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CONTENTS

TOPIC OF INTEREST - PULMONOLOGY

Recurrent respiratory infections - An approach 245
- Subramanyam L

Community acquired pneumonia – Management guidelines 258
- Gautam Ghosh

Asthma syndrome - Understanding asthma phenotypes in children 267
- Mahesh Babu R, Ilin Kinimi

Diagnosis of tuberculosis - Newer investigations 273
- Varinder Singh, Satnam Kaur

Cystic fibrosis - When to suspect and how to manage? 284
- Meenakshi Bothra, Rakesh Lodha, Kabra M, Kabra SK

Approach to recurrent pneumonia in children 294
- Dipangkar Hazarika

Parapneumonic effusion and empyema 306
- Gowrishankar NC

Flexible fiberoptic bronchoscopy 313
- Vijayasekaran D

Non-invasive ventilation - A practical approach 318
- Shrishu R Kamath, Anitha VP

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GENERAL ARTICLES

Brain death - Practical approach 326
- Devaraj V Raichur

Hypertensive crisis in children 331
- Raghunath CN, Padmanabhan, Vani HN

DRUG PROFILE

Monoclonal antibodies in pediatric therapeutics 339
- Jeeson C Unni

DERMATOLOGY

Basidiobolomycosis 351
- Madhu R

RADIOLOGY

White matter disease 358
- Vijayalakshmi G, Malathy K

CASE STUDY

Tracheal bronchus in an infant with recurrent upper lobe pneumonia 363
- Suresh Babu PS, Agarwal Nagamani S

A rare cause of eosinophilia-Anticonvulsant hypersensitivity syndrome 366
- Sudip Saha, Madhusmita Sengupta

ADVERTISEMENT 239,240,241,242,370

CLIPPINGS 266,293,305,312,325,350,357,362,369

NEWS AND NOTES 272,312,338,365

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RECURRENT RESPIRATORY INFECTIONS - AN APPROACH

*Subramanyam L

Abstract: Recurrent respiratory tract infections (RRI) is a commonly encountered problem in children. While evaluating, it is necessary to find out if they have atopy, underlying chronic disease or immuno deficiency so that their RRI can be managed better.

Keywords: Recurrent respiratory infections (RRI), Children.

A common reason for bringing an infant or child frequently to a pediatrician is recurrent respiratory tract infections (RRI). This may refer to infections that are too great in number, too severe, or too long lasting; that are associated with unusual complications; or that fail to resolve with standard therapy. Though the causes are multiple, it can be grouped into one of the following four categories (i) RRI in normal child (ii) RRI in atopic child (iii) RRI in a child with chronic disease and (iv) RRI in immune deficient child.

Major causes: The majority of children who present with recurrent respiratory infections (RRI), especially localized to one organ or system, have increased exposure, allergy, or chronic disease, including anatomic problems, rather than a defect in immune response (Table I).

The “normal” child: About 50 percent of children with recurrent respiratory infections referred for evaluation have no known significant cause for these infections.

Infants and children vary considerably as to the number of infections experienced. On an average, a child can have four to eight respiratory infections per year. Some infants and young children who are kept away from visitors have only one or two infections per year while others may have 10 to 12 infections per year, particularly if they have elder siblings or if they attend daycare or preschool. Exposure to passive smoking also increases the risk of upper respiratory infection. The mean duration of viral respiratory symptoms is about eight days, but the normal range can extend beyond two weeks, which means that the “normal” child with over 10 viral respiratory infections can have symptoms for nearly one-half of a year. With regard to the number and types of infections seen, most of the respiratory infections are viral. The commonest viral pathogens are influenza, parainfluenza, rhino, adeno and respiratory syncytial virus (RSV). These children have normal growth and development, respond quickly to appropriate treatment, recover completely and appear healthy between infections. The physical examination and laboratory tests are normal.

The child with atopic disease: About 30 percent of children with recurrent infections have atopic disease. Chronic allergic rhinitis may be mistaken for chronic or recurrent upper respiratory infections. Children with atopic disease often develop coughing and wheezing...
following viral respiratory infections. These symptoms are frequently misdiagnosed as pneumonia or bronchitis rather than reactive airways disease/asthma. These episodes respond poorly to antibiotics, but well to allergy/asthma medications. Children with atopic disease seem more likely to develop recurrent upper respiratory infections, such as sinusitis, rhinitis and otitis media. Growth and development are usually normal. These children often have characteristic physical findings, like “allergic shiners” or a transverse nasal crease.

The child with chronic disease: Ten percent of children with recurrent infections have an underlying chronic disease other than atopy or immunodeficiency. The child with a nonimmune chronic illness often presents with poor growth/failure to thrive, a sickly appearance, and physical findings characteristic of the specific chronic disease. Diseases in this category include cystic fibrosis, gastroesophageal reflux, congenital heart disease, chronic aspiration and congenital anomalies of respiratory tract.

The child with an immunodeficiency: Ten percent of children with recurrent infections have an immunodeficiency, with a defect in one or more components of the immune system. Components of the adaptive immune system include B cells (humoral or antibody system) and T cells (cellular system). The innate immune system is made up of the phagocytic cell system and the complement system. The features given in Table II should lead to suspicion of an immunodeficiency.

Primary disorders of immune function should be considered in children who have recurrent and/or complicated bacterial infections (eg, sinopulmonary infection, recurrent soft tissue or organ abscesses, two or more episodes of bacterial sepsis or meningitis); persistent oral candidiasis; infection with opportunistic, unusual, or “signature” organisms; failure to thrive; or a family history of immunodeficiency or unexplained deaths in infancy. Normally a balance exist between the hosts exposure to disease and the defence mechanism of the respiratory tract. In RRI this balance is altered. For a better understanding, pulmonary defence mechanism is discussed below.

Pulmonary defence mechanism

Normal host defence: The pulmonary host defense system is complex and includes anatomic and mechanical barriers, humoral immunity, phagocytic activity and cell-mediated immunity.

Anatomic and mechanical barriers in the upper airway comprise an important part of the host defense. Particles greater than 10 microns are efficiently filtered by the hairs in the anterior nares or their impact onto mucosal surfaces. The nasal mucosa contains ciliated epithelium and mucus-producing cells. The cilia beat synchronously, clearing the entrapped organisms in the nasopharynx via expulsion or swallowing. In the oropharynx, salivary flow, sloughing of epithelial cells, local production of complement and IgA and bacterial interference from the resident flora serve as important factors in local host defense.

An intact epiglottic reflex helps to prevent aspiration of infected secretions and the cough reflex helps to expel aspirated materials. The sharp angles at which the central airways branch cause particles of 5 to 10 micron size to impact on mucosal surfaces, where they are entrapped in endobronchial mucus. Once entrapped, the ciliary system moves the particles upward out of the airways into the throat, where they are normally swallowed.

Humoral immunity: Secretory IgA is the major immunoglobulin produced in the upper airways and accounts for 10 percent of the total protein concentration of nasal secretions. Although it is
### Table I. Recurrent respiratory infections - causes

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal child</td>
<td>Viral infections</td>
</tr>
<tr>
<td>Child with atopic disease</td>
<td>Allergic rhinitis,</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
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<tr>
<td>Child with chronic disease</td>
<td>Congenital anomalies of respiratory tract</td>
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<td></td>
<td>Cardiovascular anomalies</td>
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<td></td>
<td>Recurrent aspirations</td>
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<td></td>
<td>Gastroesophageal reflux</td>
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<td></td>
<td>Retained foreign body</td>
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<td></td>
<td>Medistinal adenopathy</td>
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<tr>
<td></td>
<td>Tuberculosis</td>
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<tr>
<td></td>
<td>Cystic fibrosis</td>
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<tr>
<td></td>
<td>Primary ciliary dyskinesia</td>
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<tr>
<td></td>
<td>Interstitial lung disease</td>
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<tr>
<td></td>
<td>Alpha-1 antitrypsin deficiency</td>
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<tr>
<td></td>
<td>Pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Child with immunodeficiency</td>
<td>Primary antibody deficiency</td>
</tr>
<tr>
<td></td>
<td>Severe combined immunodeficiency (SCID)</td>
</tr>
<tr>
<td></td>
<td>Secondary immunodeficiency (HIV/ AIDS)</td>
</tr>
</tbody>
</table>

### Table II. Pointers for suspicion of immunodeficiency

- Recurrent bacterial infections (sinopulmonary, soft tissue abscesses)
- Severe or complicated infections (Bacterial sepsis, meningitis)
- Persistent infection which fails to resolve with standard therapy
- Associated with unusual organisms - Pneumocystis jiroveci
- Adverse effects of live vaccine as well as vaccine failure
- Failure to thrive
- Family history of immunodeficiency or unexplained deaths
not a very good opsonizing agent, it does possess antibacterial and antiviral activity. IgG and IgM enter the airways and alveolar spaces predominantly via transudation from the blood and act to opsonize bacteria, activate complement and neutralize toxin. Immunoglobulins, surfactant, fibronectin and complement acts as effective opsonins to help eliminate microorganisms (0.5 to 1 micron particles) that reach the terminal airways and alveoli. Free fatty acids, lysozyme and iron-binding proteins also are present and may be microbicidal.

**Phagocytic cells:** There are two populations of phagocytic cells in the lung: polymorphonuclear leukocytes (PMNs) from the blood and macrophages. There are several distinct populations of macrophages, which vary in their location and function:- The alveolar macrophage is located in the alveolar fluid and is the first phagocyte encountered by inert particles and potential pathogens entering the lung. If this cell is overwhelmed, it has the capacity to become a mediator of inflammation and produce cytokines that recruit neutrophils. Interstitial macrophages are located in the lung connective tissue and serve both as phagocytic cells and antigen-processing cells. The intravascular macrophage is located in capillary endothelial cells and phagocytizes and removes foreign material entering the lungs via the bloodstream.

**Cell-mediated immunity:** Cell-mediated immunity is especially important against certain pathogens, including viruses and intracellular microorganisms, that can survive within pulmonary macrophages. Although relatively few in number (5 to 10 percent of the total lung parenchyma cell population), lymphocytes play three critical roles: the production of antibody, cytotoxic activity and the production of cytokines.

It is important, therefore that an underlying immunodeficiency should be considered in any child who suffers from recurrent, persistent or unusual infections of any site.

Immunodeficiency may be primary or secondary. Secondary immunodeficiencies usually occur well after infancy while most primary immunodeficiencies are inherited and present during the first year of life. Secondary immunodeficiencies are more common than primary immunodeficiencies. Common examples include HIV/AIDS, malignancy and exposure to immunosuppressive drugs. Primary immunodeficiencies most often affect B cell function, while secondary immunodeficiencies more often affect T cells (the cellular system). Almost three-fourths of the primary immunodeficiencies are caused by an antibody (B cell) deficiency or a combined antibody plus cellular (T cell) abnormality. Isolated T cell defects, as well as phagocytic cell, complement are much less common. Following are the common primary immunodeficiency diseases in children (Table III).

**History and physical examination**

**Birth history:** Pregnancy history should be explored for maternal illness (eg., HIV, CMV). Birth history should include length of gestation, birth weight and neonatal problems, such as jaundice, respiratory distress, delayed separation of umbilical cord or need for intensive care. Feeding history, should include duration of breast feeding.

**Growth and development:** Weight, height and head circumference should be plotted and followed over time. Children with chronic disease or immunodeficiency often have poor weight gain or even weight loss. Functional assessment of a child’s development should be made because chronic disease and certain primary immunodeficiencies can lead to delay in attaining developmental milestones.
Immunization history: Immunization history should be reviewed. Details include any adverse effects from a vaccine, particularly live virus vaccines (e.g., CNS complications from oral polio vaccination or diarrhoea following rotavirus vaccine) as well as vaccine failure (e.g., chicken pox in a varicella vaccinated child). The immunization record is also valuable when examination of vaccine titers is planned to evaluate antibody function.

Medications: Current and past medications (including over-the-counter medicines and supplements) should be recorded, including duration, effectiveness and adverse reactions. Use of any immunosuppressive medications, such as glucocorticoids, should be noted. If immunoglobulin has been given, the route, dose and frequency should be noted.

Past illnesses: An inquiry about past hospitalizations, injuries or accidents, surgeries, or prolonged school absences may provide clues to the present illness.

Family history: The presence of family members with similar diseases, recurrent infections, unexplained death, suggests the possibility of a genetic illness. Many immunodeficiencies have X-linked transmission (e.g., some forms of agammaglobulinemia, chronic granulomatous disease). Inquiring about consanguinity is important when considering autosomal recessive immunodeficiencies. Inquiry should also be made about infections in family members, including illnesses such as tuberculosis, hepatitis B and HIV.

Social history: The home, parents’ work environment and daycare or school should be explored for exposures, such as allergens, tobacco smoke, contaminated water supply, farm animals, solvents and toxins, as well as location near industrial plants. Prior residences and travel history may be important in exposure to infectious agents or allergens.

Physical examination: The physical examination in children with recurrent infections provides
information as to their general health and may suggest the presence of allergy, chronic disease or immunodeficiency. The child’s overall appearance and activity are the first clues to the general state of health. Vital signs (including oxygen saturation if cardiac or pulmonary disease is suspected) should be recorded. Unusual dysmorphic appearance may signify a genetic syndrome.

Growth and development is documented by growth charts and maturational milestones. Weight loss or failure to thrive is suggestive of chronic disease or immunodeficiency. The presence of acute or chronic otitis media should be determined, since upper respiratory infections are the most common recurrent infection. Hearing should be evaluated in children with recurrent otitis. Draining ears and perforated tympanic membranes suggest immunodeficiency.

Dark circles under the eyes, conjunctivitis, a transverse nasal crease, congested turbinates and clear nasal discharge suggest allergy. Purulent nasal discharge, postnasal drip and diminished gag reflex are consistent with chronic sinusitis. Pharyngeal cobblestoning may be seen with either allergic rhinitis or chronic sinusitis. Mouth ulcers, gingivitis, mucosal candidiasis and poor dentition suggest immunodeficiency. Diminished or absent tonsils and cervical nodes in the presence of recurrent respiratory infections suggest an antibody deficiency. Nasal polyps suggest cystic fibrosis.

Chest asymmetry, an increased posterior-anterior chest diameter and pectus excavatum are associated with chronic lung disease. Productive cough with digital clubbing suggests bronchiectasis. Interstitial lung disease (ILD) should be considered in any child with a normal birth history who presents with chronic cough, dyspnea, inspiratory crackles, tachypnea, chest wall retractions and exercise limitation.

Certain findings are characteristic of specific immunodeficiency syndromes (Table IV). Further analysis depends upon the age of onset, site of infection and isolation of organisms.

Table IV Clinical patterns suggestive of immunodeficiency syndromes

<table>
<thead>
<tr>
<th>Features</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers, gingivitis and impetigo</td>
<td>Chronic granulomatous disease (CGD), or leukocyte adhesion defects</td>
</tr>
<tr>
<td>Coarse features, chronic infected eczema and deep-seated abscesses</td>
<td>Hyper IgE syndrome</td>
</tr>
<tr>
<td>Petechiae, easy bleeding, eczema, and chronic draining ears</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Congenital heart disease, developmental delay and dysmorphic facies with low-set ears, hypertelorism, downturned eyes, micrognathia</td>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td>Early onset of seborrheic dermatitis and alopecia</td>
<td>Some forms of SCID</td>
</tr>
<tr>
<td>Progressive cerebellar ataxia, telangiectasia, developmental delay and immunodeficiency (IgA)</td>
<td>Ataxia-telangiectasia</td>
</tr>
</tbody>
</table>
**Age of onset**

**Birth to six months:** Infections presenting shortly after birth may be secondary to prolonged rupture of membranes, congenital infection, infection exposure during the birth process, or aspiration. Premature infants, especially those needing ventilators are at high risk for infection. Several primary immunodeficiencies are associated with early onset of severe infections, notably congenital neutropenia, leukocyte adhesion defects, severe combined immunodeficiencies and complete DiGeorge syndrome.

**Six months to two years:** Normal infants exposed to other children or to tobacco smoke are more prone to recurrent respiratory infections. Wheezing, eczema/atopic dermatitis and food intolerance suggest allergy. Persistent diarrhoea, chronic cough, or failure to thrive suggests cystic fibrosis or a primary immunodeficiency. Congenital antibody deficiencies usually present at 7 to 12 months as maternal IgG disappears.

**Two to six years:** Children developing infection in the two to six year age range may also fit into any of the four categories outlined above. Secondary immunodeficiencies resulting from malignancy, nephrotic syndrome, or gastrointestinal problems often begin at this age.

**Six to 18 years:** It is unusual for recurrent infections to first present beyond six years of age. HIV infection and other sexually transmitted diseases should be considered in adolescents. Infections associated with vasculitic lesions, arthritis and recurrent fever suggests autoimmunity.

**Sites of infection**

**Upper respiratory tract:** The upper respiratory tract (nose, throat, ears, sinuses) is the most common site of infection. Most upper respiratory infections are viral.

Chronic purulent nasal discharge and cough secondary to postnasal drainage suggest chronic sinusitis. Refractory asthma is sometimes associated with chronic sinusitis. Gastroesophageal reflux can also cause chronic cough and recurrent otitis media and sinuitis. Persistently opacified sinuses, particularly cases refractory to antibiotics, may be due to an antibody deficiency or cystic fibrosis in a small subset of patients.

Allergic disease is associated with chronic or seasonal clear nasal discharge, congestion, itchy eyes, nocturnal cough, and a poor response to antibiotics. Allergic rhinitis can be misdiagnosed as recurrent upper respiratory infections. Recurrent or persistent candidiasis, stomatitis, gingivitis, and oral ulcerations occur in T cell and phagocytic cell disorders.

**Lower respiratory tract:** Recurrent pneumonia is rare in normal children or children with allergic disease, and suggests chronic cardiopulmonary disease or immunodeficiency. Recurrent pneumonia limited to a particular anatomic region (eg., right middle lobe) is typically caused by a local anatomic abnormality (eg., foreign body, bronchial compression by mediastinal adenopathy or vascular anomaly, bronchial sequestration or cyst). By contrast, patients with sequential lower respiratory tract infections involving different regions of the lung often have an underlying systemic disorder (eg, cystic fibrosis, immotile cilia syndrome, recurrent aspiration). Reactive airway disease/asthma is often misdiagnosed as pneumonia or bronchitis in young children.

**Organisms**

Isolation of the same organism repeatedly from a single site suggests a structural defect, while isolation of an organism from a normally sterile site suggests an underlying defect in immunity. Certain immunodeficiency commonly
present with infections caused by opportunistic, unusual or ‘signature organisms’ (Table V).

In antibody deficiencies, infections of the upper and lower respiratory tracts, characteristically with encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenzae type b, are the commonest presenting feature. Deficiencies of cell-mediated immunity predispose predominantly to infections with viruses and fungi, often with opportunistic organisms such as Pneumocystis jiroveci.

Respiratory infections also occur in patients with phagocytic cell defects in chronic granulomatous disease (CGD), infections with catalase-producing bacteria are typical, whilst in the hyper-IgE (Job’s) syndrome, recurrent sinopulmonary infections with pyogenic bacteria are common. Pseudomonas sepsis may occur in phagocytic disorders or in profound antibody or T cell immunodeficiency. Pseudomonas infection also occurs in patients with cystic fibrosis. Deficiency of the third complement component (C3) are associated with pyogenic bacteria. Patients with deficiencies of the late components of complement activation (C5-9) are particularly prone to infections with Neisseria sp., including meningooccal infections. Children who present with such infections should undergo laboratory evaluation for immunodeficiency.

**Laboratory Evaluation**

Laboratory evaluation of children with recurrent infection depends upon history and physical examination findings. Screening tests may include a complete blood count, urinalysis, sedimentation rate or CRP, appropriate cultures, radiologic imaging of the infection site, immunoglobulin levels, antibody titers to vaccine antigens and complement activity. Definitive diagnostic testing should be performed if the initial screening evaluation is abnormal.

The simplest test of immune function is complete blood count which gives important information on the numbers of the major immune cell population such as neutrophils and lymphocytes. Special attention should be paid to the total absolute lymphocyte count: lymphopenia is defined as a count of <1500 cells/μL in patients over five years and <2500 cells/μL in younger children. The presence of anemia, thrombocytopenia, or an abnormal differential count warrants further investigation. Eosinophilia

<table>
<thead>
<tr>
<th>Antibody</th>
<th>T-cell</th>
<th>Phagocytes</th>
<th>Compliment</th>
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<tr>
<td><strong>Bacteria</strong></td>
<td><strong>Viruses</strong></td>
<td><strong>Bacteria</strong></td>
<td><strong>Bacteria</strong></td>
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<tr>
<td>(esp. encapsulated)</td>
<td>CMV, HIV</td>
<td>Staphylococci</td>
<td>C3: pyogenic Inf.</td>
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<tr>
<td>Strep.pneumoniae</td>
<td>Fungi</td>
<td>(esp. catalase +)</td>
<td>C5-9:Neisseria sp.</td>
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<tr>
<td>Haemophilus (HIB)</td>
<td>Candida</td>
<td>Gram-negative</td>
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<td>Aspergillus</td>
<td><strong>Bacteria</strong></td>
<td>(Pseudomonas)</td>
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<td>Pneumocystis</td>
<td>Mycobacteria</td>
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<td>carinii</td>
<td><strong>Protozoa</strong></td>
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<td>Haemophilus</td>
<td>Toxoplasmosis</td>
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| Table V Types of infection in immunodeficient patients |
suggests allergy while thrombocytosis suggests chronic inflammation.

Evaluation for infection may include: Sedimentation rate (ESR) or C-reactive protein (CRP). An elevated ESR or CRP suggests systemic or regional infection or an autoimmune process.

A chest x-ray is indicated if the child has a chronic cough or other features suggesting parenchymal involvement. Thymic size should be noted in chest radiographs of infant with recurrent infections. Sinus films with a lateral pharyngeal view for adenoidal size is indicated for the patient with suspected sinusitis or obstructive breathing. Complete absence of adenoidal tissue suggests immunodeficiency.

To detect the structural abnormalities of tracheo bronchial tree and for suspected intraluminal airway obstruction (foreign body) flexible bronchoscopy should be performed. Cardiac evaluation with an electrocardiography is required to identify a congenital heart disease. Barium swallow of cineesophagogram is usually the first-line diagnostic test for determining whether aspiration occurs with swallowing or because of GER. If gastroesophageal reflux is present it is further confirmed by oesophageal pH monitor, technetium milk scan, esophagoscopy and biopsy.

Suspected cystic fibrosis can be diagnosed by gene mutation studies and sweat chloride estimation (>60mEq/L) by quantitative pilocarpine iontophoresis method. Ciliary dyskinesia can be identified by saccharin clearance, a simple test to assess the ciliary beat frequency. The confirmatory test is by studying the nasal brush biopsy or scrapping of the nasal mucosa under electron microscope.

The absence of the alpha-1 globulin band on serum protein electrophoresis will reveal probable alpha-1 antitrypsin deficiency. Further, genetic analysis for alpha-1 anti-trypsin is performed.

Hypersensitivity pneumonitis can be diagnosed by doing lung biopsy. These patients

<table>
<thead>
<tr>
<th>Immune function</th>
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<tr>
<td>General</td>
<td>Complete blood count</td>
<td>IgG subclasses</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td>IgM, IgA, IgG, IgE</td>
<td>Specific antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Response to vaccines</td>
</tr>
<tr>
<td>Cell-mediated Immunity</td>
<td>Absolute Lymphocyte count</td>
<td>Lymphocyte function test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CD4, HIV, DTH)</td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Absolute Neutrophil count</td>
<td>Neutrophil function test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NBT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow cytometry</td>
</tr>
<tr>
<td>Complement</td>
<td>C3, C4</td>
<td>Identification of individual components</td>
</tr>
<tr>
<td></td>
<td>Complement function (CH50, AH50)</td>
<td></td>
</tr>
</tbody>
</table>

Table VI Laboratory investigation of immunodeficiency
may show gradual improvement in hospital atmosphere and relapse on returning to home when exposed to the offending antigens in the environment.

BAL (Brancho alveolar lavage) is performed when a child presents with anemia, hemoptysis and recurrent pneumonia. It may show alveolar macrophages filled with hemosiderin pigments which is suggestive of pulmonary hemosiderosis.

Evaluation for primary immunodeficiency should focus on the component of the immune system that is most likely to be involved based upon the initial assessment.

Initial tests: The screening evaluation should include both quantitative and qualitative tests. Abnormalities of the following initial tests suggest immunodeficiency and serve as a guide for subsequent investigations. Further laboratory evaluation is probably futile if these tests are all normal (Table VI).

Immunoglobulin levels: Immunoglobulin levels, including IgG, IgM, IgA, and IgE, are usually indicated. These must be compared with age-matched controls, particularly in the first two years of life.

Antibody deficiency is suggested by an IgG less than 200 mg/dL and a total Ig (IgG plus IgM plus IgA) less than 400 mg/dL, or the complete absence of IgM or IgA (after infancy).

An elevated IgE (>100 IU/mL) suggests allergy, eczema, or chronic skin infections but may occur in phagocytic disorders or hyper IgE syndrome (levels are generally >2000 IU/mL for this syndrome). Low or absent IgE levels exclude IgE-mediated allergic disease.

Antibody titers: The function of the antibody system is best assessed by checking antibody titers to previously administered vaccines. Response to protein antigens can be assessed by measurement of titers to tetanus, diphtheria and H. influenzae type b.

Complement activity: C3, C4 estimation to be done in patients with recurrent sepsis or Neisseria infection. The screening test is a total hemolytic complement determination (CH50). CH50 assay is an effective screening test for a complete deficiency of a complement of the classical pathway. AH50 assay is a screening test for alternative pathway deficiency. A normal CH50 level excludes nearly all hereditary complement deficiencies.

Further testing is warranted when screening tests are abnormal or if there is a convincing history of immunodeficiency. These intermediate tests should provide some guidance as to which specific disorders must be considered and confirmed by additional studies.

IgG subset determinations: IgG subset determinations are sometimes of value, particularly in patients with a slightly low total IgG level and poor antibody response to vaccinations. A complete absence of IgG1, IgG2, or IgG3 suggests immune dysregulation and may indicate the early onset of common variable immunodeficiency. A low level of one or more IgG subclasses does not, by itself, indicate an antibody deficiency; functional antibody studies must show a defect.

The CD4 count is the most valuable reflection of the cellular immune system. An absolute CD4 count of <500 cells/μL in a child over five or <1000 cells/μL in younger children suggests a cellular immunodeficiency. An absolute B cell (CD19) count of <100 cells/μL suggests hereditary agammaglobulinemia. A low CD 16/56 count (<2 percent) suggests a natural killer cell deficiency.

HIV testing: HIV testing, either by antibody titers or PCR, should be done in any patient suspected of a T cell deficiency.
Delayed Type Hypersensitivity (DTH) testing is a sensitive indicator of intact cellular immunity. This test measures the recall response to an intradermal injection of an antigen to which an individual has already been exposed. For these reasons DTH testing can be used as a simple and economical means to exclude a defect in cellular immunity.

Phagocytic oxidative responses: Phagocytic oxidative responses are correlated with the ability of leukocytes to kill bacteria. This is best assessed using a fluorescent dye (dihydrorhodamine) and flow cytometry. A negative response is seen in chronic granulomatous disease. This procedure is faster and more informative than nitroblue tetrazolium dye reduction assays used previously.

Complement component: Complement component assays are indicated if there is very low or absent CH50 activity on repeat testing.

**Management:** Children undergoing evaluation for recurrent infection need special care during the evaluation process. Infections must be promptly recognized and aggressively treated. Empiric antibiotic therapy should be instituted pending culture results. Prophylactic antibiotics may be administered depending upon the type of disorder suspected. Measures to prevent routine infections include education of the patient and caregivers about effective hand hygiene, meticulous attention to oral and dental care and avoidance of regular exposure to large group of patients in institutional environment. Any underlying disorder (aspiration, GOR, bronchiectasis) that may be contributing must be addressed.

Bronchiectasis is the end result of variety of conditions like cystic fibrosis and immunodeficiencies. The treatment of cystic fibrosis includes chest physiotherapy, mucolytic agents, antibiotics and anti-inflammatory agents. The main aim of nutritional management is to achieve normal growth and development of these children. It includes increasing caloric intake, supplementing fat soluble vitamins and replacing pancreatic enzymes in suspected cystic fibrosis.

The management of patients with primary immunodeficiency begins with early identification and diagnosis. Live-virus vaccines (eg, oral polio, oral rotavirus, varicella, MMR, intranasal influenza) and the live BCG vaccine must not be administered to the child, if immune deficiency is suspected. Family with affected children require counselling about the risk of same disorder occurring in future children. Intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) should not be given until there has been a thorough evaluation of the patient’s immune system. IVIG and SCIG are expensive, will negate an antibody investigation for several months and have potential adverse effects. They should be used carefully only after the evaluation is complete.

**Summary**

Recurrent respiratory tract infections pose a challenge quite frequently in clinical practice. Although alarming due to their frequency, most of these are benign infections, especially in children younger than 5 years. Besides, hyper reactive airway disease and asthma mimic infections. In this scenario, differentiating simple from serious infections or noninfective conditions need good clinical acumen and a methodical approach (Fig.1).

Schematic approach is based on two symptoms, fever and cough. Presence of fever indicates infection while cough signifies airway disease. At the outset, it is important to stress that many cases of so-called “recurrent respiratory infections” actually represent hyper reactive airway disease or asthma. In patients with hyper reactive airway or asthma, cough is the predominant symptom lasting for several days
with minimal or no fever. Episodes recur with characteristic trigger factors of upper respiratory tract infections, exercise, cold air and exposure to aeroallergens or emotional upset. Often there is personal or family history of atopy. Hyperreactive airway disease or asthma invariably does not need laboratory investigations.

Fever is the predominant symptom of acute infection. It is necessary to distinguish recurrent infections of viral and bacterial etiology clearly as the management is totally different. Recurrent viral infections are common in normal toddlers and need no specific tests or therapy.

Viral infections affect large part of respiratory system—both upper and lower respiratory tract and at times also gastrointestinal system. Thus it is typically a disseminated disease, often spreading to other family members and prevalent in the community as well. It is characterized by short lasting self-limiting fever accompanied with significant cough and/or cold but without any localizing signs on physical examination.

Unlike benign nature of recurrent viral infections, recurrent bacterial infections are always secondary to underlying structural or functional defect. Hence it is important to make
sure about presence of bacterial infection before embarking on further tests. Bacterial respiratory infection presents with high fever. Cough is not a predominant symptom and is often absent. Disease is localized to either upper or lower respiratory tract. Physical examination also corroborates localization to one part of the respiratory system.

It is important to elicit if symptoms and signs are restricted to lower respiratory tract alone (aspiration, asthma, foreign body, cardiac cause, tumour, congenital lung defects) or if it is associated with upper respiratory tract (asthma with allergic rhinitis, cystic fibrosis, Kartogeners syndrome) or with other systemic involvement (immunodeficiency, cystic fibrosis, disseminated tuberculosis). Schematic approach avoids unnecessary investigations and paves the way for rational therapy.

Points to Remember

• **Recurrent respiratory infections can be grouped into four categories, the normal child, the child with atopic disease, the child with chronic condition and the child with an immunodeficiency.**

• **Most of the respiratory infections are viral. These children have normal growth and development, recover completely and appear healthy in between infections.**

• **Many cases of so called recurrent respiratory infections’ actually represent hyperreactive airway disease. Hyperreactive airway may justify treatment but not investigations except in case of atypical presentation.**

• **Recurrent bacterial infections are always secondary to underlying structural and functional abnormalities.**

• **Bronchiectasis is the end results of a variety of conditions.**

• **Primary immunodeficiency has to be considered in any child who suffers from recurrent, persistent or unusual infections of any site with failure to thrive. The screening evaluation should include both quantitative and qualitative tests.**

• **Tuberculosis is not a recurrent infection, but it remains an important differential diagnosis in all age groups in our country.**

References

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3. Barson WJ. Epidemiology, Pathogenesis and etiology of pneumonia in children. Up to Date, 18.3; Sep 2010.
COMmUNITY ACQUIRED PNEUMONIA - MANAGEMENT GUIDELINES’

*Gautam Ghosh

Abstract: Pneumonia is the single leading cause of death in children worldwide. In developing countries, community acquired pneumonia (CAP) is usually caused by bacterial pathogens. In view of the difficulty and cost associated with identification of etiological agents, the choice of antibiotic in most cases of CAP is empirical. Management issues for pneumonia include early diagnosis, availability of appropriate antibiotics, timely and appropriate referral, monitoring and follow up. Underutilisation and misuse of antibiotics are the two key features of the present scenario which need to be addressed.

