Acute Respiratory Ailments in Pediatric Age Group and Role of CRP in Diagnosis and Management

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Abstract

Respiratory diseases account for nearly 25% of all pediatric consultations. Acute respiratory infections (ARI) in infant, children, and adolescent age group are common incidence in India and worldwide. ARI need special care and knowledge from physicians to diagnose the exact pathology. It is sometimes very challenging to cure. In the intrauterine (fetal) life, gaseous exchange of oxygen and carbon-di-oxide does not occur in lungs as the placenta helps in exchange process. After birth hypoxia, temperature fluctuations, hypercapnia, and sensitivities of chemoreceptor play important role in breathing. With increasing age, there is expansion in lung

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volume, multiplication of alveoli and vessels for better and improved lung ventilation. The patients can be presented with cough (irritation of pharynx, larynx, trachea, bronchi, and pleura), rattling (due to excessive secretion in trachea-bronchial pathway), wheezing (audible whistling sound), stridor (upper respiratory obstruction by hoarseness, retraction of chest), tachypnea (abnormally rapid respiration), and dyspnea (difficult breathing). As the children cannot expectorate smoothly, there are always higher chances of lower respiratory tract infections like bronchiolitis, pneumonia, lung abscess, etc. These infections have to be diagnosed properly with blood investigations: pulmonary functions test (PFT), bronchoscopy, and imaging (X-ray or CT scan) techniques. Arterial blood gas analysis with supportive and definitive line of management is always crucial. Serial estimation of C-reactive protein (CRP) can guide the true recovery or deteriorating phases of infections in cumulative disease conditions apart from viable signs and symptoms.

**Keywords**

Acute respiratory infections · Pneumonia · Under-five children · Pediatric respiratory illness · Asthma · CRP · Bronchitis · RSV · Coronavirus

**Abbreviation**

| Abbreviation | Description |
|--------------|-------------|
| ADA          | Adenosine deaminase |
| AIDS         | Acquired immune deficiency syndrome |
| AOM          | Acute otitis media |
| ARI          | Acute respiratory infections |
| BMI          | Basal Metabolic Rate |
| bpm          | Breaths/minute |
| CAP          | Community-acquired pneumonia |
| CBC          | Complete blood count |
| CBNAAT       | Cartridge-based nucleic acid amplification test |
| CHERG        | Child Health Epidemiology Reference Group |
| COVID-19     | Coronavirus disease 2019 |
| CRP          | C-reactive protein |
| CT scan      | Computed tomography scan |
| ED           | Emergency department |
| ESR          | Erythrocyte sedimentation rate |
| GAPP         | Global Action Plan for Pneumonia |
| GBD          | Global Burden of Diseases |
| H1N1         | Influenza type A virus |
| Hib          | Haemophilus influenzae type b |
| HIV          | Human immunodeficiency virus |
| HMPV         | Human metapneumovirus |
| Hs-CRP       | High-sensitivity C-reactive protein |
| ICU          | Intensive care unit |
| IL-6         | Interleukin-6 |
| ILI          | Influenza-like illness |
1. In pediatric age group, common upper respiratory tract infections (URTI) like rhinitis (common cold), sinusitis, ear infections, acute pharyngitis, acute tonsillitis, epiglottitis, and laryngitis are discussed.

2. The common lower respiratory tract infections (LRTIs) in children are pneumonia bronchiolitis and tuberculosis are discussed with pathogens, diagnosis, and risk factors.

3. Tuberculosis is an important disease with very high prevalence (as high as 40%) in developing countries like India. Asthma accounts for 10% of all the respiratory childhood consultations.

4. C-reactive protein (CRP) is widely used to detect bacterial infection in children. CRP level along with other clinical findings is crucial in taking important decision regarding management like de-escalation of antibiotics. Role of CRP in URTIs and LRTIs are discussed. Management strategies of acute respiratory infections (ARIs) are discussed.

5. A clinical study is included to correlate the prognostic role of CRP with RTIs and related antibiotic dosage.

### 8.1 Introduction

Acute and chronic respiratory infections and subsequent diseases represent a global public health burden because of their increasing incidence and severity worldwide (Aaronson et al. 1955). This can be featured to several factors: (1) the significant spike in the occurrence of early allergen sensitization in childhood leading to asthma; (2) the frequent reappearance of viral infections usually associated with pediatric
population (Box 8.1); and (3) the increased survival of awfully preterm and fragile children born with bronchopulmonary dysplasia. All these factors supplement to the increased risk of acute expressions/symptoms becoming chronic. The persistent lung function deterioration thus leads to the development of chronic respiratory diseases in adulthood (Cutrera et al. 2017). Acute respiratory infections (ARIs) contribute to foremost disease associated mortality and morbidity among children under 5 years. Most of these deaths are due to bronchiolitis and pneumonia. Emergence of new microbial pathogens, re-emergence of previously controlled disease(s), widespread antibiotic usage and subsequent antibiotic resistance, and suboptimal coverage by immunization even after many novel efforts are major issues responsible for high incidence of acute respiratory infections. Low-cost interventions like hand washing, breastfeeding, availability of quick and feasible array of diagnostic assays, introduction of some new vaccines, and country-wise National Immunization Schedule (NIS) may reduce the burden of ARI by some extent. Epidemiological data on the incidence of different respiratory diseases are very scarce. The admissions of children with acute respiratory diseases on hospital or emergency department are becoming a routine phenomenon (Cutrera et al. 2017).

