirosis, rickettsial diseases, HIV and lymphomas. Sometimes it may be confused with systemic onset juvenile idiopathic arthritis or even systemic lupus erythematosus.

**Investigations**

**Peripheral blood:** Anemia, pancytopenia or neutropenia and thrombocytopenia are the usual peripheral blood picture in brucellosis.

**Culture:** The definitive diagnosis of brucellosis is isolation of the organism from blood, bone marrow or other tissue. Isolation of brucella may take as long as 4 weeks; hence the laboratory should be alerted if brucellosis is suspected. It has been seen that *Brucella melitensis* is easier to culture than *Brucella abortus*. But the yield of culture varies depending on the method of culture.

**Serology:** Serum agglutination test (SAT) - Wright reaction by tube method is the standard method. It is dependent on the presence of anti-lipopolysaccharide antibody and measures the ability of serum to agglutinate killed organisms. The test should be done after 7 days of illness. A titer of 1:160 or higher in non-endemic area and titers of 1:320 or 1:640 or higher in endemic areas are considered diagnostic of brucellosis. Rose Bengal test (RBT) is a rapid screening test. The result should always be confirmed by other tests. ELISA test for brucellosis is less sensitive than SAT. PCR for brucellosis is available in few centers. It could be useful in diagnosing neuro-brucellosis where SAT is negative.

For practical purposes brucellosis can be diagnosed if any of the following laboratory criteria is present.

(a) Isolation of Brucella in clinical specimen

(b) Four-fold or greater rise in Brucella agglutination titer in serum 2 weeks apart

(c) Demonstration of Brucella by immunofluorescence in a clinical specimen

**Treatment (Table I)**

Brucella is sensitive to a number of oral and parenteral antibiotics in vitro. But treatment with a single antibiotic has resulted in relapse in many cases. Hence a combination antibiotic therapy for at least 6 weeks should be used in all cases. Doxycycline is probably the most effective agent. Doxycycline-aminoglycoside combination has not only least failure rate but also has the lowest chance of relapse and hence is the recommended regime in children above
Infected valves in children with endocarditis may need to be replaced early. Rarely the initiation of therapy may be accompanied by a Jarisch-Herxheimer type reaction due to high antigen load. This may require steroid therapy in severe cases.

**Prognosis**

Outcome is good if appropriate antibiotics are started early. Death is rare and may occur in presence of complications like endocarditis or neurobrucellosis.\(^1\)

### Prevention

Consumption of pasteurized milk and milk products are the mainstay of prevention of brucellosis. Children should be prevented from coming in close contact with sick domestic animals and adults should be educated about handling potentially infected materials.\(^1\)

### Melioidosis

Melioidosis is an infection caused by a Gram-negative bacterium, *Burkholderia pseudomallei*. It is found in soil and water and is of public health importance in endemic areas. Over the years it is expanding and becoming endemic in many parts of the world including the Indian subcontinent.

---

<table>
<thead>
<tr>
<th>Age</th>
<th>Drugs</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 years</td>
<td>Trimethoprim-Sulfamethoxazole combination PLUS Rifampicin orally for 6-8 weeks</td>
<td>Trimethoprim 10mg/kg/day (maximum 480 mg), sulfamethoxazole 50 mg/kg/day twice daily dose 15-20 mg/kg/day (maximum 600-900 mg/day)</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>Doxycycline in once daily dose PLUS Rifampicin orally for 6-8 weeks</td>
<td>2-4 mg/kg/day, maximum 200 mg/day</td>
</tr>
<tr>
<td></td>
<td>Doxycycline orally in once daily dose for 6-8 weeks PLUS Streptomycin, IM for 2 weeks</td>
<td>2-4 mg/kg/day, maximum 200 mg/day orally 15-30 mg/kg/day maximum 1gm/day</td>
</tr>
<tr>
<td></td>
<td>Doxycycline in once daily dose for 6-8 weeks PLUS Gentamicin IM or IV once daily for 2 weeks</td>
<td>2-4 mg/kg/day, maximum 200 mg/day orally 3-5 mg /kg/day</td>
</tr>
<tr>
<td>Endocarditis, osteomyelitis and meningitis (all ages)</td>
<td>Doxycycline once daily dose for 4-6 months PLUS Gentamicin IM or IV for 2 weeks PLUS Rifampicin orally for 4-6 months</td>
<td>2-4 mg/kg/day, maximum 200 mg/day 3-5 mg/kg/day 15-20 mg/kg/day, maximum 600-900 mg/day</td>
</tr>
</tbody>
</table>

---

8 years. The appropriate therapy in children below 8 years has not been established as tetracycline compounds are contraindicated in this age.\(^1\)

### Table I. Recommended treatment for brucellosis

<table>
<thead>
<tr>
<th>Age</th>
<th>Drugs</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2-4 mg/kg/day, maximum 200 mg/day 3-5 mg/kg/day 15-20 mg/kg/day, maximum 600-900 mg/day</td>
</tr>
</tbody>
</table>
Epidemiology

Burkholderia species can survive in moist environment for prolonged period. Melioidosis is seasonal, most of the cases occur during rainy season. It can be acquired by contact of abrasion or wounds with contaminated soil or water, inhalation of aerosols or dust particles containing organisms or ingestion of contaminated water or food. Percutaneous inoculation is the commonest mode of transmission. Underlying chronic disease like diabetes mellitus, renal disease, chronic pulmonary disease, thalassemia, cystic fibrosis, chronic granulomatous disease and other immunosuppressed conditions are the various risk factors. Incubation period ranges from 1 to 21 days but rarely it may be years also.

Clinical features

The clinical spectrum of melioidosis is wide, from asymptomatic infection, local infection to fulminant septicemia. The initial clinical finding may be a single primary skin lesion – vesicle, pustule, bulla or urticaria. Pneumonia is the commonest systemic presentation. Bacteremia is common. Genitourinary infections, skin infections, parotitis, septic arthritis, osteomyelitis and CNS infections including brain abscess are the other manifestations. In severe cutaneous infection, necrotising fasciitis may occur. In disseminated infection, hepatic and splenic abscesses may occur. Melioidosis should be considered in a patient with travel to endemic area at any time and having fever of unknown origin, overwhelming sepsis, single or multiple abscesses.

Investigation

Definitive diagnosis of melioidosis is by isolation of Burkholderia pseudomallei from blood or other infected sites. Organism can also be isolated by culture of sputum, throat swab or skin lesion specimens. PCR may help in rapid diagnosis. Serodiagnosis is not adequate in endemic area due to high background seropositivity.

Treatment

In acute melioidosis, ceftazidime 150 mg/kg/day q8h or meropenem 60 mg/kg/day q8h is the treatment of choice. Duration of therapy is 7 to 14 days. Oral co-trimoxazole with 8 mg/kg/day trimethoprim, q12h should be given for 3 to 6 months for eradication and to reduce the chances of recurrence. Chronic melioidosis can be treated with chloramphenicol, tetracycline or doxycycline.

Points to Remember

- Classical triad of brucellosis is fever, arthralgia or arthritis and hepatosplenomegaly.
- A combination antibiotic therapy of doxycycline-aminoglycoside for at least 6 weeks should be used in all cases to prevent treatment failure and relapse.
- Melioidosis can be acquired by contact of abrasion or wounds with contaminated soil or water, inhalation of aerosols or dust particles containing organisms or ingestion of contaminated water or food.
- Melioidosis should be considered in a patient with travel to endemic area at any time and having fever of unknown origin, overwhelming sepsis, single or multiple abscesses.
- In acute melioidosis, ceftazidime or meropenem for 7 to 14 days is the treatment of choice.

References

**CHEMOPROPHYLAXIS**

*Suhas V Prabhu*

**Abstract:** Chemoprophylaxis refers to the use of antibiotics in the prevention of infections and is an useful arm in the armamentarium to fight infections. It should be used only in select clinical situations where it has been shown to be effective. The clinical situation wherein it is recommended, the agents used, the doses required and the timing and duration of therapy are discussed.

**Keywords:** Antibiotics, Prophylaxis, Infections.

The word prophylaxis is derived from pro which is “before” and the Greek ‘phulaxis’ - ‘act of guarding’. When antimicrobials or chemotherapeutic agents are used for prophylaxis, it is referred to as chemoprophylaxis. Chemoprophylaxis is an important weapon in the fight against infections. It may be employed before the organism has invaded the host, where it is called ‘primary chemoprophylaxis’ or after the invasion has occurred (but before the symptoms/disease has occurred) in which case it is called ‘secondary prophylaxis’.

Judicious use of chemoprophylaxis can definitely reduce serious infections and their consequences in many clinical situations with high risk of infection. If not done with rational thought and correct selection, it can be counter-productive and may harm the patient by causing allergic reactions and side effects. More importantly, such misuse of antibiotics will sooner or later result in increased anti-microbial resistance in the community due to unwarranted evolutionary pressure of antibiotics on bacteria. Unfortunately, worldwide, there is even now a lot of incorrect use of antibiotics for prophylaxis, generally amounting to gross overuse and abuse. The wrong molecules are used, often in inappropriate situations and for unduly extended periods of time.

Prophylaxis aimed at infections with a single exogenous pathogen given over short period of time is likely to be more successful. Common examples where chemoprophylaxis is clinically effective to prevent some infections are: post-operative wound infections, repeated urinary tract infections, infective endocarditis, rheumatic fever, tuberculosis contacts, epidemic outbreaks and travellers to endemic areas. Enough studies have been done in many of these clinical scenarios and guidelines published which need to be scrupulously followed by clinicians. Changing scenario of infective organisms and their sensitivity patterns has resulted in repeated modifications of these guidelines and one needs to keep updated.

**Basic principles**

Chemoprophylaxis should be resorted to only if all the following three criteria are fulfilled:

- Target patient has a condition that makes him/her prone to develop the infection
- Organisms likely to cause the infection and their current drug sensitivity pattern are known
- For a finite period of time when the infection is likely to occur (and not indefinitely).

**Ideal antimicrobial agent**

The chemoprophylactic agent chosen should have a narrow spectrum targeted to the likely organism with little or no toxicity and side effects. It should achieve good bactericidal concentrations at the target site under risk of infection and additionally not alter the host’s flora or induce development of bacterial resistance. Ideally, it should be different from the agent generally used for therapy. Low cost and ease of administration (once or twice oral daily doses) are also desirable characteristics.

**Surgical site infections**

Surgical site infections occur in 2% to 5% of hospital surgeries and are associated with significant morbidity, mortality and increased healthcare costs. Therefore, prevention of these infections with judicious peri-operative chemoprophylaxis (along with other measures) is of top priority and rational use of prophylactic antibiotics is an important arm of antimicrobial stewardship as it will not only prevent infections but also thereby reduce antibiotic use. However, even in developed countries, there is still non-uniformity of surgical site chemoprophylaxis.
Following categorization of surgical procedures can provide a guide to the risk of surgical site infection and help to decide the appropriate chemoprophylaxis:

**Clean surgeries:** Elective, non-traumatic, without acute inflammation at operative site; no break or entry surgical into the gut, respiratory or urinary tracts, closed with primary suturing: Infection risk <2%.

**Clean contaminated surgeries:** Emergency surgeries with elective entry into the gut, respiratory or urinary tracts with minimal non-infected spill, minor break: Infection risk <10%.

**Contaminated surgeries:** Non-purulent inflammation/infection at site, gross spill, major break, penetrating trauma less than 4 hours, chronic wound grafting: Infection risk ~20%.

**Dirty and infected:** Purulent infection at the surgical site, pre-operative perforation of tract, penetrating trauma >4hrs. Infection risk ~40%. (Antibiotic usage in these cases can be actually considered as treatment rather than prophylaxis).

Common injuries at home or during play in a healthy child such as clean traumatic cuts, lacerations, abrasions and small superficial burns do not call for chemoprophylaxis. Wound cleaning and topical antiseptic application coupled with a keen follow-up are adequate.

**Choice of antibiotic agent**

The chemoprophylactic agent needs to be selected based on its efficacy against the possible pathogen. In clean surgeries, the usual source of infection is the skin flora (Staphylococci) and these should be the target. Therefore, a first or second generation cephalosporin like cefazolin or cefuroxime is the usual choice. Addition of vancomycin is to be considered only if the patient is colonized with methicillin resistant Staphylococcus aureus (MRSA). Vancomycin should also be considered in patients with a history of allergy to penicillins / betalactams. For surgeries in the head and neck, reproductive tract and colon/rectum addition of metronidazole is recommended to include coverage for anaerobic flora. Another option is to replace cefazolin with cefoxitin that has adequate anaerobic coverage to obviate the need to add metronidazole. An aminoglycoside may be added in gastro-intestinal (GI) surgeries if extended spectrum beta-lactamase (ESBL) producing organisms are dominant. In neonates (<72 hours of age), in order to cover group B Streptococci and Enterococci along with enteric gram negative bacilli, the recommended agents are ampicillin plus gentamicin. If the patient is already on broad spectrum antibiotics for pre-existing infections, additional chemoprophylaxis is unnecessary.

**Timing and duration**

It is obvious that one has to ensure high blood levels of the chemotherapeutic agent at the time of anticipated wound contamination i.e. at the time of the incision. The drug should therefore be administered just before the skin incision (15 to 60 minutes earlier). For antibiotics with a longer half-life and infusion time like vancomycin, administration may be started up to 2 hours prior to start of the surgery. A second dose will be needed if the surgery time exceeds twice the half-life of the antibiotic: e.g. cefazolin and cefuroxime should be re-dosed 4 hours after the first if the surgery is not over by that time. With this exception, most studies show no added benefit of extending antimicrobial prophylaxis to more than single dose and in fact contribute to the increase in antimicrobial resistance and adverse effects including C. difficile infection. The doses used are given in Table I.

**Recurrent urinary tract infection (UTI)**

Recurrent UTIs have a potential to cause renal parenchymal injury and long term deterioration of renal function. It is also known that infants and young children with a single UTI have a high recurrence rate of about 30 to 50%, mostly during subsequent 3-6 months. Use of chemoprophylaxis in such cases to prevent recurrent infections therefore appears clearly justified. There is no evidence to suggest that such long term prophylactic antibiotic use results in high rates of antibiotic resistance.

**Table I. Doses of antibiotics used for surgical prophylaxis (all given intravenously)**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose (mg/kg/dose)</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>50</td>
<td>3 g</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>30</td>
<td>2 g</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>30-50</td>
<td>1.5 g to 2g</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>40</td>
<td>1 g</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>240 mg</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15</td>
<td>1 g</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15</td>
<td>1 g to 2 g</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>10-15</td>
<td>500 mg</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10-20</td>
<td>600 mg</td>
</tr>
</tbody>
</table>
Children with congenital anomalies of kidney and urinary tract (CAKUT) such as vesico-ureteral reflux (VUR) are at even higher risk of renal damage and must receive chemoprophylaxis till the reflux resolves spontaneously or by surgery. However logical this may sound, the current evidence for the efficacy and benefits of chemoprophylaxis for recurrent UTI is conflicting and controversial. It is generally agreed that it has modest benefits in preventing recurrent febrile/symptomatic UTI but possibly without significant benefits in reduction of long term renal dysfunction and hypertension. Consequently, different regional guidelines vary in considerations and recommendations. The current Indian Academy of Pediatrics (IAP) guidelines recommend continuous chemoprophylaxis to prevent recurrent UTI. Situations calling for continuous prophylaxis include

i. UTI below 1-year of age while awaiting imaging studies

ii. VUR:
   a. For grades I and II until 1 year of age is reached. Restart prophylaxis if breakthrough febrile UTI.
   b. For grade III - V prophylaxis till age 5 years. If breakthrough occurs, consider surgery. Extend prophylaxis beyond 5 if bladder bowel dysfunction.

iii. Recurrent and frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal. Here prophylaxis should be continued for 6 months -1 year.

iv. Antibiotic prophylaxis is not advised in patients with urinary tract obstruction (e.g., posterior urethral valves), urolithiasis and neurogenic bladder and in patients on clean intermittent catheterization.

**Recommended agents:** Drugs with high urinary concentrations and least systemic levels, acting against common uro-pathogens i.e. gram-negative enteric bacteria and perineal flora, are recommended. Any one of drugs in Table II may be used as a single daily dose at bedtime

### Infective endocarditis

Infective endocarditis is a life threatening complication. Even though curable, it has the potential to significantly impair the prognosis in children with cardiac disease. Prevention of infective endocarditis in susceptible children is one of the oldest and well-established indications for chemoprophylaxis.

The latest (2007) American Heart Association (AHA) guidelines have major changes in recommendations and offer a more conservative approach based on widely accepted evidence to focus on optimal oral hygiene more than episodic chemoprophylaxis to prevent infective endocarditis. The committee felt that prophylaxis may prevent an exceedingly small number of cases of infective endocarditis, if any, in individuals who undergo gastrointestinal or genito-urinary (GU) tract and many non-invasive dental procedures and the risk of antibiotic-associated adverse events would exceed the benefit, if any, from prophylactic antibiotic therapy. Thus the new recommendations say that chemoprophylaxis

### Box 1. Cardiac conditions associated with high risk of infective endocarditis

- Acquired valvular heart disease with stenosis or regurgitation.
- Prosthetic valve replacement or repair.
- Previous infective endocarditis.
- Completely repaired structural congenital heart defect with prosthetic material or device during the first 6 months after the procedure-(period of incomplete endothelialisation).
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD, including palliative shunts and conduits.
  - Unrepaired acyanotic CHD except isolated ostium secundum atrial septal defect.
  - Repaired CHD with residual defect(s) at the site or adjacent to a prosthetic patch/device.
- Hypertrophic cardiomyopathy.
- Cardiac transplantation with subsequent cardiac valvulopathy.

### Table II. Agents for use in UTI prophylaxis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-</td>
<td>2 mg/kg/dose (Trimethoprim)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>(Above 2 months of age only)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1-2 mg/kg/dose (Above 2 months of age only)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>10 mg/kg/dose</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>20 mg/kg/ dose</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>10 mg/kg/ dose</td>
</tr>
</tbody>
</table>
should be restricted to a group of children having cardiac abnormalities that have a high risk of adverse outcome and that too for only certain dental procedures. No significant change has been reported in the infective endocarditis hospitalisation rates over the last 11 years in the United States of America (USA) after implementation of this revised guidelines.11

List of cardiac conditions associated with high risk of infective endocarditis (requiring prophylaxis) is shown in Box 1.

### Table III. Regimens for antimicrobial prophylaxis for infective endocarditis

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Route</th>
<th>Regimen: Single Dose 1/2 to 1 hour before Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>PO</td>
<td>50 mg/kg max.2 g</td>
</tr>
<tr>
<td>Unable to take orally</td>
<td>Ampicillin</td>
<td>IM/IV</td>
<td>50 mg/kg max.2 g</td>
</tr>
<tr>
<td>Allergic to penicillin</td>
<td>Cephalexin/Cefuroxime OR</td>
<td>PO</td>
<td>50 mg/kg max.2 g</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>PO</td>
<td>10 mg/kg max. 600 mg</td>
</tr>
<tr>
<td></td>
<td>Azithromycin /Clarithromycin</td>
<td>PO</td>
<td>15 mg/kg max.500 mg</td>
</tr>
<tr>
<td>Allergic to penicillins and unable to take oral medication</td>
<td>Cefazolin OR</td>
<td>IM/IV</td>
<td>30 mg/kg max. 1 gm</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone OR</td>
<td>IM/IV</td>
<td>50 mg/kg max. 1gm</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>IM/IV</td>
<td>10 mg/kg max. 600mg</td>
</tr>
</tbody>
</table>

Dental procedures for which endocarditis prophylaxis is reasonable for patients with the cardiac problems listed above are all those that involve manipulation of gingival tissue, periapical region of the teeth or perforation of the oral mucosa, biopsies, suture removal, or placement of orthodontic bands. Other dental procedures like routine anaesthetic injections through non-infected tissue, dental radiographs, placement/adjustments of removable

### Table IV. Drug choices for chemoprophylaxis to prevent recurrence of rheumatic fever

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine Penicillin</td>
<td>IM</td>
<td>1.2 million U-Wt &gt;27kg 600 000 U-Wt &lt; 27 kg</td>
<td>every 3 to 4weeks</td>
</tr>
<tr>
<td>OR</td>
<td>Penicillin V</td>
<td>Oral 250 mg</td>
<td>twice a day</td>
</tr>
<tr>
<td>Sulfadiazine or sulfisoxazole</td>
<td>Oral</td>
<td>0.5 g-wt &lt; 27 kg 1.0 g-wt &gt; 27 kg</td>
<td>once a day</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Oral</td>
<td>250 mg</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Oral</td>
<td>250 mg (6mg/kg)</td>
<td>Once a day</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Oral</td>
<td>15 mg/kg</td>
<td>Twice a day</td>
</tr>
</tbody>
</table>

### Table V. Duration of prophylaxis for people who have had acute rheumatic fever: (Recommendations of the American Heart Association)

<table>
<thead>
<tr>
<th>Category</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever without carditis</td>
<td>5 years since last episode of ARF or until 21 years of age, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever with carditis but without residual heart disease (no valvular disease)</td>
<td>10 years since last episode of ARF or until 21 years of age, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever with carditis and residual heart disease (persistent valvular disease)</td>
<td>10 years since last episode of ARF or Until 40 years of age, whichever is longer; consider lifelong prophylaxis for people with severe valvular disease or likelihood of ongoing exposure to group A streptococcal infection</td>
</tr>
</tbody>
</table>
Table VI. Recommendations for chemoprophylaxis of malaria for travellers

<table>
<thead>
<tr>
<th>Indications</th>
<th>Antimalarial agent</th>
<th>Route</th>
<th>Frequency</th>
<th>Dose</th>
<th>Timing and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All travellers to malaria endemic areas coming from non-malaria area</td>
<td>Doxycycline</td>
<td>PO</td>
<td>Once a day</td>
<td>2.2 mg/kg, max. 100 mg</td>
<td>2 days before, through 4 weeks after travel</td>
</tr>
<tr>
<td>Consider prevalent plasmodium species, local drug sensitivity/resistance status</td>
<td>Atovaquone + Proguanil (combination) <strong>Pediatric tablet</strong>- 62.5mg ato.+25mg proguanil</td>
<td>PO</td>
<td>Once a day</td>
<td>5–8 kg- ½ped.Tab, &gt;8–10 kg- ¾ped.tab &gt;10–20 kg- 1ped.Tab, &gt;20–30 kg-2ped.tabs &gt;30–40 kg 3ped.Tabs, &gt;40 kg 1 adult tab</td>
<td>2 days before, through 7 days after travel</td>
</tr>
<tr>
<td>Only in mefloquine sensitive areas</td>
<td>Mefloquine</td>
<td>PO</td>
<td>once a week</td>
<td>≤ 9kg 5 mg/kg &gt; 9–19 kg ¼ tablet &gt; 19–30 kg ½ tablet &gt; 30–45 kg ¾ tablet &gt; 45 kg 1 tablet Each tablet- 250 mg salt</td>
<td>2 weeks before, through 4 weeks after travel</td>
</tr>
<tr>
<td>Only in chloroquine sensitive area</td>
<td>Chloroquine</td>
<td>PO</td>
<td>Once a week</td>
<td>5mg/kg (base), max 300mg</td>
<td>2 weeks before, through 4 weeks after travel</td>
</tr>
<tr>
<td>Only for short travel to vivax area</td>
<td>Primaquine</td>
<td>PO</td>
<td></td>
<td>0.5 mg/kg (base) max. 30 mg</td>
<td>2 days before, through 7 days after travel</td>
</tr>
</tbody>
</table>

appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa do not require prophylaxis. The regimens recommended to be followed are listed in Table III.