Keywords: Community acquired pneumonia, Antibiotics in pneumonia.

Community acquired pneumonia is an acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting. The patient should not have been hospitalized within 14 days prior to the onset of symptoms or has been hospitalized less than 4 days prior to onset of symptoms.

This article will cover the management aspects of community acquired pneumonia.

Before dealing with management the severity of pneumonia has to be assessed (Table 1) and then decision on out patient treatment or hospitalisation has to be taken.

Severity assessment:

The first and foremost is to assess the severity of community acquired pneumonia in both infants and older children (Table 1).

Indications for hospitalization:

In infants it includes SaO₂ < 92%, cyanosis, Respiratory rate > 70 beats / min, difficulty in breathing, intermittent apnea, grunting, cyanosis and not feeding well. If the family is not able to provide appropriate observation or supervision, it is also an indication for hospitalization.

In older children: The indications for hospitalisation are SaO₂ < 92%, cyanosis, respiratory rate ≥ 50 breaths / min, difficulty in breathing, grunting, signs of dehydration, family not able to provide appropriate observation or supervision.

Malnourished children are prone to more severe disease. ARI criteria for classifying severity of pneumonia by respiratory rate cut off are kept 5 breaths/min less compared to WHO norms. Very severe pneumonia needs PICU care. Hypoxemia is a good indicator of the severity of pneumonia, and pulse oximetry should therefore be performed on every child who is ill and admitted. Transfer to PICU should be considered when there is failure to maintain SaO₂ ≥ 92% with FiO₂ > 0.6, the patient has shock, lethargy, cyanosis, head bobbing, evidence of
severe respiratory distress, exhaustion with or without raised PaCO2 or when there is recurrent apnea or slow irregular breathing.

Management protocol of CAP5

Management of CAP can be brought under the following headings.

(I) General management
(II) Supportive management
(III) Specific treatment

I. General management

Monitoring: Parents of children who are well enough to be cared for at home need information on managing pyrexia, preventing dehydration, and identifying any deterioration.

Oxygen*: Patients whose oxygen saturation (SpO2) is 92% or less while breathing room air treated with oxygen given by nasal cannulae, head box or face mask in (o) nonthreatening manner to maintain oxygen saturation above 92%. Agitation may be an indication that the child is hypoxic. In a sick child, minimal handling may reduce metabolic and oxygen requirements. SpO2 does not give idea of CO2 levels. A capnograph or ABG will give information on CO2 status if needed in ICU settings.

Feeding: Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children and especially in infants with small nasal passages. If used, the smallest tube should be passed down the nostril.

Intravenous fluids: Intravenous fluids, if needed, should be given at 80% of maintenance and serum electrolytes monitored in view of the possibility of SIADH.

II. Supportive management7

Fever: Antipyretics (paracetamol in the proper dose) can be used to keep the child comfortable.

Table.I Severity assessment

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Temperature &lt; 38.5°C</td>
<td>Temperature &gt; 38.5°C</td>
</tr>
<tr>
<td></td>
<td>RR &lt; 50 breaths/min</td>
<td>RR ≥ 70 breaths/min</td>
</tr>
<tr>
<td></td>
<td>Mild recession</td>
<td>Moderate to severe recession</td>
</tr>
<tr>
<td></td>
<td>Taking full feeds</td>
<td>Nasal flaring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent apnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grunting respiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not feeding</td>
</tr>
<tr>
<td>Older children</td>
<td>Temperature &lt; 38.5°C</td>
<td>Temperature &gt; 38.5°C</td>
</tr>
<tr>
<td></td>
<td>RR &lt; 50 breaths/min</td>
<td>RR ≥ 50 breaths/min</td>
</tr>
<tr>
<td></td>
<td>Mild breathlessness</td>
<td>Severe difficulty in breathing</td>
</tr>
<tr>
<td></td>
<td>No vomiting</td>
<td>Nasal flaring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grunting respiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signs of dehydration</td>
</tr>
</tbody>
</table>

2012; 14(3) : 259
**Cough:** Cough is a common symptom with pneumonia. Cough suppressants should be avoided. Intake of adequate fluids is encouraged. Household remedies (e.g. tulsi, ginger, honey) may be used.

**Wheezing:** Documented bronchospasm needs bronchodilators.

**Vomiting:** Most of the vomiting is post-tussive and hence needs no therapy. Persistent vomiting hindering drug intake may need antiemetics.

**Electrolyte imbalance:** Hyponatremia, hypokalemia and SIADH are rare and associated with severe pneumonia. They will need hospitalisation for correction of the same.\(^1\,^2\)

**Co-morbidities:** e.g. Diarrhea, congenital heart disease, cystic fibrosis, Immunodeficiencies, are then conditions which need special care in hospital setting.\(^7\)

**Chest physiotherapy:** Is not beneficial and should not be performed in children with pneumonia.

### III. Specific treatment\(^7\)

**a) Antibiotic therapy:** The management of a child with CAP involves a number of decisions regarding treatment with antibiotics (a) whether to treat with antibiotics (b) which antibiotic (c) by which route (d) when to change to oral treatment and (e) duration of treatment. However, there is a clear dearth of large pragmatic randomised controlled trials to provide the evidence necessary to make these decisions.

Empiric therapy should be guided by the following factors.

**1) Age guidelines:** Age is a good predictor of the likely pathogen of pneumonia and can help to narrow down the list of etiological agents (Table II)\(^8\).

**2) Sensitivity of pathogens**

- **S. pneumoniae:** S. pneumoniae is sensitive to penicillin; Semisynthetic penicillin [amoxycillin], cephalosporin (except Cefixime) macrolides, cotrimoxazole and chloramphenicol. Though antibiotic resistance in pneumococci is an emerging problem world-wide, in India it has a low but rising resistance to penicillin (1.7\%)\(^3\) and high resistance to cotrimoxazole (56\%) and chloramphenicol (17\%). Approximately 10-15% of S. pneumoniae are macrolide resistant.\(^7\)

- **b) H. influenzae:** High resistance of H. influenzae to chloramphenicol, ampicillin, co-trimoxazole and erythromycin is reported while no resistance is found against third generation cephalosporins. Newer quinolones e.g. gatifloxacin and levofloxacin have good coverage on both S. pneumoniae and H. influenzae but their use in children need more trials.\(^7\)

**3) Underlying disease:** Treatment is directed to cover the common organisms causes pneumonia in those with underlying diseases (Table III).\(^7\)

**4) Previous antibiotics:** History of antibiotics in recent past (previous 2-4 weeks) will give an idea on resistant organisms.

**5) Duration of illness:** A short duration suggests bacterial infection, while a duration beyond 2 weeks suggests atypical organism or Mycobacterium tuberculosis (TB).

**6) Parenteral therapy:** Most children with community acquired pneumonia can be treated as outpatients. Severe illness, alteration in consciousness, frequent vomiting and high risk groups will need parenteral therapy (Table IV)\(^2\). The drugs used for treatment of pneumonia and the dosages are given in Table V while Table VI gives clinical and radiological clues to the etiological diagnosis of pneumonia.

### Note

- i) III generation cephalosporin: Cefotaxime / Ceftriaxone;
- ii) Injectable aminoglycosides: Gentamicin / Amikacin;
**Table II** Age wise etiological agents for pneumonia

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacteria</th>
<th>Virus</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth - 3weeks</td>
<td>Group B streptococci, E.Coli, Klebsiella, L.monocytogenes, Staph. aureus</td>
<td>CMV, Herpes</td>
<td>Chlamydia</td>
</tr>
<tr>
<td>3weeks - 3months</td>
<td>S pneumoniae, S.aureus, H.influenzae</td>
<td>RSV, metapneumovirus, influenza, parainfluenza, adenovirus</td>
<td>Chlamydia</td>
</tr>
<tr>
<td>4months - 4years</td>
<td>S.pneumoniae, Staph aureus, H.influenzae, Group A Streptococcus</td>
<td>RSV, metapneumovirus, influenza, parainfluenza, adenovirus</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>S.pneumoniae, Staph aureus, H.influenzae, M.catarrhalis</td>
<td>Influenza, Varicella</td>
<td>Mycoplasma, Chlamydia, Legionella</td>
</tr>
</tbody>
</table>

**Table III** Organisms causing pneumonia in certain diseases.

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobinopathy</td>
<td>Pneumococcus</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Pneumococcus</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Staphylococcus, H.influenzae, Pseudomonas</td>
</tr>
<tr>
<td>HIV</td>
<td>Gram-ve bacilli, pneumocystis jiroveci, fungi</td>
</tr>
<tr>
<td>Neutropenic child</td>
<td>Gram-ve bacilli(pseudomonas), Staphylococcus, aspergillus, pneumocystis</td>
</tr>
</tbody>
</table>

iii) *A combination of ampicillin and chloramphenicol is needed as some H.influenzae strains. (below 2 years) may be resistant to one of them.

**Duration of antibiotic treatment**

Antibiotics should be given for at least 5 days in domiciliary treatment. Duration of antibiotic therapy may need to be prolonged (2 weeks) in complicated infections, such as those complicated by bacteremia or meningitis, Pseudomonas aeruginosa infection, and 4-6 weeks for empyema, necrotizing pneumonia, and lung abscess.
Table IV Empiric antibiotics of choice in CAP<sup>2</sup>

**I. Domiciliary treatment of Pneumonia.**

<table>
<thead>
<tr>
<th>Age</th>
<th>First line</th>
<th>Second line</th>
<th>Suspected Staphylococcal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3months</td>
<td>Usually</td>
<td>Severe pneumonia, and treated as inpatient</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td>3months -5 years</td>
<td>Amoxicillin</td>
<td>Co-amoxiclav or Chloramphenicol or Cefuroxime</td>
<td>Amoxicillin + cloxacillin or Cefuroxime or Co-amoxiclav</td>
</tr>
<tr>
<td>&lt;5years</td>
<td>Amoxicillin</td>
<td>Co-amoxiclav or Chloramphenicol or Macrolide</td>
<td>Amoxicillin + cloxacillin or Cefuroxime or Co-amoxiclav</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>First Line</th>
<th>Second line</th>
<th>Suspected Staphylococcus disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3months</td>
<td>III gen. cephalosporin +/--- aminoglycosides</td>
<td>Co-amoxiclav + aminoglycoside</td>
<td>III gen. cephalosporin + cloxacillin or cefuroxime + aminoglycoside or Co-amoxiclav + Aminoglycoside</td>
</tr>
<tr>
<td>3months -5 years</td>
<td>Ampicillin or Chloramphenicol or Ampicillin + Chloramphenicol or Co-amoxiclav</td>
<td>Co-amoxiclav or III gen. Cephalosporin</td>
<td>III gen. cephalosporin + Cloxacillin or Cefuroxime or Co-amoxiclav Second Line : Vancomycin / Teicoplanin + III gen. cephalosporin</td>
</tr>
<tr>
<td>&gt;5years</td>
<td>Ampicillin or Chloramphenicol or Co-amoxiclav and Macrolides (oral if mycoplasma)</td>
<td>Co-amoxiclav or III gen. Cephalosporin and Macrolides (oral if mycoplasma)</td>
<td>III gen. cephalosporin + Cloxacillin or Cefuroxime or Co-amoxiclav Second Line : Vancomycin / Teicoplanin + III gen. cephalosporin</td>
</tr>
</tbody>
</table>

Pneumonia may be treated by appropriate oral antibiotics for 10 days. If azithromycin is used, the treatment should be continued for only 3-5 days. For treatment of Legionnaires disease in immunocompetent children, azithromycin may be used for 5-10 days, and other macrolides and fluoroquinolones may be used for 10-14 days. For immunocompromised children, macrolides plus fluoroquinolones or rifampin may be used for 14-21 days.

**Monitoring in CAP<sup>1</sup>**

**Normal improvement expected after treatment**

Normal fever subsides in 2-4 days, clinical
Improvement is seen within 4 days, leucocytosis settles by 4 days, while radiological changes can take 4-6 weeks to normalise depending on the organism.

Treatment of CAP

I) Domiciliary treatment of pneumonia

1) Oral Amoxycillin for 5 days or* cotrimoxazole for 5 days

2) Observation should consider general condition, feeding, fever, vomiting and sleep. Clinical examination should look for tachypnea, air entry, chest indrawing, crepitations, rhonchi and bronchial breathing. If improvement is seen complete the antibiotic course for 5 days. If there is no improvement, consider second line drugs / macrolide. But if there is deterioration classify as severe pneumonia, hospitalise and manage accordingly.

II) Management of severe pneumonia for age > 3 months

These children need to be admitted. O₂, IV fluids, parenteral ampicillin every 6 hours have to be given. It is essential to monitor the respiratory rate, SPO₂ and work of breathing and their oral intake. After 48 hours, if child shows improvement, antibiotics are modified to oral amoxicillin to be given for 5 days. If there is no improvement treatment is modified to parenteral ampicillin with gentamicin or co-amoxyclav. Child is monitored. If child improves, complete IV antibiotics for 7 days. If there is no improvement, investigate with x-ray and modify to 3rd gen cephalosporin.

With these measures if child improves change to oral cepodoxime / cefdinir for 7 days, but if there is no improvement refer to tertiary center.

III) Management of severe pneumonia for age < 2-3 months

If there is suspicion of meningitis III gen cephalosporin with Gentamicin for 14 days is given. If there is no suspicion of meningitis IV fluids / O₂, IV ampicillin and gentamicin is given. After 48 hours child is reassessed. If the child shows improvement complete the course of injectable antibiotic for 7-10 days. If there is no improvement child needs further investigations - radiological, microbiological with continuation of antibiotics - III gen cephalosporin and gentamicin for 14 days.

IV) Management of very severe Pneumonia : (PICU)

Should be done in PICU with continuous monitoring along with O₂, IV fluids, radiology, IV ampicillin + gentamicin. If the child shows improvement at 48 hours and complete IV Antibiotic for 10 days. If not, antibiotics modified to III gen cephalosporin and cloxacillin for 7-10 days with regular reassessment to look for complications.

Approach to non-responding CAP⁸,⁹

If a child continues to be or becomes unwell 48 hours after admission, re-evaluation is necessary and the following are looked for in detail.

Inadequate dose of antibiotics, antimicrobials not effective for offending pathogen, such as antibiotic-resistant bacteria, tuberculosis, viral infection or mixed infection, extrapulmonary focus of infection, complication of pneumonia; S aureus pneumonia : Pneumatoceles / pneumothorax Mycoplasma pneumonia : Rashes / Stevens-Johnson syndrome / haemolytic anaemia, polyarthritis, pancreatitis, hepatitis, pericarditis, myocarditis and neurological complications, drug fever, immunocompromised host should be looked for.
Table V Recommended dosage of antibiotics

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Penicillin G : IM/IV</td>
<td>25mg/kg bd/tid</td>
</tr>
<tr>
<td>2. Procaine Penicillin</td>
<td>60 mg/kg OD</td>
</tr>
<tr>
<td>3. Amoxicillin</td>
<td>30-40 mg/kg/day, Po tid.</td>
</tr>
<tr>
<td>4. Cotrimoxazole (Trimethoprim(T)</td>
<td>5-7mg/kg/D + Sulphamethoxazole (S) 25-35 mg/kg/D</td>
</tr>
<tr>
<td>5. Cloxacillin</td>
<td>50-100 mg/kg/day, q6h.</td>
</tr>
<tr>
<td>6. Ampicillin</td>
<td>100-150 mg/kg/day, q8h.</td>
</tr>
<tr>
<td>7. Amoxicillin/clavulanate</td>
<td>100 mg/kg/day, iv q8h;</td>
</tr>
<tr>
<td>8. Cefuroxime</td>
<td>60-100 mg/kg/day, iv q8-12h; 20-30 mg/kg/day, po bid</td>
</tr>
<tr>
<td>9. Cefotaxime</td>
<td>100 mg/kg/day, q12h.</td>
</tr>
<tr>
<td>10. Ceftriaxone</td>
<td>50-100 mg/kg/day, OD</td>
</tr>
<tr>
<td>11. Meropenem</td>
<td>60-100 mg/kg/day, q8h.</td>
</tr>
<tr>
<td>12. Clarithromycin</td>
<td>15 mg/kg/day, q12h.</td>
</tr>
<tr>
<td>13. Azithromycin</td>
<td>10-12 mg/kg/day, OD</td>
</tr>
<tr>
<td>14. Vancomycin</td>
<td>20-40 mg/kg/day, q8h.</td>
</tr>
<tr>
<td>15. Teicoplanin</td>
<td>10 mg/kg OD (bd in serious cases)</td>
</tr>
<tr>
<td>16. Linezolid</td>
<td>20-30 mg/kg/day, q8-12h.</td>
</tr>
<tr>
<td>17. Gentamicin</td>
<td>6-7.5 mg/kg/day, bid-qd.</td>
</tr>
<tr>
<td>18. Tobramycin</td>
<td>6-7.5 mg/kg/day, bid-qd.</td>
</tr>
<tr>
<td>19. Netilmicin</td>
<td>5.5-8.0 mg/kg/day, bid-qd.</td>
</tr>
<tr>
<td>20. Amikacin</td>
<td>15-25 mg/kg/day, bid-qd.</td>
</tr>
</tbody>
</table>

Prevention

A. General principles: Reduce the risk of exposure to respiratory pathogens by droplet precautions.

B. Immunization

1. Bacille Calmette-Guérin vaccine: Follow with advice given in national immunization schedule and give routinely for all neonates
Influenza vaccine: Recommended for children older than 6 months with high-risk conditions.

Pneumococcal vaccine: 23-valent pneumococcal polysaccharide vaccine (PPV23) for children older than 2 years and 13-valent pneumococcal conjugate vaccine for children older than 2 months.

C. Preventive therapy

1. Tuberculosis: Isoniazid 5 mg/kg/day for 6 months recommended for children below 6 years with evidence of latent tuberculosis infection and a history of close contact with patients with infectious tuberculosis.

2. Haemophilus influenzae type b infection: Rifampicin 20 mg/kg (maximum 600 mg) daily for 4 days for all household contacts when at least 1 contact is younger than 4 years of age.

Points to Remember

- Pneumonia is the leading cause of mortality and common cause of morbidity in children below 5 years.

- In developing countries bacterial infections are the most common cause of pneumonia. *Streptococcus pneumoniae*, *Hemophilus influenzae* type b and *Staphylococcus aureus* are the common offenders.

- Administration of appropriate antibiotics in the early phase of pneumonia alters the outcome.

- Oral amoxicillin is the drug of choice in most cases of non-severe pneumonia. *Oral cefixime* is a poor choice.

**Table VI Clinical and radiographical clues to the aetiological diagnosis of pneumonia**

<table>
<thead>
<tr>
<th>Radiographical findings</th>
<th>Clinical circumstance</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental consolidation</td>
<td>Community-acquired</td>
<td><em>S. pneumoniae</em>, <em>M. pneumoniae</em></td>
</tr>
<tr>
<td>Lobar consolidation</td>
<td>Community-acquired</td>
<td><em>S. pneumoniae</em> (2/3 of community-acquired pneumonias)</td>
</tr>
<tr>
<td>Rounded pneumonia</td>
<td>Community-acquired</td>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>Community-acquired (winter)</td>
<td>Virus, <em>M. pneumoniae</em></td>
</tr>
<tr>
<td>Cavitation/necrosis</td>
<td>Aspiration</td>
<td><em>S. aureus</em>, <em>Gram negative bacilli</em>, <em>anaerobes</em>, <em>actinomycosis</em>, <em>S. aureus</em></td>
</tr>
<tr>
<td>Multiple cavitary nodules,</td>
<td>Post measles, malnourished</td>
<td><em>S. aureus</em>, <em>S. pneumoniae</em>, <em>Gram negative bacilli</em></td>
</tr>
<tr>
<td>Pneumatoceles</td>
<td></td>
<td><em>M. pneumoniae</em>, <em>M. tuberculosis</em></td>
</tr>
<tr>
<td>Empyema</td>
<td>Complication of pneumonia</td>
<td><em>S. aureus</em>, <em>S. pneumoniae</em>, <em>Gram negative bacilli</em></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td></td>
<td><em>M. pneumoniae</em>, <em>M. tuberculosis</em></td>
</tr>
</tbody>
</table>
All children (specially below 3 months of age) with severe pneumonia should be hospitalised and treated with parenteral antibiotics.

References
1. IndiaCLEN Task Force on Pneumonia; Rational use of antibiotics. Indian pediatr 2010;47:11-15.
5. Guideline for the diagnosis and management of community acquired pneumonia: pediatric-alberta medical association.

Nebulized hypertonic saline solution for acute bronchiolitis in infants

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants, but the standard treatment remains supportive care. This review was conducted to assess the effects of 3% saline solution administered via nebulizer, which can increase clearance of mucus, in these patients. We included seven randomized trials involving 581 infants with mild to moderate bronchiolitis. Meta-analysis suggests that nebulized 3% saline may significantly reduce the length of hospital stay among infants hospitalized for non-severe acute bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations. No significant short-term effects (30 to 120 minutes) of one to two doses of nebulized hypertonic saline were observed among emergency department patients; however, more trials are needed to address this question. There were no significant adverse effects noted with nebulized hypertonic saline when administered along with bronchodilators.

Current evidence suggests nebulized 3% saline may significantly reduce the length of hospital stay among infants hospitalized with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.

**Abstract:** Since the first National Heart, Blood, Lung Institute (NHBLI)-Asthma Management guidelines (1991), the international recommendations have been to diagnose asthma with a set of clinical parameters, and treat with a standardized approach. However, all practicing physicians, encounter children who continue to have symptoms in spite of adequate and appropriate therapy. This was identified globally within a few years of the guidelines.  

It is now realized that asthma is not a single disease, but a common manifestation of many overlapping individual diseases or phenotypes – each characterized by its own genetic and environmental interaction. Hence asthma is now classified as phenotypes. In the past 10 years, the use of the word phenotypes in asthma has increased tremendously in medical literature. However, despite widespread use of this terminology, there is no uniform understanding of what this means. Does phenotype represent superficial groups of asthmatic children with similar set of signs and symptoms or does it actually represent fundamentally separate disease entities? Going by the current available literature, the term “Phenotype” is still loosely used.

**Methods of classifying asthma phenotypes in children.** The common ways to classify the phenotypes has been based on simple criteria involving one or some clinical features (Table I).
Some popular classifications include those that are based on triggers (episodic wheezers, multi trigger wheezers, etc) and those based on retrospective symptom history and progress (Transient early) wheezers, persistent wheezers, etc) (Table II).

In the mid 90s, the Tucson group introduced a classification of children based on retrospective symptom history in the first 6 years of life. They identified 3 major groups of early wheezers:

**Transient early wheezers:** Those who wheezed in the first 3 years of life and did not have any wheeze by the time they were 6 years old. This group often wheezed with viral infections and were found to have smaller airways at birth. The predisposing factors for this group include - maternal smoking especially during pregnancy, prematurity, neonatal ventilation and bronchiolitis in the first 3 months of life. There was no increased association with atopy in this group.

**Persistent wheezers:** Those who wheezed in the first 3 years of life and continued to wheeze when they were 6 years old. Maternal asthma,
maternal smoking, rhinitis apart from colds, eczema during the first year of life and male sex were all independently associated with persistent wheezing. This group also had increased levels of IgE in the blood at 9 months of age.

**Late onset wheezers:** Those who did not wheeze in the first 3 years of life but had wheezing at 6 years of life. This group also had an increased association with a maternal history of asthma.

As this classification is based on retrospective symptom history at the age of 6, it cannot be used to guide treatment decisions for younger children. However, it has become the most widely used model in epidemiological studies.

The other classification which is getting more popular for use in clinical practice is the classification of wheezing children into 2 major groups.

**Episodic wheezers:** Episodic (viral) wheeze is defined as wheeze in discrete episodes, with the child being well between episodes. Although not unique to the preschool age group, this phenotype appears to be most common in preschool children. The most common causative agents include rhinovirus, respiratory syncytial virus (RSV), corona virus, human metapneumovirus, para influenza virus and adenovirus. Episodic (viral) wheeze most commonly declines over time, disappearing by the age of 6 years, but can continue as episodic wheeze into school age, change into multiple-trigger wheeze or disappear at an older age.

**Multi trigger wheezers:** Although a viral respiratory tract infection is the most common trigger factor for wheeze in preschool children, some young children also wheeze in response to other triggers like tobacco smoke, allergen exposure and some children may also wheeze in response to crying, laughter or exercise.

**Therapeutic implications of asthma phenotypes:** Even scratching the surface, with what has been discussed so far, it can be easily seen that all asthmatics do not represent a uniform population, but actually belong to many divergent groups with differential response to therapy. Some of the newer fallouts on the therapeutic front from the above concepts are as below:

1. **Pharmacogenetic phenotyping:** Elegant studies have shown that genetics do have a role to play at least in some of the therapeutic responses. As an offshoot of the Childhood Asthma Management Program study, it has been shown that response to inhaled corticosteroids can be altered by the variation in the child’s FCER gene (IgE receptor gene). A subset of children homozygous for the CC allele responded very well to inhaled steroids and a subset who were homozygous for the TT allele did not. So, response to primary medication in asthma—inhaled steroids, might be genetically controlled. Similar studies have demonstrated the genetic subgroups in whom leukotriene receptor antagonists will be beneficial or not beneficial.

2. **Oral Steroids for acute exacerbations of viral induced wheezing:** A short course of oral steroids to manage mild to moderate acute exacerbation of asthma is well known. However, its efficacy in treating viral induced exacerbations is controversial and no advantages over placebo have been found.

3. **Inhaled steroids used in children with viral induced wheezing:** This area is very controversial. Systematic studies have concluded high dose inhaled steroids (1600-3200 μgm beclomethasone) provide some benefit in episodic wheezers. The requirement for oral steroids reduces by 50%, but the rate of hospitalization and duration of symptoms did not change. 400 μgms of budesonide given on a daily basis to episodic wheezers did not show any benefit.
Table I Methods of classifying asthma phenotypes

Methods based on clinical features
Symptom based
  Age at onset
  Natural history
  Severity
Defined by triggers
  Allergic versus non-allergic
  Exercise induced
  Viral-triggered versus multi-triggered wheeze
Response to treatment
  Corticosteroid responsive

Methods based on pathophysiological features
Pathological tests (biopsy, induced sputum and bronchoalveolar lavage)
  Eosinophilic
  Neutrophilic
Non-invasive markers of airway inflammation
  Exhaled nitric oxide
  Exhaled breath condensate
Pulmonary function tests
  Fixed versus bronchodilator-reversible airway obstruction
  Bronchial responsiveness to exercise, cold air, chemical challenge

Table II Classification based on retrospective history and progress

<table>
<thead>
<tr>
<th>Publication</th>
<th>Wheeze Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucson Study 1995</td>
<td>Non wheezer</td>
</tr>
<tr>
<td></td>
<td>Transient early wheeze</td>
</tr>
<tr>
<td></td>
<td>Late-onset wheeze</td>
</tr>
<tr>
<td></td>
<td>Persistent wheeze</td>
</tr>
<tr>
<td>European Respiratory Society Task</td>
<td>Episodic (viral) wheeze</td>
</tr>
<tr>
<td>Force 2008</td>
<td>Multiple-trigger wheeze</td>
</tr>
</tbody>
</table>
4. Leukotriene modifiers in episodic wheezers: Montelukast is the only medication in this group which is licensed for use in the younger age group. Since inhaled and systemic corticosteroids did not have a major impact in the treatment of episodic wheezers, montelukast was tried in this age group. A trial of intermittent montelukast, started when patients developed signs of a common cold, compared with placebo in 220 children with episodic wheeze showed a 30% reduction in unscheduled health visits, but no effect on hospitalizations, duration of episode, and â2 agonist and prednisolone use. So, instead of intermittent use of montelukast, a daily preventer regimen was tried. Daily use of montelukast over a 1-yr period reduced the rate of wheezing episodes in 549 children with episodic (viral) wheeze by 32% compared to placebo.

5. Step up therapy for asthmatics already on low dose ICS: In one of the recent studies, children who were already on low dose inhaled steroids and were still symptomatic, were assigned to 3 different step up therapy options – (1) adding a LABA, (2) adding a leukotriene modifier and (3) increase the dose of inhaled steroids to moderate doses. What was interesting in this study was that they used a triple cross over design, which meant that all the children received extended periods of all three step up options, and then various parameters were analyzed. This study showed that nearly all the children had a differential response to each step-up therapy. LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up. This was expected. However, some children had a best response to ICS or LTRA step-up therapy (and not to LABA), highlighting the need for us to understand that not all children with asthma behave the same and different individuals respond better to different options.

Summary: Multiple approaches have been used to classify asthma phenotypes and new terminologies are being added rapidly. However, as discussed, one single approach might not be appropriate for all situations. This is an area where there is still much work to be done. But, it is paramount for us to understand that differences do exist amongst asthmatic children, and one treatment will not fit all.

From a clinical practice perspective, it is important to individualize each child’s management. Though we might still start with a unified approach (GINA or NHBLI guidelines), we will need to monitor the response and change strategies if need be.

Points to Remember

• There is a lack of specific biological basis for the disease heterogeneity in asthma—either genetic or causal, hence asthma is now classified as phenotypes.

• Methods of phenotyping can be based on clinical and pathophysiological features.

• Phenotyping therefore has therapeutic implications.

• It is paramount for us to understand that differences do exist amongst asthmatic children and one treatment will not fit all and it is important to individualize each child’s management.

• Though we might still start with a unified approach (GINA or NHBLI guidelines), we will need to monitor the response and change strategies if need be.

References


NEWS AND NOTES

4th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition (WCPGHAN 2012) Taipei, Taiwan
Date: November 14-18, 2012

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Abstract: Tuberculosis is one of the important infectious diseases affecting children and is responsible for disease and death in them. Inadequacies of the available diagnostic tests for tuberculosis have contributed to both under and overdiagnosis of the disease and have driven the zeal for development of new effective point of care diagnostic tools. The paucibacillary and extra-pulmonary disease among children makes the diagnosis more challenging. The current strategy is to look for novel approaches while also working for improvement in the existing diagnostics. Among the tools developed so far, those likely to have major impact on diagnosis of pediatric tuberculosis include: better specimen collection and processing techniques, improvement in microscopy and newer culture methods. Most relevant application of Nucleic Acid Amplification Tests (NAATs) appeared to be for rapid detection of mutations associated with drug resistance. And, the recently developed Xpert MTB/RIF® system holds promise as a rapid, point of care diagnostic for childhood tuberculosis. Development of Interferon Gamma Release Assays (IGRAs) in place of Tuberculin skin test (TST) has not led to any better diagnosis of disease though these tests are more specific and not affected by BCG vaccination. Skin test with recombinant dimer ESAT-6 (rdESAT-6), urinary lipoarabinomannan (LAM) assay and test for volatile organic compounds produced by mycobacteria in breath are newer promises in the diagnostics pipeline that seem attractive and need further evaluation in pediatric population.

Keywords: Childhood tuberculosis, Diagnosis, New tools, IGRAs, Rapid culture, NAATs, Xpert.

Despite being a curable disease, tuberculosis still causes 1.5-2 million deaths per year globally with pediatric cases contributing a significant burden to TB disease morbidity and mortality (15-40% of total disease burden). Both under and over diagnosis are common in pediatric population as establishing diagnosis of TB is far more tedious due to non specific clinical and radiological presentation, difficulty in obtaining specimen for microbiological confirmation and paucibacillary form of disease. Improving the performance of diagnostics and their availability is the key not only to reduce morbidity and mortality but also to limit the emergence and spread of drug resistant tuberculosis. Until recently smear microscopy and culture on solid media have been the mainstay of diagnosis of active disease and a positive tuberculin skin test (TST) as an evidence of latent infection (LTBI). However, of late considerable progress...
has been made in improving existing technologies and developing novel diagnostic tests for detecting active disease as well as latent infection. Some of these newer diagnostics have been endorsed by WHO for use in adult population. This review describes the improvement in diagnostics and their role in diagnosis of childhood disease in the light of currently available literature.