### 8.2 Epidemiology

In ARI incidence, Southeast Asia stands first in number (Wardlaw et al. 2006). Southeast Asia together with sub-Saharan African countries account for more than 80% of all incidences of ARI (UNICEF 2008). In India, due to pneumonia, more than 4 lakh deaths occur every year. Death from pneumonia account for 13–16% of all deaths in the hospital pediatric wards (Jain et al. 2001; Vashishtha 2010).

| GROUP                     | AGE                                      |
|---------------------------|------------------------------------------|
| 1. Neonate                | Birth to 28 days                         |
| 2. Post neonate           | 29 days to < 1 year                      |
| 3. Newborn                | First 4 weeks after birth                |
| 4. Infant                 | Birth to < 12 months                     |
| 5. Toddler                | 1 year to 36 months                      |
| 6. Preschool child        | 37-72 months                             |
| 7. School age child       | 73 months-12 years                       |
| 8. Adolescence            |                                          |
| i. Early                  | 10-13 years                              |
| ii. Middle                | 14-16 years                              |
| iii. Late                 | 17-20 years                              |
From 2000 to 2003, it is recorded that 10.6 million deaths annually occur in children under 5 years (Sharma et al. 2013). ARI alone accounted for 19% of children deaths and which is just over 2 million deaths. Bronchiolitis and pneumonia are the leading causes of death mostly caused by viruses (Bryce et al. 2005; Hart and Cuevas 2007). It is the most common infection in children in all age groups. Among the upper and lower respiratory tract infections, if we consider the milder form of the disease(s), in a country like India, it consists of the bulk of the cases reported from all socioeconomic status.

Sharma et al. (2013) found out that overall prevalence of acute respiratory infections (ARI) was 27% (Sharma et al. 2013). ARI was noticed more among low social class (79.3%), illiterate mothers (37.8%), those living in kutcha houses (52.6%), overcrowded houses (63.7%), use of smoky fuel for cooking (67.4%), inadequate cross ventilation (70.4%), with history of parental smoking (55.6%), low birth weight children (54.8%), and malnourished children (57.8%). Rural children (62.2%) were more affected than urban children.

Kuldeep et al. found that the overall prevalence of ARI was 32% (130/406) (Temani et al. 2016). Winter season, illiterate mother, >2 under-five children at home, overcrowding, smoker in house, family member suffering from cough and cold in last month, smoky chulhas, low birth weight (LBW), partial immunization, inappropriate breastfeeding were significant risk factors for ARI in children in India. No association was found between prevalence of ARI and age, sex, religion of child, geographic location of house in terms of main road, place of birth (home or hospital), and birth order of the child.

Pneumonia was ranked worldwide as the single largest killer of post-neonatal children in 2015. Pneumonia is attributable to nearly 15.5% of all deaths in children below 5 years of age. It is responsible for the deaths of around 900,000 children every year and is one of the most frequent causes of health facility consultation. The main cause of this disease in Southeast Asia and sub-Saharan Africa is low economic profile of population. In Bhutan, in spite of free traditional and modern medicine, the major public health challenge is acute respiratory infection (ARI) and represented 15% of the deaths in under-five children. Administration of Haemophilus influenzae type b (Hib) vaccine, pneumococcal conjugate vaccine, and childhood immunization schedule (from January 2019) were introduced to reduce ARI (Jullien et al. 2020; Liu et al. 2016; UNICEF 2018; Walker et al. 2013).

Common cold occurs round the year, but the incidence is greatest from the early fall until the late spring, reflecting seasonal predominance of viral pathogen. The recent incidence and outbreak of coronavirus infection in China and other countries started from early fall to late spring only. Young children have an average of 6–8 colds per year (Kliegman et al. 2020).

One of the leading under-five causes of mortality was pneumonia. In southern Asia and in sub-Saharan Africa, the leading cause of under-five deaths was pneumonia and preterm birth complications (Liu et al. 2016).

In 2010, estimated 120 million episodes of pneumonia (14 million of which progressed to severe episodes) in children below 5 years were noted of which
1.3 million of pneumonia led to death. *Streptococcus pneumoniae* (18.3%) is the most common cause of vaccine-preventable severe pneumonia (Walker et al. 2013).

In 2001, the Child Health Epidemiology Reference Group (CHERG), World Health Organization (WHO), and UNICEF estimated that pneumonia was the foremost cause of child mortality. This contributed to the initiation of Global Action Plan for Pneumonia (GAPP), a global effort (Rudan et al. 2013).

Williams et al. (2002) suggested that throughout the world 1.9 million children died from ARI in 2000, of which 70% reported from Africa and Southeast Asia (Williams et al. 2002).

The total number of pneumonia deaths of 1–59 months children for the year 2008 for 122 countries (with low (<85%) or no coverage of death certification) was estimated to be 1.18 M (calculated by regression model), which represented 23.27% of all 1–59 months children deaths (Theodoratou et al. 2011).