**Rheumatic fever (RF)**

Group A streptococcal (GAS) infections, mainly tonsillo-pharyngitis have a potential risk of late complications like rheumatic fever which can result in permanent damage to cardiac structures and function. Each subsequent infection with this organism can add to the cardiac risk and hence prophylaxis is warranted.

Primary prevention of first attack of RF is reliably achieved by optimum antibiotic therapy and eradication of GAS from throat. This requires a complete 10day course of oral penicillin or a single intramuscular injection of benzathine penicillin (age and weight appropriate dose). Secondary prevention of rheumatic fever is achieved by continuous antibiotic prophylaxis in children with a well-documented history of rheumatic fever and/or confirmed
**Table VII. American Academy of Pediatrics recommendations for chemoprophylaxis for contacts of high risk/invasive infection**

<table>
<thead>
<tr>
<th>Organism/disease</th>
<th>AP eligibility/indications</th>
<th>Antimicrobial Agent</th>
<th>Route</th>
<th>Frequency</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Only in high risk contacts within &lt;48hrs of exposure</td>
<td>Oseltamivir</td>
<td>PO</td>
<td>Once a day</td>
<td>3mth-1yr: 3mg/kg, &gt;1yr and&lt;15kg: 30mg, 15kg-23kg: 45mg, 23-40kg: 60mg and &gt;40kg:75mg</td>
<td>10 days</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><strong>After exclusion of active TB disease in</strong>&lt;br&gt;1 All asymptomatic contacts of TB (&lt;6 years age)&lt;br&gt;2 All neonates of mothers with TB in pregnancy&lt;br&gt;3 All MT+ve children with HIV/immunosuppressive therapy&lt;br&gt;4. All HIV infected children between age 1-5 years</td>
<td>Isoniazid*</td>
<td>PO</td>
<td>once a day</td>
<td>10mg/kg</td>
<td>6months</td>
</tr>
<tr>
<td>Meningococcal Disease</td>
<td>Close contacts (&gt;8hours,&lt;3feet) of a patient of invasive meningococcal disease or direct exposure to respiratory secretions</td>
<td>Rifampicin OR Ceftriaxone</td>
<td>PO</td>
<td>every 12hrly</td>
<td>&lt;1mth-5mg/kg&lt;br&gt;1mth-10mg/kg</td>
<td>2days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IM</td>
<td>single dose</td>
<td>&lt;15years 125mg&lt;br&gt;15years 250mg</td>
<td>Only once</td>
</tr>
<tr>
<td>Hemophilus influenza b</td>
<td>Close contact (&lt;10years age) of a patient of invasive Hib disease-household/ (&gt;4hours over 5/7days before hospitalization) Household contacts &lt;18years age with immunocompromise</td>
<td>Rifampicin</td>
<td>PO</td>
<td>once a day</td>
<td>&lt;1mth-10mg/kg&lt;br&gt;1mth – 20mg/kg (max 600mg)</td>
<td>4days</td>
</tr>
</tbody>
</table>
rheumatic heart disease.\textsuperscript{12} Again, a weight adjusted dose of benzathine penicillin given intramuscularly once every 3 weeks is the best regimen. Oral penicillin V, sulfadiazine, sulfisoxazole and macrolides are options to be considered only in situations where injectable penicillin is not possible or tolerated (Table IV). The duration for which prophylaxis is recommended depends on the extent of pre-existing cardiac involvement and is shown in Table V.

### Malaria

Malaria is a common and life-threatening disease transmitted in many tropical and subtropical areas. Travellers from non-malarial regions (who would be having no or partial specific immunity to malaria) are at risk of severe malaria during visit to any of those countries or areas where malaria is endemic. Residents of malaria endemic areas who travel to non-endemic regions are at risk of malaria if they receive a wrong dose or fail to take their medication regularly. A weight adjusted dose of sulfadoxine-pyrimethamine with a fixed dose ofFansidar (Fansidar) is the prophylactic drug of choice (Table IV). The duration of prophylaxis is determined by the length of stay in the malarial area and is shown in Table V.
endemic regions including India are immune to severe malaria due to repeated clinical and subclinical malaria episodes, hence do not require prophylaxis. Simultaneously, advocating personal protective measures against mosquito bites is also important. While complete protection from malaria cannot be guaranteed, good adherence to the recommended chemoprophylaxis significantly reduces the risk of fatal malaria disease. As the species of plasmodium causing malaria and their drug resistance patterns vary in various regions chemoprophylaxis with regard to efficacy and possible adverse effects has to be tailored to each region separately. Updated information on this is freely accessible at local/national health agency and World Health Organization (WHO) and (Centers for Disease Control and Prevention) CDC websites. For travellers to India options include daily doxycycline, weekly mefloquine or daily atovaquone and proguanil. Complete current (2017) recommendations are listed in Table VI.

Prophylaxis for Contacts of high risk/ invasive pathogens

Infectious diseases that are due to invasive pathogens with a risk of severe disease, especially those not easily amenable to treatment are indications for chemoprophylaxis. Prompt and correct chemoprophylaxis can be effective in preventing an otherwise dangerous outcome.

Apart from appropriate index case diagnosis of high-risk infection and its management, identification and evaluation of close contact with high risk population is important. The pediatrician can then offer early pathogen specific chemoprophylaxis as given in table VII. For travellers to India options include daily doxycycline, weekly mefloquine or daily atovaquone and proguanil. Complete current (2017) recommendations are listed in Table VI.

Post exposure chemoprophylaxis (PEP) for occupational exposure to human immunodeficiency virus (HIV)

This is an example of prophylaxis to prevent infection in health care personnel involved with the care of children/patients with infection with HIV. The recommendations vary with the serological status of the patient and the type or extent of the exposure.

Blood or visibly bloody fluids or other potentially infectious material (e.g. semen; vaginal secretions; breast milk and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) are the only source fluids that carry meaningful risk. Exposure to saliva, tears, sweat, or non-bloody urine or faeces does not require PEP. The risk of transmission of HIV following percutaneous exposure is around 0.3% and following mucosal exposure is 0.09%. Inspite of the low risk, PEP is recommended because of the serious nature of the HIV infection.

While the National AIDS Control Organization (NACO) of India recommends two or three drug regime based on the severity of exposure and HIV status of the host, international guidelines recommend three drug regimens for all irrespective of mucosal/ percutaneous exposure, severity of the exposure and the status of disease in the host. The common international regimes include two nucleoside reverse transcriptase inhibitors (NRTI) (tenofovir and emtricitabine) with either a boosted protease inhibitor (atazanavir/ lopinavir) or integrase strand inhibitors (raltegravir/ dolutegravir) starting as soon as possible after exposure but not later than 24 hours after exposure and continued for a period of 28 days. The health care worker should be counselled about adherence and monitored for adverse effects of the drugs. Complete blood counts, liver and renal function tests should be done 2 weeks after the initiation of therapy. HIV antibody test should be done 3 months after exposure to confirm success. Health care workers who are pregnant/ intolerant to the drugs or exposed to drug resistant HIV should be referred to a specialist. The same regimen can be given to adolescents or adults with history of sexual exposure (or rape victim) to a person with suspected or confirmed HIV infection if started within 36 hours of exposure.

Points to Remember

- **Chemoprophylaxis is an important weapon in the fight against infections.**
- **Antimicrobial chemoprophylaxis is useful only in very select clinical situations.**
- **One must follow the standard recommendations/guidelines for drug choices, doses and duration.**
- **Haphazard antimicrobial use for prophylaxis is not effective and can actually worsen the situation.**

References


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**CLIPPINGS**

*Human milk as a protective factor for bronchopulmonary dysplasia: a systematic review and meta-analysis*

A systematic review and meta-analysis were performed to summarise current evidence evaluating the effects of human milk on the risk of bronchopulmonary dysplasia (BPD) in preterm infants. Studies on human milk and BPD in English and Chinese databases were searched on 26 July 2017. Furthermore, the references of included studies were also screened. The inclusion criteria in this meta-analysis were the following: (1) preterm infants (<37 weeks); (2) human milk; (3) comparing with formula feeding; (4) the outcome included BPD; and (5) the type of study was randomised controlled trial (RCT) or cohort study. A total of 17 cohort studies and 5 RCTs involving 8661 preterm infants met the inclusion criteria. The ORs and 95% CIs of six groups were as follows: 0.78 (0.68 to 0.88) for exclusive human milk versus exclusive formula group, 0.77 (0.68 to 0.87) for exclusive human milk versus mainly formula group, 0.76 (0.68 to 0.87) for exclusive human milk versus any formula group, 0.78 (0.68 to 0.88) for mainly human milk versus exclusive formula group, 0.83 (0.69 to 0.99) for mainly human milk versus mainly formula group and 0.82 (0.73 to 0.93) for any human milk versus exclusive formula group. Notably, subgroup of RCT alone showed a trend towards protective effect of human milk on BPD but no statistical significance. Both exclusive human milk feeding and partial human milk feeding appear to be associated with lower risk of BPD in preterm infants. The quality of evidence is low. Therefore, more RCTs of this topic are needed.

CARE BUNDLE FOR PREVENTION OF ICU AQUIRED INFECTIONS

*Vasanth Kumar  
**Suchitra Ranjit

Abstract: Bundle is a collection of evidence based medical practices that help in improving outcome. Care bundles contribute to infection prevention, reduce unnecessary antibiotic usage and may limit the development of antibiotic resistance. Hand hygiene and aseptic techniques are important elements of any care bundle. The components of ventilator associated pneumonia bundle aim to prevent micro-aspiration, colonization of upper airway and gastrointestinal tract with potentially pathogenic organisms and contamination of ventilator circuit. The components of catheter associated infection prevention bundle aim to prevent extraluminal transmission of microorganisms from patient’s skin and intraluminal transmission via direct contamination of the catheter or tubing. Care bundles are relatively easy to develop and implement in hospital set up using Plan-Do-Study-Act model with help of a team member identified as a bundle champion.

Keywords: Bundle, Ventilator associated pneumonia prevention bundle, Central line care bundle, Catheter associated urinary tract infection prevention bundle, Plan-Do-Study-Act cycle

Definition

In medical practice, “bundle” is a group of care elements for a given disease / problem that are evidence-based and that, when executed together, may result in better outcomes than if implemented individually.¹

Bundle vs checklist

Though bundles and checklists appear similar, bundle has a higher clinical significance than checklist. A checklist is generally used as a reminder where multiple elements (usually >5) have to be completed. Unlike bundles, all components in checklist are not necessarily evidence based. On the contrary, a bundle brings all interventions together as a package, which must be followed for each and every patient, every single time. Moreover all the elements of the bundle are necessary and removing any one of them will result in inferior result.¹

Characteristics

(i) Each and every component of care bundle is vital for achieving the desired outcome.

(ii) If any one component of the bundle is skipped, it will result in an unsatisfactory outcome.

(iii) The individual elements in a bundle are straightforward, non-controversial, evidence-based recommendations based on randomized control trials.

(iv) Care bundle is an all or none phenomenon (i.e.) either the entire bundle is executed or not. There is no scope for partial performance.²

Types

There are several bundles available that can be employed in hospital setting. These contribute to infection prevention, reduce unnecessary antibiotic prescription and may limit the development of antibiotic resistance in healthcare facilities. This article will discuss on the three common ICU bundles employed worldwide as a part of infection control measure.

A. Ventilator associated pneumonia (VAP) prevention bundle

VAP is the second most common hospital acquired infection in PICU patients. VAP leads to increased duration of mechanical ventilation, intensive care stay, mortality risk and increase in medical costs. This implies that the primary aim of the VAP bundle is to reduce complications associated with mechanical ventilation. For this reason, ventilator bundle is regarded as an important component of patient safety in pediatric critical care patients.³
Basic practices to be followed for prevention of VAP:

Head end elevation: It is the simplest and most cost-effective method of decreasing VAP incidence. It decreases VAP by reducing the risk of aspiration of gastrointestinal, oropharyngeal and nasopharyngeal secretions. It also improves ventilation, as supine patients generate lower spontaneous tidal volumes on pressure support than those seated in upright position. For all children 30-45° elevation is the standard, but for neonates 15-30° is acceptable as it is sometimes difficult to maintain baby position.4

Daily assessment for readiness to extubate: Sedation in ventilated patients may be necessary to control anxiety, reduce pain and control oxygenation needs. The right level of sedation needs to be optimized. Too little sedation can lead to increased anxiety, increased work of breathing, decreased oxygenation and self-extubation. Excess sedation can lead to hemodynamic instability, decreased respiratory muscle function, prolonged neurological depression and delayed liberation from mechanical ventilation. Prolonged mechanical ventilation is an independent risk factor for VAP. The use of a ‘sedation scale’ to monitor the level of sedation will help to deliver the most effective sedation dose and reduce duration of mechanical ventilation and is highly recommended. Spontaneous breathing trial daily and assessment for extubation, decreases the duration of mechanical ventilation and incidence of VAP. Sedation interruptions, a strategy used in adults is not recommended in children as it may increase the frequency of unplanned extubations and reintubations.4

Oral care: Most VAP’s are caused by aspiration of bacteria colonizing the oropharynx or upper GI tract of the patient. Oral care four times a day has been shown to reduce the VAP rates. Chlorhexidine is widely used for oral care for children older than 2 months of age. Its usage in less than 2 months is limited due to its safety concern of causing irritation and systemic absorption.5

Ventilator circuit care: Ventilator heated wire circuits should be used to decrease the occurrence of condensate. The water accumulated in a non heated wire circuits should be drained away every 2-4 hours and prior to every position change and should be treated as an infectious waste. The ventilator circuits should be changed when it is visibly soiled or malfunctioning. Remember that hand hygiene is important before and after contact with ventilator circuits.5

Cuffed endotracheal tube (ET) tube and maintenance of cuff pressure: Cuffed ET tubes have been proven to be safe and found to decrease the risk of micro-aspiration. Low pressure high volume cuff is preferred. The cuff pressure and volume is maintained at the minimal occlusive settings to prevent clinically significant air leaks around the endotracheal tube, typically around 20 cm of water. ET tube with subglottic drainage ports have been found beneficial in adults. These are available from 6.0 size ET tube and hence can be used in children above 10 years of age.4

Deep throat suction before ET suction: Presence of pooled secretions above the ET tube cuff are reservoirs of potentially pathogenic bacteria. Therefore, thorough oropharyngeal suctioning should be performed before deflating the cuff to reposition the ETT or before checking cuff pressure.4

Aspiration devices: Oral aspiration device (Yankauer suction tube) should be kept in a clean non-sealed plastic bag when not in use. ET aspiration catheter should not be reused. In-line aspiration catheter systems should be changed if soiled or otherwise indicated.5

To summarise, while recommendations for pediatric VAP prevention are successfully practiced world-wide, high-level evidence for pediatric bundle components is sparse. Moreover the heterogeneity in the bundle components used by different studies makes it difficult to identify the impact of each individual component.6 For instance, though stress ulcer prophylaxis has been part of VAP bundle in adults, some studies have found that H2 blockers raise the gastric pH and increase gastric colonization rates and thereby the risk of VAP.7 Similarly thromboembolism prophylaxis is not recommended in children.4 Since stress ulcer and thromboembolism prophylaxis have gone out of favour, some have replaced them with daily oral care, ventilator circuit care and suctioning precautions.8,9

B. Central line care bundle

Central line related blood stream infections contribute to significant morbidity, mortality and health care utilization rates. Though in earlier days infections were thought as inevitable, nowadays with strict and meticulous care, the incidence has come down drastically.

Basic practices to be followed:10

(i) Check if there is a clear indication for central venous catheter insertion.

(ii) Healthcare personnel involved in insertion, care and maintenance of central venous catheters (CVCs) should be educated about Central Line Associated Blood Stream Infection (CLABSI) prevention.
(iii) Daily bathing of all ICU patients with chlorhexidine has been shown to prevent blood stream infection.

**During insertion:**

1. **Hand hygiene:** To be followed immediately before and after patient contact.
2. **Use of full barrier precautions:** Maximal sterile barriers and aseptic technique, including a sterile gown, sterile gloves and a large sterile “full body” drape.
3. **Chlorhexidine skin antisepsis:** Skin preparation with 2% chlorhexidine gluconate in 70% isopropyl alcohol is used and allowed to dry for at least 30 seconds. Povidone iodine can be a suitable alternative. Aseptic technique is maintained throughout insertion of catheter.
4. **Optimal catheter type and site:** A catheter with the minimum number of ports or lumens necessary for that patient should be selected. Any site is acceptable in children. The risk of infection with peripherally inserted central line (PICC) line is same as central venous catheter.
5. **Document details of insertion in the records (including date, location, catheter lot number and signature and name of operator undertaking insertion).**

**Post insertion**

1. Ensure appropriate nurse-to-patient ratio in ICU to manage patients with CVCs and keep the number of floating nurses to a minimum.
2. Daily review if line is necessary and prompt removal of unnecessary catheters.
3. Transparent dressings to be applied to facilitate regular site inspection. Site care can be performed with chlorhexidine-based antiseptic every 5-7 days or immediately if the dressing is soiled. The gauze dressings can be changed every 2 days or earlier if soiled.
4. **Administration sets which are not used for lipids or blood products may be left in place up to 96 hours without increasing infection risk.**
5. “**Scrub the hub**” to disinfect the access ports: All catheter hubs, needleless connectors and injection ports to be disinfected with alcoholic chlorhexidine for at least 5 seconds (ideally 20 seconds) before accessing the catheter.

**Things not considered part of CLABSI prevention**

1. Routine use of systemic antimicrobial prophylaxis at the time of insertion or when catheter is in-situ.
**Twelve step suggestions**

The following 12 steps are followed to implement care bundle in hospital setup:

1. Every hospital can try to identify a problem in a particular area so that care bundle can be implemented for the same.

2. It should be understood that bundles are not a panacea for all infection risks and should be implemented in a targeted group of patients, in a common hospital location like PICU.

3. Ensure the items in the bundle are straightforward and easy to carry out. Complex interventions can hinder the practical accomplishment of a bundle.

4. The components of a bundle should be regularly updated with changing evidence and not be static.

5. Identify members of the healthcare team (e.g. Zero VAP team) to test the execution of the proposed bundle elements.

6. Create awareness through necessary training and education and provide the team with practicable guidelines and evidence to execute the bundle.

7. Get sanction from hospital management and clearly define the goal and purpose of the desired project and communicate this message to the members of healthcare team.

8. Establish an appropriate methodology e.g. Plan-Do-Study-Act (PDSA) cycle to implement the new care bundle to practice (Fig. 1). Perform the interventions in bundle element each and every time for every eligible patient.

9. It is a good idea to have an identified person as a team leader or a bundle champion to oversee the process, troubleshoot problems and track the progress.

10. The bundle champion can track the compliance of bundle performance as an “all or none” phenomenon.

11. The tracking should be accurate, consistent and ongoing to authentically reflect hospital practice and outcome.

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**Fig.1. Model PDSA cycle for implementing a new “Care Bundle”**
feedback should be taken frequently (monthly or more frequently if possible) to encourage improvement and sustainability.

12. Address logistical concerns to make it easy to deliver the bundle as part of the system of care and workflow.

**Points to Remember**

- **Each and every component of care bundle is vital for achieving the desired outcome.**
- **Bundles contribute to infection prevention, reduce unnecessary antibiotic usage and may limit the development of antibiotic resistance.**
- **Pediatric ventilator bundle consists of head end elevation, daily assessment for readiness to extubate, daily oral care, ventilator circuit care and suctioning precautions.**
- **Central line care bundle includes hand hygiene, maximal barrier precautions, chlorhexidine for skin preparation, transparent dressing and prompt removal of the catheter.**
- **Routine antibiotic prophylaxis and routine replacement of central line or urinary catheter is not recommended.**

**References**

**SUPERBUGS**

*Dhanya Dharmapalan*

**Abstract:** Superbugs have emerged among the microbes through the evolution of “survival of the fittest”, the speed of this evolution being fuelled by injudicious use of antibiotics in humans and animals. These are multidrug resistant microbes against which the effectiveness of antibiotic armamentarium is limited and cause increased mortality and morbidity. Multidrug resistant Acinetobacter baumannii and Carbapenemase producing Klebsiella pneumoniae are the leading superbugs among Gram negative bacteria whereas drug resistant staphylococcus species, enterococcus, Streptococcus pneumoniae are the common Gram positive superbugs. Superbug forms of Salmonella typhi and Mycobacterium tuberculosis pose a great public health challenge for elimination. Treatment of these infections should be preferably guided by experts in infectious diseases and good infection control practices. An efficient antibiotic stewardship and infection control practices seem to be our only hope to buy time in the battle against these superbugs.

**Keywords:** Superbugs, Antibiotic resistance, Infection control, Carbapenemases, Methicillin resistant Staphylococcus aureus.

The term “superbugs” refers to the microbes which have undergone multiple mutations and exhibit high levels of resistance to antibiotic classes which are specifically recommended for their treatment. As a result there are very limited therapeutic options and increased morbidity and mortality caused by infections due to these multidrug resistant organisms. Irrational use of antibiotics in humans and animals compounded with poor infection control measures are the driving forces for the global increase in the superbug infections. These superbugs which know no geographical boundaries, religion and race are incessantly devising mechanisms for survival and sharing these secrets to each other. Unfortunately any bug appears to have the potential to mutate and emerge as a superbug and become resistant to every antibiotic.

**Gram negative superbugs**

Multidrug resistant Acinetobacter baumannii and carbapenemase producing Klebsiella pneumoniae have emerged as the leading Gram negative superbugs in the intensive care units. The other Gram negative superbugs are multidrug resistant pseudomonas, serratia, Citrobacter freundii, Burkholderia cepacia, Escherichia coli, etc. The mechanisms of resistance among the Gram negative bacteria to beta lactams are due to enzymatic degradation, porin loss or efflux pumps. These bacterial secrets of defence get transmitted easily to other bacteria through mobile genetic elements.

In the extended betalactamase (ESBL) producing Gram negative organisms, beta lactam-beta lactamase inhibitor (BL-BLI) combinations like piperacillin-tazobactam helps to spare carbapenem. But carbapenem are preferred for severe ESBL infections even when isolate is reported as susceptible to BL-BLI. This is so because some Gram negative organisms may produce Amp C betalactamases which are not susceptible to BL-BLI combinations. Also in severe sepsis where the bacterial load is high, there could be a phenomenon of inoculum effect due to which the antibiotic might not work efficiently. Inoculum effect is a phenomenon seen in laboratory where there is significant increase in the minimal inhibitory concentration (MIC) of an antibiotic when the number of organisms inoculated is increased. But on the other hand, exposure to a carbapenem to even a short period can increase the risk of colonisation or infection with a carbapenem-resistant (CR) organism. Widespread use of carbapenem have thereby worsened the antibiotic crisis further due to the emergence of CR superbugs. Hence, enormous efforts are underway to spare carbapenem and use targeted drug regimens.

The carbapenemases of clinical importance produced by these superbugs are:

1. Class A: Example Klebsiella producing carbapenemases (KPC)
2. Class B: Example New Delhi Metallo beta-lactamase (NDM-1), which was reported in 2007 from Klebsiella pneumoniae isolate found in a Swedish tourist who had undergone a surgery in New Delhi. The isolate showed susceptibility only to tigecycline and colistin.  

3. Class D: OXA type enzymes hydrolyse oxacillin. These are found in Acinetobacter baumannii and Enterobacteriaceae.

In the recent antimicrobial resistance (AMR) surveillance by the Indian Council of Medical Research (ICMR), CR rates varied with different organisms with least for E coli (10%) and Pseudomonas (25%) and higher for Klebsiella pneumoniae (40%) and Acinetobacter baumannii (70%).