I. Improvement in specimen collection techniques

Bacteriological diagnosis, gold standard for diagnosis of TB disease is difficult in children as they seldom produce sputum and also due to paucibacillary or extra-pulmonary nature of disease in many of them. However, in this era of MDR/XDR tuberculosis, bacteriological confirmation is becoming increasingly important. Traditionally early morning gastric aspirate has been the method of choice for diagnosis of pulmonary tuberculosis in children. Efforts have been made to innovate and develop a number of alternative methods of specimen collection. Using some of these, microbiological diagnosis is possible even in young infants.

a. Sputum Induction: Nasopharyngeal aspiration of the mucus expectorated following administration of inhaled bronchodilator and hypertonic saline has been successfully used in several countries. Recent experience has indicated that sputum induction can be a feasible and more reliable alternative to gastric aspirate (GA) with studies showing yield from sequential induced sputum (IS) specimens is significantly higher than from 3 GAs and yield from a single IS specimen is better or similar to that of sequential GAs. Specimen can be obtained even from young infants.

b. Nasopharyngeal aspiration: Nasopharyngeal aspiration may be considered as a form of sputum induction as passing a nasal canula elicits a cough reflex. Studies have suggested culture yield from aspirate to be similar to that of GA and IS. More studies are needed to study the feasibility of using NPA as a TB diagnostic in children and positive result may make it specimen of choice as it can be obtained relatively easily and less

c. String test: It consists of swallowing a gelatin capsule containing a coiled string by the child. As the capsule reaches the stomach, it dissolves and string is left in stomach for 4 hours during which time it becomes coated with swallowed respiratory secretions after which it is withdrawn and specimen is cultured. However, it is not suitable for younger children due to issues in swallowing an intact capsule and there is little data on efficacy of test in pediatric population. Another disadvantage is the time required for the test to get completed, though one study has shown that intragastric time can be reduced to 1 hour without affecting the test yield.

d. Lung flute: Recently, a new device for sputum induction called lung flute has been developed in which patient exhales into a mouthpiece and air flows over a long reed, generating a low frequency acoustic wave that travels backward into the lower airways and improves mucociliary clearance. However, there is no data for the use of this device in pediatric population.

II. Improvement in smear microscopy

Although much effort is being made to develop new diagnostics for tuberculosis, sputum smear microscopy remains and will remain the primary means of bacteriological diagnosis of TB in resource poor settings. So, considerable research has been done to optimize the yield of smear microscopy. A series of recent systematic reviews have shown that microscopy can be optimized by using the following three different approaches: chemical and physical processing and concentration of sputum; fluorescence microscopy and examination of two (and not three) sputum specimens.
a. Chemical/physical processing and concentration of sputum: Pretreatment of sputum with bleach or sodium hydroxide followed by centrifugation or passive sedimentation have been shown to increase the sensitivity (increase varying from 11-26% for the former method and 2-34% for the latter) of smear microscopy with the former method being more consistent in improving the yield.8,11 A more recent systematic review however concluded that the benefits of bleach processing are less than those described previously. Further research should focus on alternative approaches to optimizing smear microscopy, such as light-emitting diode fluorescence (LED) microscopy and same-day sputum collection strategies.

b. Fluorescence microscopy: Fluorescence microscopy has been shown to have a higher sensitivity while retaining similar specificity compared to ordinary light microscopy (average increase in sensitivity of about 10%).10,11 Also, it is less time consuming as smears can be examined at lower magnification. Recent availability of LED light source for fluorescence microscopy, which makes it far less cumbersome, promises to make it acceptable for low resource settings.

c. Examination of two (not three) specimens: Studies quantifying the incremental yield of serial sputum examination in adults have shown that approximately 80% of TB cases are detected with the first specimen with an incremental yield of 11.9% and 3.1% with the second and third specimen respectively.12 Thus third sputum sample adds very little to the overall yield and omitting it will result in lesser patient visits to the clinic and decrease the lab workload, leading to lesser patient dropout and improved quality of services.13

In view of the above, WHO and RNTCP in our country has revised its policy on smear microscopy. It, now, recommends examining two sputum specimens in places where a well functioning external quality assurance system exists and workload is very high and resources are limited.14 WHO has also recommended to phase in LED microscopy as an alternative to conventional microscopy in both high and low volume labs and to replace conventional fluorescence microscopy with LED microscopy in all the settings where fluorescence microscopy is used.13 More research is needed to support this move for pediatric TB where the bacillary load is low.

III. Improvement in culture methods

a. Automated liquid culture systems

Automated liquid culture systems are a significant advance over traditional solid culture media. These systems have unique sensing mechanisms to detect a small growth of mycobacteria such as by detecting radioactivity (BACTEC TB 460®), oxygen concentration changes (BACTEC MGIT 960®), pressure changes in the headspace of culture bottles (Versa TREK®) or CO₂ production (BacT/Alert 3D®). All of them have similar performance and operational characteristic. Liquid cultures are more rapid and sensitive than solid culture (may increase the case yield by 10% over solid media) with mean time to detection being 12.9 days with BACTEC MGIT 960 and 15 days with BACTEC 460 compared to 27 days with LJ media.15,16 These methods can be used for drug susceptibility testing (DST) as well. However, apart from being expensive and requiring expertise and infrastructure, contamination with normal flora/environmental organisms like nontuberculous mycobacteria (NTM) can be a problem in all these systems due to enrichment added to media.

WHO, now, endorses the use of liquid culture and drug susceptibility testing (DST) in a phased manner in low and middle income countries.
Recognizing the problem of bacterial contamination and increased frequency of NTM isolation using liquid media, it has also recommended that all mycobacterial isolates should be speciated at least to the level of mycobacterium tuberculosis complex (MTBC) vs NTM using rapid method of species identification.\(^\text{16}\) Rapid methods for identification of MTBC include nucleic acid hybridization methods (results within 2 hours), lateral flow assays (results in 15 min, preferred method), line probe assays and DNA sequencing.

b. Non conventional non-commercial culture and drug susceptibility testing (DST)

In view of increasing rates of drug resistant tuberculosis, rapid methods for DST are crucial. While conventional culture and DST methods entail long delays for mycobacterial growth, WHO endorsed liquid culture systems and molecular line probe assays are faster but complex, costly and require sophisticated lab infrastructure, limiting their immediate uptake in resource constrained settings.\(^\text{17}\) So, several noncommercial culture and drug-susceptibility testing (DST) methods have been developed, specifically for resource constrained settings, with the purpose of diagnosing drug resistant tuberculosis rapidly. Some of these are direct tests i.e. can be applied directly to the specimen obtained from patient after decontamination, whereas some are indirect i.e applied to mycobacterial isolates grown on conventional culture.

i. Microscopic observation drug susceptibility testing (MODS): It is a potential low cost modification to liquid culture and utilizes the markedly faster growth of Mycobacterium tuberculosis in liquid media than in solid media and the characteristic microscopic cording appearance visualized using an inverted microscope. Growth can be detected in a median of 7 days. It can be applied as a direct or indirect test. A recent meta-analysis of direct and combined (direct and indirect) testing of MODS indicates that the method is 98% sensitive and 99.4% specific for the detection of rifampicin (RIF) resistance and 97% sensitive for isonicotinic acid hydrazine (INH) resistance. Mean turn-around time was 9-9 days (95% CI 4·1-15·8) for the MODS.\(^\text{18}\) Importantly, smear-negative specimens require conventional liquid culture before MODS testing and time to detection of MDR (3-4 weeks) is not faster than with conventional DST using liquid media (3-5 weeks). Therefore, the utility of this method in primary and extra-pulmonary form of paucibacillary disease is likely to be low.

ii. Nitrate reductase assay (NRA): Also known as Griess method, it is a liquid or solid medium based technique relying on ability of MTBC to reduce nitrate to nitrite which can be detected using Griess reagent. In the presence of antibiotics at critical concentration, development of red-pink colour indicates drug resistance. As NRA uses nitrate reduction as a marker of growth, results can be obtained earlier (usually within 10 days) than by examination of microcolonies on solid media. It can also be applied both as direct or indirect test. However, Griess reagent kills the organisms when added to tube, so multiple tubes must be inoculated if further testing is required. In addition, not all the members of MTBC reduce nitrate, presence of nitrate negative AFB may require further testing. Studies on combined use (direct and indirect) have shown it to be highly sensitive and specific for detection of rifampicin (sensitivity 97%, specificity 100%) and INH resistance (sensitivity 97%, specificity 99%) and diagnostic accuracy for direct testing alone did not differ significantly from combined testing.\(^\text{18}\) NRA done on smear-positive specimens allows detection of MDR within 6-9 days.\(^\text{17}\) Smear-negative specimens require conventional solid culture before NRA testing and
time to detection of MDR (7-11weeks) is not faster than with conventional DST using liquid media.\textsuperscript{17}

iii. Colorimetric redox indicator (CRI) methods: It is an indirect test done on MTBC isolates grown from conventional culture and is based on reduction of a colored indicator added to the culture medium after mycobacteria have been exposed to the test antibiotic. Drug resistance is indicated by change in colour of the indicator which is directly proportional to the number of viable organisms remaining in the medium after exposure to the antibiotic. Different indicators used are tetrazolium salts and redox indicators alamar blue and resazurin. It is highly sensitive (97\%) and specific (99\%) for detection of rifampicin resistance and also for INH resistance (sensitivity 97\%, specificity 98\%).\textsuperscript{16}

iv. Thin layer agar (TLA): It is a direct test that uses a standard light microscope to detect microcolonies of MTBC on plates containing a thin layer of Middlebrook 7H10 or 7H11 solid medium (with or without drugs) which can be detected as early as 7 days with DST results available between 10-15 days. Though not as sensitive as liquid media, specificity for INH and rifampicin resistance have been reported to be 100\%.\textsuperscript{18}

V. Phage based assays: Novel diagnostic tests using mycobacteriophages to detect M.\textit{tb} and rifampicin resistance require only 2 days of turnaround time. While these tests have a relatively high sensitivity, the specificity is more variable with false overdiagnosis of RIF-resistance.\textsuperscript{19} In addition, when performed directly on sputum specimens, the sensitivity and specificity of the tests vary widely.

WHO has reviewed non commercial culture and DST methods and has recommended that selective use of MODS, NRA and CRI for rapid screening of patients suspected of having MDR TB as an interim measure in resource constrained settings while capacity for genotypic/automated liquid culture is being developed.\textsuperscript{16}

IV. Direct nucleic acid amplification tests (NAATs)

These tests amplify and detect the nucleic acid regions that are specific to MTBC. There are two types of NAATs in use - commercial and in-house. In-house tests lack standardization, show substantial heterogeneity in their performance are highly operator dependent and thus are not recommended. There are five commercial assays that detect MTBC isolates in patient specimens. These assays use either PCR (Amplicor\textsuperscript{®} PCR assay), transcription-mediated amplification (Amplified MTD\textsuperscript{®} assay and GenoType\textsuperscript{®} Mycobacteria Direct assay), strand displacement amplification (BD ProbeTec\textsuperscript{®} assay), or loop-mediated isothermal amplification (LAMP).

There are many theoretical advantages to using NAATs as TB diagnostic viz. high sensitivity, ability to detect very low copy number of nucleic acid, rapidity and ease to automate. However, extensive review of available literature on NAATs has shown highly variable results and limited utility in children.\textsuperscript{21-23} Several meta-analysis have shown their sensitivity to be low in paucibacillary forms of disease (smear negative, extrapulmonary) which represent the vast majority of childhood tuberculosis.\textsuperscript{23-28} A negative test, therefore, does not rule out the disease. Factors contributing to reduced sensitivity are uneven distribution of bacilli in the sample, suboptimal extraction of nucleic acid and presence of inhibitors. Also, these tests can give false positive results. Major reason for false positive results is contamination of specimen from amplicons derived from positive specimens. Patients on treatment can have mycobacterial DNA detected for long periods despite effectiveness of treatment, giving false positive results and making these tests useless for
treatment monitoring. Inability to differentiate clinically relevant disease is another concern, especially in endemic areas where latent infection with M. tb is common. Studies have reported positive PCR assay in patients with recent exposure to TB or mediastinal adenopathy observed on CT scan but with no evidence of active disease. 22, 23

Thus, NAATs have not lived up to the expectation. However, these tests have definite value in rapid detection of mutations associated with drug resistance and with increasing incidence of drug resistant tuberculosis, this seems to be their most relevant application to date.

The validity of NAATs for detection of drug resistant TB hinges on the observation that 90-95% of isolates phenotypically resistant to INH or rifampicin demonstrate common resistance mutations. Thus, theoretically it is possible to detect such resistance in over 90% of cases using these tests. The commonly used NAAT tests are detailed below:

a. Line Probe assays (LPA): LPA are NAATs to detect common mutations responsible for drug resistance by DNA hybridization. In brief, the test consists of DNA extraction, multiplex NAA, solid phase reverse hybridization on test strip and detection of resistance mutations. Commercially available LPAs include INNO-LiPa Rif TB (detects rifampicin resistance only) and MTBDR plus assay (detects INH and Rifampicin resistance). A recent review reported the sensitivities of the Inno-LiPa to be above 95% for clinical isolates and 80% for smear-positive clinical specimens, with 100% specificity. 30

MTB DRplus assay, evaluated with smear-positive specimens in a high-volume diagnostic setting in South Africa, showed sensitivities of 98.9% for the detection of rifampicin resistance, 94.7% for the detection of INH resistance and 98.8% for the detection of MDR-TB. 30 In a meta analysis, the pooled sensitivity and specificity for the MTB DR plus assay were 98.4% and 98.9%, respectively. 31 Limited data exist on performance of these tests in smear-negative samples and these tests have not been specifically evaluated in childhood TB. WHO endorses these tests for use in smear positive sputum specimens or M. tb isolates grown on conventional culture. 32

LPA on smear positive specimen allow detection of MDR TB within 48 hours. 17 However, these tests do not eliminate the need for conventional culture and DST. Moreover, they detect only MDR and conventional culture and DST is still required to detect XDR TB and to monitor treatment response of MDR TB patients.

b. Real Time PCR: Real time PCR uses hybridization with fluorescence labeled probes during amplification. Major advantages of PCR are that the whole amplification mixture is analyzed for presence of amplicons (vs LPA where only a portion of amplified product is analyzed on the strips) and reaction is occurring in a closed chamber thus minimizing chances of contamination.

c. Xpert MTB/RIF: This recently made available fully automated molecular test is useful, for simultaneously detecting M. tuberculosis and presence of rifampicin resistance in it. It uses heminested real-time PCR assay to amplify an MTB specific sequence of the rpoB gene, which is probed with molecular beacons for mutations within the rifampin-resistance determining region. Testing is carried out on the MTB/RIF test platform (GeneXpert, Cepheid), that integrates sample processing and PCR in a disposable plastic cartridge containing all reagents required for bacterial lysis, nucleic acid extraction, amplification and amplicon detection. The only manual step is the addition of a bactericidal buffer to sputum before transferring a defined volume to the cartridge. The MTB/RIF cartridge is then inserted into the GeneXpert device, which provides results within 2 hours. Given the ease
of performance and result availability within 2 hours, it may well become a point of care TB diagnostic.\textsuperscript{33,34}

Recently, the Xpert MTB system was evaluated in a large study (1462 patients-741 culture positive, 721 culture negative). For MTB/Rif resistance detection, it had overall sensitivity of 97.6\% (99.8\% for smear- and culture-positive cases and 90.2\% for smear-negative culture-positive cases). The sensitivity of the testing of a single sample from culture positive patients was 92.2\%, with increases to 96.0\% when two specimens were tested and to 99.8\% when three specimens were tested. Similarly, the sensitivity of a single sample for smear-negative, culture-positive patients was 72.5\%, with increases to 85.1\% when testing two samples and to 90.2\% when testing three samples. The overall specificities of the test to detect TB was 99.2\% for a single test, 98.6\% for two tests and 98.1\% for three tests. The test showed 99.1\% sensitivity and 100\% specificity for the detection of RIF resistance. Also, a single, direct MTB/RIF test identified a greater proportion of culture positive patients than did a single Löwenstein–Jensen culture.\textsuperscript{34} Overall, the Xpert MTB system has shown excellent performance in adults with lower biosafety requirements and simpler contamination control. In 2010 the WHO endorsed this assay as an initial diagnostic test for suspected cases of MDR-TB or HIV-TB and as a follow-up test for microscopy on AFB smear-negative suspects in settings where MDR-TB or HIV is a lesser concern.\textsuperscript{35}

In a South African study on pediatric cases, MTB/Rif tests on induced sputums using Xpert MTB\textsuperscript{®} system detected twice as many cases (75.9\%, 95\% CI 64.5-87.2) as did smear microscopy (37.9\%, 25.1-50.8), detecting all of 22 smear-positive cases and 22 of 36 (61.1\%, 44.4-77.8) smear negative culture positive cases. For smear-negative cases, the incremental increase in sensitivity from testing a second specimen was 27.8\% for MTB/RIF, compared with 13.8\% for culture. The specificity of MTB/RIF was 98.8\% (97.6–99.9). MTB/ RIF results were available in median 1 day (IQR 0–4) compared with median 12 days (9–17) for culture (p<0.0001). The authors recommend testing of two induced sputum specimens as the first-line diagnostic test for children with suspected pulmonary tuberculosis.\textsuperscript{36}

V. Advances in latent TB diagnosis

1. Interferon Gamma Release Assays (IGRAs): IGRA’s were developed as an alternative to tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection (LTBI). Two tests are currently available - Quatiferon-TB Gold (QFT-G\textsuperscript{®}) and T-SPOT.TB\textsuperscript{®}. These tests measure Interferon ã (IFN ã) released from T cells after stimulation by M.tb specific antigens (CFP-10 and ESAT-6) which are absent from all BCG vaccine strains and most NTM. QFT-G measures IFN ã release in whole blood in IU/mL using ELISA and T-SPOT.TB counts the cells releasing IFN ã visualized as spots with ELISPOT technique (therefore requires separation of peripheral blood mononuclear cells). Quantiferon - TB Gold In Tube assay (QFT-GIT\textsuperscript{®}) is a newer version of QFT-G which has been enhanced by addition of another antigen TB7.7 and entails simpler sample preparation.

Commercial IGRAs are being increasingly used and recommended for diagnosis of M.tb infection in high income, low burden countries. However, the value of IGRAs in high burden settings and children is less clear. A recent meta-analysis done to assess the value of IGRAs and TST in diagnosis of TB infection and disease in children concluded that TST and both the IGRAs have similar accuracy for the diagnosis of M.tb infection and disease in children.\textsuperscript{37} However, it emphasized several limitations like heterogenous methodology of the
included studies and lack of sufficient data from high burden countries, very young and HIV infected children and need for rigorous, standardized approaches for evaluating TB diagnostics. Another meta-analysis assessing the utility of IGRA (QFT-G only) for diagnosis of LTBI and active disease in immunocompetent children concluded that there is no clear evidence to support the use of IGRAs in place of TST for detection of LTBI. Though, there is evidence to support increased specificity of IGRAs compared to TST for diagnosing LTBI, their sensitivity is variable. Sensitivity of IGRAs for TB disease is no different from TST and a significantly reduced sensitivity was found in high burden countries compared with low burden settings. WHO discourages the use of IGRAs for diagnosis of active TB/LTBI in low/middle income countries.

2. Skin Test with rdESA T-6: This new specific tubercular skin test may form the benchmark skin test in future as it overcomes the major limitation of the conventional TST i.e. the lack of specificity of the purified protein derivative (PPD), a crude antigen mixture. Statens Serum Institute, Copenhagen, Denmark has developed this specific skin test by utilizing intradermal recombinant dimer ESAT-6 (rdESAT-6). Further work is ongoing to improve this novel skin test and to include other specific TB antigens such as CFP 10.

VI. Newer diagnostics in the pipeline

There are two novel diagnostic tests that have not been evaluated in children but are likely to be tested in this population in near future; the urinary lipoarabinomannan (LAM) assay and tests for volatile organic compounds in the breath.

1. Urinary lipoarabinomannan (LAM) assay

It is an immune-based approach detecting urinary lipoarabinomannan (LAM), a heat stable glycolipid specific to mycobacteria that is released by metabolically active bacteria and found in the urine of patients with active TB. LAM was originally detected in serum, but this test was limited by immune complex formation. Adult studies evaluating commercially available tests to detect urinary LAM by antigen capture ELISA for the diagnosis of tuberculosis have shown adequate specificity (87.8%-89%) but variable suboptimal sensitivity (38%-50.7%) with significantly higher sensitivity (62.0%) for patients coinfected with HIV with advanced immunosuppression (presumably due to higher bacterial burden and increased frequency of disseminated disease) and lower sensitivity (28%) for smear-negative patients (HIV positive and negative patients combined). Urine-based TB diagnosis is definitely attractive since urine is an easier specimen to collect and may be less variable in quality and safer to handle. The performance of this assay in TB-HIV coinfected children, in whom disseminated disease is common, will be of interest. Further work is needed to improve the LAM assay.

2. Volatile organic compounds in breath

A number of studies have identified specific patterns of volatile organic compounds produced by MTB. These compounds were first detected in the headspace of cultures of MTB, but have more recently also been detected in the breath of adult TB patients. A recent study has demonstrated sub-optimal sensitivity (84%) and specificity (65%) for one such assay, however this may improve with further development. Since breath sampling is simple and noninvasive, this would be an attractive assay system for pediatric TB. Certainly, it will be the easiest and most non-invasive manner of scenting out the disease using an electronic nose.

To conclude, while lots of innovations and progress has been made in developing and/or improving TB diagnostics, the major impact for
children is likely to happen by using better specimen collection and processing, improved technology for microscopy and cultures in combination with newer point of care NAAT tests like Xpert MTB® system.

**Points to Remember**

- **Despite the difficulties of bacteriological diagnosis in children, a sincere and active effort must be made for mycobacterial detection and isolation in appropriate clinical specimens.**

- **Smear microscopy of appropriate specimen remains the primary means of bacteriological diagnosis of TB in resource poor settings.**

- **More research is needed to support routine use of light emitting diode (LED) fluorescence microscopy in place of conventional microscopy for pediatric TB.**

- **Automated liquid culture systems are a significant advance over traditional solid culture media, but are complex, costly and require sophisticated lab infrastructure.**

- **Utility of non conventional, non commercial culture and DST methods like MODS, NRA, CRI assays in primary and extra-pulmonary form of paucibacillary disease is likely to be low and these methods need further evaluation in pediatric population.**

- **Main value of NAATs such as LPAs and PCR lies in rapid detection of mutations associated with drug resistance. Xpert MTB/RIF® may be the turning point in the role of NAATs in diagnosis of all forms of TB as a point of care test.**

- **There is no clear evidence to support the use of IGRAs in place of TST for diagnosing TB infection.**

**References**


Cystic Fibrosis- When to Suspect and How to Manage

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** Rakesh Lodha
*** Kabra M
*** Kabra SK

Abstract: Cystic fibrosis (CF) is an autosomal recessive disorder due to a mutation in the CFTR gene leading to failure of chloride conductance by epithelial cells. As a result of this, the secretions become too viscid and difficult to clear. Clinical features are variable. Common presenting clinical features include: recurrent chest infections, malabsorption and failure to thrive. CF may be suspected in a child presenting with meconium ileus, recurrent pneumonia and / or malabsorption of pancreatic origin. Other laboratory evidence supporting a possibility of CF include: hypochloremic metabolic alkalosis, airway colonization with P. aeruginosa, abnormal pancreatic function tests and obstructive azoospermia in post pubertal males. The diagnosis of CF is confirmed by the demonstration of a high sweat chloride (>60 mEq/L) on at least two occasions or by identifying two CF causing mutations or by suggestive nasal potential difference measurements.

The treatment of cystic fibrosis in children includes respiratory management, nutritional care, anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction. Airway clearance techniques include adequate hydration, chest physiotherapy and mucolytic agents. Antibiotics can be used via intravenous, oral or inhalational route, when needed. Long term use of low dose azithromycin has immunomodulatory effect. Other supportive care includes increased calorie intake, supplementation of fat soluble vitamins and replacement of pancreatic enzymes.

With improvement in multidisciplinary management of CF, life expectancy of CF patients is increasing.

Keywords: Cystic fibrosis, Hypertonic saline, Pancreatic enzyme, Pseudomonas.

Cystic fibrosis (CF) is the most common life limiting autosomal recessive genetic disorder in Caucasians. The basic defect in CF is a mutation in the gene for chloride conductance channel i.e. cystic fibrosis transmembrane conductance regulator (CFTR). The failure of chloride conductance by epithelial cells leads to dehydration of secretions, that become too viscid and difficult to clear.

Indian scenario

CF was thought to be extremely rare in India. The precise disease burden in India is not known,
but the estimated burden is between 1 in 10000 to 1 in 40000 population. However, a recent review of all reported cases of CF in literature indicate that CF is probably far more common in people of India/Indian origin than previously thought, but is under diagnosed or missed in the majority of cases.

Molecular genetics of CF

The prevalence of genetic mutations in CF patients varies from one population to other. The frequency of delta F508 mutation, the commonest identified mutation has been reported between 19 to 44% in Indian subcontinent. Due to the heterogeneity of Indian population, there are different mutation profiles in different regions of India. Hence, it is difficult to design a panel of mutations that can be used for diagnosis and prenatal diagnosis of cystic fibrosis in India.

Presentation of cystic fibrosis

The common clinical presentation include: meconium ileus in neonatal period, recurrent bronchiolitis in infancy and early childhood, recurrent lower respiratory tract infections, chronic lung disease, bronchiecstasy, steatorrhoea, diarrhoea and with increasing age - pancreatitis and azoosperma. Pancreatic insufficiency is present in >85% of CF patients manifesting as meconium ileus, meconium peritonitis, meconium pseudo cyst, malabsorption, diarrhoea, failure to thrive, rectal prolapse, pain abdomen, abdominal distention, meconium ileus equivalent and deficiency of fat-soluble vitamins. Anemia can occur along with hypoalbuminemia and ascites as a result of Vitamin E deficiency and protein malabsorption respectively.

In a report of 120 patients with cystic fibrosis from All India Institute of Medical Sciences, New Delhi, the common clinical presentation included: recurrent or persistent pneumonia, failure to thrive, and malabsorption.

CF may be suspected in a child presenting with meconium ileus, recurrent pneumonia, malabsorption of pancreatic origin suggested by significant steatorrhoea and oil droplets in stools. A combination of metabolic alkalosis, hyponatrema, hypokalemia and hypochloremia also strongly suggest a possibility of CF. Culture of Pseudomonas in sputum or respiratory secretions and development of clubbing in a child who is being treated as asthma should arouse a possibility of CF.

Diagnosis of CF

The diagnosis of CF is confirmed by the demonstration of a high sweat chloride (>60 mg/L) at least on two occasions or by identifying two CF causing mutations. Nasal potential difference measurements can be used as an adjunct to sweat test but is not widely available. As mutations are heterogenous in Indian population and there is no panel of common mutations, sweat chloride remains the gold standard for diagnosis of CF in India. But sweat chloride test is not available widely. To improve diagnosis of CF, there is need to establish sweat testing facilities widely throughout the country. To overcome the cost of sweat testing, an indigenously prepared sweat equipment can be used with acceptable results. False positive sweat test result can occur in conditions listed in Table I.

If sweat test facility is not available; CF may be suspected in children presenting with recurrent pneumonia, malabsorption or failure to thrive. An attempt may be made to document: hypokalemia, hyponatrema, hypochloremia, metabolic alkalosis or pseudomonas in airway secretions. If two or more of the above are present; a suspected CF may be diagnosed and treated with physiotherapy, appropriate antibiotics, vitamin, enzyme and salt supplementation. However a label of CF should
Table I Conditions causing false positive sweat chloride test

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Hypogammaglobulinaemia</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Klinefelter’s syndrome</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Ectodermal dysplasia</td>
<td>Mucopolysaccharidosis type 1</td>
</tr>
<tr>
<td>Familial cholestasis (Byler’s disease)</td>
<td>Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>Nephrosis</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Pseudohypoaldosteronism</td>
</tr>
<tr>
<td>Glycogen storage disease type 1</td>
<td>Psychosocial problems</td>
</tr>
</tbody>
</table>

Table II WHO List of single organ disease phenotypes associated with CFTR mutations (Joint Working Group of WHO/ICF (M)A/ECFS/ECFTN, 2001)

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated obstructive azoospermia</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Disseminated bronchiectasis</td>
</tr>
<tr>
<td>Diffuse panbronchiolitis</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Neonatal hypertrypsinogenemia</td>
</tr>
</tbody>
</table>

Table III Methods of chest physiotherapy

<table>
<thead>
<tr>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural drainage and chest clapping</td>
</tr>
<tr>
<td>Active cycles of breathing</td>
</tr>
<tr>
<td>Positive expiratory pressures (PEP)</td>
</tr>
<tr>
<td>High pressure PEP</td>
</tr>
<tr>
<td>Flutter therapy</td>
</tr>
<tr>
<td>Autogenic drainage</td>
</tr>
<tr>
<td>High frequency chest wall oscillation (HFCWO)</td>
</tr>
</tbody>
</table>
be given only after documentation of raised sweat chloride values or demonstration of two mutations.

The spectrum of CFTR mutation disorders

The clinical outcome of CF can vary significantly even for the same genetic mutation. To allow for this heterogeneity and to avoid inappropriately labeling someone with a life shortening disease it has been suggested that there should be three diagnostic categories; CF unlikely, non classic CF, and classic CF.

“Non classic” CF describes patients with a CF phenotype in at least one organ system (Table II) and borderline sweat test results with insufficient evidence from genotype or electrophysiology to support the diagnosis. Some of these patients may develop progressive lung disease as a result of chronic airway infection in adult life. Therefore, these patients need to have follow-up properly.

Prenatal diagnosis and neonatal screening for CF

With the identification of genetic mutations in a child and parents, it is possible to make a prenatal diagnosis by chorionic villous (CV) biopsy around 10-12 weeks or amniotic fluid cell culture at 15-16 weeks of gestation in future pregnancies. In addition, pre implantation diagnosis is also possible.

Management of CF

The treatment of cystic fibrosis in children includes respiratory management, nutritional care, anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction.

A. Respiratory management

The principle components of care includes airway clearance techniques, antibiotics and anti inflammatory agents.

Airway clearance techniques: Airways can be kept clear by adequate hydration, chest physiotherapy, judicious use of antibiotics and mucolytic agents. Chest physiotherapy techniques for keeping airways clean include the methods mentioned in (Table III). The method can be individualized on the basis of age of patient, clinical status, experience of physiotherapist, personal preference of patients, social issues including level of support etc. For infants and young children postural drainage and chest clapping may be more convenient. As cyclical breathing and autogenic drainage requires patient’s cooperation, they can be used in older children. Flutter therapy, positive expiratory pressure and high frequency chest wall oscillation require special devices and training. They can be used under supervision of physiotherapist.

Mucolytic agents

Various oral and inhaled mucolytic agents have been used. N-acetyl cysteine breaks the sulphydryl bonds of the mucus glyco-protein thereby reducing the viscosity of airway secretions. Because of its offensive odour and propensity to cause bronchospasm, hemorrhagic tracheitis and impaired ciliary clearance, its use is limited to selected cases where other measures fail to clear the airway.

Recombinant human DNase (rhDNase): In CF patients, there is high concentration of DNA in respiratory secretions, released by disintegrating inflammatory cells. Long term trials in patients with CF have proven that DNase, given as aerosol, increases mucociliary clearance, reduces incidence of respiratory infections, decreases rate of hospitalization, number of days missed from work or school and the frequency of CF related symptoms, with very few side effects like upper airway irritation (voice change, laryngitis, pharyngitis). There is no role for oral mucolytic drugs such as bromhexine, ambroxol.
**Hypertonic saline inhalation:** Inhaled hypertonic saline acutely increases mucociliary clearance and improves lung function in people with cystic fibrosis. In clinical trials hypertonic saline preceded by a bronchodilator has been found to be an inexpensive, safe, and effective additional therapy for all patients with cystic fibrosis including infants.¹

**Antibiotic therapy**

The commonly encountered microbial agents causing pulmonary exacerbation in children with CF include Staphylococcus aureus, Haemophilus influenzae b, Pseudomonas, Burkholderia cepacia, different viruses, mycoplasma, mycobacterium spp, and aspergillus. The organisms can be isolated by obtaining cough swab, sputum or deep throat swabs after physiotherapy (DTSP). Periodic cough swab cultures may help in empirical treatment of acute exacerbation. The treatment of acute exacerbation of infection, if the patient is known to be colonized with Pseudomonas include ceftazidime, or cefoperazone or piperacillin or imipenem or meropenem in combination with an aminoglycoside. If the colonization status is not known then a combination of drugs effective against Pseudomonas and Staphylococcus are used empirically. The duration of intravenous therapy is 2-4 weeks.