During 2000 and 2003, out of 73% of the 10.6 million yearly deaths reported in children younger than age 5 years, pneumonia accounted 19%, neonatal pneumonia or sepsis (10%), and asphyxia at birth (8%) (Bryce et al. 2005).

Study in 2008 showed that there are about 156 million new episodes of childhood pneumonia each year worldwide, of which 151 million episodes are reported in the developing world. Most incident cases occur in India (43 million), China (21 million), and Pakistan (10 million), with high numbers in Bangladesh, Indonesia, and also in Nigeria (6 million each). Pneumonia is responsible for nearly 19% of all pediatric deaths in children aged <5 years. More than 70% of the worldwide deaths of childhood pneumonia takes place in Southeast Asia and sub-Saharan Africa. The main pathogens associated with childhood pneumonia are respiratory syncytial viruses, *Streptococcus pneumoniae* and *Haemophilus influenzae*.

### 8.3 Spectrum of Respiratory Illness or Infections

Respiration is the act of breathing which consists of inspiration that means inhaling the air and expiration that is exhaling the air. Respiratory tract consists of organs which help in the action are nose, sinuses air pockets around the nose, mouth cavity, throat, larynx, trachea and its branches, bronchus and its divisions, and lungs. Depending upon the positions in the anatomy, the respiratory tract is divided into upper and lower respiratory tract. Upper respiratory tract mainly consists of nose, nasal sinuses, ethmoid, sphenoid, maxillary, and frontal. Lower respiratory tract consists of airway below the vocal cords, consists mainly trachea, bronchus, bronchiole, and lung parenchyma.

All infections of the upper (URI) and lower (ALRI) respiratory tract comes under the purview of ARI. Most of the infective respiratory viruses succumb throughout the respiratory tract without any representative clinical manifestations (Hart and Cuevas 2007).

For ARI, other allied factors are environmental (indoor air pollution, humidity), family upbringing (poverty, overcrowding, birth order, access to medical care), medical access (malnutrition, HIV/AIDS, prematurity, diarrheal disease, measles,
chronic lung disease, malaria, micronutrient deficiency), etc. (Hart and Cuevas 2007).

Each child in the first 2 years of life experiences nearly 8–9 episodes of URI per year. However in the progression from URI to ALRI, children more frequently develops acute tracheitis, laryngitis, bronchitis, bronchiolitis, and lung infections (pneumonia, tuberculosis, and empyema) (Hart and Cuevas 2007).

ALRI were assessed by WHO guidelines (Shann et al. 1984) (Fig. 8.1) and classified as mild, moderate, or severe based on the three principal signs of rapidity of breathing, chest indrawing, and inability to feed. This categorization determines therapeutic interventions. The modified assessment utilizes different thresholds for tachypnea. The threshold is 60 breaths/min (bpm) for children <2 months; it is 50 bpm in those of 2–11 months and 40 bpm in those of 1–4 years. This improves greatly the sensitivity of case identification. Any infection that affects the airways below the epiglottis is defined as ALRI and includes clinical pneumonia. The chief bacterial pathogens of pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae*. An increasing number of other pathogens (Fig. 8.2) causing clinical pneumonia or ARLI are enlisted. Vaccination against most of these pathogens has not been enrooted (Hart and Cuevas 2007; Lanata et al. 2004).

Lower respiratory tract infections (LRI) is a broad term that includes bronchiolitis and pneumonia, as defined by the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (Troeger et al. 2018; Jullien et al. 2020).

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**Fig. 8.1** The most widely clinical definition of ALRI was promulgated by the WHO. It assesses three principal signs to resolve severity namely rapidity of breathing, chest indrawing and inability to feed. From this point ALRI is grouped as mild, moderate or severe. Classification determines therapeutic interventions (Hart and Cuevas 2007; Shann et al. 1984).
About 200 antigenically distinct viruses have been suggested as causes of epidemic or sporadic respiratory infections in infants and children. Since more than 30 years rhinovirus, enterovirus, corona virus, respiratory syncytial virus and parainfluenza virus were summed up with adenovirus, influenza and measles virus as primary causes of respiratory tract infections. This list of viable pathogens was extended in 2006 with the discovery of human bocavirus, metapneumovirus and polyomavirus. The family of herpesvirus was also included as pathogen for respiratory diseases in immune-compromised patient (Brouard et al. 2007).

8.4 Risk Factors

In India, some crucial risk factors of ARI are unsatisfactory extent of breastfeeding, malnutrition of the child, suboptimal coverage of immunization, low literacy, poor socioeconomic factors, poor quality cooking fuel, indoor air pollution, and others to increase the burden of ARI among children (Acharya et al. 2003; Savitha et al. 2007; Selvaraj et al. 2014).

Mostly children are presented to hospitals or primary health care before clinicians with acute cough which may be clinically diagnosed and treated accordingly. As children could not give a clear-cut history of their illness, so diagnosis based on
visible symptoms is sometimes difficult. The causes of acute cough may be pulmo-
nary or non-pulmonary. The treatment decisions of children having acute cough or
difficulty in breathing is done on the basis of symptoms and other clinical
evaluations (Boxes 8.2 and 8.3).