Colistin used in treatment of these CR Gram negative infections has a wide spectrum of activity covering many multidrug resistant bacteria except Neisseria, Proteus, Serratia, Providencia, Brucella and Edwardsiella species, Pseudomonas mallei and Burkholderia cepacia. It has no activity against any Gram-positive bacteria or anaerobes. It causes bacterial death by damaging the cytoplasmic membrane of the bacterial cell.

Colistin is available as a prodrug called colistimethate sodium (CMS). When prescribing CMS, clinicians should pay special attention to dosage units. Depending on the country and formulation, CMS may be expressed in milligrams of “colistin base activity” (CBA), International Units (IU), or less frequently in milligrams of the chemical CMS itself. One mg of CBA is equal to 30,000 IU or 2.4 mg of CMS. CMS has a potency of 12,500 IU/mg. Loading dose of 6-9 million units (MU) is recommended in critically ill children as colistin has a long half life of 14 hours and in the absence of loading dose it may take 2-3 days to achieve a therapeutic plasma concentration. Loading dose is followed by the maintenance dose of colistin about 12-24 hours later as per the creatinine clearance. It is usually given as 75,000 - 150,000 IU/kg/day in three divided dosages in infants and children and 50,000 – 75,000 IU/kg/day in three divided dosages in neonates.

Unfortunately resistance to colistin mediated by plasmid encoding genes have also been reported. Indian data from ICMR reported high colistin resistance rate of up to 40% among CR Klebsiella pneumoniae, 10% in CR E coli and less than 5% for CR Pseudomonas aeruginosa and Acinetobacter baumannii. Colistin resistance data among children is not available. A retrospective literature review over 15 years of blood culture isolates in Indian children, mostly from intensive care settings, had reported colistin resistance of 3.8% in Klebsiella pneumoniae and 8.8% in Escherichia coli.

It is still being debated whether colistin monotherapy or colistin combination therapy is better. However, despite the low quality of evidence and in view of concerns of resistance to colistin due to its monotherapy as well as observational study of decreasing mortality with combinations, there is strong recommendation of using colistin in combination with one or more agents which have invitro activity against the pathogen. In case of absence of susceptible second or third agent, it is recommended to use combination of second or third non-susceptible agent with lowest MIC.

Though there is no data presently available in neonates and children, the role of polymyxin B appears to be promising, as it attains more rapid and higher steady state concentrations compared to colistin and has less nephrotoxicity. However polymyxin B should not be used in treatment of urinary tract infections as it does not achieve adequate levels in the urinary tract.

Tigecycline has a broad spectrum which includes MDR Acinetobacter baumannii, Carbapenem resistant E coli, klebsiella, MRSA, etc. It has no clinical utility against Pseudomonas. It is preferred for use in severe intraabdominal infections and skin and soft tissue infections caused by multidrug resistant organisms. Since it attains a low serum level, tigecycline is reserved only if alternative treatments are not available. Safety and efficacy in pediatric population has not been established.

ICMR has proposed a All India AMR surveillance at molecular level which will help guide clinicians decide targeted therapies as per the genotype of the isolate and also update the current standard treatment regimens. ICMR has rolled out capacity building plans for the next five years for determination of carbapenem MIC and microbroth dilution based MIC determination for colistin isolates, irrespective of the anatomical sites.

Carbapenem sparing measures have also been proposed through the use of beta-lactam-beta lactamase inhibitor combinations by molecular characterisation of these multidrug resistant pathogens. For example: piperacillin tazobactam is preferred in carbapenem sensitive and suspected Class A beta lactamase (CTX-M-15) producing bacteria. Ampicillin-sulbactam has been recommended for sulbactam susceptible CR Acinetobacter baumannii with class D OXA enzymes.

**Stenotrophomonas and Burkholderia**

Stenotrophomonas maltophilia and Burkholderia
cepacia are ubiquitous pathogens that can colonize skin and invasive devices like catheters, endotracheal tubes, etc., to cause severe infection in the immunocompromised and cystic fibrosis. They exhibit complex mechanisms, including biofilm formation and are often refractory to therapy. Burkholderia cepacia may be susceptible to cotrimoxazole, doxycycline and meropenem. Combination of antibiotics may be required. Cotrimoxazole remains the drug of choice for Stenotrophomonas infections.

### Salmonella typhi

India is endemic for MDR Salmonella typhi and ceftriaxone is recommended as first line for parenteral therapy. Oral treatment options are cefixime (20 mg/kg/day) for 14 days or azithromycin (20 mg/kg/day) for 7 days. But just across the border, in Pakistan is emergence of extensively drug resistant Salmonella typhi due to a novel Salmonella typhi clone harbouring resistance to three first-line drugs (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) as well as fluoroquinolones and third-generation cephalosporins. To combat this dreadful situation, the Sindh Health Commission in Pakistan has recently issued a public notice restricting use of azithromycin and meropenem. Unfortunately azithromycin is widely abused as an empiric antibiotic for respiratory infections even if other agents like betalactams are recommended for the same. It is extremely important for us to preserve this drug and use only if no other alternative as XDR Salmonella typhi epidemic will be a public health catastrophe.

### Gram positive superbugs

Examples of Gram positive superbugs are Staphylococcus species, Enterococcus fecalis and Streptococcus pneumoniae.

Vancomycin remains a first line therapy for MRSA bacteremia due to its bactericidal effect. Vancomycin intermediate Staphylococcus aureus (VISA) (MIC 4 to 8 mcg/mL) and Vancomycin resistant Staphylococcus aureus (VRSA) (MIC more than 16 mcg/mL) have been rarely reported in children.

Teicoplanin has advantages over vancomycin for MRSA infections due to lesser nephrotoxicity. Daptomycin is an alternative to vancomycin in bacteremia, right sided infective endocarditis (IE), osteomyelitis and skin and soft tissue infections. It is not FDA approved in less than one year of age. Ceftaroline has been recently approved for treatment of complicated MRSA skin and soft tissue infections in children above 2 months. It is bactericidal and binds to penicillin binding protein (PBP) i.e. PBP2A to inhibit bacterial cell wall synthesis. It has a promising role in infections caused by VISA, VRSA and daptomycin nonsusceptible coagulase positive as well as coagulase negative staphylococcus. Resistance to ceftaroline due to alterations in PBP2A has been already identified unfortunately even in geographic areas not exposed to this drug.

Options for Vancomycin resistant Enterococcus (VRE) are limited to linezolid and daptomycin.

Drug resistant Streptococcus pneumoniae is now being increasingly reported in India. A recent study from Vellore, India reported increasing penicillin resistance and cefotaxime non-susceptibility of pneumococcal meningitis thereby recommending empiric use of combination of cephalosporins and vancomycin for suspected pneumococcal meningitis.

Clostridium difficile, an anerobic Gram positive spore forming bacillus which is more common in adults is increasingly being isolated among hospitalised children as one of the important causes of antibiotic associated diarrhea.

### Tuberculosis (TB)

In children MDR-TB (resistance to isoniazid and rifampicin) is mainly due to primary transmission from the index case, rather than acquired from prior exposure to TB treatment. Extensively drug-resistant (XDR) TB is defined as MDR-TB with additional resistance to at least one fluoroquinolone and one of the injectables, i.e. kanamycin, amikacin or capreomycin. Unfortunately, the drug resistance scenario has worsened to the extent that totally drug resistant TB has been reported from India.

Presumptive diagnosis of main antibiotic class resistance can be made through molecular methods (line probe assay and Xpert MTB/RIF) within hours to two days. In all cases of confirmed MDR-TB, second-line drug-susceptibility testing (DST) should be performed to exclude XDR-TB so that individualised antibiotic regimen can be started. Standard guidelines for diagnosis and treatment of MDR TB have been released by World Health Organisation. It is important to pursue for microbiological diagnosis of tuberculosis before starting tuberculosis treatment, notify TB and preferably refer MDR TB to experienced TB experts / RNTCP programme considering the prolonged and complicated management of these patients.

### Next steps

At a global level, for the purpose of highest priority
to research and drug development, WHO has recently named the critical-priority bacteria as carbapenem-resistant Acinetobacter baumannii and Pseudomonas aeruginosa, and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacteriaceae. The highest ranked gram-positive bacteria (high priority) were VRE and MRSA. Various international health organisations are focussed on educating clinicians about antimicrobial stewardship and infection control as well as increasing public awareness about the judicious use of antibiotics.

At national level, ICMR has set up AMR surveillance, released national antibiotic guidelines and plans to strengthen the microbiology facilities across the country for determination of MIC levels of the superbugs and genotypic identification to guide antibiotic treatment. Mechanisms for peer audit of prescriptions can help to avoid irrational practices. Prohibition of over the counter antibiotics without prescriptions is a crucial step to stop self medication by common man. Indian Academy of Pediatrics (IAP) is also actively involved in educating its members with modules in rational antibiotic practices, antimicrobial stewardship and infection control in hospitals and nursing homes.

At an individual level, rational antibiotic practice evolves with the habit of questioning about the possible etiology and justifying the need and the choice of the antibiotic in every infection on a daily basis. Blood cultures reporting superbugs need to be interpreted in clinical context as true pathogen or contaminant. Infection control measures especially hand hygiene play a vital role in prevention of transmission of these bugs. In view of limited antibiotic options and the threat that such bugs cause to the existence of mankind, these infections when confirmed in a clinical setting should be made notifiable. Preferably such patients should be referred to tertiary centres with microbiologists. Pediatricians should make laboratory reports superbugs need to be interpreted in clinical context.

**Conclusion**

The super powers of the superbugs have been facilitated by the irrational use of antibiotics by humans. Poor infection control measures have only boosted their spread from the healthcare environment to common households. With few antibiotics in hand to fight them, the situation appears grim. The patients infected with superbugs should be referred to a tertiary centre where good microbiology services and infectious disease experts are available to guide the treatment. Antimicrobial stewardship and good infection control are the only defensive strategies to buy time till some wonder drugs/mechanisms are invented.

**Points to Remember**

- **Superbugs are multidrug resistant microbes whose evolution is being hastened with irrational antibiotic use and poor infection control practices.**
- **Superbugs which are increasingly encountered are multidrug resistant Acinetobacter baumannii, carbapenemase producing Klebsiella pneumoniae, vancomycin resistant enterococcus (VRE), vancomycin resistant Staphylococcus aureus (VRSA), XDR salmonella, MDR and XDR tuberculosis.**
- **The antibiotic options to infections by superbugs are extremely limited and should be treated preferably with the help of infectious disease experts and microbiologists.**
- **Antibiotic stewardship and infection control are essential to control the rise of dangerous population of superbugs.**

**Acknowledgement:** I thank Dr. T. Jacob John, retired Professor, CMC Vellore for his review inputs.

**References**


**CLIPPINGS**

**Predictive tool for intravenous immunoglobulin resistance of Kawasaki disease in Beijing**

A cohort study was done using data set (including clinical profiles and laboratory findings) of children with KD diagnosed between 1 January 2010 and 31 December 2015 to analyze the risk factors and construct a scoring system. Data set of children with KD diagnosed between 1 January 2016 and 1 December 2016 was used to validate this model. Data of 2102 children diagnosed with KD at Children's Hospital Capital Institute of Pediatrics and Beijing Children's Hospital was analyzed for responsiveness to IVIG. The predictive tool included C reactive protein ≥90 mg/L (3 points), neutrophil percentage ≥70% (2.5 points), sodium ion concentration <135 mmol/L (3 points), albumin <35 g/L (2.5 points) and total bilirubin >20 μmol/L (5 points), which generated an area under the receiver operating characteristic curve of 0.77 (95% CI 0.71 to 0.82) for the internal validation data set, and 0.69 (95% CI 0.58 to 0.81) and 0.63 (95% CI 0.53 to 0.72) for two external validation data sets, respectively. If a total of ≥6 points were considered high-risk for IVIG resistance, sensitivity and specificity were 56% and 79% in the internal verification, and the predictive ability was similar in the external validation. Hence this predictive tool is helpful in early screening of high-risk IVIG resistance of KD in the Beijing area. Consequently, it will guide the clinician in selecting appropriate individualized regimens for the initial treatment of this disease, which is important for the prevention of coronary complications.


**NEWS AND NOTES**

5th International Neonatology Association Conference (INAC 2019)

Date: 12th – 14th July, 2019  Venue: Tijuana, Mexico

Email: secretariat@worldneonatology.com
Antimicrobial resistance (AR) implies the development of resistance in pathogens to antimicrobials. These pathogens encompass bacteria, mycobacteria, fungi, viruses and parasites. Antimicrobial resistance is one of the biggest health crises facing humans today. It is estimated that AR will lead to 10 million deaths annually worldwide in 2050 as against 700,000 annual deaths in the current era. The drug pipeline is drying up and very few new drugs are on the horizon. We could be returning to the pre-antibiotic era and face the prospect of untreatable infections. Hence, it is crucial that whatever possible be done to avert/mitigate the AR crisis.

**Cause**

AR in pathogens can be innate or acquired. Innate resistance is due to certain mutations in the genome of the pathogen. Examples of innate resistance are resistance in Klebsiella to ampicillin and *Stenotrophomonas maltophilia* to carbapenems. Acquired resistance is more common, which is due to selection pressure exerted by use of antimicrobial drugs. Antimicrobials wipe out the sensitive strains and lead to selective proliferation of the resistant strains. This resistance can be due to mutant genes present in plasmids or carried on the chromosome. Irrational antimicrobial use in humans and the veterinary industry is the biggest driver of AR in the world today.

**Mechanisms**

There are four key mechanisms causing AR (Table I).

**Extent of AR**

**In bacteria:** Bacteria are commonly defined as multidrug resistant (MDR), extensively drug resistant (XDR) and pan-resistant. The epidemic of multidrug resistant and extremely drug resistant tuberculosis in India is a public health calamity. The key solution to this antimicrobial resistance crisis lies in promoting rational antimicrobial therapy and exercising antimicrobial stewardship.

### Table I. Mechanisms of antimicrobial resistance

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of inactivating enzymes that destroy the antimicrobial</td>
<td>Beta lactamases that destroy beta lactam antibiotics.</td>
</tr>
<tr>
<td>Target modification which leads to inability of the antimicrobial to act</td>
<td>Modification of penicillin binding protein (PBP) that leads to pneumococcal resistance to penicillins and cephalosporins as well as methicillin resistance in staphylococci.</td>
</tr>
<tr>
<td>Efflux of the drug from the cell</td>
<td>Drug resistance in <em>Pseudomonas</em> as well as resistance to macrolides.</td>
</tr>
<tr>
<td>Reduced entry of the drug into the cell due to modification of porin channels</td>
<td>Resistance to imipenem in gram negative organisms especially <em>pseudomonas</em>.</td>
</tr>
</tbody>
</table>
drug resistant (PDR) (Fig.1). The term MDR applies to resistance to at least one agent in ≥ three antimicrobial classes, XDR when there is resistance to all except one agent in ≤ two antimicrobial classes and PDR when the isolate is resistant to all available antimicrobials.

AR in *S. aureus*: Resistance in *S. aureus* to penicillin through production of beta lactamase emerged very early soon after the introduction of penicillin. Now, more than 95% of *S. aureus* isolates are resistant to penicillin. The penicillinase resistant penicillins (PBP) viz cloxacillin and nafcillin circumvented this resistance mechanism and are the drugs of choice for treatment of methicillin sensitive *S. aureus* (MSSA) infections. There was then emergence of methicillin resistance in *S. aureus* (MRSA). This was by virtue of modification of the PBP. MRSA infections were first described in hospital associated *S. aureus* infections (HA- MRSA). These strains are highly resistant and treatment options include the glycopeptides (vancomycin, teicoplanin), lipopeptides (daptomycin) and oxazolidones (linezolid). It is estimated that in India 60% of health care associated *S. aureus* infections are MRSA. Then came the emergence of methicillin resistance in community acquired *S. aureus* (CA- MRSA). These isolates are sometimes highly virulent by virtue of production of the Panton Valentine Leukocidin (PVL) toxin. Illnesses caused by CA- MRSA include necrotizing skin and soft tissue infections, necrotizing pneumonias and bone and joint infections. Some studies from India place prevalence of MRSA in community acquired staphylococcal infections as 20%. CA- MRSA strains are less resistant than HA-MRSA and are often susceptible to clindamycin, cotrimoxazole, tetracyclines. CA- MRSA strains are now being increasingly isolated from hospitalized patients in India blunting the demarcation between CA-MRSA and HA-MRSA.

AR in pneumococcus: Pneumococcus is the commonest bacterial cause of pediatric and adult respiratory infections and emergence of resistance in this organism is of great concern. There is high prevalence of cotrimoxazole and macrolide resistance in pneumococcal strains isolated from India making these antibiotics ineffective in bacterial respiratory infections. The emergence of resistance to penicillins and cephalosporins by modification of PBP is discussed further. There has been revision of the breakpoints for defining resistance to beta lactams in pneumococcus. For non meningeal isolates, the breakpoints have been revised upwards while there is downward revision of breakpoints of meningeal isolates (Table II). This is because the level of antibiotic achieved in the cerebrospinal fluid (CSF) is lower than serum levels. Owing to this change in definition, there has been an increase in resistance in meningeal isolates while there is decrease in resistance in nonmeningeal isolates.

In a systematic review by Singh, et al which included 7 studies published from 2009-2016 in children below 5 years, the incidence of penicillin resistance was 10% and cefotaxime resistance was 4%. In the ASIP study (Alliance for Surveillance of Invasive Pneumococcal Serotypes) in children below 5 years which included 361 isolates, penicillin resistance was 8% with no cephalosporin resistance. One of the largest retrospective study from CMC, Vellore included 861 invasive isolates from both adults and children between 2008- 2016. Among the 663 non meningeal isolates, only one was fully resistant to penicillin and 3 showed intermediate resistance. Of the 148 meningeal isolates, the overall penicillin resistance was 43.7 % (increased from 9.5% in 2008 to 42.8% in 2016) while the overall cephalosporin resistance was 14.8%.

### Table II. Definitions of resistance in pneumococcus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitive</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin breakpoints in µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old</td>
<td>≤0.06</td>
<td>0.12-1</td>
<td>≥2 (CNS)</td>
</tr>
<tr>
<td>New (Non CNS)</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
</tr>
<tr>
<td>New (CNS)</td>
<td>≤0.06</td>
<td>None</td>
<td>≥0.12</td>
</tr>
<tr>
<td>Cephalosporin breakpoints in µg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old</td>
<td>≤0.5</td>
<td>1</td>
<td>≥2</td>
</tr>
<tr>
<td>New (non CNS)</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>New (CNS)</td>
<td>≤0.5</td>
<td>1</td>
<td>≥2</td>
</tr>
</tbody>
</table>
increased from 4.7% in 2008 to 28.5% in 2016). This data indicates that standard dose penicillins and cephalosporins can be used to manage non meningeal infections while for meningeal infections the time has come to move from ceftriaxone monotherapy to ceftriaxone with vancomycin. If the MIC to ceftriaxone exceeds 4, rifampicin should also be added.

**AR in Salmonella enterica:** There are an estimated 2.1-3.4 million cases of typhoid and paratyphoid occurring annually in India and these infections contribute to 10% of all hospitalized cases of fever. AR in enteric fever is as big a problem as the disease burden. Most strains are currently resistant to fluoroquinolones. Though there is return of susceptibility to age old drugs including ampicillin, cotrimoxazole and chloramphenicol, these drugs are rarely used in treatment. The drugs most widely used in treatment are the third generation cephalosporins (cefixime and ceftriaxone) and azithromycin. There are sporadic reports of cephalosporin resistance due to production of a novel ESBL with very high minimum inhibitory concentration (MIC). Even more disturbing are the outbreaks of extensively drug resistant *S. typhi* in Pakistan due to acquisition of a plasmid encoding resistance to both fluoroquinolones and cephalosporins. Spread of this XDR strain to India and its attendant problems is a serious concern.

**AR in Shigella:** Shigella causes nearly 5-10% of all diarrhea in children below 5 years of age in developing countries including India. There is an increase in resistance in most strains of Shigella to cotrimoxazole and ampicillin. Additionally, there is high prevalence of resistance to fluoroquinolones in India. Thus antimicrobial choices for bloody diarrhea in India are fairly limited and include cefixime and azithromycin. Increase in resistance to these drugs is likely to compromise treatment even further.

**AR in other Gram negative pathogens:** Gram negative bacteria can become resistant by a variety of mechanisms including impaired penetration in the cell, increased efflux, target modification, etc. But the most dramatic of all mechanisms is the production of inactivating enzymes chiefly, the beta lactamases. These mechanisms also coexist with each other. The beta lactamases hydrolyse the beta lactam ring of penicillins, cephalosporins, monobactams and carbapenems. The first generation beta lactamases appeared even before penicillin was introduced. These were found in *S. aureus*, Moraxella, *E. coli* and *Hemophilus influenzae*. The cephalosporins were resistant to these beta lactamases and hence were widely used for therapy in the 1980’s.

This efficacy of the cephalosporins was short lived and in 1983 the first extended spectrum beta lactamase (ESBL) (TEM-3) was described. The number of ESBL’s increased phenomenally and now number more than 200. They are plasmid mediated enzymes and are grouped into four major families; TEM, SHV, CTX-M and OXA. One organism can produce more than one type of ESBL. The ESBL’s were first recognized in *E. coli* and *Klebsiella* but are now produced by other Gram negative pathogens as well. The ESBL’s hydrolyse all penicillins, cephalosporins and aztreonam. However cefoxitin, beta lactam and beta lactamase inhibitor (BL-BLI) combinations and carbapenems are effective against the ESBL’s. Even more potent than the ESBL’s were the Amp-C beta lactamases, which were chromosomally encoded enzymes produced first by the SPICE group of organisms (Serratia, Pseudomonas, Indole positive proteus, citrobacter and enterobacter). These are now known to be produced by other gram negative pathogens too. In the de-repressed mutants producing these enzymes, copious quantities are produced such that the BL- BLI combinations are ineffective and only carbapenems are effective. Then emerged the carbapenemases, the most potent of all the beta lactamase enzymes that hydrolyse cephalosporins, penicillins, carbapenems but not aztreonam. The conventional BL- BLI combinations are ineffective against these enzymes. These carbapenemases can further be classified as serine carbapenemases (KPC, OXA) and the metallo beta lactamases (NDM, IMP, VIM etc). The most common type of carbapenemases seen in India are the NDM and the OXA. The only drugs effective against carbapenemase producing organisms are polymyxins, tigecycline, fosfomycin and sometimes aminoglycosides, cotrimoxazole, etc. The new BL-BLI combinations that have recently got regulatory approval but are still not available in India and are effective against KPC producing organisms include ceftazidime avibactam and meropenem vaborobactam. However, the utility of these drugs in the Indian set up is limited since the main carbapenemase is NDM against which these beta lactamase inhibitors are ineffective. Aztreonam avibactam a drug still in trial phase is likely to be useful against NDM producing organisms.

It must be remembered that several different type of beta lactamases may be coproduced by the same organism, thus making treatment of Gram negative infections even more challenging. Beta lactamases can be classified in various ways but one classification is the Ambler system which is based on amino acid homology. Class A includes the ESBL’s and the KPC; Class B includes the metallo beta lactamases (NDM, IMP, VIM); Class C includes the Amp C beta lactamases and Class D includes the
OXA enzymes. Resistance in Gram negative pathogens in community and hospital associated infections is the most challenging problem facing India today. Studies indicate 40-50% prevalence of ESBL in E. coli causing urinary tract infections in children even in the community. Prevalence of resistance in health care associated infections is even greater. Almost 70-80% of Gram negative health care associated infections are ESBL producers. The rates of carbapenem resistance are increasing and in some tertiary care hospitals such as the author’s own institution, resistance in E. coli and Klebsiella approach 50% while those in Pseudomonas and Acinetobacter approach 80% (unpublished data). In a recently published study on neonatal sepsis from Delhi which even included newborns delivered at home and being admitted to a health care facility for the first time, the ESBL and carbapenem resistance rates approached 80%. With increase in use of carbapenems and thus resistance, there is an excessive use of polymyxins which has now resulted in emergence of resistance to polymyxins and the prospect of totally drug resistant (TDR)/pan drug resistant (PDR) pathogens.