The commonly used oral antibiotics include a drug from fluroquinolones group. These drugs may be started early and given for 2-3 weeks when acute exacerbation is suspected. An early identification of respiratory infection and administration of oral antibiotics may decrease the need for hospitalization and intravenous antibiotics. The early indications of starting oral antibacterials include increase in cough and expectoration, change in the color of expectoration, decrease in activity, impaired appetite, fever and weight loss. Fever may not be a common clinical manifestation of acute exacerbation of infections.

**Aerosolised antibiotics:** Use of aerosolised antibacterials has been shown to give good results in treating patients who are chronically colonized with pseudomonas. The drugs commonly used are colistin sulphate and tobramicin (Table IV). These drugs are delivered to lower respiratory tract by nebulizers, are continued till the two

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (years)</th>
<th>Dose (mg)</th>
<th>Frequency (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>&lt; 6 yrs</td>
<td>150</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 6 yrs</td>
<td>300</td>
<td>2</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>&lt; 5 yrs</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5-12 yrs</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 12 yrs</td>
<td>160</td>
<td>2</td>
</tr>
<tr>
<td>Colistin</td>
<td>&lt; 1 yrs</td>
<td>0.5 mega units</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1-12 yrs</td>
<td>1-2 mega units</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 12 yrs</td>
<td>2 mega units</td>
<td>2</td>
</tr>
<tr>
<td>Amphotericin</td>
<td></td>
<td>10</td>
<td>1-2</td>
</tr>
</tbody>
</table>
consecutive cough swabs or sputum cultures are negative for pseudomonas. Suggested alternative regimen includes administration of tobramycin alternate months. A recent report suggest that Colistin-tobramycin combinations are more efficient than respective single antibiotics for killing P. aeruginosa in biofilms.

**Azithromycin:** Long term use of low dose azithromycin in young patients with cystic fibrosis has a beneficial effect on lung disease expression, even before infection with Pseudomonas aeruginosa. Continuous low dose azithromycin daily or 2-3 times a week has been shown to reduce pulmonary exacerbation and preserve pulmonary function. Macrolides display immunomodulatory effects that may be beneficial in chronic inflammatory pulmonary diseases. In a randomized controlled trial it was demonstrated that 5 mg or 15 mg/ kg/ day of azithromycin were safe and were equally effective and can be used continuously.

**Bronchodilator and inhalation steroid therapy**

Bronchial hyper-responsiveness occurs in 25-50% patients, especially, during intercurrent infections and in those with poor baseline lung function. These patients may benefit with bronchodilators and inhaled steroids.

**B. Nutritional management of CF**

The main aim of nutrition management is to achieve normal growth and development of children. Nutritional management of CF can be discussed as follows:

i) Increasing caloric intake

ii) Supplement fat soluble vitamins

iii) Replace pancreatic enzymes.

(i) Increasing caloric intake: Most children will grow normally by consuming the average energy intake requirement for a child of their age group provided they get adequate enzyme supplements. The caloric demand may increase by up to 50% during acute pulmonary exacerbation. In Indian children where diagnosis of CF is delayed, malnutrition is common and their airways are colonized with pseudomonas by the time the diagnosis of CF is made. They would have suffered from frequent exacerbations of respiratory infection, hence they need more calories than their normal peers. Caloric intake can be increased by encouraging the child to eat energy rich food throughout day e.g. - full fat dairy products and fried food. Parents should be told not to restrict fat in the child’s diet.

**Oral caloric supplements** In the form of commercial preparations or home made feeds can be given, in addition to regular meals. Suggested supplements include - addition of skimmed milk powder and ice cream to milk, preparations of groundnut and jaggery, coconut and sugar, etc.

**Nasogastric and gastrostomy feeding:** Is indicated in following situations: 1) no weight gain for 6 months even with adequate caloric intake, 2) acute pulmonary exacerbation with poor oral intake, 3) consistently poor appetite and inability to maintain caloric intake, 4) before major surgical procedures, 5) during periods of increased caloric requirement e.g. puberty and pregnancy. The feeds may be home made liquid feeds or commercially available formulae. Pancreatic enzymes should always be given with supplementary feeds.

**ii) Supplementation of fat-soluble vitamins and minerals:** Children with pancreatic insufficiency are at risk of developing deficiency of fat-soluble vitamins Recommended doses of vitamin A and D are given in (Table V). Recommended doses of vitamin E are 50 mg for children below one year of age, 100 mg for children between 1-10 years and 200 mg thereafter. Vitamin K is recommended only in...
children with clinical manifestation of vitamin K deficiency and those having liver disease in a dose of 10 mg vitamin K daily. All vitamins should be given with meals and enzyme. Water-soluble vitamin deficiency is not common. Increased sweating in hot weather may result in excessive salt loss in CF patients. Sodium supplement is recommended in hot climate. There are no studies on the doses of daily salt for Indian children. Till data are available we advice daily extra salt intake of 2.5 g in children below 10 kg, 5 g in children between 11-20 kg and 7.5 g in children above 20 kg.

**iii) Pancreatic enzyme supplement:** Pancreatic enzyme preparation is given with meals in the form of enteric coated capsules or spherules, which can be sprinkled over food in infants and young children who are not able to swallow capsules. The initial doses of enzyme can be 3000 (1/3rd capsule) – 10000 IU (one capsule) per meal. Doses can be adjusted by observing stool consistency and weight gain in the child. Appropriate pancreatic replacement therapy will achieve normal or near normal absorption. Effective treatment should allow a normal diet to be taken, control symptoms, correct malabsorption and achieve a normal nutritional state and growth. There has been a search for a cheaper source of lipase as the current enzyme preparations are quite expensive.

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**C. Management of other GIT manifestations of CF**

The common GI manifestations in CF include pain abdomen, abdominal distention, meconium ileus equivalent, intussusception and meconium peritonitis.

Pain abdomen in CF may be due to pancreatic insufficiency, rectal prolapse, gastro esophageal reflux or intestinal obstruction. Pain and abdominal distention, rectal prolapse due pancreatic insufficiency respond after increasing doses of enzymes. For gastro esophageal reflux, prokinetic agents along with H-2 receptor antagonist are required. Pain abdomen secondary to constipation can be treated with oral lactulose in the dose of 1 ml/kg/day in 2 divided doses.

Meconium ileus equivalent or distal intestinal obstruction syndrome should be managed with proper hydration. Mild cases may be treated with oral lactulose. However, severe cases may be treated with following: Acetyl cysteine sachets (200 mg 3-4 times a day) or Acetyl cysteine enema (50 ml of 20% solution in water two to three times a day), oral gastrograffin: 50 ml in 200 ml of water once or twice in children below 8 years of age and 100 ml in 400 ml water in children above 8 years of age or gastrograffin enema: 50-100 ml twice a day. Child should be monitored for dehydration and should be on

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**Table. V Recommended doses of Vitamin A and D**

<table>
<thead>
<tr>
<th>Age</th>
<th>Vitamin A</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 6 weeks</td>
<td>2000 IU</td>
<td>200 IU</td>
</tr>
<tr>
<td>6 weeks to 6 months</td>
<td>4000 IU</td>
<td>400 IU</td>
</tr>
<tr>
<td>More than 6 months</td>
<td>8000 IU</td>
<td>800 IU</td>
</tr>
</tbody>
</table>

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54
intravenous fluids. Meconium peritonitis and unresponsive meconium ileus may need surgical intervention.

Management of liver disease in CF: With improved survival, liver involvement in CF is recognized more frequently. Early administration of ursodeoxycholic acid (UDCA) may improve outcome of liver disease in children with CF by improving cholestasis and hepatic dysfunction. A regular monitoring of liver function test and imaging studies should be part of management.

D. Emerging therapies for CF

Mannitol Inhalation: Mannitol as inhalation has been shown to increase mucociliary clearance by rehydrating the airway. Studies in adults have reported its safety and improved FEV1 in cystic fibrosis.14

Role of aminoglycosides: In promoting expression of CFTR: Premature stop mutations account for approximately 5% of all mutant alleles in CF patients. The aminoglycoside antibiotics can permit protein translation to continue to the normal end of the gene. Wilschanski, et al have demonstrated significant depolarization of the nasal epithelium after nasal gentamicin instillation for 2 weeks in 9 CF patients carrying stop mutations.15 Inhaled gentamicin may lead to expression of CFTR in lung epithelia.

PTC 124: PTC124 is an orally bioavailable molecule, that induces ribosomes to selectively read through premature stop codons during mRNA translation, to produce functional CFTR. Results of phase 2 trials suggest that in patients with cystic fibrosis who have a premature stop codon in the CFTR gene, oral administration of PTC124 reduces the epithelial electro physiological abnormalities caused by CFTR dysfunction.16

Heart lung transplantation: For patients with very advanced lung disease and poor life expectancy, heart lung transplantation has been performed.

Gene therapy: Currently available therapies for CF such as supplemental pancreatic enzymes and antibiotics, address the consequences of CFTR deficiency rather than the underlying cause. However, decades of research have culminated in the recent testing of therapies that address the basic defect and hold promise for significant clinical benefit. There are two main approaches to correct the underlying defect in CF. First, gene therapy attempts to replace the missing function by introducing part or all of the CFTR gene into the target epithelial cells in the lungs. Second, pharmacological compounds attempt to correct or potentiate abnormal CFTR.

Follow-up of patients with cystic fibrosis

It is desirable that patients are followed up regularly every 4-8 weeks at a center having expertise in management of various aspects of CF. The assessment of illness and monitoring for progress of illness can be done by clinical examination and various laboratory tests. Various clinical scoring systems have been developed to provide an objective assessment of patient’s status and response to treatment. The Shwachman-Kulczycki score is the most widely used one. In this scoring system, 25 points are given for each of the following categories; activity level, nutritional status, physical examination and chest radiograph changes. Points are deducted for deterioration in status; 100 is optimal and the lower the number; worse is the clinical condition. Laboratory assessment includes periodic pulmonary function test, X ray chest, chest CT scan, ultrasound abdomen, echo cardiography, blood chemistry such as glucose, calcium, vitamin levels, transaminases levels etc. It is desirable that a cough swab or throat swab after physiotherapy is taken on each visit for bacterial culture.
Prognosis

At present there is no cure for cystic fibrosis but the survival is improving over the past decades. The data of the US cystic fibrosis foundations suggest that life expectancy has increased from 31 years to 37 years over the last one decade. Similarly reports from UK conclude that with continuing improvement in survival of cystic fibrosis patients in successive cohorts prediction of median survival of >50 yrs of age for individuals born in 2000 continues to look realistic. Majority of deaths (nearly 80%) of deaths result from loss of lung function linked to inflammation caused by chronic bacterial lung infection (principally Pseudomonas aeruginosa). Survival analysis of Indian children with CF suggest that early mortality was associated with early onset (below 2 months) of symptoms, severe malnutrition at the time of diagnosis, more than four episodes of pulmonary exacerbations in a year and colonization with pseudomonas. Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in 20% of adolescents and 40-50% of adults.

Points to Remember

- **Suspect cystic fibrosis in every child who presents with recurrent respiratory tract infections, malabsorption and failure to thrive.**

- **Management of CF includes not only treating respiratory infection and improving mucus clearance from the airways but also giving proper nutritional care, supplementation of fat soluble vitamins and pancreatic enzymes.**

- **Survival of children with CF can be improved by early diagnosis, proper institution of supportive care and prompt treatment of respiratory infections.**

References


Despite recent studies failing to demonstrate the value of routine chest radiography (CXR) in the initial evaluation of the febrile neutropenic patient with cancer, this screening test is advocated by some experts. The authors evaluated the benefits of CXR for early diagnosis of pulmonary infection at St. Jude Children’s Research Hospital (SJCRH) with emphasis on early recognition of mould infections. The authors reviewed the courses of 200 consecutive febrile neutropenic pediatric patients to determine if routine CXR at initial evaluation was useful in the identification of clinically occult pneumonia. We also reviewed all cases of proven or probable mould infections from the opening of SJCRH in 1962 until 1998 when routine CXR was no longer practiced in our institution to identify cases that were first recognized by routine CXR. Of 200 febrile neutropenic patients, pulmonary abnormalities consistent with pneumonia were detected by routine CXR in only five patients without pulmonary signs or symptoms. Routine CXR was pivotal in the recognition of the mould infection in only two cases over this 36-year period. CXR is warranted in the evaluation of the newly febrile neutropenic pediatric oncology patient only when respiratory signs or symptoms are present.
APPROACH TO RECURRENT PNEUMONIA IN CHILDREN

* Dipangkar Hazarika

Abstract: Children with recurrent chest infections pose diagnostic challenge for clinicians. The causes may vary from simple recurrent viral respiratory infections to more serious underlying pathology, such as bronchiectasis. Many different disorders like asthma, cystic fibrosis, various immunodeficiency and congenital abnormalities of respiratory tract can present in similar way. The assessment of these children require close attention to history and examination, as causes are many. Early and accurate diagnosis is essential to ensure early optimal treatment and to minimize the risk of progressive or irreversible lung damage. This article focuses on the practical approach to the diagnosis of recurrent pneumonia in children.

Keywords: Recurrent pneumonia, Immune deficiency, Congenital airway anomalies, Asthma.

In developing countries pneumonia is still one of the leading causes of death. A small subset of these children develop recurrent and persistent pneumonia. Many studies have described persistent and recurrent pneumonia as a single entity. But both are different and can be defined as:

1. Recurrent pneumonia: Two episodes of pneumonia within the same year or 3 or more episodes over any period of time but with complete resolution of clinical and radiological findings between acute episodes.

2. Persistent or non-resolving pneumonia: When there is clinical and radiological evidence of pneumonia for more than a month despite a course of adequate and appropriate antibiotic therapy for 10 days.

The rate of resolution of radiological changes associated with uncomplicated pneumonia often depend on the causative agent (Table I). It may vary from 2 weeks with respiratory syncytial virus or parainfluenza virus to as long as 12 months with adenovirus. Pneumococcal pneumonia usually clears in 6 to 8 weeks. Infection with resistant, highly virulent organisms, atypical organisms and inadequate antibiotic therapy also contribute to persistent pneumonia.

The natural course of an infectious pneumonia is often unknown because the etiologic agent is not usually identified. If densities clear in hours or in one or two days, they are likely to have been sub-segmental atelectasis and not infectious pneumonia.

Etiology

It is useful to classify the recurrent pneumonia with respect to underlying disorders (Table II) which can be broadly classified into the following categories:
1. Congenital malformations - airways, lungs, cardio vascular system.

2. Recurrent aspirations.

3. Defects in the clearance of airway secretion specially cystic fibrosis, ciliary abnormalities.

4. Disorders of systemic/local immunity.

Though the causes of recurent and persistent pneumonias do overlap considerably single lobe involvement suggests local compression, malformation or inflammation, whereas more diffuse disease implies metabolic, immunological or neurologic abnormalities (Table III and IV).

**Recurrent pneumonia in a single lobe**

(i) **Intraluminal airway obstruction**: Aspiration of foreign bodies represent the most common cause. A history of choking or aspirating an object is only obtained in about 40% of patients. Other causes of intraluminal obstruction like bronchial adenomas and endobronchial lipomas are far less common in children. Both have the appearance of pedunculated tumors within the airways that may cause intermittent obstruction by a ball-and-valve effect.
## Table II: Etiologic factors for recurrent pneumonia

| **Congenital Malformations** | Cleft Palate  
Pierre Robin syndrome  
Tracheoesophageal fistulae  
Tracheomalacia |
|-----------------------------|--------------------------------------------------|
| a. Airways                  | Pulmonary hypoplasia  
Pulmonary sequestration  
Congenital adenomatoid malformation of the lung.  
Bronchogenic cyst |
| b. Lungs                    | Congenital heart disease, especially L-R shunts  
Vascular ring |
| c. Cardiovascular           | Aspirations:  
Gastro-esophageal reflux  
Foreign body  
Anomalies of the upper airways  
Swallowing abnormalities |
|                            | Defects in the clearance of airways secretions:  
Cystic fibrosis  
Abnormalities of the ciliary structure function  
Abnormal clearance secondary to infections, repair of congenital defects  
Airway compression (intrinsic/extrinsic)  
e.g., mediastinal tubercular lymphadenopathy |
|                            | Disorders of local/systemic immunity:  
Primary immunodeficiency  
Acquired immunodeficiency  
- HIV infection  
- Immunosuppressive therapy  
- Malnutrition |

(ii) **Extraluminal airway compression:**
Enlarged lymph nodes are the most common cause. Infection occurs as a result of collection of secretions in the area distal to the obstruction, which act as a nidus for infection. Common cause is tuberculosis, which may involve paratracheal, subcarinal and perihilar regions. Extraluminal airway compression can also occur in lymphomas.\(^{11,14}\)

(iii) **Structural abnormalities:** (a) Congenital: Tracheal bronchus or bronchus suis, is usually
asymptomatic but their unusual anatomy may impair drainage of the right upper lobe of the lung. Bronchomalacia is seen most frequently in premature infants and children with trisomy. Affected airways collapse easily because of inadequate cartilaginous support. They may occur in localized or generalized distributions.

(b) Acquired: Bronchiectasis may be focal or generalized. Measles, adenovirus, Bordetella pertussis and M. tuberculosis are frequently implicated.

In right middle lobe syndrome right middle bronchus has a small diameter, pliable wall and takes off at an acute angle. These factors, along with peribronchial lymph nodes in the area, may make the right middle lobe bronchus particularly susceptible to compression or collapse. It occurs with increased frequency in children with asthma and allergies, suggesting that intrinsic inflammation of the bronchus may contribute to the disease process.

Reccurrent pneumonia in multiple lobes

(i) Chronic aspiration: Chronic aspiration is the most common cause of recurrent pneumonia in childhood. It can be acute or occur on a chronic recurrent basis. There is a clear association between gastroesophageal reflux disease (GERD), aspiration and recurent respiratory diseases.

(ii) Asthma: Many children diagnosed with recurent bronchopneumonia may actually have asthma, which are either undiagnosed or poorly controlled. Diagnosis of asthma is easy in those with classic history of episodic wheezing, atopy and nocturnal or exercise induced cough, but it is difficult if there is less classic clinical presentation.

(iii) Congenital heart disease: Predisposes to recurrent pneumonia. Long standing edema with chronic pulmonary venous congestion may narrow the caliber of small airways sufficiently to reduce drainage of secretions, predisposing patients to secondary infection as well.

(iv) Pneumonia is a prominent feature of few immunodeficiency disorders. Patient with gobal deficiencies of immunoglobulin A (IgA) or IgG have increased susceptibility to bacterial pneumonia. Patients with inadequate levels of C3, C5 or properdin can experience recurrent pyogenic pneumonias that may ultimately lead to the development of of bronchiectasis.

| Intraluminal obstruction | Foreign body  
|                         | Bronchial tumor  
|                         | Adenoma, lipoma, papilloma  |
| Extraluminal obstruction | Infectious lymphadenopathy  
|                         | Tuberculosis, histoplasmosis.  
|                         | Non-infectious lymphadenopathy  
|                         | Tumors, sarcoidosis.  
|                         | Vascular rings and slings  |
| Structural abnormalities | Tracheal bronchus, bronchial stenosis or atresia, bronchomalacia, localized bronchiectasis, right middle lobe syndrome, pulmonary sequestration or congennal cystic adenoid malformation, bronchogenic cyst  |
Table IV. Abnormalities causing recurrent pneumonia in multiple lobes

<table>
<thead>
<tr>
<th>1. Recurrent microaspiration</th>
<th>a. Impaired swallowing</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>- CNS</td>
</tr>
<tr>
<td></td>
<td>Global CNS dysfunction</td>
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<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Cranial nerve injury</td>
</tr>
<tr>
<td></td>
<td>Cricopharyngeal incoordination.</td>
</tr>
<tr>
<td></td>
<td>- Neuromuscular disorder</td>
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<tr>
<td></td>
<td>Dystrophy</td>
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<tr>
<td></td>
<td>Myotonic dystrophy</td>
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<tr>
<td></td>
<td>Idiopathic cricopharyngeal achalasia</td>
</tr>
<tr>
<td></td>
<td>- Anatomic abnormalitiesx</td>
</tr>
<tr>
<td></td>
<td>Obstructive lesions of tongue/larynx</td>
</tr>
<tr>
<td></td>
<td>Submucosal cleft</td>
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<tr>
<td></td>
<td>Laryngeal cleft</td>
</tr>
<tr>
<td>b. Esophageal obstruction</td>
<td>Foreign body</td>
</tr>
<tr>
<td>c. Esophageal dysmotility</td>
<td>Achalasia</td>
</tr>
<tr>
<td></td>
<td>Traheoesophageal fistula before or after repair</td>
</tr>
<tr>
<td>d. Gastroesophageal reflux(GER).</td>
<td></td>
</tr>
<tr>
<td>2. Asthma</td>
<td></td>
</tr>
<tr>
<td>3. Immunodeficiency syndromes</td>
<td>Antibody deficiency or dysfunction</td>
</tr>
<tr>
<td></td>
<td>T-cell deficiencies</td>
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<tr>
<td></td>
<td>Phagocytic defects</td>
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<td>Complement deficiency</td>
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<tr>
<td></td>
<td>Combined</td>
</tr>
<tr>
<td></td>
<td>Immunodeficiency syndromes</td>
</tr>
<tr>
<td>4. Mucociliary dysfunction</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Ciliary dyskinesia</td>
</tr>
<tr>
<td>5. Structural abnormalities</td>
<td>Tracheobronchomegaly</td>
</tr>
<tr>
<td></td>
<td>Cartilage deficiency (Williams-Campbell syndrome)</td>
</tr>
<tr>
<td></td>
<td>Segmental bronchomalacia</td>
</tr>
</tbody>
</table>
6. Congenital heart disease

7. Bronchopulmonary dysplasia

| 8. Miscellaneous | Hypersensitivity pneumonitis |
|                 | Goodpasture’s syndrome      |
|                 | Alveolar proteinosis        |
|                 | Idiopathic pulmonary Hemosiderosis |
|                 | Wegener’s granulomatosis    |
|                 | Histiocytosis.              |

(v) Mucociliary dysfunction: Patients with mucociliary dysfunction usually presents with recurrent pneumonias, sinusitis, otitis media and male infertility. The primary ciliary dyskinesias (PCD) are a heterogenous group of conditions reflecting a range of ultrastructural and/or functional ciliary abnormalities. Affected children may have situs inversus or dextrocardia (Kartagener’s syndrome). Cystic fibrosis is an autosomal recessive genetic disorder affecting all exocrine organ systems that classically present in childhood with recurrent pneumonia, chronic sinusitis, steatorrhea, and failure to thrive.¹¹

There are limited data regarding the causes of recurrent or persistent pneumonia in children and available data are mostly from West.¹⁰ Lodha, et al reported underlying illness in 16 out of 19 (84%) children with persistent pneumonia. Most frequent causes were post-tubercular bronchiectasis and asthma.⁶ A recent study by Kumar, et al reported 41 children with persistent pneumonia where Gram negative infection is the most common cause followed by aspiration secondary to either GERD or oil instillation. Tuberculosis was the next most common cause.²¹

Recurrence pneumonia - Approach

It is important to take detailed history and physical examination before a child is subjected to the detailed workup and appropriate diagnostic studies in stepwise manner.¹⁰

History

1. Age of onset: Onset of symptoms soon after birth or in early infancy indicates hereditary/congenital disorder. Cystic adenomatoid malformation, congenital airway anomalies and congenital lobar emphysema present early in life. Disorders of humoral immunity usually present in later infancy.¹⁹ History of possible foreign body aspiration followed by recurrent episodes of pneumonia tends to occur in the 1-3 year age group.¹¹

2. Details of the episodes: Details of first episode and subsequent episodes should be obtained. Onset, nature and duration of cough, occurrence of fever, and documentation of signs by a physician and radiographic evaluation should be done. Type and duration of antimicrobial therapy (adequate/appropriate), response to therapy and need for hospitalization also should be recorded. It is important to differentiate these episodes from recurrent wheezing episodes.¹⁰

Ask about the timing of the symptoms in relation to feeding and the change in position, vomiting, irritability, and nocturnal symptoms of coughing and wheezing. Sleep disturbances may be seen in gastro-esophageal reflux and obstructive lesions, especially of upper respiratory tract.²²

3. Past history/associates complaints: Occurrence of repeated infections at other sites
suggests systemic immunodeficiency. Past history of tuberculosis and history of foreign body inhalation is important. Symptoms of malabsorption, recurrent otitis media and sinusitis and failure to thrive suggest cystic fibrosis. Presence or absence of symptoms when the child is well e.g. intercurrent wheeze may suggest poorly controlled asthma.

Patient with congenital heart disease with failure exhibit easy fatiguability, sweating over the forehead on feeding. Swallowing dysfunction can present as recurrent regurgitation of feeds and child may develop cyanosis during these episodes.\textsuperscript{23}

4. Perinatal history: Prematurity, history of prolonged exposure to oxygen and blood transfusions should be looked for. History of meconium ileus or delayed passage of meconium should arouse suspicion of cystic fibrosis. History of maternal infections such as HIV, Chlamydia or other viral illnesses should be sought.\textsuperscript{10,23}

5. Family history: Enquire about any family history of allergic disorders, asthma, cystic fibrosis, and congenital anomalies. Occurrence of early or unexplained deaths or recurrent infections in other family members may suggest immunologic disorder or other diseases with a strong genetic component. However, a negative family history does not rule out the possibility of autosomal recessive inheritance of a genetically mediated disorder. High risk behavior or history of blood transfusion in parents is essential, to rule out exposure to maternal HIV infection, in a child where immunodeficiency is suspected.\textsuperscript{10,20,23}

6. Environmental history: Crowded and polluted living environment predispose to recurrent respiratory infections. Daycare attendance, exposure to inhaled pollutants, irritants and passive tobacco smoking may provide important clues to the etiology, as well as the presence of siblings with similar problems.\textsuperscript{10,23}

7. Drug history: Many medications also may cause pulmonary problems (ACE inhibitors cough, aspirin-induced wheeze, leukotriene antagonist-associated infiltrates) and hence, a comprehensive drug history should be also be taken.\textsuperscript{11}

8. Vaccination history: Is critical because pertussis may present with prolonged cough and radiographic abnormalities.\textsuperscript{11}

9. History of sleep disturbances: Obstructive upper respiratory tract lesions present with sleep disturbances or even sleep apneas. Gastro-esophageal reflux also can have similar presentation. Some times children with pulmonary aspiration syndromes are reported to assume peculiar postures during sleep.

10. Immunodeficiency: History pointing to a systemic immunodeficiency is suspected if in addition to recurrent pneumonia, there is evidence of infection at other sites e.g., skin, gut, etc.\textsuperscript{12}

Construction of a family tree as well as a genetic counselling may be helpful in identifying a specific immunological deficiency (Table V).\textsuperscript{24,25}

Physical examination

The aim of the physical examination is not only to document presence of respiratory disease, but also localize the site of infection, and to detect any underlying etiologic factor. General physical examination should include

1. Head, neck and throat: Look for signs of chronic otitis media or sinusitis. Chronic otitis media may be associated with ciliary dysmotility syndromes or in boys with Wiscott-Aldrich syndrome. Conjunctivitis, allergic shiners, Dennie morgan’s lines and transverse creases over nose may accompany dermatitis in atopic patients, who have an increased frequency of asthma and associated pneumonia. Presence of purulent conjunctivitis may suggest a B cell immune deficiency. Phlyctenular conjunctivitis may be seen in several conditions having hyperactive
immune response including tuberculosis. Look for presence/absence of tonsillar/adenoidal tissue. Tonsils may be absent in hypo/agammaglobulinemia.

2. Periodontal disease: Can indicate phagocytic cell dysfunction, while oral candidiasis may suggest T-cell abnormalities. Abnormal dentition has been reported as a finding in hyper IgE syndrome.

3. Review of growth and development is essential and the child’s current weight and height should be plotted. Normal growth is a reassuring sign, though children may grow normally during the early stages of serious systemic diseases.

4. Clubbing may be present in chronic disorders like bronchiectasis, cystic fibrosis, and bronchiolitis obliterans.

5. Lymphadenopathy: Generalized lymphadenopathy may be present in tuberculosis, HIV infection and histiocytosis.

6. Certain morphologic features: May point towards specific disorders e.g., presence of “fish mouth” with hypertelorism in DiGeorge’s syndrome, telangiectasia of eyes/ears in ataxia telangiectasia.

7. Skin: Examined for evidence of infective foci rash or for features of atopic dermatitis. Fine and sparse hair is seen in severe combined immune deficiency.

8. Observation during feeding: Nasopharyngeal regurgitation, difficulty in sucking/swallowing and associated coughing/choking should be looked for. The palate, tongue and oro-pharynx should be inspected for any anomalies.

9. Respiratory system: A meticulous examination of respiratroy sytem including assessment of respiratory rate, evidence of distress, thoracic deformities, wheezing, stridor, the dimensions of the chest and careful auscultation of the chest to localize the infection should be done.

Table V Warning signs of primary immunodeficiency. If two or more of the following warning signs are present, there is possibility of an underlying primary immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infection within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonia within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infection.
9. Two or more deep seated infection including septicemia.
10. A family history of primary immunodeficiency.

Table V Warning signs of primary immunodeficiency.
Laboratory evaluation

It should be done judiciously and in a stepwise manner guided by history and physical examination (Fig.1).

1. **A complete blood count:** Anemia may suggest chronic disease. Thrombocytopenia can be seen in Wiskott-Aldrich syndrome.11

2. **X-ray chest:** It helps to make the distinction between recurrent and persistent pneumonia and whether consolidation is localized to a single lobe or multiple lobes. A child who has recurrent focal abnormalities may need early consideration of bronchoscopy, chest CT, MRI, or angiography as needed to rule out foreign bodies or anatomic abnormalities. If radiographs show abnormalities in diffuse or variable regions of the lungs, initial studies should be directed by the clinical history. Children with neurological dysfunction, swallowing difficulty, or vomiting should have a barium swallow to assess the adequacy of swallowing mechanism and to check for GERD.10,11
3. Mantoux test: Should be done on any child with focal changes in chest x-ray and consideration should be given to tests for fungal infection in endemic areas.

4. Computed tomography: Useful in diagnosing structural anomalies and also helps in defining the extent of involvement of the lung, especially in diseases like bronchiectasis, cystic fibrosis and interstitial lung disease. CT is the preferred method for investigating perilaryngeal or mediastinal compressive masses affecting the airway and has largely replaced conventional angiography for investigation of suspected vascular rings. High resolution CT(HRCT) needs to be done when interstitial lung disease is suspected.

5. Pulmonary function tests (PFT), commonly performed using spirometer, usually feasible only in children >5 years age. It helps to evaluate the airway hyper-reactivity. If PFT is normal and still there is strong clinical suspicion of bronchial hyper reactivity; challenge test using methacholine may be performed.

6. Bronchoscopy is indicated if abnormality of bronchial anatomy or foreign body aspiration is suspected. In addition, bronchoalveolar lavage (BAL) can be performed to identify the etiologic agent. Isolation of mucoid Pseudomonas aeruginosa is a strong pointer to the diagnosis of cystic fibrosis. Demonstration of Pneumocystis jiroveci suggests underlying immunodeficiency.

7. Barium study: Barium swallow and cine esophagogram may help in identifying the disorders of swallowing. Radionuclide scans, esophageal pH monitoring may be done to confirm GER. While demonstration of GER is easy, documentation of relationship of GER to recurrent pneumonia is difficult. Presence of lipid laden macrophages in bronchial washings has been found to be of value in confirming recurrent or chronic aspiration. Quantification of lipid laden macrophages in bronchial washing is a better marker of aspiration.

8. Sweat chloride estimation should be performed in all children with recurrent pneumonia even in patients without evidence of malabsorption or growth failure, because 20% of children with CF may have adequate pancreatic function. Earlier cystic fibrosis was thought to be extremley rare in India but in recent times, its presence is being increasingly recognized.

9. Electron microscopy: Morphologic studies are performed on nasal mucosal scraping/biopsy when ciliary abnormalities are suspected in patients with bronchiectasis or chronic sinobronchial disease after the common causes for the same has been ruled out.

10. Immunological studies: Basic Immunological investigations as given below needs to be done if immunodeficiency is suspected.

   i) Complete and differential blood counts
   ii) Quantitative serum immunoglobulin G/M/A including IgE.
   iii) Mantoux test and where available trychophyton and Candida skin tests should be used to document presence of delayed type hypersensitivity.
   iv) HIV screen by ELISA.
   v) T and B cell subset quantification. If phagocytic defects are suspected, screening tests include neutrophil count and nitro blue tetrazolium test.