**Box 8.2: Causes of Acute Cough**

- **URTI:** Common cold, rhinitis, postnasal
  discharge during sinusitis (in older children),
  hypertrophied tonsils and adenoids, laryngitis,
  pharyngitis and tracheobronchitis.
- **Whooping cough & measles.**
- **Foreign body in air passages causing allergic
  responses.**
- **Asthma & nasobronchial allergy.**
- **Pneumonia, bronchiolitis, empyema and
  pulmonary suppuration.**
- **Non pulmonary cause:** Congenital Heart
  Failure.

* [Paul and Bagga, 2019]

Children with atleast one atopic parent and atopic allergen sensitization within the
first 2 years of childhood was the major risk factor for developing asthma at 5 years.

In sinusitis, viral infections predispose the child to bacterial sinusitis and bacterial
middle ear infections. Acute rheumatic fever is one of the complications of tonsils
and adenoids. Complication of croup occurred around 15% of viral croups. The
highest risk in infants with acute bronchiolitis includes further respiratory compro-
mise in the first 48–72 h after onset of dyspnea and cough, desperate illness, air
hunger, respiratory acidosis, and apnea (Reuter et al. 2014).

In acute bronchiolitis, risk is higher for infants with young aged mother or with
mothers who smoked during pregnancy. Infants with preexistent smaller airways and
diminished lung functions are predisposed to this disease. Severe form of the disease
encompasses 12 weeks, preterm birth and underlying comorbidity (like pulmonary,
cardiovascular, neurologic, or immunologic disease) (Oymar et al. 2014). The most
common complications of common cold are acute otitis media (AOM), sinusitis, and
exacerbation of asthma along with indiscriminate use of antibiotics.

More than two episodes of either rhinovirus or respiratory syncytial virus infec-
tion or suffering, or a single lower respiratory tract infection increase the risk factor
to nearly 5–7 folds more. These children are more susceptible in developing asthma
in comparison to their atopic peers who were sensitized by allergen after 2 years.
Children, who were allergic at one year of age, are more susceptible in developing asthma at age of 14 years. Allergic sensitization was a prime risk factor below 2 years and becomes irrelevant in children >5 years (Kusel et al. 2007; Rubner et al. 2017; Cutrera et al. 2017).

Box 8.3: Treatment Decisions for Children (2 Months to 5 Years) with Difficulty in Breathing or Cough*

| Signs & symptoms | Type of disease/ Clinical condition | Therapeutic remedy |
|------------------|------------------------------------|--------------------|
| **1. COUGH OR COLD**<br>Without fast breathing<br>No chest indrawing<br>No indicators of severe illness | No Pneumonia | Remedies at home |
| **2. RESPIRATORY RATE**<br>RR/min Age<br>60 or more < 2 months<br>50 or more 2-12 months<br>40 or more 12-60 months | Pneumonia | Cotrimoxazole (at Home) |
| **3. CHEST INDRAWING** | Severe pneumonia | IV/IM penicillin (at Hospital) |
| **4. CYANOSIS**<br>Severe chest indrawing<br>Inability to feed | Very severe pneumonia | IV Chloramphenicol (at Hospital) |

* IV=Intravenous; IM=Intramuscular [Paul and Bagga, 2019].

The risk factors of sinusitis are meningitis, epidural abscess, subdural empyema, and brain abscess (Wagenmann et al. 1992). Complications of pneumonia include the widespread bacterial infections in thoracic cavity, hematological spread, and
bacteremia. Rare complications of pneumonia include suppurative arthritis, meningitis, osteomyelitis, and hematological spread of H. influenza or pneumococcal infection (Kliegman et al. 2020).

8.5 Pathophysiology of Upper Respiratory Tract Infections

Acute respiratory tract infections are not only affecting the respiratory tract but they also have systemic effects because of spreading of infection through blood (sepsis) or due to microbial toxins.

In pediatric age group, common upper respiratory ailments are rhinitis (common cold), sinusitis, ear infections, acute pharyngitis, acute tonsillitis, epiglottitis, and laryngitis. Ear infections and pharyngitis may cause complications like deafness and acute rheumatic fever.

**Common cold** is also known as rhinitis. It is mostly due to viral infection of the upper respiratory tract, children usually have runny nose (rhinorrhea), and nasal blockage are prominent. Systemic signs and symptoms such as fever, headache, body ache, fever, and lethargy are either mild or absent (Box 8.4).

**Box 8.4: Common Cold and Its Pathogens**

| PATHOGENS*       | COMMON SIGNS & SYMPTOMS                      |
|------------------|---------------------------------------------|
| Human rhinoviruses | Wheezing/bronchiolitis                      |
| Coronaviruses     | Brochiolitis in children < 2 y age         |
| Human metapneumovirus | Pneumonia and bronchiolitis               |
| Influenza viruses | Influenza, pneumonia, croup                |
| Parainfluenza viruses | Bronchiolitis                      |
| Adenoviruses      | Pharyngoconjunctival fever                 |
| Enteroviruses     | Herpangina                                 |

*Pathogens associated with common cold.
#Pathogens (relative frequency) includes all the frequent, occasional and uncommon viruses causing cold [Kliegman et al., 2016].
Viruses causing rhinitis are associated with symptoms of cough, wheezing, and fever. Most common causes of common cold are rhinoviruses. Common cold is frequently known as infectious rhinitis (rhinosinusitis) with the involvement of sinus mucosa. Nearly 200 types of human rhinoviruses are the most common pathogen of common cold. Rhinoviruses account for around 30% of URIs; respiratory syncytial viruses (RSVs), human metapneumoviruses, parainfluenza, and influenza viruses, and adenoviruses for around 35%; coronaviruses for 10%, and in <10% etiology cannot be ascertained. Enteroviruses are also the rare causes of common cold (Box 8.5).