**AR in tuberculosis:** India is currently grappling with a crises of drug resistant tuberculosis. It is estimated that prevalence of multidrug resistance (MDR, resistance to at least both isoniazid and rifampicin) in the 27,90,000 new cases of tuberculosis reported in 2016 was (5%) 147,000. Furthermore it is estimated that 10% of all cases of MDR are extremely drug resistant (XDR, MDR with additional resistance to a newer fluoroquinolone and second line injectable). MDR and XDR tuberculosis treatment is expensive and toxic with associated high morbidity and mortality. New data is challenging the efficacy of currently used second line drugs including ethionamide and para aminosalicylic acid and the toxicity of the injectable aminoglycosides. Bedaquiline and delaminid are now available. New guidelines for treatment of MDR/XDR tuberculosis with an all oral regime sans aminoglycosides have been proposed by the World Health Organization (WHO) and are also likely to be adopted by the revised national tuberculosis control program (RNTCP) in a phased manner both in older children and adults.

**AR in fungi:** There is emergence in incidence of fungal infections including Candida and Aspergillus due to increase in the population of patients with prolonged stay in critical care units, patients on cancer chemotherapy and transplant recipients. This has seen an indiscriminate use of antifungal drugs mainly fluconazole. This has led to emergence of fluconazole resistance in Candida (C. albicans, C. tropicalis) and emergence of candida species that are inherently resistant to fluconazole (C. glabrata, C. krusei and C. auris). A recent multicentric study on ICU acquired candidemia in India (2012), pegged fluconazole resistance in Candida as 12%. Current rates are higher. This rise in azole resistance has driven increased use of echinocandins with consequent increase in treatment costs. Resistance in aspergillus to azoles is not a problem at present but may increase in future.

**AR in viruses:** Resistance detection in viral pathogens entails the use of genotypic methods to detect the unique resistance causing mutations. Phenotypic tests are not used in clinical practice. There is near complete resistance in influenza to the M2 protein inhibitors (amantadine). Resistance to oseltamivir has been sporadically reported from the West but not so far from India; resistance may be present though undetected owing to requirement of sophisticated techniques and is likely to increase given the indiscriminate use of the drug. Another problem likely in the near future is resistance to ganciclovir in cytomegalovirus (CMV) due to increasing use of this drug in patients undergoing hematopoietic and solid organ transplant for pre emptive therapy and prophylaxis. Options for treatment of ganciclovir resistant CMV include cidofovir and foscarnet both of which are highly toxic and not available readily in India at present. Resistance in HIV to nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) in Indian patients failing first line treatment is in excess of 80%. We are likely to see an increase in transmitted resistance in treatment naive patients as it is now more than a decade since anti retroviral therapy has been extensively used.

**AR in malaria:** The concern here is chloroquine resistance in Plasmodium falciparum that is widespread throughout India. Resistance in P. falciparum to pyrimethamine sulfadoxine is being increasingly reported especially from the north eastern states. Sporadic reports of artemisinin resistance have been reported again from the north eastern states at the Myanmar border- one of the hotspots of antimalarial drug resistance in the world.

**Solutions to the AR crises**

The foremost is promotion of rational antimicrobial practice. This involves all stakeholders including the government, pharmaceutical industry, health care professionals and the public and includes

- Education of medical practitioners about rational antimicrobial practices right from the undergraduate level through post graduation to practicing doctors.
- Development of evidence based guidelines to treat
common infections and ensuring that they are implemented.

- Educating the public and parents about the hazards of overuse of antibiotics.
- Preventing overuse/misuse of antimicrobials in the veterinary industry.
- Legislation to prevent over the counter availability of antimicrobials and banning irrational fixed drug combinations
- Establishing antimicrobial stewardship programs in hospitals

Apart from promotion of antimicrobial stewardship, other important strategies for mitigating the AR crises include prevention of infections through promotion of sanitation, hygiene, immunization and good infection control. The other important links in the chain are tracking resistance patterns through a countrywide initiative and development of new drugs and novel treatment strategies including bacteriophages and monoclonal antibodies among others.

Conclusions

We are facing an “antimicrobial resistance” crisis. We are running out of treatment options and not many new drugs are in the pipeline. If we do not use our existing antimicrobials wisely we are destined to return to the preantibiotic era of untreatable infections.

Points to Remember

- Antimicrobial resistance compromises treatment of infections and is associated with increased morbidity, mortality, adverse effects and cost of therapy.
- AR is fuelled largely by irrational use of antimicrobials in both humans and animals.
- AR in gram negative bacteria through production of extended spectrum beta lactamase (ESBL) and carbapenemases is alarming in the Indian health care setting.
- AR in S. pneumoniae to penicillins and cephalosporins is emerging, forcing change in empiric regimens for acute bacterial meningitis.
- MDR and XDR in M. tuberculosis is a big hurdle in the elimination of tuberculosis from India.
- The impact of resistance in other pathogens including Candida, influenza, HIV and malaria should not be forgotten.

References

Maternal weight and infections in early childhood: a cohort study.

A national cohort was created by combining data from the Swedish Medical Birth Register, the National Inpatient Register, the Cause of Death Register, the Total Population Register and the longitudinal integration database for health insurance and labour market studies. 6,93,007 children born in Sweden between 1998 and 2006 were included and analyzed for the number of hospitalizations for infectious diseases during the first 5 years of life, overall and for categories of infectious diseases (lower respiratory, enteric, upper respiratory, genitourinary, perinatal, skin and soft tissue, neurological and eye, digestive tract, bloodstream and other infections). Overweight (body mass index (BMI) 25.0–29.9) and obesity (BMI ≥ 30) during pregnancy were associated with a higher overall incidence of hospitalizations for infectious diseases, adjusted incidence rate ratio (IRR) 1.05 (95% CI 1.03 to 1.06) and adjusted IRR 1.18 (95% CI 1.16 to 1.21) respectively. Overweight and obesity during pregnancy were strongly associated with perinatal infections, adjusted IRR 1.34 (95% CI 1.25 to 1.44) and adjusted IRR 1.72 (95% CI 1.57 to 1.88). In contrast, no association was observed between maternal weight during pregnancy and infections of skin and soft tissue, the nervous system, the digestive tract or the bloodstream.

NEWER ANTIBIOTICS - USE IN PEDIATRIC PRACTICE

*Jeeson C Unni
** Ranjit Baby Joseph

Abstract: There are few trials assessing the use of newer antibiotics in the neonates and children. The reality strikes that 50 times more studies are being conducted in adults than in children; 177 and 580 times more in adults than in neonates and preterm babies, respectively. Though there are 2-5 new drugs being introduced for each group of antibiotic, only 2 antibiotics - carbavance and solithromycin - have been investigated in 1 and 2 ongoing clinical trials respectively in pediatric patients.

Keywords: Newer antibiotics, Drug resistance, Pediatric trials.

Ninety-one years after the invention of penicillin, a silent epidemic of resistance to many antibiotics is emerging. There is a dearth of new antibiotics to fall back upon. Newly approved antibiotics tend to be reserved as a last line of defence against multi-drug resistant infections, thus minimizing its sales value. Drugs on which millions are spent on research and development sometimes, do not see the light of the day. This is a major deterrent for investment in research and development by pharmaceuticals which has resulted in a bleak future for development of new antibiotic molecules.

‘Innovation gap’ is the expression that has been used to describe the lack of novel structural classes introduced to the antibacterial armamentarium since 1962. Since 2000, only 3 new classes of antibiotics have been introduced to the market for human use, with one limited to topical use. Recently, Infectious diseases society of America (IDSA) supported a program, called “10 X 20 initiative” to develop ten new systemic antibacterial drugs within 2020 through the discovery of new drug classes, as well as to find possible new molecules from already existing classes of antibiotics.

The three classes of drug-resistant bacteria that are a major cause of concern are a) Methicillin Resistant Staphylococcus aureus (MRSA), b) Multi drug-resistant (MDR) and pan drug resistant (PDR) Gram-negative bacteria, which include strains of Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa and c) a third class comprising of MDR and extensively-drug-resistant (XDR) strains of Mycobacterium tuberculosis (MDR- TB and XDR-TB).

The XDR bacteria include the ESKAPE pathogens - Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae.

World over, there are only few clinical trials being conducted on newer antibiotics in the pediatric age group with 76 clinical trials investigating one or more antibiotics recruiting children between 0 and 18 years of age in comparison to 4078 trials in adults. Of these 76 trials, only 23 have recruited neonates and among them only 8 clinical trials globally recruited preterm neonates. These clinical trials are for complicated intra-abdominal infections (cIAI), complicated UTI (cUTI) and complicated skin and soft tissue infections (cSSTI). Respiratory and systemic infections, the most common clinical indications for antibiotics in pediatrics, are not currently being evaluated.

Of the 37 antibiotics listed in the May 2016 edition of the Pew Charitable Trusts Antibiotic Pipeline, five had an agreed pediatric investigation plan (PIP) e.g. Imipenem / Cilastatin+Relebactam, cadazolid, carbavance (Meropenem+Vaborbactam), eravacycline and solithromycin. As of 8th November 2016, only two (carbavance and solithromycin) of these 37 antibiotics listed were being investigated in 1 and 2 ongoing clinical trials in pediatric patients, respectively. A PIP was agreed for carbavance in 2015 for treatment of Gram-negative infections and for solithromycin in 2016 for the treatment of gonococcal infection, anthrax, tularemia and bacterial pneumonia. PIPs were agreed in 2015 for the treatment of UTI and complicated IAI with eravacycline and in 2016 for the treatment of clostridium difficile infection with cadazolid and of gram-negative bacterial infection with imipenem/cilastin+relebactam. Despite this, no registered
trials of these antibiotics were identified. Relatively newer antibiotics in use in pediatric population are listed in Table I.

**Cefepime**

It is a 4th generation cephalosporin with excellent aerobic Gram positive and Gram negative coverage including Pseudomonas aeruginosa and other bacteria producing Amp C beta-lactamases. Gram positive activity is similar to ceftriaxone. Indications include empirical broad-spectrum antibiotic treatment for febrile neutropenia, severe septicemia and respiratory, urinary tract, biliary and pancreatic infections by resistant Gram positive and negatives not responding to first line drugs. It has a limited effect in meningitis. It is a relatively safe - the more common adverse events being headache, diarrhea, nausea, vomiting, pruritus and rash. Rarely, reversible cefepime induced encephalopathy has been reported with confusion, hallucinations, agitation, convulsions, tremor, delirium and coma with regression of symptoms within two to seven days of stopping the drug. Almost all these patients with cefepime induced encephalopathy had renal failure and had received higher than the recommended dose. There is a risk of super infections with organisms like candida, enterococcus, MRSA, Pseudomonas aeruginosa, Clostridium difficile, etc. while on cefepime.

**Meropenem**

It is a carbapenem antibiotic with broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative infections including pseudomonas resistant to other antibiotics. It is easier to remember organisms that it does not cover: MRSA and methicillin-resistant coagulase-negative staphylococci, most vancomycin-resistant Enterococcus (VRE) spp, atypicals, Stenotrophomonas (carbapenem use is a risk factor for Stenotrophomonas infection). It is the preferred carbapenem for treatment of CNS infections.

**Linezolid**

Linezolid is effective against Gram-positive bacteria including MRSA, VRE and Streptococcus pneumoniae, Mycobacterium tuberculosis and Nocardia. It is considered to be an ideal reserve drug for treatment of VRE, vancomycin-resistant Staphylococcus aureus (VRSA) and penicillin-resistant Streptococcus pneumoniae (PRSP). Ideally should be reserved for treating such infections as there are very few drugs in our armamentarium to effectively treat these organisms. Linezolid will be an important component of treatment for children with the worst forms of DR-TB. It is used in treatment of pneumonia and endocarditis, as well as skin and soft tissue.

**Table I. Newer antibiotics already in use in children**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>Febrile neutropenia – Resistant Gram +ve and Gram -ve bacteria</td>
</tr>
<tr>
<td>Meropenem/ Imipenem</td>
<td>Gram +ve and Gram -ve bacteria - P. aeruginosa and anaerobes. No activity against Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td>Linezolid</td>
<td>MRSA, Vancomycin resistant enterococci (VRE) and Streptococcus pneumoniae, Mycobacterium tuberculosis and Nocardia</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Gram +ve and Gram -ve bacteria and anaerobes</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Gram +ve: MRSA; Enterococcus faecalis</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Gram –ve and aerobic bacteria, Enterobacteriaceae and Pseudomonas aeruginosa (No Gram+ve cover)</td>
</tr>
<tr>
<td>Polymyxin E (Colistin)</td>
<td>Last-resort antibiotics for MDR Psuedomonas, Klebsiella pneumoniae, Acinetobacter. New Delhi metallo betalactamase (NDM-1) MDR Enterobacteriaceae have also shown susceptibility</td>
</tr>
<tr>
<td>Levofloxacin/Moxifloxacin</td>
<td>Gram +ve and Gram -ve bacteria and atypical bacteria; penicillin resistant S Pneumoniae</td>
</tr>
<tr>
<td>Piperacillin - Tazobactam</td>
<td>Gram +ve and Gram -ve bacteria, P aeruginosa</td>
</tr>
</tbody>
</table>
central nervous system and osteoarticular infections. It may sometimes pose serious adverse effects like bone marrow suppression, peripheral and optic neuropathy, lactic acidosis and serotonin syndrome.

**Tigecycline**

Tigecycline is useful against Gram+ve, Gram -ve and anaerobes. It is licensed to use in adults with complicated skin and skin structure infections (cSSSI) due to *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible only; VSE), MRSA, *Streptococcus anginosus* group, *Streptococcus pyogenes* and *Bacteroides fragilis*. It has got restricted approval for use in children.13

**Aztreonam**

Aztreonam is a β-Lactam (monobactam) antibiotic. Spectrum includes Gram-negative aerobic bacteria, Enterobacteriaceae, and *Pseudomonas aeruginosa*. It is useful in penicillin and cephalosporin allergies as no apparent cross-reactivity occurs. Expected side effects are rash, thrombophlebitis and eosinophilia. It is excreted via kidney and has notable drug interaction with probenecid.14

**Colistin**

Colistin (Polymyxins) is an antibiotic with a general structure consisting of a cyclic peptide with a long hydrophobic tail. They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids. They are produced by non-ribosomal peptide synthetase systems in Gram-positive bacteria such as *Paenibacillus polymyxa* and are selectively toxic for Gram-negative bacteria due to their specificity for the lipopolysaccharide molecule that exists within many Gram-negative outer membranes. The global problem of advancing antimicrobial resistance has recently led to a renewed interest in their use.15

Newer antibiotics in different stages of development are listed in Table II.

**Oxazolidinones**

Linezolid, which was the first in class to be approved this millennium has stimulated significant efforts to discover new agents in the oxazolidinone class. New drugs like Tedizolid phosphate is currently in phase 3 clinical trials for acute bacterial skin and skin structure infections (ABSSSI), cadazolid is in phase 3 for *Clostridium difficile*-associated diarrhea (CDAD) and radezolid is in phase 2 studies for uncomplicated skin and skin structure infections and community-acquired pneumonia. Another drug called MRX1 is being evaluated for Gram+ve like MRSA, penicillin resistant/intermediate *Streptococcus pneumoniae* and vancomycin resistant enterococcus. Sutezolid, another new member of this class is now in phase 1 studies for extensively resistant TB (XDR TB) following the bedaquiline and delamanid way. AZD5847, another upcoming drug in this class is in phase I studies as antitubercular drug. The efficacy of AZD5847 was additive when tested along with a variety of conventional TB agents.16

Cadazolid is a new hope in treatment of *Clostridium difficile*-associated diarrhea in children. There are trials comparing its efficacy to vancomycin. In phase I and II

---

**Table II. Newer antibiotics in pipeline**

| Oxazolidinones | Radezolid, tedizolid, cadazolid, MRX-1 |
| Glycolipopeptides | Oritavancin, dalbavancin, surotomycin |
| Streptogramins | NXL 103 |
| Quinolones | Nemonoxacin, delafloxacin, avarofloxacin |
| Beta-lactam antibiotics | Ceftaroline, ceftobiprole |
| Beta-lactam / beta-lactamase inhibitors | Ceftolozane / Tazobactam, Ceftazidime / Avibactam, Imipenem / Relebactam, Meropenem/Vaborbactam |
| Carbapenems | Ertapenem, doripenem |
| Tetracycline | Omadacycline, eravacycline |
| Macrolides | Modithromycin, solithromycin |
| Aminoglycosides | Plazomicin |
trials, cadazolid was shown to be safe, well tolerated and efficacious, positioning itself as a potential future viable therapeutic option. Phase II study indicates that the effect of all doses of cadazolid were numerically similar to, or better than vancomycin. Phase III trials have raised questions about the drug’s efficacy. International Multi-Center Program Assessing Cadazolid Treatment (IMPACT 1) study met its primary endpoint, while the second phase III study, IMPACT 2, did not.\textsuperscript{17}

In various systematic reviews, tedizolid was found to be superior to vancomycin for clinical response at end of therapy and post therapy evaluation. It is suggested that tedizolid provides an alternative option for the management of serious skin infections caused by suspected or documented MRSA. Newer oxazolidinones (tedizolid and radezolid) also showed mild adverse effects in Phase II and III clinical trials.\textsuperscript{18}

**Newer glycolipopeptides**

Daptomycin is a lipopeptide antibiotic with unique action on cell membrane. It is effective against Gram+ves like enterococci [including glycopeptide-resistant enterococci (GRE)], MRSA, streptococcus, corynebacteria and stationary phase Borrelia burgdorferi persisters. It is used in skin and skin structure infections caused by Gram+ves, S. aureus bacteremia and right-sided S. aureus endocarditis. It binds avidly to pulmonary surfactant and so cannot be used in the treatment of pneumonia. Daptomycin resistance is still uncommon, but has been increasingly reported in GRE. When used for prolonged period for MRSA like infections there is risk for reversible and often asymptomatic myopathy.\textsuperscript{19}

There are few other agents in this group which deserve attention. Telavancin is useful against MRSA and Gram+ves. FDA has approved the drug in September 2009 for cSSSI and in June 2013 for hospital-acquired MRSA and ventilator associated pneumonias (VAPs) caused by S aureus. Prolonged use of this agent, especially in patients with severe renal impairment has shown increased toxicity compared to vancomycin.\textsuperscript{20}

Oritavancin is approved by FDA in August 2014 for acute bacterial skin and skin structure infections (ABSSSI) and also MRSA (OD dosing). Dalbavancin is also approved by FDA in August 2014 for ABSSSI and also for MRSA and methicillin resistant streptococcus (once a week dosing). Dalbavancin and oritavancin offer extended dosing intervals and are cheaper. They have lower rates of adverse effects when compared to telavancin.\textsuperscript{21} Suromycin is under phase 2 trial for Clostridium difficile-associated diarrhoea (CDAD) in children.\textsuperscript{22} However, further studies are needed to establish its appropriate pediatric dosage before they can be licensed for use in newborns and children.

**New streptogramins**

Dalfopristin-quinupristin is already in use for infections with MRSA, coagulate negative staphylococcus (CONS), penicillin-susceptible and penicillin-resistant S. pneumoniae and vancomycin-resistant E. faecium but not E. faecalis and vancomycin intermediate resistant staphylococcus aureus (VISA). NXL-103, a combination of florphistin and linopristin is under evaluation for CAP and cSSSI spectrum - S aureus (including MRSA), S pneumoniae, S pyogenes, E faecium, E faecalis, H influenzae and H parainfluenzae. No systematic review of their use in children is available at present.\textsuperscript{23}

**Newer quinolones**

As of now, no significant clinical trials are done in children for any of these newer quinolones. Many of the new fluoroquinolones have anti-pseudomonal activity and additional anti- MRSA activity. Nemonoxacin is active against Gram positive, Gram negative, MRSA, vanco resistant pathogens and C.difficile isolates that are resistant to other quinolones. It is also more potent than levofloxacin or moxifloxacin. It is less active against Gram negatives like E coli, P mirabilis, and P aeruginosa causing CAP and skin infections.\textsuperscript{24}

Delafloxacin is approved by FDA in June 2017 for cSSSI covering both Gram positive, Gram negative, spectrum.\textsuperscript{25} Gemifloxacin is useful against Gram positive (Strep, Staph) and atypical pathogens (Chlamydia pneumoniae, mycoplasma, legionella) but less against pseudomonas when compared to ciprofloxacin. It has anaerobic activity and has poor action against mecticillin-resistant strains. The drug has high affinity for DNA gyrase and topoisomerase IV. It is also noted to have good activity against fluoroquinolone- resistant strains including fluoroquinolone resistant H. Influenzae.\textsuperscript{26} Other newer agents still under trial include avarofloxacin, finafloxacin and zafobloxacin.\textsuperscript{27} Besifloxacin is another novel topical quinolone which is found to be useful in bacterial conjunctivitis.\textsuperscript{28} Gatifloxacin has been banned due to the risk of severe hyperglycemia and trovafloxacin has been withdrawn from the market due to risk hepatotoxicity.

**Newer beta-lactam antibiotics**

Cefditoren pivoxil is a 3\textsuperscript{rd} generation oral cephalosporin which is effective against S. pneumoniae,
H influenzae, M catarrhalis, S aureus (not MRSA strains) and Streptococcus pyogenes (penicillin-susceptible strains only). The main indication is in rhinosinusitis.\textsuperscript{29} Ceftaroline and ceftobiprole are ‘5th-generation’ cephalosporins useful against MRSA, pyogenes, agalactiae, and pneumoniae, hVISA and VRSA – Gram negative -ceftazidime-susceptible E. coli and K pneumoniae, β-lactamase positive and negative H influenzae. It has got synergistic action when combined with amikacin, tazobactam, meropenem and aztreonam. Ceftaroline can be used in children aged above 2 months having acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. The spectrum of organisms covered is staphylococcal and streptococcal infections, including MRSA and penicillin-resistant Streptococcus pneumoniae.\textsuperscript{30}

**Newer beta-lactam/beta-lactamase inhibitors**

Ceftolozane/tazobactam combination has superior in vitro activity against ceftazidime resistant Escherichia coli, K. pneumoniae and enterobacter and citrobacter species when compared with ceftriaxone, cefepime, and piperacillin/ tazobactam and also has significant action against ESBL-producing Proteus mirabilis. Ceftazidime/avibactam is another combination effective against multidrug-resistant Gram negative; all Enterobacteriaceae, including ceftazidime-resistant strains and Burkholderia cepacia complex. It can be used in complicated intra-abdominal infections (cIAI) along with metronidazole and complicated urinary tract infections (cUTI). Data in children are extremely limited for both these antibiotics.\textsuperscript{31}

Imipenem/Relebactam combination is used against E coli, Klebsiella pneumoniae, Enterobacter spp. including K. pneumoniae carbapenemase (KPC) producing Enterobacteriaceae and MDR Pseudomonas aeruginosa. The main indication is complicated urinary tract infection (cUTI).\textsuperscript{32} Meropenem / Vaborbactam, another newly developed combination useful against E coli, Klebsiella pneumoniae and Enterobacter spp., including MDR KPC-producing strains. Relebactam and vaborbactam serve to broaden the spectrum of imipenem and meropenem, respectively, against β-lactamase-producing Gram-negative bacilli.\textsuperscript{33} The exact roles for imipenem-relebactam and meropenem-vaborbactam combinations will be defined by efficacy and safety data from further clinical trials. Potential roles in therapy for these agents include suspected or documented infections caused by resistant Gram negative bacilli-producing ESBL, KPC, and/or AmpC β-lactamases. It is also useful in carbapenem-resistant Enterobacteriaceae (CRE) infections and P. aeruginosa infections.\textsuperscript{34}

**Newer carbapenems**

Ertapenem was approved for use by the FDA in the year 2001. Its spectrum includes Gram positive and negative aerobic as well as anaerobic bacteria excluding the non fermenters, MRSA and drug-resistant enterococci. It is effective against most resistant enterobacteriaceae producing ESBLs and/or AmpC-type α-lactamases and is noted to have limited in vitro activity against P aeruginosa and Acinetobacter species, not suitable for the empiric treatment of serious infections acquired nosocomially. It is recommended for prophylaxis of surgical-site infection following elective colorectal surgery. Unlike imipenem, ertapenem does not require co-administration with cilastin.