To conclude, a thorough and careful investigation will direct the physician to a useful therapeutic approach. Therapy for specific illness associated with recurrent pulmonary infections including asthma, chronic aspiration, GERD and immunodeficiencies should follow the standard guidelines. Nutritional support, chest physiotherapy and avoiding exposure to smoke
or allergens are all important. Those with congenital anatomic abnormalities or acquired focal disease involving a single lobe or segment may benefit from surgical resection of that part.

**Points to Remember**

- **Resolution of radiological changes in pneumonia depend on causative agents.**
- **Chronic micro-aspiration and poorly controlled asthma have to be ruled out in a child with recurrent pneumonia involving multiple lobes.**
- **History and physical examination are important part of evaluation in such children.**
- **Immunodeficiency is suspected if in addition to recurrent pneumonia, there is evidence of infection at other sites.**

**References**


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**CLIPPINGS**


The early management of patients who have sustained traumatic brain injury is aimed at preventing secondary brain injury through avoidance of cerebral hypoxia and hypoperfusion. Especially in hypotensive patients, it has been postulated that hypertonic crystalloids and colloids might support mean arterial pressure more effectively by expanding intravascular volume without causing problematic cerebral edema. The authors conducted a systematic review to investigate if hypertonic saline or colloids result in better outcomes than isotonic crystalloid solutions, as well as to determine the safety of minimal volume resuscitation, or delayed versus immediate fluid resuscitation during prehospital care for patients with traumatic brain injury. They identified nine randomized controlled trials and one cohort study, examined the effects of hypertonic solutions (with or without colloid added) for prehospital fluid resuscitation. None has reported better survival and functional outcomes over the use of isotonic crystalloids. The only trial of restrictive resuscitation strategies was underpowered to demonstrate its safety compared with aggressive early fluid resuscitation in head injured patients and maintenance of cerebral perfusion remains the top priority.
Abstract: Parapneumonic effusion (PPE) occurs as a complication mainly in bacterial pneumonia. It can be simple or complicated. Early identification of complicated, parapneumonic effusion and appropriate treatment helps to reduce the associated morbidity and mortality. Pleural fluid pH, glucose, LDH levels, Gram stain and culture are the investigations to be done along with ultrasound of chest. Management includes institution of appropriate antibiotics with tube thoracostomy, intrapleural fibrinolytics or video assisted thoracoscopy (VATS).

Keywords: Parapneumonic effusion, Pleural fluid analysis, Antibiotics, Tube thoracostomy, VATS

Pneumonia is the leading cause of death in children worldwide. Effusion into the pleural space can occur as a common complication in pneumonia. Parapneumonic effusions (PPE) constitute a major proportion of childhood pleural effusions. Simple parapneumonic effusion is defined as pleural effusion associated with lung infection due to spread of inflammation and infection to the pleura. But if the treatment is not appropriate and adequate or if the infection is caused by a virulent organism, progression of the infective process from the lung parenchyma to the pleural cavity occurs which leads to complicated parapneumonic effusion. Empyema (accumulation of pus in a body cavity) represents the end stage of a complicated para pneumonic effusion. The development of complicated parapneumonic effusion is determined by a balance between host resistance, bacterial virulence and timing of presentation for medical treatment. Malnutrition, measles or infection with antibiotic-resistant organisms do increase the risk of severe pneumonia with complicated parapneumonic effusion. Studies in children with empyema thoracis and parapneumonic effusion in developed countries have shown the mean age to be between 3-6 years with 50% to 80% of cases occurring in males. In India, one-third of hospitalized children with complicated PPE were less than 5 years of age.

The etiologic agents have changed over a period of time. The common infective agents include Streptococcus pneumoniae, Staphylococcus aureus, community-acquired methicillin-resistant Staphylococcus aureus (MRSA) that produces toxins (Panton-Valentine leukocidin) and Hemophilus influenzae type b. Other organisms implicated in PPE and empyema include coagulase-negative staphylococcus, streptococcus viridans, group A streptococcus, alpha-hemolytic streptococcus, Actinomyces species and fungi, anaerobes including bacteroides and fusobacterium species (empyema associated with aspiration pneumonia in neurologically impaired children children) and Pneumocystis jiroveci in immunocompromised host. Parapneumonic effusions have also been reported in up to 10% of viral and 20% of mycoplasma
Pneumonia. Pleural effusion can occur due to infection by Mycobacterium tuberculosis also. Effusion due to viral infections are usually asymptomatic and resolve without therapy.6

Pathophysiology

The pleural space between the parietal and visceral pleura is a potential anatomic space having a small amount of fluid which is filtered by the parietal pleura and absorbed by the visceral pleura. When there is an imbalance between the hydrostatic and oncotic pressure, fluid accumulates in the pleural cavity. Normally small amounts of protein which ooze into the pleural space are readily removed by the lymphatic system. But when large amounts of protein leaks into the pleural space due to increased capillary permeability as in pneumonia, the lymphatic system will be unable to handle the excess load leading on to the development of exudative pleural effusion.

The inflammatory process in pleural infection follows a characteristic cascade of events. Three stages in the natural course of empyema has been described. This includes-a) exudative, b) fibrinopurulent and c) organizing phases.7

Simple (uncomplicated) parapneumonic effusion is the clinical correlate of exudative phase. In this exudative phase, pleural fluid is derived from pulmonary interstitial fluid that is associated with lung infection and inflammation. This fluid crosses the visceral pleura and accumulates in the pleural space. It is usually not infected. This stage can last from 24 to 72 hours. The characteristic biochemical and microbiologic features of this uncomplicated PPE are pH > 7.2, lactate dehydrogenase < 1000 IU/L, glucose > 2.2 mmol/L and no organisms in Gram stain or culture.8

Complicated parapneumonic effusion is the clinical correlate of the fibrinopurulent phase. In this phase there is a disturbance of the physiologic equilibrium between clotting and fibrinolysis within the pleural space.9 The organism invades the pleural cavity through the damaged endothelium leading to more migration of neutrophils and activation of the coagulation cascade. This leads to increased procoagulant and depressed fibrinolytic activity. The net effect is the coating of the pleural surfaces with fibrin and fibrin strands with development of adhesions and loculations resulting in poor drainage of pleural fluid. The continuing inflammatory process is aggravated by more bacterial death and phagocytosis. The combination of all these events leads to increased lactic acid production, causing a drop in pleural fluid pH, increased glucose consumption and a rise in lactate dehydrogenase (LDH) levels resulting from leukocyte death. All these are reflected in the pleural fluid of complicated parapneumonic effusion where pH < 7.20, glucose < 2.2 mmol/L, lactate dehydrogenase > 1000 IU/L, and possible positive Gram stain and/or bacterial culture. This stage usually lasts 7 to 10 days. If left untreated, empyema develops which is the end stage of complicated PPEs.

The fibrinopurulent phase is followed by the organizing phase, in which there is proliferation of fibroblasts. A solid pleural peel replaces the soft fibrin, preventing lung reexpansion and causing lung function impairment.

Clinical features

Persistent fever, malaise, decreased appetite, cough, chest pain and dyspnea are the most common symptoms. Also if a child continues to be febrile or ill 48 hours after initiation of antibiotic therapy for pneumonia one should suspect development of complication like PPE. Children with complicated PPE usually lie on the affected side so as to splint the involved hemithorax and provide temporary analgesia. Usually children
with complicated PPE appears ill but sometimes are toxic. These children have tachypnea with shallow breaths to minimize pain. Chest examination may reveal mediastinal shift to the opposite side of involvement and also a small degree of “new” scoliosis, related to the child’s splinting the affected side. Usually respiratory system examination shows dullness on percussion of chest with diminished breath sounds on the affected side. Early recognition of a developing para pneumonic effusion is challenging. Children with pneumonia presenting with prolonged fever, tachypnea, pain on palpating abdomen and high CRP are pointers to development of PPE.

**Investigations**

The basic investigations include complete blood count, CRP, blood culture, blood glucose, liver enzymes, biochemistry, Mantoux test, resting gastric juice/induced sputum for AFB. The specific investigations can be grouped into biochemical, microbiological and radiological investigations.

**Biochemical**

Biochemical analysis of the pleural fluid helps to diagnose, classify and manage parapneumonic effusions properly. Pleural fluid protein was earlier used to classify effusion into transudate and exudate and manage accordingly. But now pleural fluid pH, glucose and LDH levels are used to differentiate simple and complicated PPE. The most sensitive pleural fluid measurement that indicates a complicated PPE is the pleural fluid pH, which drops to below 7.20 even before the glucose drops below 60 mg/dL or the LDH becomes more than three times the upper limit of that in serum (Table 1). It is important to emphasize that the pleural fluid pH needs to be measured with a blood gas machine.

**Microbiology**

The pleural fluid has to be sent for gram stain and culture. A large proportion of children with complicated PPE and empyema do not grow any organism in their pleural fluid which suggests that culture alone may not be a very good test to find the etiology in these children. One common reason may be due to the widespread use of antibiotics which also includes inappropriately chosen or dosed antibiotics. To improve the diagnostic yield pneumococcal antigen detection test (Latex agglutination test), broad range or specific polymerase chain reaction test in pleural fluid to detect pathogens, direct and enrichment culture for aerobic and anaerobic organisms can be done in the pleural fluid.

<table>
<thead>
<tr>
<th>Simple PPE</th>
<th>Complicated PPE</th>
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<tbody>
<tr>
<td>Pleural pH &gt; 7.2</td>
<td>Pleural pH &lt; 7.2</td>
</tr>
<tr>
<td>Pleural LDH &lt; 1000 IU/L</td>
<td>Pleural LDH &gt; 1000 IU/L</td>
</tr>
<tr>
<td>Pleural fluid glucose &gt; 2.2 mmol/L</td>
<td>Pleural fluid glucose &lt; 2.2 mmol/L</td>
</tr>
<tr>
<td>Gram stain - negative</td>
<td>Gram stain +/-</td>
</tr>
<tr>
<td>Culture - no growth</td>
<td>Culture +/-</td>
</tr>
</tbody>
</table>
Imaging

Chest radiography is the easily available investigation which is always done in those suspected to have parapneumonic effusion (Fig.1). An opaque hemithorax with a shift of the mediastinum indicates a large effusion. A parapneumonic effusion is seen in an anteroposterior view as a consolidation / pneumatic change along with fluid collection with a convex border medially. Obliteration of the costophrenic angle, the “meniscus sign” (a rim of fluid ascending the lateral chest wall) are common findings. Often there is an ipsilateral concave scoliosis as the child avoids movement of the affected hemi-thorax with illness of more than one week’s duration. Radiographs alone cannot differentiate empyema from parapneumonic effusion. It is advisable to do ultrasound chest if an effusion is seen in the chest radiograph.

Ultrasound will not only confirm the pleural fluid but is also useful in the detection of early loculations and septations, the determination of the nature of the effusion, quantification of the effusion and the localization of optimal sites for thoracentesis or chest tube insertion.12

CT chest should be done only in difficult cases wherein both chest radiography and ultrasound cannot differentiate a loculated empyema from a lung abscess or necrotising pneumonia. Contrast-enhanced CT scan of the chest can demonstrate the location of the effusion and often typical enhancement of the thickened parietal pleura. But CT can neither show septations nor can predict the viscosity of the effusion.13 It is always preferable to have a chest CT scan before thoracoscopy to provide anatomic information about the size and extent of the empyema cavity.

Treatment

The natural history of a complicated parapneumonic effusion is to develop a single loculus or multiple loculations and then progress to an empyema cavity in untreated or inadequately treated patients. Hence, the aims of specific treatment are drainage of the pleural fluid and treatment of the primary condition- pneumonia which has caused this complication. Despite improvements in diagnostic tests, management of complicated PPE still has its share of debate as to which modality of treatment medical or surgical is best while treating a child with complicated PPE. There are several options available for the management of the pleural fluid in patients with parapneumonic effusion: these include therapeutic thoracentesis, tube thoracostomy, tube thoracostomy with intrapleural fibrinolytics, thoracoscopy, and thoracotomy. It is advisable to have the definitive treatment performed within the first 10 days of hospitalization.14

Supportive care in children with parapneumonic effusion include antipyretics, analgesics to reduce the pleuritic pain, increased caloric intake to take care of the increased metabolic demands and IV fluids to maintain the hydration but taking care not to overload because of the possibility of syndrome of inappropriate ADH secretion (SIADH).

Intravenous antibiotics needs to be given to all children with parapneumonic effusion.
Empirical treatment covering the common organisms causing pneumonia in that community should be started and antibiotics modified after the culture reports. A third generation cephalosporin - ceftriaxone along with cloxacillin is an ideal choice for empiric treatment, but when there is suspicion of resistant organisms vancomycin or clindamycin can be used in place of cloxacillin.

Intercostal chest tube drainage (tube thoracostomy) with underwater seal system should be done for those with complicated PPE. It should be in place till all the fluid drains out or till the drainage is less than 10 ml-15ml/24 hours. Smaller size chest tube can be used to drain the complicated PPE as there is no advantage of using a large sized chest tube. The advantages of the smaller tube are that it is less painful to the patient and is easier to insert. Successful closed-tube drainage of complicated parapneumonic effusions is evidenced by improvement in the clinical and radiologic status within 24 hours (Fig.2a & b). If the patient does not show significant improvement within 24 hours of initiating tube thoracostomy, the possibilities are either the pleural drainage is unsatisfactory or the patient is not receiving appropriate antibiotic. Unsatisfactory pleural drainage can be due to the tube being in the wrong location, ICD tube block occlusion of the pleural fluid, or a fibrinous coating of the visceral pleura, which prevents the underlying lung from expanding.13

Fibrinolytic drugs- urokinase, streptokinase, and tissue plasminogen activator (tPA)- to lyse the fibrinous strands are used in complicated PPE. Streptokinase can provoke fluid accumulation even in a normal pleural cavity. Though intrapleural administration of streptokinase or urokinase significantly increases drainage volume, fibrinolytics have not been shown to reduce mortality. Intrapleural urokinase has been shown to be marginally better when compared with tPA. There is also emerging evidence that a combination of intrapleural tPA and and DNAse is significantly superior to tPA or DNA alone in improving pleural fluid drainage. But there is no difference in clinical outcome between intrapleural fibrinolysis and VATS in childhood empyema.15

Video-assisted thoracoscopy (VATS), minithoracotomy and decortication are the three surgical procedures that have been used in the management of complicated PPE. In children with a complicated parapneumonic effusion with fibrin formation, early tube thoracostomy may avoid a subsequent surgical intervention. In children with a fibrin septated parapneumonic effusion, an initial VATS is recommended to shorten the duration of fever and hospital stay.14 But intrapleural fibrinolysis is a more cost-effective treatment option compared with VATS.

The minithoracotomy is almost similar to VATS but the difference is that it is an open...
procedure which leaves a linear scar. Decortication is done if the child develops a thick pleural membrane, entraps the lung and prevents its expansion. This is usually reserved only for children who are referred late. Decortication involves the removal of all fibrous tissue from the visceral pleura and parietal pleura, and the evacuation of all pus and debris from the pleural space.

Long-term follow-up studies suggest that less than 10% children have residual symptoms. The rate of residual radiologic or pulmonary function abnormalities is, but these are usually mild and children are usually asymptomatic (Fig. 3).

Points to Remember

- **PPE should be looked for in every child with pneumonia who do not show a response at the expected time after starting treatment.**

- **Prompt treatment with appropriate systemic antibiotics and chest tube drainage are the first line of the management in complicated PPE.**

- **If the child does not improve within 24-48 hours of tube thoracostomy, suspect loculations and evaluate further with radiological investigations.**

  - **Intrapleural fibrinolytics administration is safe.**

  - **Consider early VATS in complicated PPE and empyema.**

References


CLIPPINGS


Despite recent studies failing to demonstrate the value of routine chest radiography (CXR) in the initial evaluation of the febrile neutropenic patient with cancer, this screening test is advocated by some experts. The authors evaluated the benefits of CXR for early diagnosis of pulmonary infection at St. Jude Children’s Research Hospital (SJCRH) with emphasis on early recognition of mould infections. The authors reviewed the courses of 200 consecutive febrile neutropenic pediatric patients to determine if routine CXR at initial evaluation was useful in the identification of clinically occult pneumonia. We also reviewed all cases of proven or probable mould infections from the opening of SJCRH in 1962 until 1998 when routine CXR was no longer practiced in our institution to identify cases that were first recognized by routine CXR. Of 200 febrile neutropenic patients, pulmonary abnormalities consistent with pneumonia were detected by routine CXR in only five patients without pulmonary signs or symptoms. Routine CXR was pivotal in the recognition of the mould infection in only two cases over this 36-year period. CXR is warranted in the evaluation of the newly febrile neutropenic pediatric oncology patient only when respiratory signs or symptoms are present.

NEWS AND NOTES

National conference of Pediatric Rheumatology (NCPR 2012)
Rheumatology Chapter of Indian Academy of Pediatrics
Date: 24\textsuperscript{th} & 25\textsuperscript{th} August, 2012,  Venue: Christian Medical College, Vellore

Contact
Dr. Sathish Kumar, Organizing Secretary
http://www.ncpr2012.org/
FLEXIBLE FIBEROPTIC BRONCHOSCOPY

*Vijayasekaran D

Abstract: Flexible pediatric bronchoscope is an important tool in the diagnostic armamentarium of respiratory diseases in children. As it is not available freely, the importance of this investigation is less well known. This article will give an overview of flexible fiberoptic bronchoscopy.

Keywords: Flexible bronchoscopy, children.

The value of flexible fiberoptic bronchoscopy (FOB) in children is increasing day by day. It is still underutilized even in many advanced institutions. It is a safe procedure even in infants, provided the procedure is performed by skilled personnel. Modern ultrathin scopes offer new diagnostic and therapeutic opportunities. Understanding the normal anatomy of the airway and the basic pathophysiology of lung diseases by the scopist is the important prerequisite for successful bronchoscopy. Flexible fiberoptic bronchoscopy can be better understood if the following issues are discussed.

• Equipment
• Advantages
• Prebronchoscopic preparation
• Procedure
• Indications

Role in intensive care
• Bronchoalveolar lavage
• Complications
• Cleaning and disinfection

Equipment

Flexible bronchoscopes are expensive and fragile instruments that require delicate handling. Three kinds of pediatric fiberoptic bronchoscopes are available to suit the age and body weight. The versatile one is with the external diameter of 3.5 mm, which can be used even in newborn. The one with external diameter of 2.8 mm along with working channel of 1.2 mm, meant for low birth weight and preterm babies. Larger size fiberoptic bronchoscope with external diameter of 4.9 mm has a larger working channel (2.2 mm). Since the safety of flexible bronchoscopy is of great concern, untrained persons should not be allowed to handle the bronchoscope.

Advantages

The advantages of the FOB are direct visualization of the airway lumen and the ability to obtain samples from the lower airway for bacteriologic investigations. Other advantages of FOB over rigid scopy are (a) it does not require general anaesthesia, (b) relatively an atraumatic procedure, (c) does not require mobilisation of a sick patient to the operating room (d) visualisation of bronchial orifices up to the fifth order and of upper lobes.

Prebronchoscopic preparation

The child may be admitted either as a day care or as an inpatient depending on the general condition of the patient or likelihood of
complications expected. A thorough history and complete physical examination should be done as it may give the necessary background information for the bronchoscopy. Fasting prior to the procedure is 4-6 hours for older children and 3 hours for infants.

**Procedure**

The preparation and practice of flexible bronchoscopy varies greatly for each bronchoscopist. Majority of flexible bronchoscopies are performed under topical anesthesia or conscious sedation. Assessment of the airway during spontaneous ventilation is essential to diagnose dynamic airway compression as well as alterations in vocal cord movement.

Bronchoscopy is done transnasally after applying 4 % lignocaine locally into the selected nostril. The scope is passed through the nostril for about one inch or till resistance is met, then tilted about 40 degrees downwards at the outer end of the nares and pushed in gently with a downward pressure to enter nasopharynx.

During the procedure lignocaine solution in the dose of 5 mg/kg has to be instilled by “spray and proceed technique” through the working channel. Supplemental humidified oxygen is administered by keeping the oxygen catheter closer to the other nostril and saturation is continuously monitored by pulse oximetry.

Navigation of vocal cord should be done through the posterior aspect to avoid injury, which is the difficult aspect of bronchoscopy. Once the tip of the bronchoscope crosses the carina, the complete examination of all lobes and segments is usually completed in 30 seconds to avoid complications of hypoxemia.

Anesthetist or a doctor trained in airway skills should be available throughout the procedure to monitor the oxygen saturation, heart rate and vital signs of the child. It may be better to complete the bronchoscopic examination by doing a series of short inspections, rather than one prolonged procedure to avoid hypoxemia.

**Indications**

Fiberoptic bronchoscopy is indicated when the benefits outweigh its risks and when it is the best way to obtain diagnostic information. FOB can be performed for diagnostic and therapeutic purposes or in order to obtain secretions and cells from the lungs.

Bronchoscopy at the proper time may avoid many indirect and costly investigations. In investigating pediatric patient with pulmonary infiltrates, the use of flexible bronchoscopy is indispensable.

Indications for fiberoptic bronchoscopy can be broadly classified into five categories and each category includes both congenital and acquired conditions. Category (A): evaluation of upper airway (UAW), Category (B): evaluation of lower airway (LAW), Category (C): evaluation of pulmonary infiltrates, Category (D): use in intensive care and Category (E): Bronchoalveolar lavage (Table I).

(A) Upper airway evaluation

Stridor or noisy breathing reflects partial obstruction of the upper airways which is the most common indication for FOB in infants.

Prolonged stridor may be associated with vocal cord paresis, sub glottic stenosis that requires bronchoscopic confirmation. Though mild laryngomalacia may not require FOB, it is indicated in severe laryngomalacia to document the synchronous lower airway anomalies.

A recent study reported that 48% infants with moderate to severe laryngomalacia are associated with synchronous lower airway anomalies, of
which tracheomalacia is found to be the commonest lower airway anomaly (Fig.1).²

(B) Lower airway evaluation

Persistent wheezing that does not respond to bronchodilator and anti-inflammatory therapy requires FOB, especially in infants. It is often caused by congenital malformations of the tracheobronchial tree such as primary tracheomalacia and bronchomalacia. Rare causes like tracheal stenosis, vascular compression, H-type tracheoesophageal fistula or congenital cysts may pose a difficulty in diagnosis, where FOB adds a significant contribution.

The airway malacia disorders are an important cause of respiratory morbidity in children. Malacias of the lower respiratory tract are being recognized more frequently than in the earlier days and fiberoptic bronchoscopy done under local anesthesia is the gold standard for the diagnosis of such dynamic airway lesions.⁵ The diagnosis of airway malacias presents a clinical challenge because of the frequent overlap of symptoms with more common childhood respiratory illnesses like asthma.⁴ Infants with congenital airway malacias presenting with wheeze may not improve with beta agonist nebulization because in such lesions, beta agonists by reducing the muscle tone can aggravate the pathology.⁷

### Table.I Fiberoptic bronchoscopy - Indications

<table>
<thead>
<tr>
<th>(A) UAW evaluation</th>
<th>(B) LAW evaluation</th>
<th>(C) Pulmonary infiltrates</th>
<th>(D) Intensive care</th>
<th>(E) BAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged stridor</td>
<td>Persistent wheeze</td>
<td>Persistent pneumonia</td>
<td>Difficulty in weaning from ventilator</td>
<td>cytology</td>
</tr>
<tr>
<td>Vocal cord paresis</td>
<td>Equivocal foreign body</td>
<td>Refractory atelectasis</td>
<td>Difficulty in Weaning from oxygen support</td>
<td>microbiology</td>
</tr>
<tr>
<td>laryngeal web</td>
<td>Tracheo-bronchomalacia</td>
<td>Bronchiectasis</td>
<td>Post thoracic surgery</td>
<td></td>
</tr>
<tr>
<td>Sub glottic stenosis</td>
<td>Endobronchial pathology</td>
<td>Difficulty intubation</td>
<td></td>
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</tr>
</tbody>
</table>

![Fig.1. Bronchoscopic view of laryngeal web, tracheomalacia and central foreign body](image-url)
Foreign body aspiration should be suspected in every child with acute onset of cough or wheezing with or without dyspnea (Fig. 1). Localized monophonic wheeze may be present in a child with foreign body aspiration. A foreign body in the airway can also mimic asthma. Foreign body aspiration can be excluded with FOB, but foreign body extraction in children should be performed with the rigid bronchoscope.8

(C) Persistent pulmonary infiltrates

FOB has an important role in the evaluation of pulmonary infiltrate which include refractory atelectasis, recurrent pneumonia, mass lesions or bronchiectasis.

Mucus plugs in the airways causing atelectasis and therapeutic role of FOB in the restoration of airway patency is a known fact. The therapeutic role of fiberoptic bronchoscopy in segmental atelectasis due to mucus plug occlusion in wheezing children has been substantiated as 28.5% infants with refractory atelectasis showed a resolution of the atelectasis after bronchoscopy.9

(D) Intensive care

Indications for bronchoscopy in pediatric intensive care include endobronchial toilet, assisting in a difficult intubation, assessment of lobar collapse or focal hyperinflation and assessment of stridor on extubation. Management of pneumonia in immunocompromised host or ventilator-associated pneumonia are the other important indications.10

Ventilator dependent children in intensive care particularly after thoracic surgery may pose problem during weaning. The small caliber of airway and weak cough in such children make them more easily to develop accumulation of mucus secretion and formation of mucus plug in small airway, resulting in partial airway obstruction and refractory wheezing.11

Evaluation of pulmonary infiltrates in infants with congenital heart disease can safely be done with FOB with due precautions which reinforces the utility of FOB in the investigatory workup of critically ill infants.12

(E) Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) is a technique used to study the local cellular, biochemical and immunological changes occurring in the lower respiratory tract. During BAL, the bronchoscope is wedged into the affected segment. Instilling of 2 to 5 mL/kg sterile saline (in three equal aliquots) and aspirating back into suction trap is done but the technique requires at least two persons. BAL is carried out in the most-affected area in the localized disease but in diffuse disease the right middle lobe is preferred because this area offers better fluid recovery.13

The etiology of pulmonary infections in immunodeficient children who do not respond to empirical antibiotic treatment may be diagnosed by bronchoalveolar lavage (BAL) but the recommended sterility has to be maintained.

BAL can not only wash some small fragment, powdery foreign bodies, or inflammatory section, but also help to investigate pathogens (e.g. bacterial culture, viral pathogen detection and DNA of Mycoplasma pneumoniae and chlamydia).14

BAL is helpful in diagnosing opportunistic infections like Pneumocystis jiroveci, Cytomegalovirus, Aspergillus fumigatus and M. tuberculosis. The demonstration of hemosiderin laden macrophages (alveolar haemorrhage), lipid laden macrophages (lipoid pneumonia) and Periodic acid-Schiff positive milky material (alveolar proteinosis) are useful in the respective conditions.

Complications

Complications in pediatric bronchoscopy are rare. Hypoxia is common particularly during BAL.
In children with severe hypoxia, uncontrolled bleeding diathesis, cardiac failure or severe pulmonary hypertension due precautions should be taken and the procedure should be performed by an experienced person. Nosocomial infection or overdosing with local anesthetics are usually over looked.

**Cleaning and disinfection**

Immediately after use, the suction channel should be rinsed with water or saline to remove blood, tissue and secretions. Two per cent alkaline glutaraldehyde (cidex) is the disinfectant of choice for flexible endoscopes and immersion for 20 minutes is considered sufficient to kill virtually all pathogens surviving on a well cleaned bronchoscope. Periodically, samples obtained from the suction channel of the bronchoscope should be sent to the microbiological lab to exclude contamination.

Respiratory diseases are a major cause of mortality and morbidity in children. Detailed history taking and methodical clinical examination help arrive to a closer diagnosis but to confirm, investigations are required of which fiberoptic bronchoscopy plays a significant role. Though the size is the limiting factor, advances in instrumentation will make therapeutic procedures possible endoscopically even in infants soon.

**Points to Remember**

- *FOB is an important diagnostic tool to evaluate pediatric respiratory diseases.*
- *It is safe and can be done at bedside also in ICU setting.*

**References**

NON-INVASIVE VENTILATION – A PRACTICAL APPROACH

*Shrishu R Kamath
*Anitha VP

Abstract: Non-invasive ventilation (NIV) refers to provision of ventilator support through the patient's upper airway using a mask or similar device. There is an increasing use of NIV in adults and there are pediatric studies which document the use of NIV. NIV is the best for patients who are not too sick. NIV is good option over conventional ventilation in selected patients in select conditions.

Keywords: Non-invasive ventilation, Nasopharyngeal CPAP, Mask.

Non-invasive ventilation (NIV) refers to the provision of ventilator support through the patient's upper airway using a mask or similar device. This technique is distinguished from those which bypass the upper airway with tracheal tube, laryngeal mask or tracheostomy and so are considered non invasive. (Fig.1) shows NIV with face mask.

CAP and NIV

CPAP refers to non-invasive application of positive airway pressure using face or nasal mask or similar such device. CPAP provides only just positive airway pressure on which the patient breathes. NIV can provide CPAP as well as bi-level pressure (Inspiratory positive airway pressure-IPAP and expiratory positive airway pressure-EPAP) thus generating the pressure support and tidal volume. There is still controversy as to whether providing CPAP in respiratory failure constitutes ventilator support, but for all practical purposes both are included in non-invasive ventilatory support. Nasopharyngeal CPAP is shown in (Fig.2).
NIV and negative pressure ventilation

NIV is positive pressure ventilation given in a non-invasive manner. Negative pressure ventilation includes application of sub-atmospheric external pressure to the trunk or thorax, thus imitating physiological negative inspiratory pressure swings (Fig.3). Theoretically this may be advantageous in children with right heart failure but clinically is quite cumbersome and have no monitoring devices. The role of negative pressure ventilation in clinical practice has been quite limited.

NIV in PICU

NIV can be provided in either pediatric intensive care unit (PICU) as well as in high dependency unit (HDU) set up. It is advisable not to provide NIV in a ward set up as it requires constant monitoring. Most of the recent conventional ventilators have a NIV mode available which can deliver NIV. There are standalone NIV ventilators which are small, easy to handle and user friendly. CPAP can also be provided using conventional ventilators, non-invasive standalone ventilators as well as by using bubble CPAP machines.

The major indications in the pediatric age groups are as follows:

a. Acute respiratory failure: This is the most common cause for the use of NIV. It is necessary that children with moderate respiratory failure like pneumonia, atelectasis, collapse of lung, acute exacerbations in chronic conditions like asthma, cystic fibrosis may be selected for receiving NIV. The children in such conditions should be carefully monitored as no improvement in the clinical features should immediately prompt intubation rather than increasing settings of NIV.

b. To facilitate early extubation: Children who are on ventilator, whose disease condition is improving but has not resolved completely and still need moderate support can be extubated on to NIV. This is particularly useful especially in children who undergo cardiac surgery especially in conditions like post-operative Glenn or Fontan surgery. The use of non-invasive forms of ventilation in these conditions has some intriguing possibilities by combining spontaneous respiration with some positive distending pressure, thereby combining “the best of both worlds”.

c. Obstructive airway disease: These include patients with laryngomalacia and tracheomalacia. The disorder should be a dynamic airway collapse and not fixed one. There is no role of NIV in fixed airway obstruction like subglottic stenosis and webs.

d. Neuromuscular disorders: NIV was first used in children with Duchenne muscular dystrophy. Since then it is extensively used in various neuromuscular disorder where there is no bulbar or upper airway reflex involvement. NIV helps in preventing ventilatory dependency by improving the functional residual capacity, trains the muscles and prevents disuse atrophy.

e. Cardiogenic pulmonary edema: CPAP has shown to be effective in patients with cardiogenic pulmonary edema. It improves work of breathing by recruiting fluid filled alveoli, thus improving compliance and oxygenation. BiPAP can be used if CPAP fails to show any improvement. If the child is still worsening he will need intubation and invasive ventilation.
f. Immunocompromised hosts: NIV has shown to have maximum benefit in these patients. NIV has been shown to reduce the incidence of invasive ventilation, ventilator associated pneumonia, ICU stay and mortality.

g. Hypoventilation and obstructive sleep apnea (OSA) syndrome: The hypoventilation disorders may present in variety of ways ranging from insidious onset in adolescent age group to respiratory failure in infancy. Nocturnal hypoventilation may be asymptomatic and have varied symptoms. Pulmonary function test may suggest respiratory compromise but the best way to assess nocturnal respiratory insufficiency is by polysomnography. Bedtime CPAP/BiPAP is one of the few measures which will help in reduction of the symptoms.