These viral diseases show seasonal variation, in a tropical country like India. Rhinoviral infection is very common just before rainy season in June and July and also from October to February (Matthew et al. 2009).

Small children are more vulnerable to common cold, in India usually 4–6 episodes per year of common cold reported in children. However, incidence decreases as they grow up. Most of the common cold viruses are spread by aerosol, the small particles of biological fluid that form when we talk, sneeze, or cough. Viruses causing common cold are spread by direct hand contact, inhalation of air-borne aerosols from coughing or deposition of larger size aerosols deposited during sneezing on nasal or conjunctival mucosa. It has been shown that rhinovirus and RSV spread by direct contact also. Symptoms of virus infected common cold usually have throat irritation, pain in throat, runny nose, cough, fever, and malaise. Few viruses may also cause ear pain with infection of middle ear. Infections with adenoviruses and rhinoviruses result in development of serotype-specific immunity. Due to the presence of distinct serotype of each virus, repeated infections occur. The interaction of coronaviruses with host immune system is not clear-cut, but the distinct serotype variants of coronaviruses induce short-term protective immunity (Ulrich et al. 2020).

Routine blood studies are not recommended either useful for treating common cold, most of the time disease is self-limiting or remission occurred with minimal
supportive treatment. Viral culture in secretion is costly and not cost worthy in a developing country like India. In nasal secretion, neutrophil predominance may be seen which does not mean bacterial superinfection should be remembered.

Sinusitis is one of the complications of common cold (Box 8.6). It is a common illness of childhood and adolescence. Both bacterial and viral pathogens cause acute sinusitis. The maxillary and ethmoidal sinuses are present in a child since birth but only ethmoidal sinuses contain air within the cavities of sinus which are well developed. Maxillary sinus is solid and does not contain cavity since birth, the maxillary sinus contains cavity and air after 4 years of age. The sphenoidal sinuses develop after 5 years and frontal sinuses develop after 8 years. These sinuses are linked with nasal cavity by small ducts which drain sterile secretion by ciliary cleaning movements. So sinusitis is essentially a complication in children who are generally 5–8 years or older. Common viral infection can give rise to secondary bacterial sinusitis in 2–4% of the patients. About 70–80% of etiologies of infection in sinusitis are due to three bacteria, *Streptococcus pneumoniae* (~30%), *Moraxella catarrhalis* (~20%), and nontypeable *Haemophilus influenzae* (~20%). Child with sinusitis presented with nasal stuffiness, purulent nasal discharge, runny nose, fever, and cough. *Staphylococcus aureus*, other streptococci and anaerobic bacteria are uncommon causes of sinusitis. Acute bacterial sinusitis can occur in any age with upper respiratory infections and allergic rhinitis. Viral infection produces a viral rhinosinusitis.

Acute Pharyngitis, the inflammation of pharynx, indeed the name is misleading but this is the actual upper airway tract infection where a child has typical throat pain or discomfort, classically known as sore throat. Common etiological bacterial agents
are Group A beta hemolytic *Streptococci*, *Aracnobacterium haemolyticum*, *Fusibacterium necrophorum*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Francisella tularensis*, rarely *corynebacterium diphtheriae*, *Neisseria*, etc. Viral infectious agents are adenovirus, coronavirus, cytomegalovirus, enterovirus, etc. (Kliegman et al. 2020).

Pharyngitis differs etiologically according to the season; in winter season, it is mostly due to viruses, children with all age groups are equally involved. Whereas bacterial infection, mainly streptococcus infection, is present throughout the year and it is more common in children from 3 to 14 years. In adolescent children, arcanobacterium may cause many cases of pharyngitis.

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**Box 8.7: URTI Pharyngitis**

Child with pharyngitis presented with fever, sometimes very high grade, erythema, edema, pain in throat which causes difficulty in deglutition, generalized malaise, sometimes vague abdominal symptoms also accompany these symptoms. Tonsil becomes enlarged, oral mucosa and palatal wall become congested. The lymph nodes drain oral cavity and tonsil becomes swollen and painful.

The viral pharyngitis is distinct and can be clinically diagnosed as they present more with nasal stuffiness, nasal discharge, conjunctivitis, vesicle in pharyngeal mucosa.
The lymphatic tissue around our opening of gullet and glottis, means around the oral cavity and nasopharynx is called Waldeyer’s ring, palatine tonsils are part of this ring. Small collection of lymphoid tissue in posterior part of tongue is called lingual tonsil, also a part of this ring. Other members are scattered collection of tissue in posterior pharyngeal wall, the adenoids, a small collection between nasal septum and nasopharynx.