Doripenem was approved for use by the FDA in 2007. Its spectrum is more similar to that of meropenem and imipenem than of ertapenem. Thus, it is effective against gram-positive and negative aerobes and anaerobes including Pseudomonas aeruginosa, Acinetobacter species, but not MRSA, VRE and other strains resistant to imipenem and meropenem. It is effective against β-lactamase producing strains of enterobacteriaceae. Doripenem is approved for the treatment of intra-abdominal infections and complicated urinary tract infections including pyelonephritis. Dosage adjustment is required in renal failure patients.\textsuperscript{35}

**Newer tetracyclines**

Tigecycline is the most common newer tetracycline currently used. Apart from this there are a few under development. Omadacycline is a newer one that circumvents common tetracycline resistance mechanisms. It is useful in Gram positive infections including MRSA, penicillin and MDR Streptococcus pneumoniae, VRE and also in Gram negative infections, anaerobes, atypical bacteria including Legionella spp. and Chlamydia spp. It is currently in phase III for its use in CSSSI and community acquired pneumonia (CAP). Eravacycline is another agent in phase III studies for its use in complicated intra-abdominal infections (cIAI) with good Gram positive and Gram negative (multi-drug resistant) spectrum. Data in children are extremely limited for both these new drugs.\textsuperscript{36}

**Newer macrolides**

The use of Telithromycin in CAP has dropped substantially following reports of severe hepatotoxicity and strengthened safety warnings. Fidaxomicin is a newer drug that is minimally absorbed, bactericidal especially in selective eradication of pathogenic Clostridium difficile with minimal disruption to the multiple species of bacteria that make up the normal, healthy intestinal flora thereby reducing recurrence.\textsuperscript{37} Modithromycin is another agent useful in Gram positive and Gram negative (multi-
drug resistant) infections with notable effect in MDR Neisseria gonorrhoeae infections.38

Solithromycin is a “fourth-generation” macrolide which is useful against multidrug-resistant Streptococcus pneumoniae and nontypeable Haemophilus influenzae (NTHi).39 Until hepatotoxicity issue is resolved, ketolides are unlikely to replace established antibacterials for CAP, or lipoglycopeptides and oxazolidinones for gram-positive infections.

**Newer trimethoprim-related drug: Iclaprim**

It has got a spectrum covering S. aureus and S. pneumoniae, including several resistant strains. Its effectiveness against H. influenzae, Moraxella catarrhalis and Legionella pneumophila may also make it useful in respiratory tract infections. It is being developed as an intravenous as well as oral formulation. Iclaprim has undergone Phase III trials in adults and yet to undergo any trials in children.40

**New aminoglycoside: Plazomicin**

Plazomicin has action against Gram positive and Gram negative infections. It has in vitro synergism with daptomycin and ceftobiprole against MRSA, hetero vancomycin-resistant S. aureus (hVRSA) and vancomycin-intermediate Staphylococcus aureus (VISA). It also has synergistic activity with doripenem, imipenem, piperacillin/ tazobactam and cefepime against P aeruginosa. It has undergone Phase II trial in patients with cUTI and acute pyelonephritis, including cases with concurrent bacteremia. Safety and efficacy are not established in children below 18 years.41

**Points to Remember**

- **About 41 new antibiotics are in development.**
- **Only about 60% of drugs that enter phase III end up getting approval and based on the pipeline analysis is very clear that there are not enough new drugs that are available to patients.**
- **Although the bacterial resistance is developing rapidly newer antibiotics in pipeline provides us some hope; and we need more research in this regard in neonates, children and adolescents.**
- **Judicious use of the antibiotics is the need of the hour to present rapid development of extensive drug resistance.**

**References**


AMAZING INTERACTION OF VITALS – ORGAN CROSS TALK

Abstract: Air, water and energy are essential for sustaining life. Different systems, organs and tissues of the body function together to maintain homeostasis. The main function of the respiratory system is ventilation, oxygenation and acid base balance. Breathing is controlled by complex mechanisms involving respiratory centres, central and peripheral chemoreceptors. The function of the circulatory system is to provide adequate oxygen and nutrients to meet the metabolic demand of the tissues. The role of kidney is filtration, reabsorption, secretion, excretion as well as volume and osmoregulation, where as nutrition and energy is regulated by the gastrointestinal system. To maintain homeostasis all systems of the body are interacting with each other which can be assessed by the vital signs.

Keywords: Vital signs, Ventilation, Perfusion, Oxygenation, Circulation, Energy

The concept of homeostasis was discovered by Claude Bernard which is the best example of interaction among the organs of the human body. Organ cross talk is a concept which refers to complex interaction between systems which helps to maintain homeostasis.

For sustaining healthy life three basic things are essential i.e., air, water and energy for which all systems must function optimally. The respiratory system takes care of ventilation, oxygenation and maintain normal blood gas, while the circulatory system distributes oxygen and nutrients to all the tissues. It also carries waste from the tissues to the kidneys and lungs for elimination. If the respiratory and the cardiovascular system are functioning optimally, all the end organs have the scope to perform optimally. Normal respiratory rate and heart rate in different ages are shown in Table I.

Table I. Age appropriate heart rate and respiratory rate

<table>
<thead>
<tr>
<th>Age</th>
<th>RR/min</th>
<th>HR/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>30-40</td>
<td>120-160</td>
</tr>
<tr>
<td>1 year</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>10 year</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Adult</td>
<td>18</td>
<td>72</td>
</tr>
</tbody>
</table>

The initial assessment of a child relates to respiratory and circulatory systems, followed by assessment of the major end organs-brain and kidneys. The main function of the kidney is not only filtration, reabsorption and excretion but also volume regulation and osmoregulation. Respiratory rate and tidal volume are regulated by central nervous system (CNS) through a complex interaction of controllers, sensors and effectors. All these can be assessed clinically by vital signs (respiratory rate, heart rate, blood pressure, temperature, oxygen saturation) in health and disease state.

Relationship of ventilation and perfusion

Effective gas exchange depends on adequate volume of air reaching the alveoli (ventilation) and sufficient blood flow (perfusion) through pulmonary capillaries leading to diffusion of gases across the alveolar capillary membrane. The association is called ventilation perfusion (V/Q) ratio. Minute ventilation (MV) is the product of tidal volume (TV) and the respiratory rate (RR), which in adults equals 9 litres/min [MV = TV (500ml) X RR (18/min)].

The respiratory rate and tidal volume both in health and disease are adjusted to achieve the desired minute ventilation with the least expenditure of energy. Alveolar ventilation is defined as that portion of the minute ventilation that participate in gas exchange. This gas exchange occurs in the respiratory bronchioles and alveoli (useful ventilation) while the remaining airways serve as conducting tubes. The volume contained in the conducting areas is known as the anatomic dead space since it is not taking part in gas exchange. Normally 30% of each tidal breath fills the anatomic dead space (i.e. about 180 ml in adults). Infants, with a TV of 6ml/kg have a dead space of 2mL/kg.
Alveolar ventilation = Alveolar volume (320 ml) X RR (18) = 5.760 litres

Dead space ventilation = dead space volume (180 ml) X RR (18) = 3.240 litres

Cardiac output (CO) is the product of stroke volume (SV) (which is the volume of blood ejected with each cardiac contraction) and heart rate which in adults is around 5.760 litres [CO = SV (80ml) x HR(72)]. In a healthy adult, every minute 5 to 6 liters of air reaches the alveolus and 5 to 6 liters of blood is reaching capillaries and gas exchange takes place.

Why does an adult need a respiratory rate of 18/min and heart rate of 72 / min (Fig.1) and how RR : HR Ratio 1: 4 ( Box 1)?

**Ventilation**

Alveolar ventilation: Alveolar volume X RR
320x18 (5760 mL)

**Perfusion**

Cardiac output: Stroke volume X HR
80x72 (5760 mL)

**Box 1. RR and HR – Basis of ratio**

How RR: HR = 1:4?

320 X 18 = 5760 80 X 72 = 5760
Alveolar Vol: Stroke Vol 4 : 1
Respiratory rate: Heart rate 1 : 4

**Oxygenation**

Inspired oxygen from the environment moves across the alveolar-capillary membrane into the blood and is then transported from the lungs to the peripheral tissues through blood for aerobic cellular metabolism. This process can be conceptualized as three steps: a) oxygen delivery, b) oxygen extraction and c) oxygen consumption.

**Oxygen delivery**

Oxygen delivery (DO₂) is the rate of oxygen transport from the lungs to the peripheral tissues. DO₂ (ml/min)  = Q x CaO₂ where Q is the cardiac output and CaO₂ is arterial oxygen content (Fig.2).

Normal arterial blood oxygen content (CaO₂) is 20ml/100 ml of blood while normal mixed venous blood oxygen content (CvO₂) is 15ml/100ml of blood.

**Oxygen extraction**

Oxygen extraction (OE) is the proportion of arterial oxygen that is removed from the blood as it passes through the microcirculation (Box 2).

**Box 2. O₂ extraction ratio**

\[(\text{CaO}_2 - \text{CvO}_2)/\text{CaO}_2\]

\[(20ml - 15ml) / 20 ml\]

Normal OE ratio range : 0.25 to 0.30

**Oxygen consumption**

Oxygen consumption (VO₂) is the rate at which oxygen is removed from the blood for use by the tissues. Normal VO₂ in a resting person is approximately 5ml O₂/kg/min. Children have a high metabolic rate, so O₂ consumption in infants is high compared with adults. O₂ consumption in infants is 6 to 8 ml/kg per minute, compared with 5 mL/kg per minute in adults. Therefore, hypoxemia and tissue hypoxia can develop more rapidly in a child than in an adult if inadequate alveolar ventilation occurs.

DO₂ to the tissues is a product of CO and CaO₂. When hemoglobin is 15 gms and fully saturated (100%) CaO₂ is 20 ml for each 100ml of blood. While 100ml of oxygenated blood passing through tissues 5ml of oxygen extracted by

Cardiac output (CO) X Oxygen content (CaO₂)

Stroke volume(SV) X Heart rate (HR) 1.34 x Hb x SaO₂ + (0.003x PaO₂)

**Fig.2. Oxygen delivery (DO₂)**
the tissues. The balance of 15ml of CaO$_2$ passes to the mixed venous blood. Normal healthy adult needs 250ml - 300 ml of O$_2$/min at resting stage for which tissues receives 5-6 litres of cardiac output /min. Aerobic metabolism produces 80ml carbon dioxide for each 100ml oxygen consumed; this respiratory quotient (RQ) of 0.8 means that the normal adult produces 200 ml carbon dioxide for each 250 ml oxygen consumed every minute.

**Normal O$_2$ requirement and how supplied**

Normal oxygen requirement is 5ml/kg/min. Healthy adult needs 250-300ml of O$_2$/min at resting stage for which tissues receives 5-6 litres of cardiac output /min. As 100 ml of oxygenated blood supplies 5 ml of O$_2$, 5-6 litres of blood supply around 250-300 ml of O$_2$.

**RR and HR more in infants - Why?**

Infants have lower lung volumes and capacities while children have decreased lung reserves. Growing infants have a higher BMR so their oxygen requirements are higher.

**Circulation**

The total body water (TBW) in most adults is between 50% and 60% of total body weight. Approximately two-thirds of TBW is in the intracellular space and one-third in the extra-cellular space. The extra-cellular space comprises of two compartments; interstitial space (75%) and plasma or vascular space (25%).

The electrolyte content within each compartment is distinctly different from that of the other. The extracellular fluid (ECF) contains sodium as its primary cation, with chloride and bicarbonate as its primary anions. The intracellular fluid (ICF) contains potassium as a primary cation with phosphate as the primary anion. Water moves freely across cell membranes to ensure equal osmolalities in ECF and ICF (Normal 290).

**Regulation of blood pressure**

The two hormones, angiotensin-II and atrial natriuretic peptides (ANP) contribute to the regulation of blood pressure and therefore GFR. When blood pressure and GFR decrease, juxtaglomerular cells and macula densa cells of juxtaglomerular apparatus detect decreased stretch and decreased delivery of Na$^+$, K$^+$ and water respectively. The juxtaglomerular cells then secrete ‘renin’ which acts on angiotensinogen (a large plasma protein produced by liver) and forms angiotensin I. As angiotensin-I pass through lungs, the enzyme - angiotensin converting enzyme (ACE) converts it to angiotensin-II, an active hormone which causes vasoconstriction of arterioles, stimulates aldosterone secretion, stimulates thirst center and ADH secretion. This helps in restoring systemic and renal blood pressure, which normalizes GFR.

The other hormone that influence glomerular filtration and other renal process is atrial natriuretic peptide (ANP). ANP promotes both excretion of water and Na$^+$. Secretion of ANP is stimulated by increased stretching of atra which occurs when blood volume increases. ANP increases GFR, perhaps by increasing the permeability of the filter or by dilating afferent arterioles. It also suppresses secretion of ADH, aldosterone and renin.

Blood pressure is the product of cardiac output and systemic vascular resistance. The normal blood pressure in different age groups is given in Table II. Physiologic variables that the body can manipulate to compensate for compromised perfusion include cardiac output and systemic vascular resistance.

Cardiac output is the product of stroke volume and heart rate. Hence, tachycardia is a common sign of decreased perfusion and early shock. Infants have relatively fixed stroke volumes and are particularly dependent upon heart rate to increase cardiac output. Stroke volume is determined by preload, cardiac contractility and after load. Compensatory mechanisms that improve stroke volume include increased venous smooth muscle tone (improves preload by shunting blood to the heart) and increased cardiac contractility (resulting in more complete emptying of the ventricles) (Fig.3).

As cardiac output decreases, blood pressure is maintained as long as SVR increases. In children with shock, this compensatory mechanism can be so effective that systolic blood pressure may initially remain normal or even slightly elevated. Pulse pressure, the difference

<table>
<thead>
<tr>
<th>Age</th>
<th>Systolic BP</th>
<th>Mean BP (Minimum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>50 -70</td>
<td>40-60</td>
</tr>
<tr>
<td>6 yr</td>
<td>80-116</td>
<td>60-90</td>
</tr>
<tr>
<td>10 yr</td>
<td>90-130</td>
<td>60-90</td>
</tr>
<tr>
<td>18 yr</td>
<td>104-135</td>
<td>65-100</td>
</tr>
</tbody>
</table>

*Adult normal BP - 120/80mm of Hg; MAP (diastolic + 1/3rd pulse pressure) – 93; Minimally acceptable SBP (> 5th centile) =70+ (age X 2); Acceptable SBP (>50th centile) = 90+( age X 2)
between the systolic and diastolic blood pressure, is often narrowed because an increase in SVR raises the diastolic pressure. In contrast, if SVR is low (as in sepsis), diastolic blood pressure decrease and pulse pressure widens.

**Distribution of circulation**

Parameters that determine adequate oxygen delivery to tissues include blood flow to tissues (cardiac output), the regional balance between blood flow and metabolic demand. Organ systems generally receive portions of the total cardiac output that are proportional to that organ’s metabolic demand (Table III). In a simplified fashion then, metabolic demands may be equated with organ system oxygen consumption except in three organ systems: a) kidneys, b) skin, and c) heart. The kidneys normally receive about 20% of the cardiac output while utilizing only 10% of the body’s total oxygen consumption. This disparity is in response to the kidney’s role in filtering metabolic waste products from the blood. The skin normally receives about 10% of the cardiac output while using only 5% of the body’s total oxygen consumption. This is secondary to the role of cutaneous circulation as a temperature regulator. The heart normally receives about 5% of the cardiac output while utilizing 10% of the body’s total oxygen consumption. This necessitates a large extraction of oxygen from the coronary blood supply and results in extremely desaturated coronary sinus blood. The clinical implication is that, because there is normally very little available oxygen remaining in coronary sinus (venous) blood, oxygen supply to the heart is vitally dependent on maintenance of adequate coronary blood flow.

At a glomerular filtration rate (GFR) of 125ml/min, the kidneys produce 180 litres of filtrate daily. Yet the average urine output is only 1000 to 1500 ml. Through reabsorption, 99% of the glomerular filtrate is returned to the bloodstream. Reabsorption of fluid and solutes contribute to the regulation of blood pressure.

**Renal autoregulation**

The ability of kidneys to maintain a constant blood pressure and GFR despite changes in systemic arterial pressure is called renal autoregulation. Wherever blood pressure drops afferent arteriole dilates and efferent arteriole constricts. This increases net filtration pressure (NFP) and GFR. In the presence of high blood pressure, afferent arterioles constrict as NFP and GFR are higher.

How normal urine output (1-2 ml/kg/hr) is maintained?
Cardiac output - 5-6 litres / min
Renal perfusion 20% of CO - 1 litre / min

**Table III. Individual organ perfusion**

<table>
<thead>
<tr>
<th>Organs</th>
<th>Percent of cardiac Output (%)</th>
<th>ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>14</td>
<td>700</td>
</tr>
<tr>
<td>Heart</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>Bronchi</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Kidneys</td>
<td>22</td>
<td>1100</td>
</tr>
<tr>
<td>Liver</td>
<td>27</td>
<td>1350</td>
</tr>
<tr>
<td>Muscle (Inactive)</td>
<td>15</td>
<td>750</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>250</td>
</tr>
<tr>
<td>Skin (cool weather)</td>
<td>6</td>
<td>300</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0.5</td>
<td>25</td>
</tr>
<tr>
<td>Other organs</td>
<td>3.5</td>
<td>175</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>5000</td>
</tr>
</tbody>
</table>
Table IV. Compensatory mechanisms in shock

<table>
<thead>
<tr>
<th>Compensatory mechanisms</th>
<th>Tissue / organ</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased heart rate</td>
<td>Heart</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Increased SVR</td>
<td>Skin</td>
<td>Cold, pale, diaphoretic</td>
</tr>
<tr>
<td></td>
<td>Circulation</td>
<td>Delayed capillary refill</td>
</tr>
<tr>
<td></td>
<td>Pulses</td>
<td>Weak peripheral pulse, narrow pulse pressure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>elevated DBP</td>
</tr>
<tr>
<td>Decreased splanic flow</td>
<td>Kidney</td>
<td>Oliguria</td>
</tr>
<tr>
<td></td>
<td>Intestine</td>
<td>Vomiting, ileus</td>
</tr>
</tbody>
</table>

Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) - intracranial pressure (ICP). Normally ICP is less than 10 mm Hg. An ICP of above 20 mm Hg is harmful to brain cell leading to altered consciousness which can be assessed by AVPU.

Assessment of circulation

Assessment of the adequacy of systemic perfusion is an essential part of rapid cardio pulmonary assessment in every child (healthy or distressed). It is accomplished by evaluation of pulse, blood pressure, capillary refill and mental status. Tachycardia and prolonged refill time are clinical manifestations of compensatory mechanisms to maintain a normal arterial perfusion pressure in the face of cardiopulmonary compromise.

A discrepancy between central (carotid, brachial, femoral) and peripheral (radial, dorsalis pedis) pulses may be an early sign of decreased cardiac output and diminished peripheral perfusion. Hypotension is a late finding in children with cardiopulmonary compromise. When \(O_2\) delivery to the tissues is compromised, blood flow is redirected or shunted from non vital organs and tissues (e.g. skin, skeletal muscles, gut, kidneys) to vital organs (e.g. brain, heart). This redirection occurs by a selective increase in SVR (vasoconstriction) and clinically this manifests as reduced peripheral perfusion (i.e. delayed capillary refill, cool extremities, less easily palpable peripheral pulses), and reduced perfusion to the kidneys (decreased urine volume). Change in the level of consciousness of a child may indicate decrease in cerebral oxygenation and/or perfusion (Table IV).

Types of shock include hypovolemic shock (characterized primarily by reduction in preload, as result of fluid loss), distributive shock (decreased SVR with abnormal distribution of blood flow as a result of sepsis or anaphylaxis) and cardiogenic and obstructive shock (pump...
failure as a result of cardiomyopathies, arrhythmias or blood flow obstruction). Patients may have “warm shock” with decreased systemic vascular resistance (SVR), bounding pulses and normal or flash capillary refill or “cold shock” with poor peripheral perfusion due to increased SVR (decreased capillary refill, decreased peripheral pulses as compared with central pulses).

**Pulse oximetry**

Pulse oximetry is often called as the fifth vital sign. Pulse oximetry is a tool to monitor the percentage of the hemoglobin that is saturated with O$_2$ (SpO$_2$). Pulse oximetry uses the differential absorbance of light by oxyhemoglobin and deoxyhemoglobin to estimate the oxygen saturation. Pulse oximetry is indicated in any setting where hypoxemia can occur. SaO$_2$ 94% on room air indicates adequate oxygen. It detects hypoxemia before cyanosis appears.

**Regulation of acid - base**

The main function of respiration is to maintain normal blood gas homeostasis to match the metabolic needs of the body with the least amount of energy expenditure. Once CO$_2$ is released by tissues it enters the blood. Most of the CO$_2$ (95%) is carried by RBC. While the remaining (5%) in the plasma. Virtually 99.9% of the plasma CO$_2$ is in the form of dissolved CO$_2$ (dCO$_2$). Approximately 0.1% is in the form of carbonic acid (H$_2$CO$_3$). The major blood acid is carbonic acid which is a volatile acid that is controlled by the ventilatory system.

All other potential sources of hydrogen ions are nonvolatile (or fixed) acids and therefore, regulated by the kidneys and liver. The major sources of nonvolatile acids are dietary acids, lactic acids and keto acids (Fig.4).

The primary blood base is bicarbonate (HCO$_3^-$). Hydrogen ion is produced in the renal tubular cells by the following reaction: CO$_2$ + H$_2$O $\rightarrow$ H$_2$CO$_3$ $\rightarrow$ HCO$_3^-$ + H$^+$

The presence of carbonic anhydrase in the renal tubular cells allows the reaction to take place rapidly and completely. It is the total amount of hydrogen ion secreted that is significant to metabolic acid-base balance. Since the kidneys have limited capability to acidify urine, the urine buffers play an important role in secreting large amounts of hydrogen ion. The most important urine buffer is phosphate. In glomerular filtrate, 80% of the phosphate is in the dibasic form (HPO$_4^{2-}$). In the urine 99% of the phosphate is monobasic (H$_2$PO$_4^-$). The hydrogen ions attached to phosphate do not change urine pH. Ammonia and the ammonium ion is another important buffer system. The time required for the kidneys to change affect blood pH significantly over hours, in contrast to the respiratory mechanism, which can make significant changes in seconds.

**Water and energy**

Water transports nutrients and oxygen to all tissues and cells in the body. Also, water removes the waste and toxic materials from the body through urine, sweat, respiration and stools. Water is also involved in thermoregulatory mechanism and thereby regulates body temperature.