The other miscellaneous conditions in which NIV has been useful include acute severe asthma, bronchiolitis, end of life support for terminally ill patients and chest trauma (data only from adults). There are no current pediatric guidelines on NIV and so most of the indications have been extrapolated from adult guidelines.

NIV - contraindications

NIV should not be used in the following conditions:

a. NIV should not be instituted in children with multi-organ dysfunction ie it needs to be instituted in children with only respiratory involvement and without any other organ involvement. It should be instituted when there is moderate respiratory failure. Prompt intubation and invasive ventilation should be done if the respiratory failure becomes severe. This mandates that NIV be instituted only in critical care setting wherein monitoring facilities are available inters of equipment and manpower. An exception to the rule is cardiogenic pulmonary edema where in initial careful institution of NIV can be planned. Even here worsening clinical scenario mandates invasive ventilation.

b. NIV should not be used in patients with recent facial or upper airway surgery, in terms of facial abnormalities such as burns or trauma or if the patient is vomiting or has fixed upper airway obstruction.

c. Contraindications to NIV also include recent upper gastrointestinal surgery, inability to protect the airway, copious respiratory secretions and inability to protect from it, life-threatening hypoxemia, severe co-morbidity and confusion/agitation or bowel obstruction.

d. Relative contraindication to NIV also include when patient is not able to tolerate the mask or the tube through which NIV is delivered.

Delivery of NIV

This has been discussed above. Only two primary modes of ventilation are available in NIV which are CPAP and BiPAP. BiPAP has two levels of pressure which include IPAP and EPAP. The difference between the two generates the tidal volume and pressure support. When NIV is delivered from a conventional ICU ventilator the inspiratory and expiratory gas mixtures are separated. This prevents re-breathing and allows monitoring of inspiratory pressure and exhaled minute ventilation on which monitoring and alarm limits are based. When NIV is delivered from a free standing device, there is only one tubing. The exhalation is either active (when exhalation valve opens) or is passive (when exhaled air is forced to exit through a port by the continuous bias flow due to EPAP from the ventilator). The single tubing can cause re-breathing. Similarly, the presence of exhalation valve can increase work of breathing. The presence of a small port can cause rebreathing if the set EPAP levels does not drive the exhaled gas out of the port or the port is accidently closed. It is necessary to ensure that the exhalation port is properly fitted and functioning well. There is increased risk of hypercapnia through rebreathing if this is not considered.
Difference between conventional CPAP and Bubble CPAP?

Conventional CPAP can be set on a ventilator or through NIV machines. Bubble CPAP is a specialized system in which the CPAP is generated by inserting the tube in a column of water (Fig. 4). A continuous oscillatory positive airway pressure similar to the mean airway pressure is generated. In addition to CPAP, positive pressure oscillations due to the bubbles are also administered. The use of bubble CPAP has been studied predominantly in neonatal and infant populations. It can be used in infants with mild to moderate respiratory distress like mild bronchiolitis.

Humidified high flow nasal cannula (HHFNC)

HHFNC therapy is provided by delivering high flow gases (in the ranges generally between 2 and 8 L/min) via the humidifier and supplied circuit to the nasal cannula that has been secured to the face with the cannula prongs in the nares (Fig. 6). Gas flow rate is adjusted according to clinical response. It has been speculated that HHFNC works by providing airway pressure, improving mucosal perfusion or stimulation of respiratory drive. The positive airway pressure may range from trivial to excessive relatively unpredictable unregulated related to flow, prong size, and patient size and likely to produce effective heated humidification; and sufficient to produce clinical effects and/or changes in respiratory distress.

Indigenous Bubble CPAP?

The material required for the indigenous bubble CPAP is depicted in (Fig. 5). It includes a bottle with distilled water or saline, tubing and a humidifier. This is extremely useful in limited resource setting and also is cost effective. It is prudent that it is applied only in infants and children with mild to moderate respiratory distress, eg. bronchiolitis. The progressive increase in respiratory distress mandates invasive ventilation.
pulmonary function in neonates. Based on these characteristics, HHFNC should not be regarded as a form of CPAP. Currently, there is no data to support its use as pressure generating device in older pediatric age groups.

Modes of NIV

The available standalone ventilators are either volume targeted or pressure targeted ventilators; the former is more common. The pressure targeted ventilators are flow or time triggered, pressure limited, flow or time cycled ventilators. They improve minute ventilation and gas flow either by increasing IPAP (range: 2-30cms of H$_2$O) or EPAP (range: 2-30cms of H$_2$O). Following modes are available on the pressure targeted ventilators:

a. **CPAP mode**: The patient breathes spontaneously over the baseline set pressure i.e the CPAP. The patient controls both the rate and depth of breathing. A continuous bias flow is generated in the machine and this helps to drive the exhaled gases through the exhalation port. When the patient’s respiratory effort is sensed by the flow sensors, flow through the circuit is increased to maintain a stable pressure.

b. **Assist / Spontaneous mode(S)**: One need to set the EPAP and the IPAP on the machine e. EPAP is the lower pressure akin to CPAP and when the patient makes an inspiratory effort a set IPAP is delivered. The difference in the two pressures generates the pressure support and the tidal volume. The drawback of this mode is that if the patient were to become apneic there is no back up rate which the ventilator can generate. Therefore this mode can be only used in patients with a stable respiratory drive.

c. **Assist control / Spontaneous-timed mode (S/T)**: This is similar to the assist mode but has a back-up rate which needs to be set. If the patient fails to make an inspiratory effort within a set interval, the machine triggers inspiration to the set IPAP.

d. **Control mode**: It delivers the pre-set pressure targeted breaths based on the control settings and not on patient efforts. The clinician sets the IPAP and EPAP, the number of breath per minute and the inspiratory time percent (IPAP %). The breaths are time triggered and based on the set rate. IPAP then cycles to EPAP based on the IPAP% period. The tidal volume will depend on the gradient between IPAP and EPAP, the inspiratory time, the patient’s inspiratory effort and lung mechanics.

“Ramp” “Ramp start” and “Inspiratory rise time”.

“Ramp” is a feature that may increase patient comfort when therapy is started. The ramp feature reduces the pressure and then gradually increases (ramps) the pressure to the prescription setting, so you can fall asleep more comfortably especially when used in night. This feature also helps in pediatric age group as children may not tolerate the sudden gush of flow of air when the machine is started and slow ramp up of the flow may help in better acceptance of NIV.

“Ramp Start” is a feature that indicates the starting pressure at which the ramp up starts. This is usually set below EPAP or CPAP. The Ramp function will start at this pressure slowly increasing it to the EPAP or CPAP in a graded fashion. “Inspiratory rise time” is the time required by the ventilator to reach the maximum pressure (IPAP) from EPAP.

Interfaces for NIV?

An interface is a device which connects the tubing of the machine to the patient. The interfaces that are currently available are:

a. Nasopharyngeal tubes that can deliver CPAP. An endotracheal tube inserted with
depth of insertion from nose to tragus can also be used.
b. Oro-nasal or nasal masks are available.
c. Full nasal masks.
d. Helmets.
e. Nasal prongs.
In addition, mouth seals and nasal seals are available that can prevent mouth leakages during nasal ventilation. The mask should be appropriately selected to minimize the dead space and to facilitate trigger function. Tightening the mask straps, to minimize the leak, to the extent that skin injury and cranial deformation occurs, should be avoided. Some leakage is acceptable; the ventilators used for non-invasive support always work well in the presence of leaks. In fact, some of them require leak to function correctly.

Oxygenation and ventilation with NIV

The issue with each of the above is as follows

Oxygen delivery in NIV is variable. The FiO₂ is never measured on the NIV machine. When additional oxygen is required it needs to be provided through the mask or through the port in the mask. The FiO₂ thus varies and is dependent on oxygen flow rate, type of leak port in the system, site where the supplemental oxygen is introduced in the system, IPAP and EPAP. It is not possible to predict the exact FiO₂ that is delivered to the patient. The only way to wean the FiO₂ is to wean the main oxygen supply flow to the NIV machine. This should not be lowered below 5L/min of oxygen. If lowered below the same it is possible that patient has improved and his distress is less and he may not require NIV.

If the NIV machine uses single tubing circuit, then rebreathing of CO₂ is a concern. The exhalation occurs through a single leak port and the wash out of CO₂ will depend on the flow of the gas in the circuit. If gas flow is inadequate then the flushing of the exhaled gas may be inadequate. The flow of the gas will depend on the EPAP settings and the patient’s I : E ratio.

Humidifier and in NIV

It is essential for humidifier be present in NIV. The dryness of upper airway is common complaint from users of NIV. This not only increases the resistance of the air through the nose but also makes it extremely difficult for small children to breathe. It also increases the chances of mouth breathing in the child and increasing the chances of leaks if nasal mask is used. If CPAP through the nasopharyngeal tube is used the chances of tube getting blocked is increased. This can be even dangerous and may need frequent tube changes if the tube is blocked. Heated humidifiers are better compared to pass over humidifiers. The addition of humidifier though will add to the resistance but nevertheless is useful.

Acceptance in NIV

The initiation of NIV needs lot of support from the parents as well as co-operation, especially in older children. The child will not accept the tightly applied interfaces with high gas flow blasting on the face. The help of a parent to make the child understand that this support is essential will be useful. The NIV can be slowly initiated with lower settings and then gradually increased. A nasogastric tube can also be inserted that will help in decompressing the stomach as well as starting early enteral feeds. A mild sedative like trichlorofos will help in better acceptance. This should be done with caution as hypoxia may be another cause of agitation.

Monitoring in NIV

The monitoring will include usual PICU
monitoring of heart rate, respiratory rate, saturation of the oxygen, breathing pattern, breath sounds, air entry and chest excursion. Arterial blood gases are not necessary but can be done based on the clinical scenario. A decrease in heart rate by 20% and respiratory rate by 10% indicates that the child is tolerating the NIV and will benefit from the same.

A child on NIV needs frequent monitoring compared to a child on invasive ventilation. This is extremely important since a deteriorating child or one who fails the NIV can progress to severe respiratory failure and death as well. Any child who does not tolerate NIV or is progressing to severe respiratory failure must be immediately shifted to invasive ventilation. The doctors and nurses looking after a child with NIV must be fully aware of signs of deterioration.

**Weaning from NIV**

The child is weaned once there is clinical improvement. The weaning can be done in two ways. The first method employs weaning of NIPPV settings by lowering the IPAP levels first and then lowering the EPAP levels. The second option is intermittent discontinuation of the NIV for a brief periods and then gradually increasing the period off NIV for 3-4 hours. Eventually NIV is provided only during the night times when the patient is asleep. This helps in better conditioning of the respiratory muscles and prevents fatigue of the muscle.

**Complications**

The following complications may be noted in children on NIV:

- a. Mask discomfort like excessive leak around the mask or pressure sores.
- b. Nasal and oral dryness, congestion or even epistaxis.
- c. Intolerance due to gas flow.
- d. Aerophagia and gastric distension
- e. Aspiration
- f. Mucus plugging
- g. Hypotension due to use of excessive pressures.
- h. Sinusitis.

**NIV at home**

Parents can use NIV on select children at home. Children with neuromuscular disorders usually adapt and use NIV very effectively at home. Parents need to have a good understanding of the machine when using on the children. It needs to be emphasized that parents should not over rely on NIV and when in doubt that it may be not helping the child, the parents need to seek medical help as soon as possible.

**Precaution with NIV**

NIV can be life threatening in following cases:

- a. The expiratory ports are closed.
- b. Over reliance on NIV when disease is worsening
- c. Despite maximum support if the patient continues to demonstrate continued respiratory distress, hemodynamic instability or excessive secretions then immediate intubation is necessary or else the patient can progress to cardiorespiratory failure or death.

**Points to Remember**

- *NIV should be used carefully in select pediatric patients only.*
- *Careful monitoring is the rule when children are started on NIV.*
- *In the event of child failing NIV then he should be urgently intubated.*
**NIV is best for patients who are not too sick. NIV is good option to conventional ventilation in carefully selected patients in select conditions**

**Bibliography**

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**Nagy B et al. Efficacy of methylprednisolone in children with severe community acquired pneumonia Pediatric Pulmonology, 05/29/2012**

The 5–day methylprednisolone therapy with imipenem was found effective in children having severe community–acquired pneumonia (CAP). The additive methylprednisolone treatment significantly reduced the duration of fever with 2.5 days, the WBC counts (P=0.014), the hsCRP levels showing a 48.7% decrease and the length of hospital stay with 5.2 days versus the placebo group.

Moreover, patients treated on imipenem alone had twice more complications and four times more invasive interventions compared to those on the combined therapy. However, trials with larger cohorts are needed to study further beneficial effects of corticosteroids in children with CAP.

**Ong EHM et al Mechanical CPR devices compared to manual CPR during out-of-hospital cardiac arrest and ambulance transport: a systematic review Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 06/19/2012 Evidence Based Medicine**

The authors found insufficient evidence to support or refute the use of mechanical Cardio–Pulmonary Resuscitation (CPR) devices in settings of out–of–hospital cardiac arrest and during ambulance transport. While there is some low quality evidence suggesting that mechanical CPR can improve consistency and reduce interruptions in chest compressions, there is no evidence that mechanical CPR devices improve survival, to the contrary they may worsen neurological outcome.

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BRAIN DEATH: PRACTICAL APPROACH

* Devaraj V Raichur

Abstract: Perfect understanding of death has not been easy anytime. The concept of brain/brainstem death - permanent loss of all functions of whole of brain/brainstem has made it possible to take decisions regarding organ donation and stopping inapt life-support measures. Now many countries, including India, recognize it to be equivalent to death. Determining brain/brainstem death in patients basically depends on a set of clinical criteria and ancillary studies. There is considerable variation among institutions in using these criteria. India needs locally applicable guidelines to confidently diagnose brainstem death.

Keywords: Brain, Brainstem, Death, Criteria.

Great debates have occurred over centuries as to what is death and when a human being should be considered dead. These discussions have straddled across the fields of medicine and philosophy. To confirm death several innovative but weird, in today’s standards, methods were proposed historically.1 Despite the noticeable achievements of the modern medicine, the diagnosis of death sometimes is not straightforward, even today.2

It is not uncommon in pediatric and adult intensive care units (ICUs) that deeply comatose patients with severe brain damage often have clinically absent brain function and are being kept ‘alive’ by mechanical ventilators. Many of them may not show signs of recovery over many days. It is important, in this context, to recognize irreversibility of the damage to the brain to decide on further course of actions regarding withdrawing life support measures and when possible, harvesting organs for organ transplantation.

Brain death (also called ‘whole brain death’) is said to have occurred when whole of the brain has totally and permanently lost its function while heart continues to beat and other body functions are maintained artificially.3 It is necessary that absence of brain function is accompanied by evidence of irreversibility.

Concept of death, brain death and brainstem death

Brain death and death: It is wonderful to know why and how concepts on brain death have evolved. In a situation like that of preintensive-care-days, if a person dies, there is hardly any appreciable dissociation between cessation of breathing, cardiac activity and brain function. All these happen simultaneously or within a span of less than five minutes. Introduction of ventilatory support and drugs to support cardiac functions has divided this relationship and made real the possibility of dissociation among these functions. Although the prime intention of such support measures is to support the cardiorespiratory function till the brain regains its function, their development has led to the need for revising the understanding and definition of death.
Unfortunately when brain function is irreversibly lost, life support becomes a futile attempt and proving ‘death’ becomes a difficult and sensitive task particularly when the heart is beating. This also carries a lot of emotional, legal and medical implications. The intention of certification of brain death may be (i) to plan for organ donation, (ii) stopping the life support to end the agony of the family as it matters no difference for the patient’s survival, or (iii) to divert the life support to some other child who may be benefitted by that.

Brain death or ‘whole brain death’ implies that all functions of the cerebrum and brainstem are lost and has been accepted legally as equal to death of a person in the USA and many other countries. In the UK and India, the ‘brainstem death’—permanent loss of all the functions of the brainstem – is used legally to be equivalent to death. This is based on the argument that brainstem allows the brain to function as a unit, and the bedside clinical tests to diagnose brain death focus on brainstem function. Brain death and brainstem death are practically equivalent terminologies as the brain stem is the physiological hub containing all the vital centers. Brain death is diagnosed when there is irreversible loss of consciousness, apnea and absence of all brain stem reflexes.

What happened in other countries?

Availability of Intensive Care Units, and of organ transplants in developed countries necessitated the discussion on brain/brainstem death much earlier, resulting in development of well conceived guidelines and recommendations. Criteria for diagnosing the whole brain death and brainstem death have been delineated, and periodically updated, by medical bodies in the USA and the UK respectively. It is also important to note that often, in the same country, different institutions use slightly different criteria to diagnose neurologic death. In this regard, we are lagging behind in our country and have to follow these guidelines till Indian medical and legal bodies formulate similar guidelines in our context.

Initiating the brain stem evaluation: This fact is raised when a patient on ventilatory support fails to initiate spontaneous breathing, or pupils are dilated and non reactive or when there is no cough reflex or remained unresponsive after stopping the sedation or muscle relaxants. This thought occurs first in the mind of a resident or nurse or those closely attending on these patients in intensive care units.

Following are the requisites to commence the procedure of brain death certification or brain stem function evaluation.

a) All reversible medical conditions which could depress the brain functions should be corrected, namely: hypotension, hypothermia, metabolic functions such as hypoglycemia, electrolyte disturbances, high ammonia, intoxication and drug overdose. Western guidelines do not include transient complete paralysis leading to peripheral locked in syndrome caused by snake bite. This can be also included in the list.

b) All sedatives, analgesics, neuromuscular blocking agents and anticonvulsants should be discontinued for a reasonable period of time or serum levels are confirmed to be not in the supra therapeutic range.

Evaluation should be postponed for atleast 24 to 48 hours or longer following CPR after cardiac arrest or severe acute brain damage of any cause.

Components of brain stem function assessment: Brain death and brain stem deaths are practically equivalent terminologies as the brain stem is the physiological hub containing all the vital centers. Brain death is diagnosed when there is irreversible loss of consciousness, apnea and absence of all brain stem reflexes.

1. Neurological examination: This forms the assessment of level of consciousness and brain stem reflexes and demonstration of flaccid tone and absence of movements (excluding the spinal cord events)
2. Apnea test

3. Ancillary tests: (EEG and radionuclide cerebral blood flow studies). These are done more than once at an interval of 12-24 hours, depending on the age of the child, to establish the diagnosis of brain death. There are clear guidelines on this – how many persons to assess, who should be in the team, how frequently examination is repeated.

**Loss of brainstem reflexes**

a) Pupils are dilated or in mid position and fixed; pupillary reaction to bright light in both the eyes is absent.

b) Absence of movement in bulbar musculature: The normal grimacing or facial muscle movement in response to deep pressure over the condyles at the temporomandibular joint or over the supraorbital ridge is absent.

c) Absence of cough and gag reflex: Cough reflex is tested by inserting the suction catheter into the trachea up to carina followed by suction attempts. Pharyngeal gag reflex is demonstrated by stimulating the posterior pharyngeal wall with a tongue depressor.

d) Absent corneal reflex: Gently touching the cornea with a cotton thread normally causes twitching of eyelids; this should be absent. This should be done carefully without causing any damage to cornea.

e) Absent oculovestibular reflex: This is elicited by irrigation of the each ear separately with cold water, at a temperature of $30^\circ$. This test can be done only after ensuring the patency of external auditory canal and the intactness of tympanic membrane. There should not be any movement of eyes during the one minute observation period. After few minutes test can be repeated in other ear.

**Apnea test:** This test is done to determine the responsiveness of the brainstem to the elevated carbon dioxide levels, in principle, 20 mmHg above the basal level for the individual. The test is performed by preoxygenating the patient with 100% oxygen and adjusting the ventilator settings to bring the PaCO2 to 40 mmHg, pH to normal and then disconnecting from the ventilator. The patient is provided with oxygen at 6 L/min through a tracheal catheter, tip of which is preferably placed at the carina. The PaCO2 is allowed to rise while monitoring for development of hypoxia or hypotension. At the end of 10 minutes, an arterial blood gas analysis is done to confirm a PaCO2 > 60 mmHg or > 20 mm above the baseline. Throughout the entire procedure heart rate, blood pressure and O2 saturation are monitored with careful observation for any spontaneous respiratory effort. Presence of any spontaneous respiratory efforts is inconsistent with brainstem death. If hypoxia (SpO2 < 90%), bradycardia or hemodynamic instability occur any time during the test, the test should be discontinued.

**Number of examination, examiners and observation period**

Two neurological examination including apnea test should be done to ensure irreversibility and also to avoid observer related errors. It is preferably done by two different physicians managing the ventilator care of the child.

Recommended observation period at different ages: (i) 24 hours for neonates (37 weeks gestation to term infants 30 days of age). (ii) 12 hours for infants and children (beyond 30 days upto 18 years). Longer interval is needed if there are any inconsistencies or concern in the examination.

The first examination recognizes the criteria for brain death and the second examination preferably done by a second examiner confirms that the child fulfills the criteria for brain death, by testing irreversibility.
Ancillary studies: EEG and radionuclotide cerebral blood flow (CBF) studies are not substitute for clinical examination and if available, they are performed only after the completion of clinical examination and apnea test. They are used to assist the clinician in making the diagnosis of brain death. Ancillary tests are very useful (i) when neurological examination cannot be completed safely because of the underlying medical condition or if there is any uncertainty about the results or (ii) if there is a possibility that medication effect may interfere with the evaluation or (iii) to reduce the observation period.

If the ancillary tests are equivocal or if there is any concern about the validity, all components of the evaluation – neurological examination, apnea test and ancillary studies should be repeated after a waiting period of 24 hours. Complete supportive care should be continued without any compromise during this period till the declaration of brain death. All aspects of the evaluation should be appropriately documented.

Diagnosis of brain death in infants

Criteria in infants younger than 7 days of age and for premature neonates have not been described; they should be at least as rigorous as for those 7 days to 2 months of age. It is often difficult to diagnose brain death in premature infants; the wait period should be at least 72 hour. In term infants (37 weeks of gestation to 30 days) both EEG and CBF studies are less sensitive and CBF study may be preferred among the two. Beyond 30 days and up to 18 years both have equal sensitivity.

Brain/brainstem death and law

In India, the transplantation of Human Organs Act, 1994 defines that “brain-stem death” means the stage at which all functions of the brain-stem have permanently and irreversibly ceased and “deceased person” means a person in whom permanent disappearance of all evidence of life occurs, by reason of brain-stem death or in a cardiopulmonary sense, at any time after live birth has taken place. For the purpose of removing the organs for transplantation, after brainstem death, the act compels “Where any human organ is to be removed from the body of a person in the event of his brain-stem death, no such removal shall be undertaken unless such death is certified, in such form and in such manner and on satisfaction of such conditions and requirements as may be prescribed, by a board of medical experts consisting of the following, namely: (i) the registered medical practitioner, in charge of the hospital in which brain-stem death has occurred; (ii) an independent registered medical practitioner, being a specialist, to be nominated by the registered medical practitioner specified in clause (i), from the panel of names approved by the appropriate authority (iii) a neurologist or a neurosurgeon to be nominated by the registered medical practitioner specified in clause (i), from the panel of names approved by the appropriate authority; and (iv) the registered medical practitioner treating the person whose brain-stem death has occurred.” It is understandable that such a rigid rule is essential for preventing misuse of the concept of brainstem death to unduly favor organ transplantation. It must be noted that the act leaves the decision on, what criteria should be used and how many physicians should examine to confirm brainstem death, to the board of medical experts constituted. However across India, as of today, diagnosing brainstem death for the purpose of discontinuation of the life-support measures - to ensure appropriate use of economic, social and family resources-is a far more common situation than the situation of organ transplantation. Further, neurologists or neurosurgeons are not available in all intensive care unit settings. The act is silent with respect to the situations where organ transplantation is not an issue and no rules are available on the number of physicians to be
involved in certifying brainstem death. In this context, it is appropriate for an Indian medical organization to take the responsibility of formulating the criteria to be used in India for diagnosing brainstem death, with due consideration to the prevalent health care situation in India.

**Communication with the parents and relatives**

The issue of death with a beating heart is not easy to comprehend for all. Appropriate emotional support should be provided to the parents. Whole process of evaluation should be done with sensitivity, precision and honesty. The parents and relatives need to be counseled about the patient’s condition when brainstem death is suspected and once a diagnosis of brainstem death has been made, they should be explained about its implications in unequivocal terms. When relevant, a request for organ donation should be made; for this the physician needs to have excellent communication skills, considering the state of the parents. The option of organ donation should not be discussed with the family till the brain death is certified.

If the request for the organ donation is accepted, further care of the brainstem dead ‘person’ should be the responsibility of the organ transplant team, both medically and financially. In other situations, removal of life-support measures should be addressed. It must be emphasized to the parents/relatives that the purpose of withdrawing life-support measures is not to let the patient die but because their continuation makes no difference for a patient who is already dead.

**Points to Remember**

- The concept of brain/brainstem death has been equated to death, legally, in many countries.
- Considerable variation exists in criteria used to diagnose brain/brainstem death across the world and among the institutions.

**References**

HYPERTENSIVE CRISIS IN CHILDREN

* Raghunath CN
** Padmanabhan
*** Vani HN

Abstract: Hypertensive crisis is not uncommon in children a potentially life threatening medical emergency. Hypertensive crisis are situations when marked elevations in blood pressure is associated with progressive or impending target organ damage. Most children with hypertensive crisis have an underlying secondary cause for hypertension. The “Fourth Report on High blood pressure provides updated normative data for BP for healthy children aged 1 to 17 years according to age, gender and height. This review article aims to help practitioners and pediatricians to know the manifestation of this crisis and its effective management.

Keywords: Hypertensive crisis, Hypertensive emergency.

Hypertensive emergencies occur rarely in children. The estimated incidence of persistent hypertension in pediatric population is approximately 1 to 3%. Hypertensive crisis are situations when marked elevations in blood pressure is associated with progressive or impending target organ damage. The term hypertensive crisis is used to indicate either hypertensive emergency or urgency. One to two percent of the patients with hypertension do develop hypertensive crisis at some point during the life time. Hypertensive crisis in pediatric patients is a medical emergency. It is prudent to look for secondary causes of hypertension in children with hypertensive crisis.

Definition

The “Fourth Report on High Blood Pressure in Children and Adolescents” provided updated normative data for BP for healthy children aged 1 to 17 years according to age, gender, and height for fiftieth, ninetieth, and ninety-fifth and ninety-ninth percentiles. The report defined normal BP as systolic and diastolic values less than the ninetieth percentile.

Prehypertension is defined as an average SBP or DBP between the ninetieth and ninety-fifth percentiles or if BP exceeds 120/80 mm Hg, even if below the ninetieth percentile.

Hypertension is defined as average SBP or DBP that is ninety-fifth percentile on three or more occasions. The report also defined the stages of hypertension in children.

Stage 1 hypertension is defined as an average systolic or diastolic BP between the ninety-fifth and ninety-ninth percentile + 5 mm Hg.

Stage 2 hypertension is defined as a persistent BP above the ninety-ninth percentile + 5 mm Hg.
There is no level of systolic or diastolic blood pressure to define hypertensive crisis as this alone cannot predict the severity of the problem. The 1993 report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure established an operational classification of hypertensive crises as either emergencies or urgencies. Hypertensive emergency is defined as acute elevation of blood pressure with presence of end organ damage and hypertensive urgency as elevated blood pressure without the presence of end organ damage, although these patients may still manifest symptoms such as headache and nausea. Distinguishing hypertensive urgencies from emergencies is important in formulating a therapeutic plan. Etiology of hypertensive crisis in children are shown in Table I.

**Pathophysiology of hypertensive crisis**

The pathogenesis of hypertensive crises is not well understood. Hypertensive crisis is thought to be initiated by an abrupt increase in systemic
vascular resistance likely related to humoral vasoconstrictors. The subsequent increase in BP generates mechanical stress and endothelial injury leading to increased permeability, activation of the coagulation cascade and platelets, and deposition of fibrin. With severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue. This process results in ischemia and the release of additional vasoactive mediators generating a vicious cycle of ongoing injury.

The renin-angiotensin system is often activated, leading to further vasoconstriction and the production of proinflammatory cytokines such as interleukin-6. The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency.\textsuperscript{5,6,7}
Table II Signs pointing to words secondary causes of hypertension

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Tachycardia, Decreased lower extremity pulses; difference in BP from upper to lower extremities</th>
<th>Hyperthyroidism, pheochromocytoma, mocyctoma, neuroblastoma, primary hypertension Coarctation of the aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Retinal changes</td>
<td>Severe hypertension, more likely to be associated with secondary hypertension</td>
</tr>
<tr>
<td>Ear, nose and</td>
<td>Adenotonsillar hypertrophy</td>
<td>Suggests association with sleep-disordered breathing (sleep apnea), snoring</td>
</tr>
<tr>
<td>Height, weight</td>
<td>Growth retardation</td>
<td>Chronic renal failure</td>
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<td></td>
<td>Obesity (high BMI)</td>
<td>Primary hypertension</td>
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<td></td>
<td>Truncal obesity</td>
<td>Cushing syndrome, insulin resistance syndrome</td>
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<tr>
<td>Head and neck</td>
<td>Moon facies</td>
<td>Cushing syndrome</td>
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<tr>
<td></td>
<td>Elfin facies</td>
<td>Williams syndrome</td>
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<td></td>
<td>Webbed neck</td>
<td>Turner syndrome</td>
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<td></td>
<td>Thyromegaly</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Skin</td>
<td>Pallor, flushing, diaphoresis</td>
<td>Pheochromocytoma</td>
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<tr>
<td></td>
<td>Acne, hirsutism, striae</td>
<td>Cushing syndrome, anabolic steroid abuse</td>
</tr>
<tr>
<td></td>
<td>Café-au-lait spots</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td></td>
<td>Adenoma sebaceum</td>
<td>Tuberous sclerosis</td>
</tr>
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<td></td>
<td>Malar rash</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td></td>
<td>Acanthosis nigricans</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Chest</td>
<td>Widely spaced nipples</td>
<td>Turner syndrome</td>
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<tr>
<td></td>
<td>Heart murmur</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>Friction rub</td>
<td>Systemic lupus erythematosus (pericarditis), collagen-vascular disease, end stage renal disease with uremia</td>
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<tr>
<td></td>
<td>Apical heave</td>
<td>Left ventricular hypertrophy/chronic hypertension</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Mass</td>
<td>Wilms tumor, neuroblastoma</td>
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<tr>
<td></td>
<td>Epigastric/flank bruit</td>
<td>Pheochromocytoma</td>
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<tr>
<td></td>
<td>Palpable kidneys</td>
<td>Renal artery stenosis</td>
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<tr>
<td></td>
<td></td>
<td>Polycystic kidney disease, hydronephrosis, multicystic-dysplastic kidney, mass (see above)</td>
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<tr>
<td>Genitalia</td>
<td>Ambiguous/virilization</td>
<td>Adrenal hyperplasia</td>
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<tr>
<td>extremities</td>
<td>Joint swelling</td>
<td>Systemic lupus erythematous, collagen vascular disease</td>
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<tr>
<td></td>
<td>Muscle weakness</td>
<td>Hyperaldosteronism, Liddle syndrome</td>
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</table>
Table III Investigations

<table>
<thead>
<tr>
<th>I. Diagnosis: primary or secondary</th>
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</thead>
<tbody>
<tr>
<td><strong>A. Laboratory</strong></td>
</tr>
<tr>
<td>Complete blood counts</td>
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<tr>
<td>Peripheral smear</td>
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<tr>
<td>Urine routine,</td>
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<tr>
<td>Urine culture</td>
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<tr>
<td>Serum urea, creatinine</td>
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<tr>
<td>Serum electrolytes</td>
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<tr>
<td>Serum calcium, phosphorus</td>
</tr>
<tr>
<td>ASO, ANA, serum C3</td>
</tr>
<tr>
<td>Urine catecholamines</td>
</tr>
<tr>
<td><strong>B. Radiology</strong></td>
</tr>
<tr>
<td>Chest X ray</td>
</tr>
<tr>
<td>Voiding cystourethrogram</td>
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<tr>
<td>Cardiac catheterization,</td>
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<tr>
<td>Renal ultrasound,</td>
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<tr>
<td>Renal scan</td>
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<tr>
<td>Renal arteriography</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Tests for target organ damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine analysis</td>
</tr>
<tr>
<td>Chest X ray</td>
</tr>
<tr>
<td>Echocardiogram</td>
</tr>
<tr>
<td>CT scan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Tests for associated risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum lipid profile</td>
</tr>
<tr>
<td>Serum uric acid</td>
</tr>
<tr>
<td>Urinary catecholamine, etc.</td>
</tr>
</tbody>
</table>

The figure outlines the underlying pathophysiology of hypertensive emergency.