Common episodes of pharyngotonsillitis are caused by viruses. Tonsillitis can be acute or chronic infection. Acute tonsillitis, the most common bacterial cause is Streptococci, β hemolytic group A. Other uncommon are Staphylococcus aureus, Neisseria, and Corynebacterium. The chronic infection may be due to polymicrobial, both aerobic and anaerobic. In aerobic, Haemophilus influenzae is common whereas Peptostreptococcus is common among anaerobes as it is a normal commensal present in oral cavity.

Clinical manifestation of tonsillitis is fever, sometimes high grade and with malaise, bad breath may be present, pain in throat, difficulty in deglutition, enlarged neck glands may also present. In Chronic Tonsillitis, all symptoms may be present but more indolent together with may be foul smelling or cheesy discharge present.

Parapharyngeal and retropharyngeal abscess are formed due to infection in and around neck in the soft tissue. In neck, there are glands which are deeply situated; infection and inflammation are due to the draining organs; nodes infected can give rise to pus formation and abscess formation; depending upon the place of pus discharge the abscess is known as parapharyngeal or retropharyngeal abscess.

These are more common in 3–5 years of age group. A patient who has fever, neck pain, and stiffness will refuse to eat. In some cases, the child may be very ill with respiratory difficulty and stridor.

Bacteria which invade directly into the surrounding from infected tonsil can infect the deep tissues around the tonsil and form peritonsillar abscess. This is more common in the adolescent groups with history of tonsillitis. The child usually has fever, neck pain, and throat pain. Streptococcus and anaerobes bacteria of mouth are the most common offending agents.

Inflammation of the vocal cords and the structures inferior to the vocal cords are known as laryngitis, laryngotracheitis, and laryngotracheobronchitis. Laryngotracheobronchitis is also known as Croup. Croup is a heterogeneous group of acute and infectious reactions symptomized by brassy cough, hoarseness, respiratory distress, and inspiratory stridor. This is mainly a viral disease of children in which upper airway in and around glottis is affected, but if it does not resolve of its own within a week, superadded bacterial infection can occur. Croup affects larynx, trachea, and bronchi. The affected children usually have fever which may be low grade to very high grade in few instances, a typical barking cough, runny nose, and throat pain. Pathogens associated with croup are influenza A and B, respiratory syncytial virus, adenoviruses, and measles; rarely with Mycoplasma pneumonia.

Spasmodic croup is a variety of croup which is common in lower age group (1–3 years age), clinically similar to acute laryngotracheobronchitis, but mostly viral in origin. Also some psychological and allergic factors are associated with spasmodic croup. The occurrence of symptoms are often sudden and occur in late
evening or nighttime where the child awakens with metallic cough, characteristic barking, noisy inspiration, respiratory distress with frightened and anxious behavior.

**Acute Epiglottitis (supraglottitis)** is an acute condition, life threatening sometimes as the child develop acute airway obstruction due to disease. The child has fever, prostration, sore throat, dyspnea, drooling of saliva, and difficulty in swallowing. The child may go into severe respiratory distress with stridor (harsh, high-pitched respiratory sound) suddenly, with cyanosis. Diagnosis is by visualization of a large and swollen epiglottis by laryngoscopy.

**Acute laryngitis** is mainly due to viral etiology (diphtheria is an exception), the child presented with fever, cough, pain in throat, and characteristic hoarseness. The illness is generally mild where respiratory distress is quite unusual. Bacterial laryngitis is uncommon and in past mostly due to diphtheria, which is rare now even in developing countries.

**Bacterial Tracheitis** is the acute infection (upper airway tract) of trachea mostly due to bacteria such as *Moraxella catarrhalis, Streptococcus pneumoniae, Haemophilus influenzae*, and some anaerobic organisms. The most common pathogen is *Staphylococcus aureus*. It takes place between 5 and 7 years of age, with a slight predominance toward male population. It is often referred to as bacterial complications of viral disease, not just a primary bacterial illness.

The children usually have high fever with expectoration (brassy cough), purulent airway secretions, they usually do not have difficulty in deglutition or drooling of saliva as the upper airway inflammation is relatively absent. The cough is typical, brassy in nature with different grade of respiratory difficulty.

### 8.6 Role of CRP in Upper Respiratory Tract Infections

In a study by Appenzeller et al. (2002) (van der Meer et al. 2005), 9205 cases of common cold studied, 5788 (62.9%; 3394 men and 2394 women) patients tested positive for respiratory virus (RV) (Appenzeller et al. 2002).

In RV-positive cases, the rate of abnormal CRP levels was 62.8% (3633 of 5788 cases). In cases of single RV infection, the rate of abnormal CRP levels was 61.9% (2855 of 4610 cases), whereas in cases of viral co-infection (two or more infections), the rate of abnormal CRP levels was 66.0% (778 of 1178 cases). Abnormal CRP levels were observed in 66.0% (695 of 1053 cases) of double-infection cases and in 66.4% (83 of 125 cases) of ≥triple-infection cases.