The body loses water primarily by excreting it through urine and stools. Water is also lost daily as sweat and in exhaled air through the lungs. The body obtains water primarily by absorbing it from the digestive tract. This water is called exogenous (outside) water, which comes from both the food we eat as well as the water and fluids we drink. Additionally, some amount of water is produced by the body during metabolism, called metabolic water produced in the body.

During breakdown (oxidation, using oxygen in the blood) of CHO, proteins and lipids in the tissues for energy release, 6 molecules of water and 6 molecules of carbon dioxide will be released as follows:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O + \text{energy released}$$

This CO$_2$ will be transported through blood the lungs for excretion through exhaled air. During oxidation of 100g of CHO, lipids and proteins in the body for energy release, 55g, 110 g and 40g of water is produced respectively. As such 350 to 400ml (1ml=1g) of metabolic water is produced daily in the body, depending on the energy requirement and the nature of food consumed. The daily water requirement for each individual varies from 2 to 3 liters per day, of which nearly 8-10% is from metabolic water, 20-25% from foods and the remaining 65-72% is from drinking water and other fluids.
Holliday-Segar method estimates the fluid requirements based on the amount of kilocalories expended and is therefore indirectly related to the patient’s weight. Accordingly for every 100 kilocalories expended for metabolism, 100 mL of fluid is needed in normal children (Table V).

### Table V. Holliday-Segar formula for calculation of maintenance of calories and fluids

<table>
<thead>
<tr>
<th>Weight</th>
<th>kcal/d or mL / d</th>
<th>kcal/d or mL / h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 kg</td>
<td>100/kg/day</td>
<td>4kg/hour</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>1000 + 50/kg/day*</td>
<td>40 + 2/kg/hr*</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1500 + 20/kg/day**</td>
<td>60 + 1/kg/hr**</td>
</tr>
</tbody>
</table>

* for each kg >10  ** for each kg >20

### Basal metabolic rate (BMR)

Basal metabolism is the energy expended for cellular and tissue processes that maintain life. It is measured under standard conditions of thermoneutrality, immobility and fasting. The components of energy expenditure are basal metabolic activities (such as heat production for maintenance of body temperature, maintenance of ionic gradients across cells, cardiac and respiratory function), the thermic effect of food (thermogenesis) and physical activity (Table VI). The energy expenditure of physical activity is determined by the time spent on an activity and the intensity of effort, is defined as the ratio of total energy expenditure over BMR and is expressed as multiples of BMR.

### Table VI. Components of energy expenditure

<table>
<thead>
<tr>
<th>Components of energy expenditure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal metabolic rate</td>
<td>70%</td>
</tr>
<tr>
<td>Thermogenesis</td>
<td>15%</td>
</tr>
<tr>
<td>Activity</td>
<td>15%</td>
</tr>
</tbody>
</table>

### How to calculate daily energy requirements?

About 2000 calories are the basic calories needed for a person, with zero physical activity i.e. basal metabolic rate (BMR). BMR have to be multiplied with the body activity factor; which ranges from 1.2 to 1.9, depending on their physical activity. Factor of 1.2 to 1.4 for low physical activity or sedentary habits, 1.5 to 1.6 for moderate physical activity and 1.7 to 1.9 for high physical activity. The formula for energy calculations is given in Box 3.

### Box 3. Energy (Kcal) calculation - Formula

- Sedentary person – Wt (kg) x 30
- Moderately active person- Wt (kg) x 40
- Active person (athlete) – Wt (kg) x 50

During exercise, increased oxygen consumption (VO$_2$) and carbon dioxide production (VCO$_2$) occur immediately with exercise. During aerobic metabolism, glucose and fats utilize oxygen to form adenosine triphosphate (ATP), the ultimate source of energy. There is very little oxygen stored in the body, so aerobic metabolism requires continuous delivery of oxygen from the atmosphere to the blood. Without oxygen, glucose is metabolized anaerobically and the yield of ATP per glucose molecule is much less; in addition, lactic acid which is generated as a by-product, when buffered generates carbon di-oxide in excess of that from aerobic metabolism. So hyperventilation occurs as compensation for the lactic acidosis. The metabolic changes during exercise in aerobic and non aerobic metabolism are given in Box 4.

### How much energy is needed and at what ratio?

A healthy man with sedentary habits needs 1800 to 2000 kilo calories/day of energy/day and a healthy woman with sedentary habits needs 1600 to 1800 kilo calories/day which is roughly equivalent to about 30 Cal/kg body weight/day. On the other hand, growing children, sports persons, pregnant and lactating women need >35 Cal/kg/day. Caloric intake should be proportioned among the three macronutrients: carbohydrates, proteins, and fats. In a healthy adult’s diet, these daily recommended calories must be obtained from CHO, lipids and proteins, in the ideal ratio of 57:30:13 respectively. Growing children, athletes, pregnant and lactating women need more calories from protein and lipids. Hence, for them the ratio will be 53:32:15.

### How much CHO, lipids and proteins do we need daily?

### Box 4. Metabolic changes - Exercise

**Aerobic metabolism:**

i. Substrate - Glucose

\[ C_6H_{12}O_6 + 6 \, O_2 \rightarrow 6CO_2 + 6H_2O + 36 \, ATP \]

ii. Substrate - Fatty acid

\[ C_{16}H_{32}O_2 + 23 \, O_2 \rightarrow 16 \, CO_2 + 16 \, H_2O + 130 \, ATP \]

**Anaerobic metabolism:**

Glucose + 2 ADP $\rightarrow$2H$^+$ + 2 ATP
In a healthy diet, 2000 calories must be derived from CHO, lipids and proteins, in the ratio of 57:30:13. This is equivalent to 1140 + 600 + 260 calories of energy from CHO, lipids and proteins, respectively. At the rate of 4, 9 and 4 Kcal of energy/g of CHO, lipids and proteins respectively, a person needs 285g of CHO, 66 g of lipids and 65 g of proteins (about 1g protein/kg body weight/day) daily.

**Fever**

Elevated body temperature may result from fever (increased body temperature with elevated hypothalamic set-point) or hyperthermia (increased body temperature with normal hypothalamic set-point). Fever is induced by cytokines activated during inflammation and controlled by thermoregulatory center located in anterior hypothalamus. Temperature of deep tissues of the body is “core”. Normal core temperature is 98.4°F (± 1°F or ± 0.6°C).

Normal body temp is balanced by heat production by metabolic activity of muscle and liver and heat loss by the skin and lung. However, the newborn has a much greater heat loss than the older child or adult, because heat loss is largely determined by the ratio of body surface area to body weight and are heavily dependent on the environment to retain body heat. The environmental temperature is extremely important for infants. Most infants that are sick are placed in a neutral thermal environment (NTE), which is the environmental temperature at which oxygen consumption is lowest.

Benefits and harms - Whether fever is beneficial or harmful is disputed. Fever is an integral part of the inflammatory response and, as such, may have a role in fighting infection. However, defence mechanisms can go awry. Even if fever does have a role in defending the host against infection, it may still be that, in some circumstances, fever does more harm than good.

**Potential benefits** – Potential benefits of fever include retardation of the growth and reproduction of some bacteria and viruses (perhaps related to decreased serum iron) and enhanced immunologic function at moderately elevated temperatures, although some of the benefits are reversed at temperatures approaching 40°C (104°F).

**Potential harms** – Fever can make patients uncomfortable. It is associated with increased metabolic rate, oxygen consumption, carbon dioxide production, and demands on the cardiovascular and pulmonary systems. For the normal child, these stresses are of little or no consequence. However, for the child in shock or for the child with a pulmonary or cardiac abnormality, the increased demands can be detrimental and may offset any immunologic benefit from the fever.

**Conclusion**

This is how cardiopulmonary, cerebro-renal, gastro and metabolic systems are working together in health and diseases to maintain homeostasis of the body as “Unity in Diversity”. Recording of vital signs is essential for diagnosis and monitoring in a sick child. The skin changes, the sensorium and the urine output assess the end organs that are being supplied by the respiratory and the cardiovascular systems. The others are direct assessments of the respiratory and cardiovascular systems.

Thus, we realise that the parents can monitor the behaviour of the child and urine output; in other words, they can monitor the well being of the end organs such as brain and the kidney. We as physicians, can evaluate the wellbeing of the respiratory and the circulatory system. In this manner one can ensure that any child can be easily and quickly evaluated for deviation from normal physiology.

**Points to Remember**

- **Oxygen requirement is 5 ml / Kg/min.**
- **Normal healthy person of 50-60 kg needs 250-300ml of O2/ min for which tissue receives 5-6 litres of cardiac output/ min**
- **Alveolar volume: stroke volume is 4:1 , that is why RR: HR is 1: 4**
- **MAP is a better indicator for organ perfusion than systolic pressure.**
- **Normal urine output is 1 to 2 ml /Kg/hr.**
- **To arrive at normal fluid and calories requirement Holliday Segar formula is used.**
- **Oxygen consumption is lowest at neutral thermal environment**

**Bibliography**


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**NEWS AND NOTES**

**Advances in acute and chronic dialysis for children in South Asia**

**RRT KIDS 2019**

organized by

Department of Pediatric Nephrology

Mehta Multispeciality Hospitals India. Pvt. Ltd. Chennai

Date: 19th – 21st July, 2019

Venue: Hotel Radisson Blu, Egmore, Chennai.

**For registration**

Mobile: 91-8754414275, 91-9840109117

Email: rrtkids2019@gmail.com

Website: www.rrt.kids.org

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**The 17th ASEAN Pediatric Federation Congress (APFC) 2020 & the 23rd Annual Congress of Vietnam Pediatric Association (VPA)**

**Dates:** 22nd – 24th October, 2020  **Venue:** Hanoi, Vietnam

**E-mail:** secretariats.apfc2020@gmail.com
**STEROID MODIFIED DERMATOPHYTOSIS IN CHILDREN - AN UPDATE**

*Madhu R*

**Abstract:** Superficial dermatophytosis has evolved as a difficult to treat, chronic, recurrent, widespread recalcitrant infection and has emerged as a major public health problem in our country over the last 5-6 years. Current scenario of dermatophytosis is considered to be due to factors relating to environment, host, etiological agents and antifungal resistance with the most important factor being the rampant abuse of topical steroid antifungal/antibacterial combination creams procured by patients over the counter or as prescribed by practitioners. Potent steroid molecules in the combination creams cause local immunosuppression, barrier dysfunction and increase multiplication of the dermatophytes resulting in persistent infection. The term ‘Steroid modified dermatophytosis’ is used when the clinical morphology of dermatophytosis can be recognised in spite of application of topical corticosteroids. The term ‘Tinea incognito’ refers to the situation in which the clinical morphology is so altered that dermatophytosis is unrecognizable, due to the application of topical corticosteroid creams or use of systemic steroids. Clinical morphology, adverse effects, approach to a patient with steroid modified dermatophytosis and management strategy have been discussed.

**Keywords:** Steroid modified dermatophytosis, Tinea incognito, Local immunosuppression, Tinea pseudoimbricata.

Dermatophytosis is the most common superficial fungal infection caused by dermatophytes belonging to the three genera namely Trichophyton, Microsporum and Epidermophyton, the other two common superficial mycoses being pityriasis versicolor and candidiasis. Dermatophytes are keratinophilic in nature and thus invade the keratin of the skin, hair and nails. The infection spreads by direct contact from infected human beings (anthropophilic), animals (zoophilic), soil (geophilic) or indirectly through fomites. There has been an increase in the occurrence of superficial dermatophytosis among the adults across the country over the last 5-6 years and this has reflected in the increased prevalence of this infection among the children.1,2

This increasing trend would have been of no concern at all, if dermatophytosis was easily amenable to treatment as has been in the past. On the contrary, this has emerged as a major public health problem because it has evolved as a difficult to treat infection that runs a chronic, recurrent and refractory course with extensive involvement, much to the dismay of the medical fraternity and patients alike. Conventional dose and duration of systemic antifungal agents mentioned in the standard textbooks have been found to be ineffective to result in clinical cure. Current scenario of dermatophytosis is considered to be due to a plethora of factors relating to environment, host, etiological agents, antifungal drugs and antifungal resistance with the most important factor being the rampant abuse of topical steroid antifungal/antibacterial combination creams procured by parents either over the counter or as prescribed by practitioners.3 The steroid component in these combination creams is most often a potent steroid molecule such as clobetasol propionate or mometasone. These interfere with the host immunity causing local immunosuppression resulting in a conducive atmosphere for the florid multiplication and deeper penetration of the dermatophytes. Among a total of 1066 brands of topical steroids sold in our country, combination cream containing clobetasol, ofloxacin, ornidazole and terbinafine stood second in the sales with a turnover of Rs 110 crores in 2013.4 Free availability of these irrational combination creams, lack of qualified medical personnel, ignorance about the adverse effects of the steroids and practice of sharing of prescriptions among family members, friends and relatives have led to the widespread use of these creams in children and also by the parents. The terms ‘Steroid modified dermatophytosis and steroid modified Tinea’ are used when the clinical morphology of dermatophytosis can be recognized in spite of application of topical corticosteroids. The term ‘Tinea incognito’ which was described by Ive and Marks in 1968, refers to the situation
in which the clinical morphology is so altered that dermatophytosis is unrecognizable, due to the application of topical corticosteroid creams or use of systemic steroids.\textsuperscript{\textcircled{1,2}} Subsequently, this term was also used to denote the altered picture due to the application of topical calcineurin inhibitors.\textsuperscript{\textcircled{6}}

**Epidemiology**

In the past, studies have shown that tinea capitis is the most common clinical presentation of dermatophytosis seen in children aged less than 10 years. But, at present, tinea corporis has been increasingly observed among children including infants.\textsuperscript{\textcircled{7,8}} Multiple site involvement, extensive lesions and involvement of the face, more often steroid - modified mark the current trend of dermatophytosis in children.\textsuperscript{\textcircled{8}} There is a paucity of literature on the clinico-mycological aspects of steroid modified tinea in children but in a study on childhood dermatophytosis, 51% of children gave history of application of double/ triple/ quadruple combination creams containing corticosteroids and antifungals.\textsuperscript{\textcircled{9}} In a study done at Bhubaneswar, 61.1% of children had used these combination creams.\textsuperscript{\textcircled{10}} Abuse of topical steroid creams for dermatophytosis is more rampant in northern India compared to the south. It was found from a study at Jhansi, North India, 86% of children had used topical creams containing clobetasol propionate (Group I potent steroid) which should not be used in children even in the presence of steroid responsive dermatoses.\textsuperscript{\textcircled{8}} History of contact with infected family members was present in 83% to 91.95% of children in these studies, which clearly reiterates the significant role played by fomites in the transmission of dermatophytosis among the contacts.\textsuperscript{\textcircled{8}-\textcircled{10}} Most often, primary source of infection was found to be the mother followed by sibling and father.\textsuperscript{\textcircled{9}} It was also observed that children who had applied potent topical steroids for a longer duration presented with extensive lesions compared to those children with limited infection.\textsuperscript{\textcircled{8}}

**Pathophysiology in steroid modified dermatophytosis**

First and foremost step in the acquisition of dermatophytosis is adherence of the arthroconidium to the keratinocyte, followed by germination and penetration. Moisture is an important factor that facilitates germination of arthroconidia. Prolongation of hyphae occurs in a radial direction resulting in the classical annular lesion of tinea corporis, wherein there is an active margin in the periphery and central clearing which is due to the elimination of the fungi by the host immunity. Dermatophytes grow in a centrifugal pattern and multiply at a rate faster than the rate of epidermal turnover, which is about four times in the active margin with inflammation. By virtue of persistence of immunological surveillance, already infected skin remains clear of the infection. Application of topical corticosteroids interferes with this normal phenomenon resulting in atypical presentations that pose difficulty in diagnosis.\textsuperscript{\textcircled{11}}

Topical corticosteroids are known for their anti-inflammatory, local immunosuppression, vasoconstriction and anti-proliferative effects. Hence, there is a profound modification by topical corticosteroids of the local host cell mediated immunity induced by dermatophytes compared to systemic steroids. In addition, topical corticosteroids also cause atrophy of the epidermis, reduction in size of the keratinocytes, increase in transepidermal water loss (TEWL) and decrease in ceramides, free fatty acids and cholesterol, all of which cause epidermal barrier dysfunction.\textsuperscript{\textcircled{12,13}} In addition, antibiotic components in the topical steroid combination creams interfere with the normal microflora and affect the barrier function. The net result of all these factors is florid multiplication of the dermatophytes unchecked by the local host immunity resulting in a chronic infection that does not respond to treatment even with systemic antifungals given in the conventional dose and duration.

On the contrary, there has been a recommendation by a European Expert panel for the use of topical antifungal-corticosteroid cream at the initiation of treatment of dermatophytosis for 1-2 weeks to reduce the inflammation followed by antifungal monotherapy. But the steroid molecules present in these combination creams were hydrocortisone or diflucortolone valerate which are less potent unlike the potent molecules such as clobetasol propionate/mometasone present in the steroid combination creams used in India among the patients with dermatophytosis. However, the experts had clearly stated that the incorrect use of these creams may lead to treatment failure and adverse effects.\textsuperscript{\textcircled{14}} Hence, in our country, there is no role for use of topical steroid combination creams in the treatment of dermatophytosis even for a short duration as it will only worsen the menace of tinea.\textsuperscript{\textcircled{1}}

According to patients with dermatophytosis who use topical corticosteroid creams their physicians can recognize the use of steroids, even if they fail to give the details of topical medications. Patients apply these creams initially for a few days which results in rapid control of itching and temporary resolution of inflammation, following which application is stopped. Within a few days after cessation of treatment, lesions become more active and erythematous resulting in a flare-up, due to the increased load of the
fungi in a background of local immunosuppression and barrier dysfunction and this cycle gets repeated.\textsuperscript{11}

**Clinical features**

**Steroid modified tinea:** Duration of abuse of the topical steroid/ topical steroid antifungal/ antibacterial combination creams is directly proportional to the severity of the clinical morphology of the lesions. Characteristic presentation of an annular lesion with active margin and scales with central clearing is conspicuous by its absence in the children with steroid modified tinea. Wide spread, ill-defined, erythematous lesions in bizarre shapes with absence of scales and central clearing are more often seen. Intermittent application of the topical steroids result in waves of the growth of dermatophytes in a centrifugal manner with ineffective clearance of the fungi due to the profound local immunosuppression resulting in ‘Tinea pseudoimbricata’ wherein multiple concentric rings are seen representing the activity or at times ‘double edged tinea’ or ‘ring within ring appearance’. Follicular papules and pustules may be present.\textsuperscript{1,11,15}

**Tinea incognito:** Clinical morphology is totally altered and hence, a high degree of suspicion is required to make a clinical diagnosis. Bizarre morphology with ill-defined borders, discrete papules, pustules, follicular papules etc mimicking various dermatoses like rosacea, psoriasis, systemic lupus erythematosus, photo sensitive rash, seborrheic dermatitis, atopic dermatitis, diaper dermatitis, contact dermatitis, eczema, folliculitis, impetigo, urticaria, pityriasis rosacea, granuloma annulare, Hansen’s disease, erythema annulare centrifugam and erythema migrans may be seen.\textsuperscript{6,16,17}

**Adverse effects of corticosteroids**

Common adverse effects of topical corticosteroids include striae, atrophy, telangiectasia, post inflammatory hypopigmentation/ depigmentation and acniform eruptions. Other side effects are rosacea, perioral dermatitis, hypertrichosis and exacerbation of skin infections. In the recent times, it is not unusual to see adolescents with extensive striae and iatrogenic Cushing’s disease.\textsuperscript{18,19}

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**Table I. History and its relevance in steroid modified dermatophytosis**

<table>
<thead>
<tr>
<th>History</th>
<th>Reasons</th>
</tr>
</thead>
</table>
| Environment factors          | • Overcrowding / occupation (children of migration workers; adolescents working - Metro work / construction / hotel industry)  
• Poor living conditions and water scarcity (Poor personal hygiene) |
| Host factors                 | • Duration of infection / Number of episodes  
• Family members affected - Number  
• Probing to find out the common source of infection  
• Sharing of fomites – towels, clothes, soaps, bed linen  
• Frequency of washing these clothes / washing infected and non-infected clothes together  
• Bathing frequency, cold/hot water bath, Wiping dry after bath  
• Clothes dried in sunlight vs indoors – particularly hostel students  
• Children with tinea cruris lesions – V shaped inner garments  
• Wearing of waist / wrist bands  
• Sharing of prescriptions  
• Lifestyle – long hours in synthetic uniforms / tight garments  
• Long hours spent playing in sun |
| Treatment history            | • Topical steroid antifungal (TSAF) combination creams – Number of tubes used/ frequency/ duration  
• Systemic corticosteroid – Injections/Intralesional  
• Poor compliance  
• Doctor hopping - Suboptimal duration of therapy will result in clinical failure |
Diagnosis

Whenever there is dilemma over the diagnosis of dermatophytosis, it is essential to do a direct microscopic examination of skin scrapings in 10% potassium hydroxide wet mount. Dermatophytes are typically seen as hyaline, long, branching septate hyphae with or without arthrospores. Culture in modified Sabouraud’s agar medium with chloramphenicol and cycloheximide could be done when feasible, to know the current epidemiological trend of the organism.

Approach to a patient with steroid modified dermatophytosis

Most often, children with steroid modified tinea tend to present with chronic infection of more than 6 months duration or recurrent episodes with history of irregular treatment. Hence, it is very important to take a detailed history with regard to factors related to the environment, host and treatment taken (steroids and antifungals) (Table I).

Detailed examination of the skin (extent of infection), hair and nails has to be done, as the latter acts as a reservoir for the infection. Counseling given during the first visit regarding the adherence to general measures (Table II) and drugs is the cornerstone of successful management of this infection.

Table II. General measures - Do’s and don’ts²⁰

<table>
<thead>
<tr>
<th>Do’s</th>
<th>Don’ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To bathe twice daily in cold water and wipe dry after bath</td>
<td>• Hot water bath is best avoided as it will worsen the epidermal barrier function</td>
</tr>
<tr>
<td>• Lukewarm water bath is preferable during winter and for the children living in hilly terrain</td>
<td>• Damp clothes should be never worn as the moisture acts as a fertile ground for dermatophytes</td>
</tr>
<tr>
<td>• Infected clothes to be washed separately in hot water at 60°C and dried in good sunlight inside out as sunlight is the best disinfectant. If drying in sunlight is not possible, ironing could be done.</td>
<td>• Synthetic, tight garments- jeans, leggings etc are to be strictly avoided</td>
</tr>
<tr>
<td>• Cotton clothing is always preferable</td>
<td>• Children with tinea cruris should avoid wearing V- shaped inner garments</td>
</tr>
<tr>
<td>• To ensure regular washing of towels, clothes and bed linen</td>
<td>• Waist/ wrist bands to be removed.</td>
</tr>
<tr>
<td>• Regular wet mopping of the floor</td>
<td>• Strict avoidance of sharing of fomites - towels, soaps, clothes etc</td>
</tr>
</tbody>
</table>

Systemic antifungals

Children with steroid modified tinea need a longer duration of treatment than the conventional duration mentioned in the standard text books. This is an experience based observation than evidence based. Literature states that it takes about 3 weeks for the reversal of immune response to occur after cessation of steroid when used for a period of 2-4 weeks. This explains the lack of response or slow response in the initial few weeks to antifungal drugs.²¹ Details of systemic antifungals is given in Table III.
Principles of systemic treatment:

- Ideal to start on a drug that has not been used early or in the recent past
- If good response - Conventional dose; Longer duration
- Duration of treatment is always individualized
- End point should be clinical cure
- Terbinafine / Itraconazole preferred in oily or sebum rich skin
- Fluconazole or griseofulvin is preferred in dry skin (Fluconazole - drug of choice in infants, toddlers and young children by virtue of its safety profile).