Assessment of children with hypertensive crisis

A focused history, physical examination and investigations are central to the initial assessment of a child presenting with hypertensive crisis.

**History and physical examination**

History should include the duration and severity of hypertension, symptoms like headache, chest pain, breathlessness, visual disturbances, decreased urine output, edema, passing of cola colored urine, altered sensorium, seizures, weakness and epistaxis and a detailed drug history. Blood pressure should be measured using the proper technique. Specific signs to identify the secondary causes of hypertension should be looked as illustrated in the Table II.

Also the end organ damage has to be assessed. The common end organs involved are eyes, brain, CVS, kidneys.

**Eyes:** Retinal hemorrhages and exudates, papilledema.

**CNS:** Hypertensive encephalopathy, Intracranial hemorrhage, lacunar infarcts, stroke. Hypertensive encephalopathy is characterized by the insidious onset of headache (often occipital and worse in the morning), nausea, and vomiting, followed by alterations in mental status, lethargy, and restlessness/agitation. Can progress to seizures and coma if untreated. It is generally characterized by the lack of localizing neurologic signs.

**CVS:** Pulmonary edema, unstable angina/myocardial infarction, acute aortic dissection.

**Renal:** Malignant nephrosclerosis, leading to acute renal failure, hematuria, and proteinuria. Activation of the renin-angiotensin system can further exacerbate the hypertension.

**Hematologic:** Hemolytic anemia can occur with severe hypertension.

**Investigations**

Investigations have to be done to determine the cause of hypertension, associated risk factors,
Table IV Antihypertensive drugs used for management of severe hypertension in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose†</th>
<th>Route</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most useful</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>β-blocker</td>
<td>100–500 mcg/kg/min</td>
<td>iv infusion</td>
<td>Very short-acting constant infusion preferred. May cause profound bradycardia. Produced modest reductions in BP in a pediatric clinical trial</td>
</tr>
<tr>
<td>Hydralazin</td>
<td>Vasodilator</td>
<td>0.2–0.6 mg/kg/dose</td>
<td>i.v.i.m</td>
<td>Should be given every 4 hours when given iv bolus. Recommended dose is lower than FDA label</td>
</tr>
<tr>
<td>Labetalol</td>
<td>α- and β blocker</td>
<td>bolus: 0.2–1.0mg/kg/dose up to 40mg/dose infusion: 0.25–3.0mg/kg/hr</td>
<td>iv bolus or infusion</td>
<td>Asthma and overt heart failure are relative contraindications.</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Calcium channel blocker</td>
<td>1–3 mcg/kg/min</td>
<td>iv infusion</td>
<td>May cause reflex tachycardia.</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Vasodilator</td>
<td>0.53–10 mcg/kg/min</td>
<td>iv infusion</td>
<td>Monitor cyanide levels with prolonged (&gt;72 hr) use or in renal failure; or coadminister with sodium thiosulfate</td>
</tr>
<tr>
<td><strong>Occasionally useful‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Central α-agonist</td>
<td>0.05–0.1 mg/dose may be repeated upto 0.8 mg total dose</td>
<td>po</td>
<td>Side effects include dry mouth and sedation.</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>ACE inhibitor</td>
<td>0.05–0.1 mg/kg/dose up to 1.25 mg/dose</td>
<td>i.v bolus</td>
<td>May cause prolonged hypotension and acute renal failure, especially in neonates</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Dopamine receptor agonist</td>
<td>0.2–0.8 mcg/kg/min</td>
<td>i.v infusion</td>
<td>Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 years.</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Calcium channel blocker</td>
<td>0.05–0.1 mg/kg/dose</td>
<td>po</td>
<td>Stable suspension can be compounded</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Vasodilator</td>
<td>0.1–0.2 mg/kg/dose</td>
<td>po</td>
<td>Most potent oral vasodilator; long-acting.</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; im, intramuscular; iv, intravenous; po, oral.
* Useful for hypertensive emergencies and some hypertensive urgencies.
† All dosing recommendations are based upon expert opinion or case series data except as otherwise noted.
‡ Useful for hypertensive urgencies and some hypertensive emergencies.
end organ damage and magnitude of damage

Table III.

Management

Management requires prompt recognition and appropriate management to prevent further complications. Hypertensive emergency requires ICU admission while hypertensive urgency could be managed in the wards with oral medications. The oral agents should be slowly titrated using lower doses and preventing excessive reduction in blood pressure. The goal of the treatment is to reduce the blood pressure over days.

Treatment of hypertensive emergencies is tailored according to the extent of end organ damage. ABC should be focused as in other emergent situations. Vascular access should be obtained and the patient should be placed on continuous cardiac monitoring with frequent blood pressure measurements. Neurologic status, fluid and electrolyte balance of the patient must be monitored carefully and frequently. An arterial line is indicated in children as potent intravenous antihypertensives require frequent monitoring and titration. Goal of treatment is not to rapidly reduce the blood pressure to a “normal” level. Such actions can result in hypoperfusion of end organs. The goal is to reduce the mean arterial pressure (MAP) by less than 25% over the first 2 to 8 hours and gradually normalize the blood pressure over the next 24 to 48 hours.

Pharmacotherapy

There are several available agents, and choice of a specific agent depends on the clinical presentation and current medical condition of the patient (Table IV).

Conclusion

Severe hypertension resulting in hypertensive emergencies and urgencies occurs infrequently in children. Proper management of this potentially life-threatening condition and prevention of its complications depends on prompt recognition and treatment. Most children who present with hypertensive crisis have secondary hypertension. Renal parenchymal disease is the commonest underlying etiological factor. With the increase in the prevalence of obesity in children, the incidence of hypertension among children is also on rise. Successful treatment of hypertensive crises requires rapid recognition and appropriate management to prevent complications. Patient’s age, rapidity of rise in blood pressure and etiology of the hypertensive emergency, determine the optimal therapy in children.

The goal of treatment is not immediate return of blood pressure to normal, but reduction to a safe level. Rapid reduction is not recommended due to sudden hypotension, failure of autoregulatory mechanisms, and the possibility of cerebral and visceral ischemia. Asymptomatic children with hypertensive urgency require less aggressive approach and blood pressure can be brought down more gradually. Practitioners should be aware of the pediatric blood pressure norms, techniques for accurate measurements and early recognition of signs of hypertensive crisis and proper management of this condition for better outcome.

Points to Remember

- **Distinguishing between hypertensive emergency (associated with acute target organ damage) and urgency (no target organ damage) is crucial to appropriate management.**

- **Diagnosis of hypertensive emergency requires a through history (evidence of target organ damage, illicit drug use and medication compliance) as well as a complete physical examination, basic laboratory date and electrocardiogram to**
assess for the presence of target organ damage and determine its severity.

- Hypertensive urgency is managed using oral antihypertensive drugs in outpatient or same day observational settings, while hypertensive emergency is managed in an intensive care unit or other monitored settings with parenteral drugs.

- The initial goal in hypertensive urgency is a reduction in mean arterial pressure by no more than 25% within the first 24 hours using conventional oral therapy in hypertensive emergency, mean arterial pressure should be reduced by less than 25% over the first 2 to 8 hours and gradually the blood pressure should be normalized over the next 24 to 48 hours.

- Various medications are available for the treatment of hypertensive emergency appropriate therapy should be based on specific target organ involvement and underlying patient’s comorbidities.

References


MONOCLONAL ANTIBODIES IN PEDIATRIC THERAPEUTICS

*Jeeson C Unni

Abstract: Monoclonal antibodies (mAbs), developed just 4 decades ago, have become a necessary treatment modality in some childhood illnesses that do not responded to standard first line therapy. New molecules are being recognized and as a consequence, a number of trials using these drugs are being conducted and published. A review of applications of a few important molecules in this category is presented.

Keywords: Monoclonal antibody, abciximab, adalimumab, alemtuzumab, basiliximab, infliximab, omalizumab, palivizumab.

Monoclonal antibodies (mAbs) are proteins that target specific antigens (as against polyclonal antibodies that target multiple antigens) and are produced in large amounts by hybrid cells (hybridomas). This capacity of the hybridoma persists indefinitely and they can be stored frozen and reconstituted at any time. Various processes including chromatography and recombinant technology are then employed to make the antibody as small as functionally possible; able to target two or more antigens (as in cancer therapy to target the cancer cell and the anticancer drug to reduce its toxicity); bispecific (contain fragments of two different mAbs and consequently bind to two different types of antigen); or less immunoreactive (humanized). Since it is a vast and relatively recent development in pediatric therapeutics, the article will first enumerate its applications citing relevant studies and then describe a few more commonly used mAbs in some detail.

Uses

Table I is a list of the 32 monoclonal antibodies that have been studied and found useful in certain specified conditions. They are not first line therapy for most pediatric indications which include

i) Malignancies - a) acute lymphoblastic leukemia - marrow relapse\textsuperscript{26} relapsed/refractory ALL\textsuperscript{7}, mature B cell, Burkit’s, B precursor ALL\textsuperscript{39}, post transplant relapse\textsuperscript{11} b) non Hodgkin lymphoma - recurrent\textsuperscript{23}, intermediate-risk (Stage III/IV) B-cell non-Hodgkin lymphoma\textsuperscript{40} c) refractory or relapsed acute myeloid leukemia\textsuperscript{22} d) High risk neuroblastoma\textsuperscript{14} and e) recurrent or refractory Ewing sarcoma\textsuperscript{37}. They are usually included in combination therapy. Studies are still ongoing and the most researched among these is rituximab.

ii) Autoimmune diseases - a) JIA\textsuperscript{4,5,24,44,45} in cases that do not respond to conventional therapy and most studies are on adalimumab, rituximab with methotrexate and in cases with ankylosing spondylitis, infliximab b) SLE-though rituximab is used, further data is required before establishing its use in SLE protocols\textsuperscript{46} and a lot of expectation is placed on belimumab as it became the first biologic agent and the first of any class of drug to be approved in 55 years for this multi-system

* Consultant Pediatrician Dr Kunhalu’s Nursing Home, Cochin.
disease by the US Food and Drug Administration\textsuperscript{10,11} c) Crohn’s disease - combination therapy of infliximab with immunosuppressives\textsuperscript{25,26} and adalimumab\textsuperscript{3} have been found effective in refractory cases d) ulcerative colitis not responding to standard therapy - infliximab with immunosuppressives could be tried\textsuperscript{26,27,28} e) prevention of organ transplant rejection – basiliximab\textsuperscript{8,9} and daclizumab\textsuperscript{16} have been used f) kawasaki disease - IVIG resistant disease with infliximab\textsuperscript{29} and use of abciximab to prevent myocardial infaraction and remodel the affected coronaries\textsuperscript{1,2} g) bronchial asthma – omalizumab may have a place in therapy of asthma not controlled with recommended standard protocols and guidelines\textsuperscript{35,34} h) psoriasis – infliximab and adalimumab\textsuperscript{6} tried but their efficacy reported to diminish with time.

\textbf{iii) Infectious diseases} - a) immunoprophylaxis of respiratory syncytial virus bronchiolitis in high-risk infants with palivizumab\textsuperscript{35,36} b) prevention of hemolytic uremic syndrome by shiga-like toxin of E coli by urtoxazumab\textsuperscript{47} c) invasive fungal infection - efungumab in combination with other antifungals is an option in sick children.\textsuperscript{20}

\textbf{iv) Others} - a) type 1 diabetes mellitus - teplizumab is a drug being investigated for its ability to prevent a decline in \(\beta\)-cell function and achieve glycemic control.\textsuperscript{44}

Drugs that will be discussed in detail are abciximab, adalimumab, alemtuzumab, basiliximab, infliximab, omalizumab and palivizumab.

\textbf{Pharmacokinetics}

Majority of mAbs are IgG1 molecules. Due to high molecular mass most mAbs are administered IV, rapidly achieving maximum serum concentrations. Since IV infusions require admission, other parenteral routes are preferred - subcutaneous (adalimumab, rituximab); IM (palivizumab). Absorption following IM or SC administration is slow and, for some antibodies, dose dependent. Monoclonal antibodies often demonstrate target-mediated disposition, where antibody–antigen binding influences the rate and extent of antibody distribution and elimination. Clearance of mAbs via the reticuloendothelial system is regulated through interaction with various Fc receptors. FcRn protects IgG antibodies from elimination, but this protection system is saturable. Because of these possible capacity limitations in catabolism, most antibodies demonstrate nonlinear, dose-dependent pharmacokinetics. Half life of mAbs depends on the source - chimeric: 4-5 days, humanized: 3-24 days; recombinant human 11-24 days; human mouse antibody (HAMA) response develops 7-10 days after exposure to murine antibody. The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

\textbf{Abciximab}\textsuperscript{50}. Two hrs after IV bolus, over 80\% of glycoprotein receptors are blocked and platelet aggregation is almost nonexistent. The blockade may be maintained by continuous IV infusion of 0.125 \(\mu\)g/kg/min (maximum of 10 mcg/min). The initial elimination half-life is \(<10\) min, with a second-phase half-life of about 30 min. When infusion is stopped, a rapid decline in plasma conc. occurs in 6 hrs, followed by a slower decline. Bleeding time usually declines to 12 min. or less within a day in most recipients. Some receptor blockade may persist for \(>10\) days after discontinuation of infusion.

\textbf{Adalimumab} - The maximum serum concentration. and the time to achieve it were 4.7 \pm 1.6 mg/ml and 131 \pm 56 hours respectively, following a single SC dose of 40 mg with a bioavailability of 40\%. Following IV administration, distribution volume ranged from 4.7 to 6.0 L; synovial fluid conc. ranged from 31- 96\% of serum levels. The systemic clearance is
approximately 12 ml/hr. The half-life is approximately 2 weeks, ranging from 10 to 20 days. Mean steady-state trough concentrations of approximately 5 mg/ml and 8 to 9 mg/ml, were observed without and with methotrexate respectively.

**Alemtuzumab**\(^1\)\(^{,2}\) - pharmacokinetics is characterized by a two-compartment model with nonlinear elimination with large inter-patient variability in all parameters. Higher serum levels are associated with better treatment responses. Several patient-specific factors, such as disease status, tumor burden and soluble CD52 levels, appear to influence serum level. The probability of achieving a complete or partial response was ≥50% when the maximal trough concentration exceeded 13.2 \(\mu\)g ml\(^{-1}\) or when \(\text{AUC}_{0-T}\) exceeded 484 \(\mu\)g h\(^{-1}\) ml\(^{-1}\).

**Basiliximab** - After the peak serum concentration is reached, basiliximab is gradually eliminated from the blood with a mean half-life of 7.06 days. CD25+ T-lymphocytes in the peripheral blood were suppressed completely with serum conc. of over 0.2 \(\mu\)g/ml for 40.3-51.7 days (mean +/- SD; 45.8 +/- 4.9).\(^5\)

**Infliximab**\(^6\) - The apparent volume of distribution of the high-molecular-weight infliximab is low and represents the intravascular space. The long persistence in this compartment (elimination half-life 7-12 days) is due to the very low systemic clearance of about 11-15 ml/hr. Elimination of infliximab is most probably accomplished through degradation by unspecific proteases. During multiple infusions (every 4-8 weeks), no accumulation was observed, and serum conc. and the AUC increases in proportion to the infused dose, indicating linear pharmacokinetics. Trough concentrations above 1 mcg/ml could be used as a kind of therapeutic target.

**Omalizumab** exhibits a similar pharmacokinetic profile in adults, adolescents, and children.

After intramuscular administration of 15 mg/kg palivizumab, the mean serum conc. at 30 days was 49 ig/mL and 69.4 ig/mL 30 days after the second dose.\(^6\)

**Mechanism of action**

Three different pharmacodynamic principles of action have been recognised for mAbs - apoptotic (lysis), coating and inactivating activity depending on type of antigen and antigen-antibody reaction. The disease specific antigen is present on the surface of the cell for abciximab, alemtuzumab, basiliximab, palivizumab and rituximab and they exert their effect by lysis and death the target cell. Occasionally, only coating occurs resulting in down regulation of the antigen. Adalimumab and rituximab are directed against soluble substances as antigens and they block the antigen binding receptor and thereby inactivate the target cell function.

**Dose**

**Abciximab**\(^6\) - 0.25 mg/kg intravenous bolus, followed by 0.125 \(\mu\)g/kg/min infusion for 12 hours. Platelet counts and coagulation time must be monitored. Preferably used by specialist experienced in its use.

**Adalimumab** (with methotrexate or alone if methotrexate inappropriate) - Subcutaneously child 13-17 yr - 40 mg alternate week; review treatment if no response in 12 wks.\(^5\)

**Alemtuzumab** - No standard dosage schedules in children are available on pediatric formularies and BNF for children advices to ‘consult local treatment protocols for details’. One study used initial infusions with a low dose of 0.06mg/kg [max 3mg]; increased over 5 days to 6mg/kg [max 30mg] over 2 hours, 5 times per week for 1 week, then 3 times per week for 3 additional weeks.\(^7\)

**Basiliximab**\(^5\) - IV inj. or IV infusion - >1yr and < 35kg – 10mg within 2 hrs before transplant and
Table I Monoclonal antibodies studied in children with indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Source</th>
<th>Target</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>Fab</td>
<td>chimeric</td>
<td>CD41 (integrin alpha-IIb)</td>
<td>Kawasaki(^1,2)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>mab</td>
<td>human</td>
<td>TNF-α</td>
<td>Crohn's Disease(^3), JIA(^4), Enthesitis-related arthritis(^5), Chronic childhood uveitis(^4), Psoriasis(^6)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD52</td>
<td>relapsed /refractory ALL(^7)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>mab</td>
<td>chimeric</td>
<td>CD25 (α chain of IL-2 receptor)</td>
<td>prevention of organ transplant rejections(^8,9)</td>
</tr>
<tr>
<td>Belimumab</td>
<td>mab</td>
<td>human</td>
<td>BLyS-specific inhibitor</td>
<td>SLE(^10,11)</td>
</tr>
<tr>
<td>Blinatumomab (MT103)</td>
<td>Bi-specific T-cell engagers (BiTEs)</td>
<td>Human</td>
<td>CD3 CD19</td>
<td>post-transplant relapsed acute lymphoblastic leukemia(^12)</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>mab</td>
<td>human</td>
<td>IL-1?</td>
<td>cryopyrin-associated periodic syndrome (CAPS)(^13)</td>
</tr>
<tr>
<td>Ch14.18</td>
<td>mab</td>
<td>chimeric</td>
<td>Anti-GD2</td>
<td>High risk neuroblastoma(^14)</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD25 ) (α chain of IL-2 receptor)</td>
<td>Pediatric multiple sclerosis(^15), pediatric kidney transplant(^16)</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>mab</td>
<td>humanized</td>
<td>C5 syndrome(^17)</td>
<td>Atypical hemolytic uremic</td>
</tr>
<tr>
<td>Edobacomab</td>
<td>mab</td>
<td>mouse</td>
<td>endotoxin</td>
<td>sepsis caused by Gram-negative bacteria(^18)</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>mab</td>
<td>humanized</td>
<td>LFA-1 (CD11a)</td>
<td>Atopic dermatitis(^19)</td>
</tr>
<tr>
<td>Efungumab</td>
<td>scFv</td>
<td>human</td>
<td>Hsp90</td>
<td>Invasive candidiasis(^20)</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD22</td>
<td>ALL in marrow relapse(^21)</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>mab</td>
<td>humanized</td>
<td>CD33</td>
<td>Refractory or relapsed acute myeloid leukemia(^22)</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Source</td>
<td>Target</td>
<td>Uses</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Ibritumomab tiuxetan</td>
<td>mab</td>
<td>mouse</td>
<td>CD20</td>
<td>Recurrent CD20+ non-Hodgkin's lymphoma&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infliximab</td>
<td>mab</td>
<td>chimeric</td>
<td>TNF-a</td>
<td>JIA&lt;sup&gt;24&lt;/sup&gt;, psoriasis&lt;sup&gt;6&lt;/sup&gt;, Crohn's disease&lt;sup&gt;25,26&lt;/sup&gt;, ulcerative colitis&lt;sup&gt;26,27,28&lt;/sup&gt;, Kawasaki disease&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inolimomab</td>
<td>mab</td>
<td>mouse</td>
<td>CD25 (α chain of IL-2 receptor)</td>
<td>Steroid-refractory acute graft-versus-host disease&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Motavizumab</td>
<td>mab</td>
<td>humanized</td>
<td>respiratory syncytial virus</td>
<td>respiratory syncytial virus - prevention&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Muromonab -CD3</td>
<td>mab</td>
<td>mouse</td>
<td>CD3</td>
<td>prevention of organ transplant rejections&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>mab</td>
<td>humanized</td>
<td>IgE Fc region</td>
<td>allergic asthma&lt;sup&gt;33,34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>mab</td>
<td>humanized</td>
<td>respiratory syncytial virus</td>
<td>respiratory syncytial virus - prevention&lt;sup&gt;35,36&lt;/sup&gt;</td>
</tr>
<tr>
<td>R1507</td>
<td>mab</td>
<td>human</td>
<td>Insulin-like growth factor-1 receptor (IGF-1R)</td>
<td>Ewing’s sarcoma&lt;sup&gt;37&lt;/sup&gt;</td>
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<tr>
<td>Reslizumab</td>
<td>mab</td>
<td>humanized</td>
<td>IL-5</td>
<td>Eosinophilic esophagitis&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rituximab</td>
<td>mab</td>
<td>Chimeric</td>
<td>CD20</td>
<td>ALL&lt;sup&gt;39&lt;/sup&gt;, B-cell non-Hodgkin lymphoma&lt;sup&gt;1&lt;/sup&gt;, SLE&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>Siplizumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD2</td>
<td>Graft-versus-host disease - prevention&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Talizumab (TNX-901)</td>
<td>mab</td>
<td>humanized</td>
<td>IgE</td>
<td>allergic reaction&lt;sup&gt;43&lt;/sup&gt;</td>
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<tr>
<td>Teplizumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD3</td>
<td>Type 1 diabetes mellitus&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>mab</td>
<td>humanized</td>
<td>IL-6 receptor</td>
<td>Rheumatoid arthritis&lt;sup&gt;45,46&lt;/sup&gt;</td>
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<tr>
<td>Urtoxazumab</td>
<td>mab</td>
<td>humanized</td>
<td>Escherichia coli</td>
<td>E. coli diarrhoea - prevention of HUS&lt;sup&gt;47&lt;/sup&gt;</td>
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<td>Visilizumab</td>
<td>mab</td>
<td>humanized</td>
<td>CD3</td>
<td>Steroid-refractory acute graft-versus-host disease&lt;sup&gt;48&lt;/sup&gt;</td>
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<tr>
<td>Zolimomab aritox</td>
<td>mab</td>
<td>mouse</td>
<td>CD5</td>
<td>Graft-versus-host disease&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
4 day after surgery; >35kg - 20mg within 2 hrs before transplant and 4 day after.

**Infliximab** - Severe active crohn’s - IV infusion 5mg/kg single dose over 2 hr. If recurrence occurs readminister within 14 weeks after 1st dose. Beyond this point chances of delayed hypersensitivity are high.58,59

**Omalizumab** - The recommended starting dosage is 150-375 mg SC every two or four weeks. Dosages and frequency of dose administration are determined by total serum IgE level, measured before the start of treatment, and body weight.

**Palivizumab** - 1mth – 2 yrs age - IM 15mg/kg once monthly, starting just prior to the beginning of the RSV season, for a total of 5 doses in high risk cases.

**Administration**

Abciximab - Visually inspect parenteral products for particulate matter and discoloration prior to administration. Do not shake vials containing abciximab. Intravenous bolus injection: Withdraw dose of abciximab through a sterile, non-pyrogenic, low protein-binding (0.2 or 0.22 micrometer) filter into a syringe. Give bolus over 1 minute. Continuous IV infusion: Abciximab should be infused through a separate line; do not add other medications to infusion solution. The solution for continuous infusion should be filtered either upon admixture using a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 micrometer syringe filter or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 micrometer filter. Withdraw the necessary amount of abciximab into a syringe. Inject into 250 ml of NS or D5W. A common dilution is 9 mg (4.5 ml) in 250 ml of NS or D5W to produce a final concentration of 36 mcg/mL. Infuse at the calculated rate via a continuous infusion pump. Discard unused solution at the end of the infusion.

**Contraindications**

**Abciximab** - Absolute contraindications are aneurysm, arteriovenous malformation, bleeding, coagulopathy, dextran therapy, GI bleeding, intracranial bleeding, intracranial mass, murine protein hypersensitivity, retinal bleeding, surgery, thrombocytopenia, trauma and vasculitis. Recent thrombolytic therapy, hypertension or allergic reaction to abciximab, mouse or human proteins, other medicines, foods, dyes, or preservatives are relative contraindications. It is recommended that abciximab not be used during pregnancy unless clearly indicated.

**Basiliximab** - adequate contraception must be used during treatment and for 16 weeks after last dose.

**Infliximab** is contra-indicated in any patient with tuberculosis or other severe infection, patients with moderate or severe heart failure or in patients with a history of hypersensitivity to infliximab, to other murine proteins or to any of the excipients. Infliximab has been associated with acute infusion-related reactions including anaphylactic shock and delayed hypersensitivity reactions; anaphylaxis kit must be readily available. Monitor patients closely for infections, including tuberculosis, before, during and after treatment with infliximab59.

**Omalizumab** - autoimmune disease; susceptibility to helminth infections-discontinue if infection does not respond to anthelmintic.

**Palivizumab** - The only contra-indication is an anaphylactic reaction to a previous dose of this preparation, its constituents or any other humanized monoclonal antibody. Care should be taken in patients with thrombocytopenia or any coagulation disorders due to the IM route of administration. Not licensed in children with congenital immunodeficiency or in children born at 35 weeks gestation or less.
Side Effects

**Abciximab** - Allergic reactions like skin rash, urticaria, itching, angioedema face, lips, or tongue, breathing difficulty, chest pain, unusual bleeding or bruising. Milder side effects include back pain, dizziness, headache, nausea and abdominal pain. Drug induced thrombocytopenia is reported with Abciximab.

**Basiliximab** - Severe hypersensitivity reactions and cytokine release syndrome reported. Withhold second dose if severe hypersensitivity or graft loss occurs.


**Omalizumab** is generally well tolerated in children with allergic asthma. Adverse events most commonly observed are injection-site reaction, viral infection, upper-respiratory-tract infection, sinusitis, headache, and pharyngitis.

**Palivizumab** - Occasionally it may give rise to mild local reactions, fever and irritability.

Drug interactions

**Abciximab** - Aspirin and aspirin-like drugs, clopidogrel, dipyridamole, herbal products containing garlic, ginger or horse chestnut, thrombolytics like alteplase, reteplase, streptokinase, and urokinase, anticoagulants like warfarin, enoxaparin, dalteparin, tinzaparin, argatroban, bivalirudin, and lepirudin, NSAIDs like ibuprofen or naproxen, ticlopidine.

Methotrexate reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively. It also delayed the decline in the serum concentrations of infliximab.

**Infliximab** - Avoid concomitant use with live vaccines, abatacept and anakinra.

**Palivizumab** - As the antibody is specific to RSV, there is no interaction with active vaccines.

Conclusion

Monoclonal antibodies are a new genre of drugs in the armamentarium of pediatric super specialists for the management of difficult-to-treat ailments in oncology, rheumatology, organ transplant, infectious disease, cardiology, nephrology, dermatology and endocrinology. It may be near impossible for a general pediatrician to keep updated on the newer
indications of these drugs as even the expert in the subject could find it difficult to keep pace with the rapid developments in this field.

**Points to Remember**

- **Monoclonal antibodies are not first line drugs in treating pediatric illnesses.** Under expert advice disease specific antibody may be administered in treatment of the following conditions when standard therapy fails
- **Malignancies - acute lymphoblastic leukemia, non Hodgkin lymphoma, neuroblastoma**
- **Autoimmune disorders - Juvenile idiopathic arthritis, SLE, Crohn’s disease, ulcerative colitis, Kawasaki disease**
- **Prophylaxis against organ transplant rejection and RSV infection in high risk cases**
- Since they are large molecules they need to be administered by parenteral route.
- **Potential risks of therapy are vulnerability for infection (including tuberculosis) and in a rare occasion the induction of autoimmune disease.**

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**CLIPPINGS**


Kawasaki disease (KD) is an acute, self-limiting, idiopathic form of vasculitis. The preventive effect of early therapy on coronary artery aneurysms, the hallmark of the disease, is well established. The spectrum of complication includes not only cardiac involvement but also central nervous system lesions. This is a report of a 4-year-old boy with a clinical presentation suggestive of KD treated with intravenous immunoglobulin and acetylsalicylic acid. Clinical manifestations regressed within 24 hours and cardiac anomalies were not seen. Two weeks later, the parents noticed a sudden absence of response to sound stimuli. Investigations confirmed bilateral severe sensorineural hearing loss for which oral steroid therapy was given. This resulted in an improvement only on the right side, with severe hearing loss persisting on the left. The authors conclude that sensorineural hearing loss is an uncommonly reported complication of KD and pediatricians should be aware of this potential complication to allow for early intervention.


A randomised double-blind study was performed to compare the efficacy of intravenous paracetamol (1 g) and 0.1 mg/kg morphine in patients with renal colic. The efficacy of the study drugs was measured by a visual analogue scale and a verbal rating scale at baseline and after 15 and 30 min. The adverse effects and need for rescue medication (1 μg/kg intravenous fentanyl) were also recorded at the end of the study. Intravenous paracetamol is effective in treating patients presenting with renal colic to the emergency department.
**BASIDIBOLOMYCOSIS**

*Madhu R*

**Abstract:** Subcutaneous phycomycosis also called as Basidiobolomycosis or chronic subcutaneous zygomycosis or Entomophthoromycosis basidiobolae is a rare entity, but it is the most common subcutaneous fungal infection that occurs in children. It is caused by Basidiobolus ranarum and is characterized by the presence of a painless, slowly progressive well defined swelling/plaque, firm in consistency. Swelling can be lifted from the underlying structures and fingers can be insinuated beneath the margins, which is indeed the diagnostic feature. This condition is often misdiagnosed as an abscess, soft tissue tumour, etc, resulting in unnecessary surgical intervention. Diagnosis is clinched by the characteristic clinical presentation with a confirmation by histopathological examination and mycologic culture. Complete resolution occurs with potassium iodide, which is the gold standard therapy for this infection. Itraconazole and trimethoprim and sulfamethoxazole have been tried and found to be effective.

**Keywords:** Subcutaneous fungal infection, Basidiobolomycosis, Splendore-Hoeppli material, Potassium iodide.

Entomophthoromycosis, a rare subcutaneous fungal infection caused by Entomophthorales encompasses Basidiobolomycosis and Conidiobolomycosis. The Entomophthorales derive their name from the Greek word “Entomon,” meaning insect, reflecting their original identification as pathogens or parasites infecting insects. Entomophthorales belong to the same class of fungi, Zygomyctes as Mucorales that cause mucormycosis. But they differ in that they cause chronic, slowly progressive, localized granulomatous infection in immunocompetent individuals with no angioinvasion unlike the latter that cause life threatening infection in immunocompromised persons. At present, basidiobolomycosis has been reported in immunocompromised hosts too. Basidiobolomycosis is predominantly seen in childhood and adolescence, but may be occasionally seen in adults, while Conidiobolomycosis occurs exclusively in adults. Basidiobolomycosis is also referred to as chronic subcutaneous zygomycosis/subcutaneous phycomycosis or Entomophthoromycosis basidiobolae. This infection is prevalent in the tropical and subtropical regions of Africa, South America and Southeast Asia (India, Indonesia, Burma, Pakistan) and Northern Australia. In South India, subcutaneous zygomycosis is said to be the second most common deep mycosis after mycetoma. The first case of basidiobolomycosis in humans was described by Lei-Kian Joe in 1956 in Indonesia. In India, first case was reported by Mukerji, et al in Bombay (Mumbai) in 1962.