The differences in abnormal CRP rates between overall positive cases and cases of co-infection were not statistically significant ($P = 0.28$), and no significant differences were observed between single infection and ≥ double infections ($P = 0.48$ and $P = 0.37$, respectively). The average CRP levels were $2.80 \pm 4.87$ mg/dL in all RV-positive patients, $2.82 \pm 4.94$ mg/dL in patients with single infections, and $2.71 \pm 4.56$ mg/dL in patients with double infections.

But the fact can be appreciated that even if it is in abnormal range still it is quite low than bacterial infection.
Schalek et al. did a study between positive culture from middle meatus and sinuses with CRP level; they found that positive middle nasal meatus cultures were observed in 24 (30%) patients while the remaining 56 patients were culture negative. The most common bacteria cultured was *S. pneumoniae* (12 patients), followed by *H. influenzae*, *S. aureus*, and *M. catarrhalis* (six, four, and two patients, respectively) (Schalek et al. 2015).

CRP values ranged from 0 to 101 mg/L, (\(\bar{x} = 23.70; \text{SD }\pm 24.74\)). The distribution of individual CRP levels was 0–20 mg/L in 46 patients (57.50%), 21–100 mg/L in 33 patients (21.25%), and in one patient the CRP value was greater than 100 mg/L (1.25%). The correlation coefficient was \(r = 0.221\) (\(P = 0.0498\)). Therefore, there was a significant.

In a study by Andreeva et al. shows that in 179 subjects use of CRP reduces usage of antibiotics significantly without compromising recovery (Andreeva and Melbye 2014).

In a study by Calvino et al. a total of 149 patients were enrolled. The most frequent etiology found was group A streptococcus, present in 83 cases (55.7%) (Calviño et al. 2014). The highest CRP concentration was observed among patients with group C streptococcus infection, with a mean of 56.3 mg/L (95% confidence interval, 25.7–86.5 mg/L). For patients with group A streptococcus infection, the mean CRP value was 34.4 (95% confidence interval, 25.6–43.3 mg/L). So they conclude that CRP concentrations are not associated with group A streptococcus infection in patients with acute pharyngitis. The use of this point of care test is therefore not useful for distinguishing patients who require antibiotic therapy.

In a study by Melby et al., 41 subjects are studied; an etiological agent was established in 23 of the 41 included subjects. These were: influenza A, influenza B, rhinovirus, and other agents. Among the 15 patients examined on both the second and the third day of illness, the median CRP value increased from 7 to 10 mg/L, and the mean value was from 19 to 24 mg/L between day 2 and day 3. Peak CRP values were reached on days 2–4. Higher CRP values were found in those infected with influenza A and B than in the other subjects (\(P < 0.001\)). A CRP value >10 mg/L was found in 26 subjects during the first 7 days, compared to five subjects after 1 week (Melbye et al. 2004).

Evidence of a secondary infection with group A streptococci was found in two of these five subjects. The development of the symptoms of sore throat, fatigue, clamminess, and pain from muscles and joints followed a similar course as the CRP response, while stuffy nose, cough, sputum production, and dyspnea tended to persist after the CRP values had approached the normal range.

A moderately elevated CRP value (10–60 mg/L) is a common finding in viral upper respiratory tract infection, with a peak during days 2–4 of illness.

Moderately elevated CRP values cannot support a diagnosis of bacterial infection when the illness has lasted <7 days, but may indicate a complication of viral infection after a week.

In a retrospective study by Cetin et al., evaluated medical records of 12 pediatric (<18 years old) cases diagnosed with deep neck abscess or abscess containing suppurative lymphadenitis and treated with only medical therapy between 2010
and 2015 (Çetin et al. 2017). They found that the laboratory examinations resulted in a high count of white blood cell (WBC), CRP, and ESR before the beginning of the medical treatment. All of the patients underwent intravenous (iv) antibiotic therapy immediately. The mean values of the baseline (the first day of hospitalization and parenteral treatment) WBC, CRP, and ESR were 18,050/μL (10,600–25,200), 99.8 mg/L (9–190), and 73.1 mm/h (39–100), respectively. Subsequent laboratory tests which are performed with a 2 or 3 days’ interval showed a declining trend in WBC, CRP, and ESR. The mean values of the last control (the day before the discharge from hospital) WBC, CRP, and ESR were 8166/μL (5200–12,000), 34.1 mg/L (2.1–101), and 35.3 mm/h (8–60), respectively, which proves that the infective markers are quite high in deep neck abscesses.

A moderately elevated CRP value (10–60 mg/dL) is very common in viral common cold, which peaks after 2–4 days of illness (van der Meer et al. 2005). Since sinusitis is mostly the bacterial infection, the blood culture and specimen culture yield good results. High level of serum CRP has also been observed.

Like other etiological factors the diagnosis of pharyngitis is aided by the patients’ history, and it has been shown in many studies that usage of antibiotics can be lowered with serum CRP level and chest radiograph. In case of viral etiology, the CRP level is generally low as compared with the bacterial etiology.

Diagnosis of tonsillitis and adenoid is essentially dependent on patient’s history, different clinical assessment with direct visualization of the tissue with laryngoscopy with history. Culture from throat swab and CRP values are helpful in diagnosis of bacterial infection. At high CRP values, antibiotics should be started.