After initiation of treatment, parents should be advised to bring the child for review at the end of 3 weeks to monitor the clinical response and ensure the adherence to general measures. It would be ideal to continue the systemic antifungal drug for one week beyond clinical resolution.

### Table III. Systemic antifungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin</td>
<td>10-20 mg/kg in 2 divided doses</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3 mg/kg twice weekly</td>
<td>6 -8 weeks</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>5mg/kg/day</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>10-20 kg - 62.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-40 kg - 125 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;40 Kg - 250 mg</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5 mg/kg/day</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

### Indian Association of Dermatologists, Venereologists and Leprologists and topical steroid abuse

Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) through its two task forces namely ITATSA (IADVL Task Force Against Topical Steroid Abuse) and ITART (IADVL Task Force Against Recalcitrant Dermatophytosis) has taken a lot of efforts to fight against the topical steroid abuse in our country. ITATSA has filed a public interest litigation and has represented to the Drug Controller General of India to bring the topical corticosteroids under Schedule H and to ban the irrational topical steroid combinations. ITART has organized continuing medical education programs to create an awareness about topical steroid abuse and proper management of dermatophytosis among the practitioners and circulated public education posters displaying the Do’s and Don’t’s of general measures to be followed by patients with dermatophytosis in 12 languages across the country with an educational grant. Topical steroid abuse is a big battle to fight and the efforts are being continued in a big way.

### Conclusion

There has been an increase in the prevalence of dermatophytosis of the glabrous skin among the children in India in the recent years. Current practice of rampant abuse of topical steroid antifungal combination creams by the adults (parents) has victimized the children resulting in an upsurge of chronic, extensive, steroid modified tinea in children. Counseling regarding strict avoidance of topical steroid combination creams/ sharing of fomites/ prescriptions is of utmost importance in the management of this difficult to treat infection. Appropriate antifungal therapy for an extended duration may be required to result in clinical cure in these patients. Need of the hour is a collective effort from the medical fraternity, irrespective of the specialty to commit and fight against the steroid menace, which has become a huge financial burden to the affected families with indirect implications on the economy of our country.

### Points to Remember

- Steroid modified tinea is on the rise among the children.
- Clinical morphology of dermatophytosis may be recognizable in steroid modified tinea but is unrecognizable in Tinea incognito.
- Direct microscopy in 10% potassium hydroxide has to be done in case of clinical suspicion.

### Box 1. Various topical antifungal agents

- Azoles - 1% Clotrimazole, 2% Ketoconazole, 1% Bifonazole, 1% Oxiconazole, 2% Miconazole
- Newer azoles - 2% Sertaconazole,1% Luliconazole, 1% Eberconazole
- Allylamines - 1% Terbinafine
- 0.25% Amorolfin
- 1% Ciclopirox olamine
- Whitfield’s ointment
• Immediate cessation of combination containing topical steroid / antifungal/ antibacterial cream is the first step.

• Counseling regarding the compliance and strict adherence to general measures will play a pivotal role in the successful outcome.

• Reversal of immune response takes about 3 weeks after stopping the steroids and hence the initial slow response or lack of response in the first few weeks.

• Persistence of infection due to local immunosuppression warrants a longer duration of treatment.

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**DISORDERS OF GLANS AND PREPUCE**

*Sushmita Bhatnagar*

**Abstract:** An understanding of normal anatomy and function of the parts of the phallus is important to interpret the pathophysiology of the several conditions/diseases of the phallus. This article describes the normal and abnormal status of the phallus in children and discusses the ideal management of the different conditions, involving glans and prepuce such as balanitis, balanoposthitis, phimosis and paraphimosis.

**Keywords:** Phallus, Balanitis, Balanoposthitis, Phimosis, Paraphimosis.

**Glans**

**Anatomy and physiology:** The terminal end of the penis or phallus is the glans penis and is a sensitive bulbous structure. The shape of the glans penis may differ slightly in different individuals but largely it is conical in shape. The proportional size of the glans penis can vary greatly from one child to another. The glans is made of an expanded cap of corpus spongiosum tissue and moulds and fuses with the distal ends of both corpora cavernosa. The surface is composed of mucocutaneous tissue and remains moist when covered by prepuce. The base of the glans forms a rounded projecting border which is called corona glandis behind which is the neck of the penis. The urethral meatus is located at the tip of the glans penis.

**Clinical significance:** Since the epithelium of the glans penis is mucocutaneous tissue, application of irritants such as vigorous washing with strong soaps or irritant solutions may dry the mucous membrane and cause inflammation as well as dermatitis. The moistness of the glans remains intact when it is covered by foreskin, and hence in those children who are circumcised, the glans is permanently exposed, becomes dry and is replaced by cutaneous tissue.

**Prepuce**

**Anatomy and physiology:** Prepuce, also known as foreskin, is a double layered covering of the glans penis. The outer layer is skin and the inner layer is mucocutaneous tissue. On the ventral aspect, the prepuce is bound to the undersurface of glans in the midline by frenulum which is a richly innervated sensitive tissue. The prepuce provides cover and protection to the glans penis and the urethral meatus. When retracted completely in the erect state, it provides adequate cover to the entire length of the shaft.

The prepuce is densely innervated by somatosensory innervation by the dorsal nerve of the penis and branches of the perineal nerve (including the posterior scrotal nerves). Autonomic innervation of the prepuce arises from the pelvic plexus, the parasympathetic fibers arise from the sacral center (S2-S4), while the sympathetic preganglionic afferent and visceral afferent fibers arise from the thoracolumbar center (T11-L2). All the innervations provide a good fine touch sensation on the prepuce.

At birth, normally the mucosa of the glans is fused with the inner lining of the prepuce and this separates gradually and spontaneously over years. On examination, just the urethral meatus on the tip of glans is seen after very gentle retraction of prepuce which is completely normal. As the child grows there could be various situations in which either the mucosal separation is delayed or stopped or the preputial orifice may not open adequately. The hormones/growth factors for this separation have been studied but still not clearly understood.

Glands present on prepuce and glans produce secretions - the smegma which is thick and whitish. Smegma helps to lubricate as well as protect from infections including HIV due to the presence of lysozymes, cathepsin B, chymotrypsin, neutrophil elastase, cytokine and pheromones such as androsterone.

**Clinical significance:** As mentioned by many researchers, prepuce is necessary for normal sexual function as it is an erogenous tissue because of the rich nerve supply and the complex interaction between the preputial and glanular protopathic sensitivity.
If this normal anatomy and physiology is not understood, physicians may advise either forcible retraction of the prepuce or advise surgical intervention such as circumcision erroneously and unnecessarily. If circumcision is done in the neonatal period when normal separation of the mucosal lining has not happened spontaneously, the mucosa of the glans is torn and may cause cicatrix formation on the glans.

Infections of the glans and prepuce

Balanitis and balanoposthitis

Balanitis is inflammation of the glans penis and can occur in boys at any age. Balanoposthitis is inflammation of both glans and prepuce. In infants and toddlers, balanitis can occur along with diaper ammoniacal dermatitis when diapers are not changed frequently after being soaked with urine in both circumcised and uncircumcised boys.

Incidence of balanitis in uncircumcised boys is about 4% during pre-school years. In boys less than 5 years, it was found that incidence of balanitis was much higher in those who were not circumcised and had associated phimosis (25%) when compared to circumcised boys (6%). As described by Herzog in a survey of 272 uncircumcised boys, balanitis was diagnosed in 6% and irritation of the glans or prepuce in 4%, of which non-specific balanoposthitis was the most common cause. Even though the incidence of other systemic conditions and sexually transmitted diseases is quite low, a high index of suspicion should be maintained for appropriate diagnosis.

Etiology: It is multifactorial in children and often results from poor personal hygiene. Secondary infection by both Gram positive and Gram-negative bacteria complicates the situation. Occasionally trauma, lack of aeration, irritation due to chemical irritants/soaps, excessive washing or other diseases such as sexually transmitted diseases could be an etiological factor. E.Coli has been found to be the most common organism followed by Proteus and Klebsiella. Candida has also been reported in some studies varying from 1-3.5%.

Clinical features: Patients with balanitis or balanoposthitis usually present with complaints such as pain, swelling of the prepuce and occasionally the phallus, redness over the prepuce, crying during micturition, dribbling of urine, itching and in severe cases urinary retention and fever with associated urinary tract infection.

Clinical examination can reveal redness, swelling, serous or purulent discharge and/or foul odor. Discharge maybe evident only after gentle retraction of the prepuce or milking of the phallus. With streptococcal infection, pain associated with excessive redness and moist glistening transudate or exudate is seen over the prepuce or glans. Incidence of N. gonorrhea or chlamydia infections is higher in children after puberty and the diagnosis needs to be confirmed with culture and tests such as rapid antigen tests, DNA probes, etc of the discharge.

Prepuce may be nonretractable, but does not always signify pathological phimosis. In very severe cases, signs of urinary retention such as distended palpable bladder may be found necessitating the child to be admitted.

Treatment

The treatment of balanitis and balanoposthitis is mainly conservative. Complete resolution of symptoms occurs with appropriate therapy once the organism causing the infection is identified. The mainstay of conservative therapy is local hygiene, Sitz bath, topical antibiotic ointments after gentle cleaning of preputial sulcus or glans or occasionally oral antibiotics depending on the severity of clinical features. In suspected or proven candidial infection, antifungal creams are also required. Hydrocortisone cream 0.5% strength can also be used in mild cases or can be used once the active infection and inflammation subsides. For streptococcal balanitis and balanoposthitis, the treatment of choice is oral administration of penicillin-V for a period of 10 days or till the condition completely resolves. For N gonorrhea or chlamydial infections, the recommended treatment is ceftriaxone or oral macrolide respectively.

In certain cases, saline wash to the preputial sulcus may be given from the preputial opening with the help of a small sized catheter or tip of butterfly IV needle set after cutting off the needle. In cases of acute urinary retention, hospitalization is necessary and treatment with intravenous antibiotics, sitz bath and topical antimicrobial ointments usually suffice. Catherization leads to introduction of ascending infection when there is balanitis and balanoposthitis. Hence conservative methods to relieve the retention must be attempted before contemplating catheterisation which is rarely necessary.

Surgical intervention is indicated in situations of recurrent or recalcitrant balanoposthitis in which there are more than two acute episodes of proven infection. Circumcision or prepucioplasty may be done in such cases. The incidence of recurrent balanoposthitis requiring circumcision was 23%.

Phimosis

Phimosis is defined as the inability to retract the prepuce (foreskin). Phimosis can be classified into
(a) physiologic phimosis and (b) pathologic phimosis. Based on state of the prepuce, phimosis is categorised as normal, cracking, scarred and balanitis xerotica obliterans.

According to Meuli, et al, phimosis can be graded into 4 categories

Grade I - Fully retractable prepuce with stenotic ring in the shaft,

Grade II - Partial retractability with partial exposure of the glans,

Grade III - Partial retractability with exposure of the meatus only and

Grade IV - No retractability.

According to Kikiros et al, the grading of phimosis is

Grade 0 - Full retractability

Grade 1 - Full retraction but tight behind glans

Grade 2 - Partial exposure of glans

Grade 3 - Partial retraction with meatus just visible,

Grade 4 - Slight retraction but neither meatus nor glans visible and

Grade 5 - Absolutely no retraction

Physiologic phimosis: At birth, almost all (96%) boys are born with physiologic phimosis. Gradually as prepuce starts opening up between the glans and its inner layer, it starts retracting. This separation occurs due to gradual deposition of smegma also called as foreskin pearl as well as the spontaneous erections which occur in boys. The process of the entire prepuce completely retracting generally ends by 6-7 years of age of which about 90% resolve by 3-4 years of age and more than 99% by 17 years of age.

On examination and gentle retraction of healthy prepuce, there is a slight pouting and the urethral meatus along-with some portion of the glans is visible. This can be differentiated from pathological phimosis in which gentle retraction of the prepuce leads to a cone-shaped structure with distal narrowing which is white and fibrotic along-with a pin point meatal opening.

Pathologic phimosis

A clinical differentiation between physiologic and pathologic phimosis is absolutely essential so that appropriate treatment is given and infants/children are not subjected to unwarranted surgical intervention. Medical professionals dealing with children should be able to distinguish between these two types of phimosis as otherwise parents are also subjected to unnecessary anxiety and financial burden of an unindicated surgical intervention.

Several mechanisms which cause pathologic phimosis are as follows:

a. Forceful retraction of prepuce causes tearing and scarring of the skin which not only leads to tight ring formation at the meatus but also problems such as straining during micturition, ballooning, itching, urinary tract infection, etc.

b. Infections leading to balanitis, posthitis or balanoposthitis may ultimately lead to balanitis xerotica obliterans (BXO).

It has been reported that of all the cases referred to surgeons for circumcision, only 8-14.4% of children actually had phimosis for which operative intervention was carried out. Thus, the rate of mis-diagnosis is as high as 85-90% and this situation should be rectified so that children are offered appropriate treatment.

Management

Precise diagnosis is absolutely essential for appropriate management. The management of phimosis can be done by several ways and means. No tests are required to diagnose phimosis and investigations are needed only if there are co-morbid conditions. Management algorithm is shown in Fig.1.

Conservative treatment

Physiological phimosis does not need any treatment. For those with pathological phimosis, therapy depends on the grade or severity of phimosis. Conservative therapy must be initiated in the form of local hygiene, Sitz bath twice a day and betamethasone cream/ointment 0.05% twice a day on the preputial opening after retracting the prepuce gently. In case of associated morbid conditions such as urinary tract infection, oral antibiotics can be initiated. Child needs to be reviewed in a week’s time for assessment of compliance and response to therapy. Betamethasone cream has to be continued for 6-8 weeks with regular follow-ups and assessment of status of phimosis. The response rates to betamethasone cream as mentioned by Steadman et al., has been between 65-95% in which there is complete resolution of phimosis. Low response rates could be multifactorial, of which, poor compliance has been the major influence on the outcomes.
If phimosis recurs, steroids can safely be continued or up to 3 months.

Alternative method of faster relief is preputial adhesiolysis with a metallic probe or artery forceps in the OPD settings. This can be done only when the child is older, is cooperative and local anesthetic creams are available for the procedure. It has been found by many authors that this method is safe and effective.

**Surgical treatment**

The surgical alternatives available are: a) Circumcision and b) Prepucioplasty

**Circumcision** is the procedure in which the prepuce is completely excised thus exposing the glans for the rest of the life of the child. Numerous techniques for circumcision are available with or without the use of bells, rings and clamps. High rate of complications have been noted worldwide with this surgery which range from immediate and minor infection, bleeding to even death. Hence, judicious selection of patients with appropriate indications for surgery is of utmost importance.

**Prepucioplasty** is an alternative surgical procedure in which the prepuce is repaired at the level of constriction and is not excised. Different types of procedures are described depending on the site of incision on the prepuce such as dorsal slit prepucioplasty, lateral slit prepucioplasty etc. Those who are firm proponents of preserving the preputial skin are resorting to these techniques of prepucioplasty. The author has devised an innovative technique in which a ventral vertical incision is taken to completely open up the tight preputial ring and repair the prepuce in such a manner so as to allow the prepuce to retract with great ease. The prepucioplasty enthusiasts have even attempted this surgical procedure on sclerotic phimosis group with considerable success.

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**Fig.1. Phimosis - Management algorithm**

**Table I. Criteria for selection of type of surgical procedure**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prepucioplasty</th>
<th>Circumcision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent balanitis</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Recurrent balanoposthitis</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Cracking preputial skin</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Scarred preputial ring</td>
<td>✓</td>
<td>+/-</td>
</tr>
<tr>
<td>Balanitis xerotica obliterans</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Recurrent UTI</td>
<td>✓</td>
<td>+/-</td>
</tr>
<tr>
<td>Failure of conservative therapy</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>
To simplify the understanding the criteria of patient selection for either of the procedures, Table I is a quick assist tool.

**Balanitis Xerotica Obliterans (BXO)**

This condition also known as lichen sclerosus deserves a special mention as the management of this condition differs from that of balanitis in children. It appears as white patches on the preputial skin causing fibrosis and narrowing of the preputial opening. It can extend to the urethral meatus on the tip of the glans causing metal stenosis. The etiology is unknown and the condition is usually progressive most commonly occurring in boys between 9-11 years. Globally, the incidence is around 35% of children who have been circumcised and the confirmatory diagnosis is based on histopathology.\(^{30}\)

The treatment of choice is circumcision with or without meatoplasty. Conservative therapy as well as prepucioplasty is not effective in adequate treatment in a majority of cases. In early cases of BXO, prepucioplasty can be attempted with a clear understanding that there could be recurrence of symptoms and child may develop a much tighter preputial ring.

**Paraphimosis**

In children, paraphimosis is a dire emergency. It is an extremely painful condition wherein the prepuce is retracted proximally, gets entrapped proximal to the coronal sulcus and is unable to be pushed down to the normal position. The blood supply of the prepuce as well as the glans is compressed resulting in rapidly increasing swelling and further constriction of the glans. As the swelling increases over both the prepuce and the glans, retraction of the prepuce becomes more and more difficult.\(^{31}\)

**Clinical presentation**

In infants and young children, paraphimosis presents with sudden onset excessive crying, pain and inability to retract the prepuce to the normal position after possibly being retracted during bathing and cleaning the area. Occasionally this condition occurs post catherization as an iatrogenic complication, either in children who are on CIC (Clean Intermittent Catherisation) or during hospitalization. In older children and adolescents, masturbation or sexual intercourse can lead to this condition. The dreaded complications of this condition are necrosis of glans penis and partial amputation of the penis.\(^{32}\)

**Management**

It is essential that the paraphimosis is reduced as early as possible. Step-wise management guideline is described as follows:

**Step 1: Pain management**

1. Systemic analgesics – Fentanyl, ketamine, nitrous oxide
2. Topical anesthetics with compression of the part – lidocaine 2% gel or EMLA (lidocaine 2.5% and prilocaine 2.5%) cream may be used and left for some time (approximately about half an hour) following which further compression and reduction may be attempted.
3. Regional nerve block – Dorsal penile nerve block as described by Flores et al under ultrasound guidance followed by compression and reduction of the paraphimosis.\(^{33}\)

**General anesthesia** – in cases where swelling is massive and there has been delay in presentation, general anesthesia with reduction is the most suitable option.

**Step 2: Reduction of paraphimosis**

Several methods for reduction may be employed, with or without the use of other agents. If a simple compression with wet gauze does not reduce the paraphimosis, other techniques need to be utilized. The options available are as follows:

1. Osmotic agents – various osmotic agents have been tried and tested such as 20% mannitol soaked gauze, granulated sugar, and use of 50% glucose soaked gauze.\(^{34}\)
2. Iced glove technique – after placing iced water in the thumb of glove, the penis is placed in that portion of the glove and held in place for sometime till the edema decreases and reduction can be achieved.
3. Hyaluronidase injection – 1 ml of hyaluronidase is injected in multiple sites of the swollen prepuce to reduce the edema following which reduction can be achieved.\(^{35}\)
4. Multiple puncture technique – also known as Perth-Dundee technique wherein fine needle 26G is used to puncture the swollen foreskin at multiple sites for drainage of edema fluid thus making the reduction feasible.\(^{36}\)
5. Aspiration of glans – after applying tourniquet to the shaft of the penis, a 20G needle is inserted into the glans and about 10 ml of blood is aspirated to reduce the size of the glans.
6. Dorsal slit procedure - Incision of the prepuce dorsally similar to prepucioplasty may be rarely indicated if other non-operative techniques are unsuccessful in reducing the paraphimosis.

7. Emergency circumcision – very rarely indicated.

All children who develop paraphimosis need not be circumcised and a close short-term follow-up for about 3 months is essential. Prevention of the condition is important by counselling the parents/caregivers and the child if old enough.

**Conclusion**

With good local hygiene various infective and inflammatory lesions of the glans and prepuce can be prevented. Disorders of the prepuce especially phimosis has to be clearly understood as a precise diagnosis is the foundation of appropriate treatment. Subjecting the neonate, infant and child to unwarranted surgical intervention is better avoided. All attempts should be made to conserve the preputial anatomy and function by conservative means.

**References**


Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis

Coronary artery aneurysms (CAA) are a serious complication of Kawasaki disease. Treatment with intravenous immunoglobulin (IVIg) within 10 days of fever onset reduces the risk of CAA from 25% to <5%. Retrospective multicenter study was done including children who had CAA with a \( z \) score \( \geq 2.5 \) and \(< 10\) at time of diagnosis and who received primary therapy with IVIg alone or in combination with either corticosteroids or infliximab within 10 days of onset of fever. Of 121 children, with a median age of 2.8 (range 0.1–15.5) years, 30 (25%) received primary therapy with corticosteroids and IVIg, 58 (48%) received primary therapy with infliximab and IVIg, and 33 (27%) received primary therapy with IVIg only. Median coronary \( z \) scores at the time of diagnosis did not differ among treatment groups \((P = .39)\). Primary treatment intensification with either corticosteroids or infliximab were independent protective factors against progression of coronary size on follow-up (coefficient: “1.31 [95% confidence interval: “2.33 to “0.29]; coefficient: “1.07 [95% confidence interval: “1.95 to “0.19, respectively). Among a high-risk group of patients with Kawasaki disease with CAA on baseline echocardiography, those treated with corticosteroids or infliximab in addition to IVIg had less progression in CAA size compared with those treated with IVIg alone. Prospective randomized trials are needed to determine the best adjunctive treatment of patients who present with CAA.

ANGRY ADOLESCENT

**Preeti M Galagali**
**Jayshree K**

Abstract: Anger is common in adolescence. Anger outbursts may present for the first time in adolescence or may be a part of the continuum since childhood. It can lead to aggression, violence, high risk behavior, crime and death. It has many causes. A thorough clinical evaluation is essential to make a precise diagnosis and plan further management. A multidisciplinary team involving pediatrician, parents, teacher and mental health professional is required for appropriate management.

Keywords: Specific learning disability, Attention deficit hyperactivity disorder, Oppositional defiant disorder, Screening for childhood anxiety related emotional disorders.

Anger is a common behavioral issue in adolescence. Parents and adolescents often seek guidance from their primary care pediatrics for managing anger and familial conflicts. Mild feelings of anger can be normal in adolescence and may indicate an increase in life stressors. Severe and prolonged episodes of anger and aggression, first seen, in adolescence are clinical pointers towards emerging mental disorders like bipolar disorders or depression.

Poorly managed anger can lead to aggression, violence, self harm, drug use, rash driving, juvenile delinquency and even death. In India, juvenile crime rate has increased by 69% in the period from 2001 to 2015. There has also been a rise in gender based violence. Currently, westernization, materialism, individualism, intense competition, unsupervised excess media usage and breakdown of joint family system have resulted in increased display of anger and frustration, especially in those individuals and families who lack adequate coping skills. Anger management is a challenge for teens, their parents and health professionals.

Definition

Anger is defined as a feeling of annoyance, displeasure or antagonism. It is an intense emotional response to frustration or provocation characterised by heightened autonomic activity, changes in central nervous system activity and cognitive labeling.

Excessive and uncontrolled anger can lead to aggression and violence. Aggression is a harmful behavior which violates social conventions. It may include behavioral traits like deliberate intention to harm and injure another individual or object. Girls tend to exhibit more of indirect aggression like name calling or rumour mongering while boys exhibit more of direct aggression like kicking, pushing, pulling and physical fighting. Adolescents with proactive aggression may have serious psychopathology with criminal intent. Violence is a form of severe aggression resulting in injury, death, psychological harm or social deprivation. Sexual violence, adolescent relationship abuse, shooting, assault and murder are heinous forms of violence.