The causative agent, *Basidiobolus ranarum* was earlier also known as Basidiobolus haptosporus or *B. meristosporus* or *B. heterosporus*. *B. ranarum* is a normal
inhabitant of soil and has been identified as saprobe and as parasite, living off of decaying vegetation, insects, woodlice and the intestines of frogs, toads, reptiles, fish, insectivorous bats, horses, dogs and other animals from whose faeces they have been isolated. Infected insects are eaten by reptiles and amphibians, which subsequently pass the spores in their excreta. Both humans and animals are infected through inoculation, ingestion and inhalation. Minor trauma, scratches and insect bites pave way for the transmission by implantation of spores.\textsuperscript{1,2,4,5,7} Direct inoculation of perineum may occur from the use of contaminated toilet leaves in which Basidiobolus ranarum may be present.\textsuperscript{2} Gastrointestinal infection has been reported to occur through ingestion. Stomach, duodenum and colon are mainly affected.\textsuperscript{1,4} Inhalation is said to play a role in patients with palatal and maxillary sinus involvement.\textsuperscript{1,4} Iatrogenic infection through injection and possible inoculation during appendicectomy has been reported.\textsuperscript{1,8,10} Muscle invasion was reported by Kamalam, et al in 1984.\textsuperscript{11} Regional lymphadenopathy may be present.\textsuperscript{1,8,12} Dissemination is very rare. No predisposing factors are known.\textsuperscript{1}

Though the organism is ubiquitous, only a small number of cases have been reported worldwide leading to the postulation that the individuals who develop this infection tend to have a subtle defect in their immunity to this group of organisms.\textsuperscript{2} It has been suggested that invasive and progressive infection in previously healthy individuals may result from transient immunosuppression during viral infections or following surgery. Extracellular proteinases and lipases like phospholipase A produced by B. ranarum contribute to the survival of the organism under various growth conditions. Lysolecithin produced by hydrolysis of phosphotidylcholine by phospholipase A has the capacity to digest human serum proteins. Protein components of liberated extracellular contents digested by proteinases produced by B. ranarum serve as nutrients for growth of the organism.\textsuperscript{1}

**Clinical features**

Basidiobolomycosis usually occurs in children younger than 10 years and a male preponderance has been reported.\textsuperscript{1,7} Constitutional symptoms are absent or minimal. Arms, thighs, gluteal regions and trunk are the usual sites of involvement. Infection starts as a nodule which expands and spreads locally. There is no haematogenous spread. Classical clinical presentation is characterized by the presence of a painless, well defined plaque or disc shaped swellings attached to the skin, with a firm India rubber consistency. The border of the subcutaneous mass is smooth, rounded, lobulated, well defined and it is possible to insinuate the fingers at the margins and raise the swelling (Fig. 1). It is freely mobile beneath the overlying skin. Satellite lesions may develop at the advancing margins. Swelling slowly increases in size and may envelop part or whole limb. Skin over the surface may be normal, tense, edematous, scaly or pigmented (Fig. 2). Pain may be present in old lesions.\textsuperscript{4,8,13,14} Ulceration may occasionally occur.\textsuperscript{4,15,16} Due to the progressive increase in size and subsequent pressure effects, complications like reversible obstructive hydronephrosis, persistent lymphedema, bone and muscle invasion have been reported.\textsuperscript{4,8,11,17} Spontaneous resolution may occur.\textsuperscript{4,8}

Gastrointestinal basidiobolomycosis is rare when compared to the subcutaneous type. Infected patients present with fever, abdominal pain with mass, diarrhea, constipation, bloody mucous discharge, vomiting and weight loss. Stomach, small intestine, colon or rectum is affected and is associated with mural thickening, nodular masses and ulcerations of the intestine that resemble Crohn’s disease. Typical presentation of fever, abdominal mass associated with pain and eosinophilia is most often misdiagnosed as chronic granulomatous diseases.
or malignancy.\textsuperscript{1,12,18} Other organs affected by B. ranarum are palate, maxillary sinus, abdominal viscera and lung.

**Differential diagnosis**

As subcutaneous phycomycosis is not so common infection, it is most often misdiagnosed and the infected children are unnecessarily subjected to surgical treatment. Early lesion is many a times mistaken for an abscess and incision and drainage is done. Progressive increase in the size of the mass with firm consistency has led to the diagnosis of soft tissue tumour, synovial sarcoma, lymphosarcoma, burkitt’s lymphoma, fibrosing panniculitis, subcutaneous malignant lymphoma, etc. Other conditions that are considered are chronic abscess, bacterial cellulitis, localized morphoea, sarcoidosis, keloid, neurofibroma, sporotrichosis, filarial elephantiasis and atypical mycobacterial infection.\textsuperscript{1,4, 8,10,14, 15,19,20,21}

**Diagnosis**

Though Basidiobolomycosis has a characteristic clinical presentation, being a rare entity, it is often misdiagnosed. Hence, a high index of clinical suspicion is required for an early diagnosis. Diagnosis is confirmed by biopsy and mycological identification of the organism through wet mount of the teased biopsy tissue in 10% KOH and culture in Sabouraud’s Dextrose Agar (SDA) medium without cycloheximide when possible. As it is a subcutaneous infection, a deep biopsy is a must for mycopathological examination and culture of the organism.
Histopathology of basidiobolomycosis is characterized by the presence of an eosinophilic granuloma. Granuloma formation and fibrosis reflects the type 1V delayed hypersensitivity response to the fungus. The deeper dermis and subcutaneous tissue are mainly involved and are replaced completely by granulomatous inflammatory infiltrate consisting of plenty of eosinophils, foreign body giant cells, Langhans giant cells, epithelioid cells, histiocytes, plasma cells and a few lymphocytes. The fungal filaments are seen as poorly stained or unstained haloes and tubes with eosin stained thin wall and infrequent septa surrounded by eosinophilic granular material known as Splendore Hoepli material, embedded in the necrotic eosinophilic microabscesses. Fungal hyphae may be present within the giant cells. Blood vessels are not invaded by the fungus unlike in mucormycosis. The fungal hyphae are better visualized with special stains like PAS - Periodic acid Schiff (purple) and GMS- Gomori Methanamine Silver (black) (Fig.3 & 4). The eosinophilic infiltration that is present has been postulated to be due to a mixture of Th1 (granuloma) and Th2 type of immune response which causes the release of cytokines like IL-4 and IL-10 which in turn are helpful in recruiting eosinophils to the affected site. It is important to remember that the presence of plenty of eosinophils which is the histopathologic characteristic feature of basidiobolomycosis, may also be seen in some parasitic infections. Hence, it becomes imperative to look for the fungal filaments surrounded by the eosinophilic granular Splendore Hoepli material.\(^3,4,8\)

Wet mount of the biopsy tissue in 10% KOH reveals broad coenocytic (non septate or infrequently septate) hyphae with thin walls. Culture in SDA medium without cycloheximide shows a rapid growth visualized as waxy cream or yellow colonies with many radial folds. Microscopic colony morphology shows broad coenocytic hyphae and zygospores with conjugation beaks. In addition, unicellular sporangia / sporangiola are formed, which are forcibly ejected into the air from the tip of the sporangiophore.\(^2,14\)

Serological tests are not widely available. Khan et al detected B ranarum antibodies with immunodiffusion and ELISA tests. Kaufman, et
al devised an immunodiffusion test to detect Basidiobolus and Conidiobolus. Immuno- florescence techniques using fungal specific antibody conjugated to fluorescein can be useful for identification of the fungus when biopsy material is unavailable for culture.

**Treatment**

Potassium iodide is considered as the gold standard in the treatment of entomophthoromycosis (basidiobolomyosisis and conidiobolomycosis) by virtue of its efficacy and affordability, in spite of the advent of the newer antifungal agents. Experience with this drug has shown that there is a dramatic response with complete resolution of the infection. It gets localized at the sites where the organisms are present. Potassium iodide has a direct antifungal effect, anti fibrotic effect and is said to enhance the proteolytic activity of myeloperoxidase enzyme system of the polymorphonuclear leukocytes. It is given in the dosage of 40-60mg/kg body weight as mixture. Potassium iodide mixture is dispensed as 10 grains (600mg) in 1 ounce (30 ml) or approximately 2 gm in 100 ml of purified water. This should be administered along with fruit juice in two to three divided doses. Initially, patient is started on 5 drops three times a day for 3 to 5 days and is observed for evidence of iodism like lacrimation, rhinorrhoea. Then the dosage is gradually increased according to the weight of the child. The solution should be stored in a brown colored bottle to prevent exposure to sunlight. The drug has to be given for several months or 1 to 2 months following complete resolution of the lesion. Patients should be monitored for evidence of iodism and potassium toxicity.

Trimethoprim sulfamethoxazole alone or in combination with potassium iodide has been found to be effective. In case of slow clinical response, combination of potassium iodide with azoles namely itraconazole, ketoconazole or trimethoprim sulphamethoxazole may be beneficial. Itraconazole is preferable to ketoconazole by virtue of the higher concentration achieved in the subcutaneous tissues. It is given in the dosage of 5mg/kg body weight while ketoconazole is to be given as 4mg/kg. In case of intolerance to potassium iodide, itraconazole or ketoconazole alone may be given. Treatment of gastrointestinal basidiobolomycosis includes surgery and long course of itraconazole up to 1 year.

**Conclusion**

Subcutaneous phycomycosis or basidiobolomyosisis is a rare fungal infection of the subcutaneous tissues, which primarily occurs in children. Diagnosis is often missed or delayed resulting in advancement of the disease and unnecessary surgical intervention, which causes physical and mental turmoil to the children and parents and extra financial burden on the family that could have been avoided. Characteristic clinical presentation and definite histopathological features clinch the diagnosis. Awareness, early recognition and correct diagnosis will help prevent unwarranted surgical treatment of this infection, which is completely curable by medical management.

**Points to Remember**

- **Basidiobolomycosis is a rare subcutaneous fungal infection, primarily seen in children.**
- **Characteristic clinical features – Painless, slowly progressive, well demarcated subcutaneous mass/plaque, firm in consistency, attached to the skin, freely mobile over the underlying structures. Fingers can be insinuated at the margins of the swelling, which can be lifted from the underlying deeper structures.**
• **Diagnostic HPE finding**: Granulomatous infiltrate with plenty of eosinophils and fungal elements seen as unstained tubes and haloes surrounded by eosinophilic fringe (Splendore Hoeppli granular material).

• **Potassium iodide (KI) is the gold standard treatment. Trimethoprim - Sulpha methoxazole and itraconazole either alone or in combination with KI are effective.**

• **Early, correct diagnosis will prevent unnecessary surgical intervention.**

References


This review critically assesses recently published literature on predicting asthma exacerbations in children, while also providing general recommendations for future research in this field.

Recent findings: Current evidence suggests that every effort should be made to provide optimal treatment to achieve adequate asthma control, as this will significantly reduce the risk of severe disease exacerbations. Children who have had at least one asthma exacerbation in the previous year are at highest risk for subsequent exacerbations, regardless of disease severity and/or control. Although several tools and biomarkers to predict asthma exacerbations have been recently developed, these approaches need further validation and/or have only had partial success in identifying children at risk.
WHITE MATTER DISEASE

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The central white matter in the brain and cerebellum consists mainly of myelinated axons. Axons are essential for transmission of signals within the nervous system for co-ordinated function. Myelin is an insulator, increasing the speed of transmission that is essential for co-ordination. Myelination begins by about the 8th month of intrauterine life, continues after birth and is complete by 2 years. At birth the dorsal brainstem, ventral thalamus, lentiform nuclei, central corticospinal tracts and posterior portion of the posterior limb of the internal capsule are myelinated. Myelination progresses from central to peripheral, caudal to cephalad and from dorsal to ventral regions. Thus, the occipital lobes of the cerebral hemispheres myelinate early while the frontal lobes myelinate later.

In CT, unmyelinated white matter is more hypodense than normal white matter. This is the normal finding in small infants. If the same is seen after the period by which myelination is complete it is white matter disease. The involvement may be focal or diffuse and ultimately results in cerebral atrophy. MRI is more precise in mapping the extent of disease and narrowing the differential diagnosis. The normal progression of myelination and the changing appearance in MRI has to be recognized to correctly interpret white matter abnormalities. White matter changes are best seen in T1 weighted images up to the age of 6 to 8 months and T2 images are best, later.

Primary white matter diseases are divided into two. One group is “dysmyelinating disorders (metabolic)”- in which normal myelin fails to develop. They are due to disorders in lipid metabolism, enzymatic deficiencies (including mucopolysaccharidoses), mitochondrial disorders and aminoacidopathies. The other group is “demyelinating disorders”, in which normal myelin which has formed is later destroyed by ischemia or injury. The imaging appearances of all white matter disease are often non-specific and the

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Fig. 2. MRI - Metachromatic leukodystrophy. Leopard skin appearance.

Fig. 3. MRI - Metachromatic leukodystrophy. Tigroid appearance.

Fig. 4. Adrenoleukodystrophy. Extensive white matter hyperintensity is seen (arrows).

Fig. 5. Adrenoleukodystrophy. Cerebellar white matter is also involved.

Fig. 6. Adrenoleukodystrophy. Enhancing middle zone (arrows).

Fig. 7. Baby with hypoglycemia. Note the white matter hypodensities in the parieto-occipital regions.
Diagnosis is made with other information like clinical history, physical findings and laboratory investigations. Certain features may help. Macrocephaly is a feature of Alexander’s disease and Canavan’s disease. A posterior distribution in the early stages is in favour of adrenoleukodystrophy. Canavan’s disease usually spares the internal capsule.

Dysmyelinating disorders are broadly grouped into lysosomal disorders, peroxisomal disorders and mitochondrial disorders. The list of disorders under each heading is found in many textbooks.

Lysosomes are intracellular organelles which contain enzymes that digest phagocytosed particles. Depending on the enzyme there may be abnormal accumulations resulting in sphingolipidoses, glycoproteinosis, mucopoly saccharidoses or mucolipidoses. Metachromatic leukodystrophy is an example of lysosomal type, where there is a deficiency of the lysosomal enzyme “arylsulfatase A”. Biochemical diagnosis is by demonstrating low levels of arylsulfatase A in peripheral blood leucocytes and urine. Commonly the age of onset is between 12 and 18 months (“late infantile”). There is also a “juvenile” and “adult onset” type. Clinically it begins with muscle weakness. Deteriorating intellect, unsteady gait, quadriplegia and decerebrate posturing follow. Death occurs in 6 months to 4 years from the onset of disease. Fig.1 is a CT picture showing non-specific white matter hypodensity. MRI is more specific and shows the characteristic “tigroid and leopard skin” appearance of the white matter in the periventricular region and the centrum semiovale. The demyelinated white matter is hyperintense in T2 weighted images with hypointense spots (leopard skin) and streaks (tigroid appearance) (Fig.2 & 3). This is due to sparing of the myelin in the perivascular white matter. The corpus callosum, internal capsule and the cerebellar white matter can also be involved. Finally there is cerebral atrophy as in all white matter disease.

Some other lysosomal disorders are Krabbe’s disease, mucopolysaccharidoses and mucolipidoses. In mucopolysaccharidoses there are low signal intensity foci representing perivascular accumulation of mucopolysaccharides.

Peroxisomes are also intracellular organelles and peroxisomal disorders are due to deficiency of certain enzymes involved in gluconeogenesis, lysine and glutaric acid metabolism. One prominent entity in this group is adrenoleukodystrophy. This is an X-linked disorder that affects the white matter, adrenal cortex and testes. The enzyme that is deficient is “acyl CoA synthetase”. Demyelination starts in the peritrigonal area, spreads along the corpus callosum and then cephalad and outwards. The subcortical white matter or U-fibres are spared initially. Fig.4 shows extensive demyelination seen as bright or hyperintense white matter in frontal and occipital regions. Fig.5 shows involvement of the cerebellar white matter also. Fig.6 is a gadolinium enhanced T1 weighted image. The affected white matter shows an enhancing middle zone that is pathognomonic of this condition. Peripheral enhancement is also a feature of Alexander’s disease and is not seen in other types.

Zellweger’s syndrome is another peroxisomal disorder with multiple enzyme deficiencies. There is dysmyelination with polygyria or pachygyria.

Mitochondrial disorders are a group of complex neuromuscular disorders. One of the well recognized disorders is ‘MELAS’ characterized by vomiting, seizures and stroke like events. These children are normal at birth. MR imaging shows multiple cortical and subcortical infarct like lesions that cross vascular
boundaries. Follow up will show resolution and reappearance of the same pathology.

Canavan disease is an autosomal recessive disorder of aminoacid metabolism caused by deficiency of N-acetyl aspartase. There is an accumulation of N-acetyl aspartic acid in the urine, plasma and brain. There is hypotonia followed by spasticity, cortical blindness and macrocephaly. It is rapidly progressive. MRI shows subcortical and then deep white matter involvement.

Alexander disease is of unknown etiology characterized by macrocephaly, psychomotor retardation and seizures. There are characteristic frontal lobe hyperintensities which progress posteriorly. There maybe mild enhancement near the frontal horns.

There are vascular causes for white matter abnormalities in children. Ischemic injury in the preterm baby is seen in the periventricular white matter that represents the water shed area between vessels radiating from the centre and vessels penetrating from the cortex. Loss of white matter volume results in dilated ventricles. In the term neonate the watershed areas are parasagital cortex, basal ganglia and sometimes the brain stem and hippocampus. These watershed areas are areas of high metabolic demand and therefore sites of hypoglycemic injury. Fig.7 is that of a patient who had hypoglycemic seizures. CT scan showed white matter hypodensities in typical parieto-occipital distribution. MRI Fig.8 shows hyperintensity in the corresponding areas. Though only histological examination will differentiate between ischemic and hypoglycemic injury, the absence of localized hemorrhages on MR images is a feature of hypoglycemic encephalopathy. This is in marked contrast to the presence of minor hemorrhages in “post ischemic-anoxic encephalopathy”.
Another important multifocal white matter disease is “multiple sclerosis”. Though it is mostly prevalent in the 20-40 year age group it can also occur in the first and second decade. T1 weighted images show hypointense lesions typically in the corpus callosum. T2 images show hyperintense lesions in callosal, pericallosal and periventricular areas. “Acute disseminated encephalomyelitis (ADEM)” is considered as a monophasic analog of multiple sclerosis. This postinfectious demyelinating disease is usually seen in children and young adults. It is an autoimmune mediated white matter inflammation and demyelination presenting 1 to 3 weeks following exposure to a virus or vaccine. Fig. 9 is a FLAIR sequence of ADEM showing high intensity areas in the subcortical and deep white matter. Brainstem, cerebellum, basal ganglia and thalamus can also be involved. Fig. 10 shows high intensity areas in the medulla and spinal cord. Gray matter involvement is more common in ADEM than in multiple sclerosis. Encephalitis may resemble ADEM. Pial enhancement is a feature of meningoencephalitis and is not seen in ADEM. ADEM is steroid responsive while encephalitis is not.

White matter abnormalities can also be caused by trauma. “Diffuse axonal injury” where there is shearing between various brain parenchymal components causes demyelination in the subcortical white matter, gray-white matter interface, corpus callosum and brainstem. Focal hemorrhages and hemosiderin deposition are evidence for injury.

Imaging appearances are not adequate to identify a particular white matter disease. Inflammatory exudates, vasogenic edema and neoplasia can also mimic white matter disease. Only clinical history and laboratory investigations help in proper diagnosis.

**CLIPPINGS**

**Elective (regular) versus symptomatic intravenous antibiotic therapy for cystic fibrosis**

Chronic infection of the airways by Pseudomonas aeruginosa in people with cystic fibrosis is associated with deterioration in respiratory function. Intravenous antibiotics are the standard therapy for pulmonary exacerbations caused by this micro-organism. Many centres advocate the use of elective (regular) three-monthly antibiotics to reduce the frequency of exacerbations and therefore slow the deterioration of lung function. Alternatively, intravenous antibiotics are only prescribed when symptoms indicate. Elective therapy may encourage multi-resistance to antibiotics. This review aimed to identify randomised and quasi-randomised controlled trials that evaluated the results of the two different approaches. No clear conclusions were identified.

Studies are insufficient to identify conclusive evidence favouring a policy of elective intravenous antibiotic administration, despite its widespread use, neither are the potential risks adequately evaluated. The results should be viewed with caution, as participant numbers are small. Clearly there is a need for a well-designed, adequately-powered, multicentred randomised controlled trial to evaluate these issues.

TRACHEAL BRONCHUS IN AN INFANT WITH RECURRENT UPPER LOBE PNEUMONIA

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Abstract: Tracheal bronchus is an aberrant bronchus that arises most often from the right lateral wall of the trachea above the carina and directed to the upper lobe territory. This congenital anomaly may remain asymptomatic or present with wheezing, stridor, cough, recurrent or persistent right upper lobe pneumonia. We report a case of tracheal bronchus in a 9-month old female infant who presented with recurrent right upper lobe pneumonia.

Keywords: Tracheal bronchus, Recurrent upper lobe pneumonia

Tracheal bronchus is an aberrant bronchus that arises most often from the right lateral wall of the trachea above the carina and supplies entire upper lobe or its apical segment. It is usually an incidental finding during broncho-scopy or chest tomography. The incidence ranges between 0.5 to 2% in children undergoing bronchoscopy.

Case Report

A 9 month old female infant presented with recurrent episodes of acute respiratory infections from the first month of life. She was born at term by normal delivery to non-consanguineous parents. She weighed 1.7kg at birth. She developed fever, cough and hurried breathing at one month of age and was admitted. Her chest radiograph showed right upper lobe pneumonia and she was given parenteral antibiotics following which she improved. Subsequently she presented with recurrent episodes of acute respiratory infection. Chest radiograph done at 4 months of age again showed right upper lobe pneumonia which was treated with antibiotics. She had no stridor or wheeze at anytime. Her complaints during the present admission were fever, cough and fast breathing. Clinical examination revealed failure to thrive, facial dysmorphism (low set ears and depressed nasal bridge) and bilateral scattered crackles. She had leukocytosis with neutrophilic predominance. Chest radiograph once again showed right upper lobe consolidation (Fig.1). She was given parenteral antibiotics for two weeks. Repeat chest radiograph taken after three weeks showed incomplete resolution of pneumonia. There was no history of contact with tuberculosis. Mantoux test and human immuno deficiency virus (HIV) serology were negative. 2 Dechocardiography and USG examination of abdomen were normal. Since the common causes of recurrent upper lobe pneumonia were ruled out, congenital malformations of the lung and tracheobronchial tree were considered. Ultrasonography of the thorax showed right upper lobe collapse-consolidation with a right paratracheal solid mass.
Computed tomography of the thorax showed a homogenous opacity with crowding of air bronchogram within the opacity in the right upper lobe suggestive of collapse consolidation. On multiplanar reconstruction of the CT images, a bronchus was seen to arise directly from the right wall of the trachea 2 cm above the carina suggestive of tracheal bronchus (Fig.2).

**Discussion**

Tracheal bronchus was first described in 1785 by Sandifort. In a majority of cases, tracheal bronchus arises from the right wall of the trachea. Out of 35 cases of tracheal bronchus reported by Ghaye, et al, 28 originated from the right wall and 7 from left. The reported incidence varies between 0.5 to 2% of pediatric endoscopic studies. It may be associated with other bronchopulmonary anomalies like tracheomalacia, tracheal stenosis, congenital cystadenomatous malformation, congenital lobar emphysema and pulmonary sequestration. Extrapulmonary manifestations include congenital heart disease, diaphragmatic hernia and malformations of the ribs and vertebrae.

Children with genetic syndromes like Down’s syndrome and DiGeorge syndrome have increased incidence of tracheal bronchus and other structural airway anomalies. In a study by Ignacio, et al 6 out of 52 patients with tracheobronchial anomalies had more than one anomaly. Most of the tracheobronchial anomalies were localized to the right upper lobe.

Majority of young patients with tracheal bronchus have clinical manifestations like recurrent cough, stridor, wheezing, recurrent or persistent upper lobe pneumonia and atelectasis which result from narrowing at the origin of the tracheal bronchus. In a recent report of 7 children with tracheal bronchus, 4 patients had retained secretions in the tracheal bronchus which was responsible for symptoms of cough, wheezing and bronchial obstruction.

Our patient had right sided tracheal bronchus originating 2 cm above the carina. She presented with recurrent episodes of acute respiratory infection from early infancy. Apart from minor facial dysmorphic features, she did not have any other extrapulmonary congenital anomalies and was treated...
Conservatively. Congenital anomalies of the lung and tracheobronchial tree were considered in view of recurrent involvement of the same lobe. Bronchoscopy is the diagnostic tool of choice for tracheal bronchus and other tracheobronchial anomalies. Chest CT especially by techniques of multiplanar reconstruction, three dimensional reconstruction and three dimensional virtual bronchoscopy are good non-invasive alternatives for newborns and infants.1,8

Treatment is based on the severity of symptoms. Most patients with tracheal bronchus can be treated conservatively, but in patients with recurrent upper lobe pneumonia, atelectasis and air trapping, surgical excision of the involved segment and aberrant bronchus may be necessary.9

We report this case in view of its practical importance as a causative factor in recurrent or persistent right upper lobe pneumonia in children.

References

A RARE CAUSE OF EOSINO
PHILIA- ANTICONVULSANT
HYPERSENSIVITY SYNDROME

* Sudip Saha
** Madhusmita Sengupta

Abstract: The term “anticonvulsant hypersensitivity syndrome” refers to a severe, idiosyncratic cutaneous reaction to drugs, which leads to long-lasting skin eruptions in combination with facial edema, lymphadenopathy, fever, multivisceral involvement, eosinophilia and lymphocytosis. So far, numerous drugs such as sulfonamides, phenobarbitone, sulfasalazine, carbamazepine and phenytoin have been reported to cause DRESS syndrome (Drug rash, Eosinophilia, systemic symptoms). It usually appears acutely in the first 4-8 weeks after initiation of the drug and persists in some cases for months and is potentially life threatening with a mortality rate of 10%. We report a rare cause of eosinophilia due to anticonvulsant hypersensitivity syndrome.

Keywords: Eosinophilia, Syndrome, Carbamazepine.

4-year-old female was admitted with fever, exudative conjunctivitis, sub-conjunctival hemorrhage, raw red lips and inflamed oral mucosa for the previous three days along with raised maculo-papular rash all over the body including palms and soles simulating vascular purpura (Fig. 1).

Past history revealed that patient was admitted 14 days back with complex partial seizures on EEG and had been prescribed carbamazepine (with advice to attend) outpatient department after 2 weeks. Patient had taken carbamazepine for 8 days before the present symptoms appeared.

Fever subsided after 3rd day. Patient was started on intravenous antibiotics avoiding penicillin group of antibiotics. Carbamazepine was stopped after admission. Investigations revealed: Haemoglobin 9.8gm%, total leucocyte count 17,600/cubic mm (eosinophils 32%; neutrophils 45%; lymphocytes 21% and monocytes 2%). The absolute eosinophil count was 10,400/cubic mm, platelet count 1,86,000/cu.mm, C Reactive Protein 5.8mg/dl, ESR 20mm/1st hr. No immature or atypical cells were present in the peripheral blood. Blood biochemistry (Liver function test: SGPT- 36IU/L, SGOT- 54IU/L, ALP- 229IU/L, Bilirubin 0.9mg/L, protein 6.7g/dL, albumin 3.4g/dL) and culture for bacteria was negative and no evidence for parasitic infestation noted. ECG, chest X-ray and abdominal ultrasound examination did not reveal any abnormality. Histological examination of skin biopsy showed a non-specific picture consisting mainly of a moderate lymphohistiocytic infiltrate in the dermal papillae and around dermal blood vessels, with papillary edema.
Three diagnostic possibilities of Kawasaki disease, Steven Johnson syndrome, anticonvulsant hypersensitivity syndrome were thought of as there was a history of carbamazepine intake with 8 days gap before appearance of rash which was papular in nature involving palms and soles with exudative conjunctivitis.

Following admission, the patient was started on methylprednisolone intravenously 30mg/kg/day for 5 days and sodium valproate 300 mg orally daily. Five days after initiation of therapy, the patient’s erythema started showing a dusky hue and the scaling decreased markedly. The total leukocyte count and eosinophil count decreased to 9,000/cu.mm and 3,150/cu.mm respectively after one week and to 6,200/cu.mm and 124/cu.mm respectively after 2 weeks of steroid therapy. Oral prednisolone was started following intravenous methylprednisolone and tapered and stopped over a period of 3 weeks as the erythema and scaling completely subsided, leaving behind post-inflammatoty hyper pigmentation. The patient was treated in relative isolation with emollients, anti-histamines, paracetamol and a high protein diet.

Discussion

Anticonvulsant hypersensitivity syndrome (DRESS [drug rash, eosinophilia, systemic symptoms] syndrome) is a multisystem reaction that appears about 4 weeks to 3 months after starting phenytoin, carbamazepine, phenobarbitone, or primidone. Although initially described with anticonvulsant therapy, other drugs, and most commonly, antibiotics, have been implicated. The mucocutaneous eruption may be identical to that of Erythema Multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, but the reaction also typically includes lymphadenopathy, as well as fever, hepatic, renal and pulmonary disease along with eosinophilia, and leukocytosis.

Patients presenting with eosinophilia pose a large number of differential diagnosis to pediatricians (Table I). Considering dermatological diseases, a maculopapular rash in combination with eosinophilia may occur among patients with atopic dermatitis, hypereosinophilic syndrome (HES), malignancies, eosinophilic cellulitis (Wells’syndrome) or hypersensitivity reactions to drugs (Table II).

Our patient had lymphadenopathy and eosinophilia, skin and eye lesions which were typical of DRESS syndrome. It has recently been linked with lamotrigine. Most cases of lamotrigine-associated anticonvulsant hypersensitivity syndrome occur in the first 8 to 12 weeks of treatment, with the onset of fever, lymphadenopathy, and cough. The diagnosis should be suspected in any patient who presents with symptoms of an upper respiratory tract infection after recently starting lamotrigine treatment.

Several cutaneous and hematological adverse reactions have been observed during carbamazepine therapy. The various cutaneous eruptions caused by carbamazepine include...
Table I Eosinophilic disorders

<table>
<thead>
<tr>
<th>Atopic diseases</th>
<th>Atopic eczema, atopic rhinitis, atopic asthma</th>
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<td>Allergy</td>
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<td>Malignancies</td>
<td>Hodgkin’s disease, myeloproliferative disorders, acute myeloid leukemia (M4)</td>
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<td>Skin disorders</td>
<td>Wells’ syndrome, hypereosinophilic syndrome (HES), eosinophilic fasciitis</td>
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<td>Pulmonary diseases</td>
<td>Churg-Strauss syndrome, eosinophilic pneumonia</td>
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<td>Gastrointestinal disorders</td>
<td>Eosinophilic gastroenteritis</td>
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Table II Differential diagnosis in skin disorders associated with eosinophilia

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<tr>
<th>Medical history</th>
<th>Laboratory test</th>
<th>Systemic symptoms</th>
<th>Skin lesion</th>
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<tr>
<td>DRESS syndrome</td>
<td>Drug initiation or change within the past 2 months</td>
<td>Eosinophilia, leukocytosis, elevated liver enzymes, high ECP levels</td>
<td>Liver failure, renal failure, arthralgia, diarrhea</td>
<td>Maculopapular rash, exfoliative dermatitis, edema of the face</td>
</tr>
<tr>
<td>HES</td>
<td>No association with drugs</td>
<td>&gt; 6 months, in some cases leukocytosis, elevated liver enzymes, high ECP levels</td>
<td>Endocarditis, congestive heart failure, thrombosis, strokes, peripheral neuropathy, encephalopathy, hepatosplenomegaly, diarrhea, arthralgia</td>
<td>Erythroderma, edema, pruritus</td>
</tr>
<tr>
<td>Wells’ syndrome</td>
<td>In some cases relation to drugs or insect bite at lesional site</td>
<td>&gt; 50% of cases, leukocytosis and thrombocytosis may occur</td>
<td>None</td>
<td>Erythema and edema in initial phase, pruritic papular, annular plaques and urticaria-like eruptions, sometimes vesicles and blisters</td>
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morbilliform eruptions, urticaria, erythoderma, purpura, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug induced lupus, and photosensitivity. Various hematological side effects of carbamazepine include leukocytosis, persistent leucopenia, eosinophilia, agranulocytosis, aplastic anemia, and thrombocytopenia. The incidence of hematological reactions to carbamazepine has been estimated to range between 1:10,800 to 1:38,000 per year.\textsuperscript{9} In view of the significant mortality rate of the DRESS syndrome, which is about 10\%,\textsuperscript{10} the correct and fast early diagnosis of this entity is of great importance.

References


CLIPPINGS

Choi SW, Han JM, Bae YJ, Lee YS, Cho YS, Moon HB, Kim TB; Lessons from two cases of anaphylaxis to proton pump inhibitors. Journal of Clinical Pharmacy & Therapeutics (May 2012)

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VIJAYAKUMAR M

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