Developmental trajectory of anger and aggression

Children aged 2 to 3 years have the highest rate of aggression due to immature verbal skills and cognitive control. With neurodevelopmental maturity, aggression declines from 70% at 2 years to 12% at 8 years. Severe aggressive behavior in childhood is a highly stable behavioral trait that usually persists in adolescence and adulthood. Adolescents with aggression usually follow two developmental courses i.e. life course persistent and

Fig. 1. Adolescent aggression-types
adolescence limited (Fig.1). Differences between the two types of aggression are highlighted in Table I.

Adolescence is a period of rapid biopsychosocial changes. Adolescents need help from parents and caretakers to cope with these changes, failing which they develop feelings of anger and frustration. Adolescence is also a phase of heightened emotions, autonomy bids, identity crisis, moving away from the family towards peers, sensation seeking behavior and questioning authority and testing limits. Such normative changes may not be completely understood by caretakers and parents which may be perceived as defiance and 'aggression'.

Adolescents may have difficulties in managing their emotions and behavior because the brain is still under development and processes information differently compared to adults (Box 1).

### Table I. Differences between life course persistent aggression and adolescence limited aggression

<table>
<thead>
<tr>
<th>Factors</th>
<th>Life course persistent aggression</th>
<th>Adolescence limited aggression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>Usually have psychological abnormality like disruptive behaviour disorder or family pathology.</td>
<td>Socially well adjusted childhood</td>
</tr>
<tr>
<td></td>
<td>Severe childhood aggression.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have not learnt societal norms.</td>
<td></td>
</tr>
<tr>
<td>Causative factors</td>
<td>Genetic predisposition, disruptive parenting, poor impulse control and hostile attribution bias</td>
<td>Affiliation with anti social peers and poor parental monitoring</td>
</tr>
</tbody>
</table>

As the brain is malleable during adolescence, it can be trained to recognize and control intense emotions including anger, felt during this period and to control behavior. If the adolescent develops enough cognitive control capacity, the impulsive reaction that arises from dispositional anger can be reduced resulting in diminished risk-taking behaviors.

### Socioecological determinants

The causes of adolescent anger and aggression are multifactorial. The important socioecological determinants are depicted in Fig.2.

### Individual factors

Poor attachment with caretakers in infancy, difficult temperament and ‘normative’ emotional lability in adolescence, childhood onset disruptive behavior disorders and emerging mental disorders (Table II) predispose to anger outbursts. An increase in testosterone hormone with onset of puberty results in aggression in boys. Adolescents with special needs and those with poorly controlled chronic disorders like diabetes mellitus, asthma, epilepsy and juvenile rheumatoid arthritis are prone to anger and frustration. High emotional and social quotient and involvement in spiritual pursuits promotes emotional well being.

### Interpersonal and community factors

Poverty and violent parents, teachers, peers and neighborhoods are risk factors for anger and aggression while strong parent and school connectedness are protective factors (Fig.2).

---

**Box 1. Increased emotional reactivity in adolescence - Causes**

- Highly reactive limbic and reward systems
- Poorly developed prefrontal cortex that controls emotions
- Poor stress management due to immature hypothalamic pituitary axis
- Responding to emotional cues by activation of amygdala rather than prefrontal cortex
- Lack of effective coping experience
- Misinterpretation of ‘facial expressions’ (e.g. expressions of fear are interpreted as anger resulting in a hostile response)
Fig. 2. Socio ecological determinants of adolescent aggression

Table II. Neurodevelopmental and mental disorders associated with anger and aggression

<table>
<thead>
<tr>
<th>Childhood onset</th>
<th>Adolescent onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>Intermittent explosive disorder</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>Depression</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Autism spectrum disorders</td>
<td>Schizophrenia</td>
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<td>Learning disability</td>
<td>Disruptive mood dysregulation disorder</td>
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<td>Intellectual disability</td>
<td>Anxiety disorders</td>
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<tr>
<td>Gaming addiction disorders</td>
<td>Obsessive compulsive neurosis</td>
</tr>
<tr>
<td></td>
<td>Substance use disorders</td>
</tr>
<tr>
<td></td>
<td>Gaming addiction disorder</td>
</tr>
</tbody>
</table>
Policy making

Governmental policies that promote establishment of adolescent friendly clinics and mental health and counseling services reduce anger, aggression and violence in the adolescents and society. Violent content on the media and violent video games promote aggression. Well managed juvenile centres can promote reintegration of the juvenile into the society and decrease violent and criminal episodes.¹¹

Management

Cognitive behaviour therapy model of stress inoculation therapy is an example of evidence based anger management program that can be adopted in clinical practice. The steps are shown in Box 2.⁵

Assessment

A detailed history is taken from the parents, adolescent and from school teachers / management regarding:

- Onset and duration of anger outbursts, triggers and consequences. This is called the Antecedent, Behavior, Consequence (ABC) approach of behavioral analysis. Details of reactive and proactive aggressive behavior are noted. Effect of the aggressive behavior on adolescent and family functioning is closely scrutinized.
- Change in academic performance and behavior. This may be a pointer towards mental disorder.
- Chronic diseases like anemia, diabetes mellitus, asthma, etc. Current status and disease severity along with compliance to medication is assessed.

Table III. HEEADSSS psychosocial history

<table>
<thead>
<tr>
<th>Item</th>
<th>Key points</th>
</tr>
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<td>Eating habits</td>
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<td>Activities</td>
<td>Hobbies, type and duration of media usage and physical activity, time spent with peers and outdoors, quantity and quality of sleep, any recent loss of interest in activities, spiritual and religious practices</td>
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<td>Substance Use</td>
<td>Attitude towards drug use, drug use amongst peers, type and frequency of drug use</td>
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<tr>
<td>Safety</td>
<td>Indulgence in violent acts, run away behaviour</td>
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A detailed systemic and mental health examination is conducted to diagnose and assess chronic physical and mental disorders. Different psychological assessment tools and rating scales can be used to assess anger and aggression in an objective manner and to rule out neurodevelopmental and mental disorders. These include DSM-5 questionnaires, childhood inventory of anger, ADHD rating scales, Beck’s depression inventory, Screen for Child Anxiety Related Emotional Disorders (SCARED) tool, behavioral assessment for children, children’s hostility inventory, child behaviour checklist, Stanford Binet intelligence test and NIMHANS battery for specific learning disability.

Further therapy depends on the identified cause(s). Pediatricians should consider referral to mental health professionals if there is psychosis, suicidal behavior, severe depression, severe substance use disorder, multiple mental disorders and criminal activity.

Goals to be achieved after the therapy are discussed with parents and adolescents and documented. Intensive multisystemic therapy targeting different determinants of adolescent aggression and drug therapy is required to manage severe antisocial behaviour. Anger associated with mental disorders is treated with drugs, like methylphenidate for ADHD, fluoxetine for depression and risperidone for bipolar disorder and schizophrenia.

An anger management program usually requires 12 to 18 weekly sessions. Before beginning the program, adolescents, parents and teachers are counseled about the importance of ensuring age appropriate nutrition, outdoor physical activity, sleep, limiting media usage, pursuing hobbies, meditation, stress management techniques and a nurturing school and family environment.

A few general principles of anger management are elucidated below:

**Psychoeducation**

Adolescents learn to recognise anger by being aware about their negative thoughts and bodily reactions in the form of palpitations, facial flushing and stomach rumblings. They also analyse the various triggers and consequences of poor anger control.

**Skill acquisition**

Adolescents learn skills of self talk, cognitive reappraisal, assertive communication, venting of feelings, humor, problem solving and relaxation to defuse anger and avoid aggression. By inculcating life skills, they are motivated to choose prosocial calm solutions to deal with

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**Box 3. Assertive skill training**

Rules for direct verbal expression of anger
- Say what happened: Don’t generalize/ guess motives
- Say how you feel: Don’t unleash an outburst/ insult
- Say exactly what you want the person to do: Don’t ask for too many or big changes/ assume that only he/she has to change
- Say why: Don’t threaten/bully/ be ashamed to say why you want the change

**Box 4. Components of parent management training**

- Normal development
- Positive attention
- Social reinforcement
- Negotiable versus non negotiable rules
- Behavioral management and positive discipline
- Effective communication, negotiation, problem solving
- Monitoring
- Stress management
- Positive connection with school
anger triggers and to speak in an assertive manner. An example of assertive skill training in verbal expression of anger is shown in Box 3.\textsuperscript{15}

**Application training**

In the last step, role plays and situational analysis are used to practically apply the anger management techniques in various anger provoking scenarios. Research has shown that involving both parents and adolescents for prolonged periods will improve the long term efficacy of an anger control program. Components of a parent management training program are given in Box 4.\textsuperscript{2,5} The program emphasizes on building positive parental communication, role modeling and teaching techniques of discipline in context of normal adolescent development. Teachers and remedial educators of adolescents with learning problems are also to be involved in therapy sessions. A few examples of a well researched module and workbook based anger management programs include ‘The Coping Power Program’ and ‘Keeping Your Cool’.\textsuperscript{9} Such programs are known to improve behavior in adolescence and prevent development of antisocial personality even in those known to have a stable aggressive trait from childhood.\textsuperscript{16}

**Primary prevention**

Pediatricians have an important role to play in health care settings and in community in the prevention of adolescent aggression and violence. In the clinic, anticipatory guidance and screening for severity of anger outbursts, mental disorders, learning problems and reinforcing parental connectedness and communication will prevent escalation of normative adolescence anger into aggression and crime. In schools and community, pediatricians can conduct life skill programs for parents, teachers and adolescents emphasizing on anger management, stress management and healthy interpersonal relationships. Pediatricians should also advocate for effective and accessible adolescent friendly health services at the governmental policy level.

As pediatricians have a good rapport with adolescents and their families, they are often consulted for anger management. There is a lack of mental health professionals in our country and a stigma attached to seeking help from them. As the most preferred primary care health professionals, pediatricians should provide basic evidence based mental health care to promote emotional and social wellbeing of adolescents and their families.

**Acknowledgement:** Figures and tables have been adapted from the following article (with permission), Galagali P. Teen Aggression. In: Gupte S, Gupte SB, Gupte M. Recent Advances in Pediatrics Hot Topics. New Delhi: Jaypee Brothers; 2018; pp165-173.

**Points to Remember**

- **Anger is a common behavioural in adolescence.**
- **Uncontrolled anger can lead to aggression, violence, crime and death.**
- **Causes of anger are multi factorial.**
- **Frequent anger outbursts are pointers towards mental disorders.**
- **Pediatricians should provide anticipatory guidance regarding anger management.**
- **Evidence based anger management programs for adolescents that include parents are effective.**

**References**


NEWS AND NOTES

MADRAS PEDICON 2019

44th Annual Conference of IAP-TNSC

Organised By

Indian Academy of Pediatrics – Chennai City Branch (IAP-CCB)

Conference: 16th to 18th August, 2019

Pre Conference Workshops: 15th August, 2019

Venue for the Conference: The New Kalaivanar Arangam, Wallahjah Road, Chennai.

Conference Secretariat

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8th Singapore Pediatric & Perinatal Annual Congress

Date: 27th – 28th July, 2019

Venue: Grand Copthorne Waterfront Hotel, Singapore

Email: secretariat@sps.org.sg; Website: www.sps.org.sg
Cerebrospinal fluid (CSF) fills the ventricles and the subarachnoid cisterns. In the previous issue we saw that the block to out flow of CSF causes dilatation of the ventricles. In this article we will discuss about the cisterns. The cisterns are CSF filled local expansions of the subarachnoid space between the pia and the arachnoid membrane. These cisterns are naturally found in the base of the brain where the surface of the skull is very rough and the brain needs to be protected. Fig.1 shows the star shaped suprasellar cistern while Fig.2 is a T1 film showing grey cisterna magna in the posterior fossa below the cerebellum. The others are interpeduncular cisterns between the two cerebral peduncles, collicular cistern, pontine cistern, cerebello-pontine angle cistern, carotid cistern and Sylvian cistern. These cisterns are related to the structures in their names.

The intracranial compartment is a rigidly enclosed space once the sutures are fused. Any change in pressure is quickly evident clinically in the form of headache. With further increase in pressure, there is vomiting, abnormal posturing, abnormal breathing patterns, hypertension or cranial nerve findings. The balance between the cranium and its contents namely the brain, blood and CSF is delicate. If one of the contents increases, the others have to give way to maintain intracranial pressure. The CSF spaces in the brain are the first to allow for extra space when there is a rise in volume of the contents. Any space occupying lesion, inflammation or injury can raise the intracranial tension (ICT). Mild increase in ICT is usually offset by obliteration of the cisterns. Further increase can soon overwhelm autoregulation leading to fatal cerebral herniation.

Fig.3 shows an obliteration of the cistern around the midbrain and pinched ventricles as the brain is swollen. Also there is no grey white matter distinction. In this case, there is generalised brain swelling increasing the parenchymal volume and hence the cisterns have flattened. At this stage anti-edema measures are required to prevent brain herniation. The subarachnoid space follows the contour of the pia as it dips into the sulci. Superior cuts normally show well-defined, dark grey, wavy patterns of the CSF filled sulci. In raised ICT these sulci are also obliterated. On the contrary, if brain volume reduces as in cerebral atrophy, cisterns dilate to keep up the volume. Fig.4 shows large cisterns and sulcal spaces.

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sheath (Fig.6). Normally the perioptic nerve space is continuous with the subarachnoid space of the brain and shows a white ring of fluid around the optic nerve.

In idiopathic intracranial hypertension the perioptic subarachnoid space is distended. Distension of the optic nerve sheath of greater than 2mm is significant. This is measured 1cm anterior to the optic foramen. There is flattening of the posterior part of the globe because of protrusion of the intraocular portion of the optic nerve head. Another important finding is vertical tortuosity of the optic nerve and its sheath (Fig.7).

Since the optic nerve is fixed at either end raised intracranial pressure elongates the optic nerve which therefore becomes tortuous. Chronic intracranial hypertension also leads to escape of CSF through the diaphragm sella into the pituitary fossa. Accumulation causes compression of the pituitary gland or partial empty sella. When severe it is called empty sella where the pituitary is not visualised. CT and MRI of the brain provide anatomical information, which along with clinical assessment can be used to infer the state of intracranial tension.

**Fig.5. Chronic intracranial hypotension. Distended dural venous sinuses**

**Fig.6. Chronic intracranial hypotension. No fluid around optic nerve**

The subarachnoid space can sometimes lose CSF due to spontaneous leak or injury to the dura. This can also happen following shunt procedure and over drainage of CSF. In this situationthere is intracranial hypotension and the cisterns are obliterated due to negative pressure. To make up for this loss of intracranial volume the dural venous sinuses dilate (Fig.5). Next to the cisterns, it is the dural venous sinuses with supple walls that can be recruited to balance the intracranial pressure. Other findings are descent of the thalamus and cerebellar tonsil and also the lack of normal CSF surrounding the optic nerve in the optic sheath (Fig.6).

**Fig.7. Intracranial hypertension. Tortuous optic nerve**

### CLIPPINGS

*Levetiracetam versus phenytoin for second line of treatment of convulsive status epileptics in children (ConSEPT): an open label, multicentric, randomized controlled trial.*

For pediatric convulsive status epilepticus, researchers ascertained the usefulness of two drugs phenytoin and levetiracetam for second line treatment. Children studied were aged between 3 months to 16 years with status epilepticus. The authors studied 639 children with status epilepticus and finally recruited 233 children including both the groups. First line drug was benzodiazepine. Children were randomised into two groups one received 20 mg/kg of phenytoin and the other received 40 mg/kg of levetiracetam. The authors concluded that levetiracetam is not superior to phenytoin for second line management of pediatric convulsive status epilepticus.

CASE REPORT

SKIMMED BREAST MILK IN THE MANAGEMENT OF IDIOPATHIC CONGENITAL CHYLOTHORAX

*Sunil Joghee
**Suja Mariam
***Siddartha Buddhavarapu

Abstract: Conservative management of congenital chylothorax involves intercostal drainage, low fat infant formula and somatostatin infusions. Availability and cost of low fat infant formulas is a limiting factor in developing countries. A preterm male diagnosed antenatally with non-immune hydrops fetalis was postnatally diagnosed to have congenital chylothorax. He was given fat free breastmilk prepared by removal of fat layer after centrifugation, and fortifying with simyl MCT oil. There was good response to fat free breast milk with resolution of chylothorax. Breast milk can be centrifuged with locally available equipments and can be a good alternative to low fat infant formulas in congenital chylothorax.

Keywords: Chylothorax, Non-immune hydrops, Skimmed milk, Breastfeeding.

Case report

A male baby was delivered by LSCS to non-consanguineous parents at 34 weeks in view of fetal distress. Routine antenatal USG at 32 weeks had showed polyhydramnios and fetal hydrops with bilateral pleural effusion. He weighed 2460 grams at birth and was severely depressed needing extensive resuscitation. Therapeutic pleural fluid tapping was done bilaterally which revealed clear fluid. There was minimal ascites and gross subcutaneous edema with no other dysmorphic features or congenital anomalies. Chest x-ray showed massive bilateral pleural effusion and bilateral chest tubes were inserted. He was managed with inotropes and high frequency oscillatory ventilation. Initial investigation showed hemoglobin of 17.9 g/dL, WBC count of 19,590 cells/cu.mm (N 60, L 34, M 5, E 1). 2D echocardiography, liver enzymes and renal function were normal. Serum albumin was 1.5 g/dL with A/G ratio of 1.5. Pleural fluid analysis on day 2 showed WBC of 508 cells/cu.mm (L-80%) with lymphocytic predominance and low triglycerides (20mg/dL) which increased to 734 mg/dL on reaching feeds of 40ml/kg/day of breast milk on day 7 of life. The baby was kept nil per oral again. Special formula was not available locally. As mother requested to feed her own milk, an attempt was made to skim the breast milk.

Mother’s expressed breast milk was collected in volumes of 50 ml in separate feeding bottles and refrigerated for 6 hours. They were packed in sterile covers and centrifuged at 3000 rpm for 20 minutes using hospital blood bank’s centrifuge machine (Cryofuge, Thermo Fisher). Once centrifuged, the creamy layer was removed using a 10 ml syringe. The fat free milk yield was around 70% of total volume centrifuged (Fig.1a & 1b). Pre and post processing milk were analyzed using automated turbidimetric method for proteins, sodium and triglycerides (Table I) which showed a 50% reduction in fat content. Simyl MCT oil was added to this milk. Milk was centrifuged every 6 hours. The baby was given low-fat breast milk for 3 weeks and then directly breast fed from 4th week onwards. No other supplementary formula was used for feeding. There was no recurrence of effusion and ICD was removed on day 12. He was discharged on breast feeds.
Discussion

Nutritional management of CCT has an important role in avoiding need of surgical intervention. Where available, initiation of enteral nutrition with low fat special formulas has been recommended. The availability and cost of such commercially available infant formulas remains a limitation in resource limited set up. Some investigators have used commercially available skimmed milk powders fortified with MCT oil. Chan et al used fat free milk by centrifuging mother’s milk and removing the top layer of fat for 7 infants with congenital and acquired chylothorax. There was no re-accumulation of chylothorax in any infant when feeding was started at 1 month. Lopez compared infants fed with fortified skimmed breast milk to those fed with specialized formula in post-operative chylothorax and found no statistically significant difference in protein-energy intake, feeding tolerance and growth parameters. Refrigerated centrifuge method is more effective in fat separation from milk compared to non-refrigerated centrifuge and refrigeration methods. Using a syringe to remove the fat is superior to using a spoon. The same method was opted for our case. Low fat breast milk was opted for this baby only after a worsening of effusion with unprocessed breast milk. We employed equipments available with the hospital’s blood bank in a cost-effective technique. Adequate precautions were taken to prevent cross contamination. No blood products were centrifuged along with milk. We were able to manage this neonate on mother’s milk alone. This shows that skimmed breast milk is still an option even when dedicated equipments are not available.

Table I. Comparison of milk before and after fat separation and removal

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<td>Protein (per 100 g of milk)</td>
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<td>Fat (per 100 g of milk)</td>
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<td>Triglycerides (per dL)</td>
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<td>Sodium (per 100 g of milk)</td>
<td>28 mg</td>
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References

FAILURE TO THRIVE IN A YOUNG CHILD
- A RARE CAUSE

*Sumathi B
**Nirmala D
***Sunil Kumar KS

Abstract: Failure to thrive in children has heterogenous causes and needs extensive evaluation based on clinical symptoms and signs. We report a rare cause of failure to thrive in a young child due to abetalipoproteinemia.

Keywords: Fatty liver, Abetalipoproteinemia, Small intestinal biopsy, Children.

Case Report

Two and half years old girl born to consanguineous parents was referred for failure to thrive. There was no history of recurrent fever, vomiting, loose stools, repeated respiratory tract infections jaundice, seizures and altered bowel habits. Developmental milestones were normal. Clinical examination showed anemia, weight falling at 3 SD, height between 0 to -2SD with soft hepatomegaly. Investigations showed Hb 8 gm/dL and acanthocytes in the peripheral smear (Fig.1). Blood sugar, renal function tests, liver function tests, chest X-ray were normal. Mantoux, resting gastric juice for AFB and retroviral screening were negative. Lipid profile showed cholesterol 91 mg/dl, triglycerides 110mg/dl, high density lipoproteins 25mg/dl, low density lipoproteins 65mg/dl and apolipoprotein B 6 mg/dl indicating low lipid profile values. Ultrasound abdomen showed fatty change in the liver. Stool examination showed significant fat globules. Differential diagnosis of fatty liver and failure to thrive include nutritional cause, juvenile diabetes mellitus and less common conditions like abetalipoproteinemia, intestinal lymphangieactasia. Upper GI endoscopy showed whitish smoky appearance of the entire duodenal mucosa suggestive of excessive oozing of lymph. Biopsy of the duodenal mucosa showed lipid laden intestinal cells suggestive of abetalipoproteinemia (Fig.2). Visual acuity, fundus examination were normal. ERG and fluorescein angiography studies were not done. Genetic mutation analysis could not be done due to financial constraints. The child was started on high dose vitamin E, along with other fat soluble vitamin supplementation and dietary advice. She has gained weight of 2 kg over 3 months and on regular follow up.

Discussion

Abetalipoproteinemia, also known as Bassen-Kornzweig syndrome was first reported by Bassen and Kornzweig in 1950. It is a rare inherited autosomal recessive disorder of fat metabolism due to mutations in
the microsomal triglyceride transfer protein (MTTP) gene. This results in deficiencies in the apolipoproteins B-48 and B-100, which are essential for the synthesis and exportation of chylomicrons and VLDL.  

This case is being submitted for a rare cause of failure to thrive where small intestinal biopsy helped in identifying the cause.

References


Clinical Practice Guideline for the Management of Infantile Hemangiomas.

Infantile hemangiomas (IHs) occur in as many as 5% of infants. This clinical practice guideline for the management of IHs emphasizes several key concepts. Earlier intervention is the key for The rationale being that the most rapid growth of hemangiomas occurs before eight weeks of age, and treatment before the completion of this proliferative phase may prevent poor outcomes. Early intervention and/or referral (ideally by 1 month of age) is recommended for infants who have potentially problematic IHs. When systemic treatment is indicated, propranolol is the drug of choice at a dose of 2 to 3 mg/kg per day. Treatment typically is continued for at least 6 months and often is maintained until 12 months of age. Topical timolol may be used to treat select small, thin, superficial IHs. Surgery and/or laser treatment are most useful for the treatment of residual skin changes after involution and, less commonly, may be considered earlier to treat some IHs.

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