In parapharyngeal abscess, CT scan may be helpful in diagnosis and aspiration of pus and different routine culture is helpful in identifying the microbe(s). In peritonsillar abscess patients, CRP is generally high as the level of bacteremia is very high.

The diagnosis of laryngotracheobronchitis is essentially based on different clinical tests. Since most of them are viral, the CRP value is of little help in the diagnosis.

In acute epiglottitis, CRP level is normal to high depending upon the course of the disease since this disease developed very fast so CRP value nearly remains normal when the child is first presented in healthcare facilities. CRP level is often normal in acute laryngitis and diagnosis is by clinical examination of the child.

Diagnosis of bacteria tracheitis is usually done by clinical examination and patient’s history. The CRP level is usually high due to bacterial preponderance.

8.7 Pathophysiology of Lower Respiratory Tract Infections

Acute bronchiolitis is caused by obstruction in the flow by internal narrowing of the airways. It is predominantly a viral disease where 50% of the incidence is caused by RSV. Other pathogens include adenovirus, rhinovirus, human metapneumovirus, human bocavirus, parainfluenza, and Mycoplasma. Bronchiolitis is rarely a bacterial cause. Huge numbers of children below 1 year are hospitalized with RSV infection. The disease is common among boys, in crowded population and in children who...
have not been breastfed. It is characterized by bronchiolar obstruction, edema, mucus, and cellular debris. Infants with acute bronchiolitis who are having respiratory distress (inability to take oral feeding, apnea, tachypnea, hypoxia) should be hospitalized.

**Pneumonia** is an infection which involves different pathological inflammatory process in lung parenchyma; the causes are varied from infection through microbes to non-infective causes also. It is the leading cause of death worldwide among children younger than age 5 year. Community-acquired pneumonia is actually the direct invasion of the lung by the bacterium present in environment. This can be attributed to both viruses and bacteria. Nearly one third of the cases are due to multiple infective organisms.

*Streptococcus pneumoniae* and respiratory syncytial virus are the most common offending agents. Apart from that *Streptococcus* pyogenes, *Staphylococcus aureus*, and *Haemophilus influenzae* type b are the major bacterial causes. Other common viral infective pathogens are influenza, parainfluenza, and adenovirus. In developing countries, *S. pneumoniae*, *H. influenza*, and *S. aureus* are the prime causes of hospitalization and deaths of children from bacterial pneumonia.

These pathogenic organisms directly invade the lower airway tract and destroy local immunity. The microbes proliferate and cause destruction of alveoli to form exudates in the alveolar cavity which give rise to the classical radiological impression of consolidation.

Classical pneumonia with classical radiological consolidation is becoming rare now particularly in pediatrics age group due to use of prophylactic antibiotics, especially in a country like India.

Clinically, the child may have history of other upper respiratory tract infection, few days prior to pneumonia. The child usually having fever, often high grade, cough, chest pain, in advanced stage respiratory difficulty is profound.

Abscess is due to infection or inflammation of certain region of lungs as a result of which the central part of necrosis of tissue occurs and a cavity is filled with material in radiograph. Children with **lung abscess** are mostly due to reflux disease, secondary infection with bacteria, developmental anomaly like trachea esophageal fistula, and pneumonia itself can cause abscess.

Bacterial lung abscess is due to fusobacterium, bacteroides, and other anaerobes which are present in reflux material. The child usually present with cough, fever, respiratory difficulty, and hemoptyis.

A lung abscess is an infectious pulmonary disease accompanied by pus-filled (or often air-fluid) cavity formation. Polymicrobial and multiple anaerobic bacteria are the causes of primary lung abscesses. The most common organism reported in lung abscess cases in Asia is *Klebsiella pneumonia*, but now *Staphylococcus aureus, Streptococcus pyogenes*, and *Actinomyces* are some new pathogens that are included in the spectrum. Other factors include unhygienic oral cavity, alcoholics with poor oral hygiene, and different dental diseases (Guo et al. 2019; Wang et al. 2005).

**Exacerbation of asthma** is a potentially serious complication of cold, but it is relatively uncommon. It is mostly associated with common cold. Since mostly
asthma exacerbation are related to non-infective causes, discussion of which is beyond scope of this chapter; we can concentrate on infective causes of asthma. The treatment of common cold is not always used as preventive therapeutics in exacerbation of asthma. Indiscriminate use of antibiotics causes complications in common cold. **Childhood asthma** is a reversible airway disease which is caused by bronchial hypersensitivity due to various factors that result in airway flow limitation.

Most common infective cause of exacerbation of asthma is viral, mostly by RSV (respiratory syncytial virus); other viruses are adenovirus, parainfluenza, and rhinovirus. Bacterial infection is not so common with asthma and whenever present is due to secondary to lower body immunity that is due to the disease itself.

Child present with all symptoms of allergic upper respiratory tract involvement like rhinorrhea, fever, coughs with wheezy respiration. Viral prodrome may precede the acute exacerbation by days to weeks.

**Tuberculosis** is a disease caused by *Mycobacterium tuberculosis* complex. In India, its prevalence is 40%, that means 40% people are exposed in general population with these bacilli in some form or the other and they are tuberculin skin test positive.

Generally, in lower age group according to wallgrens calendar extra-pulmonary (mainly pleural effusion and meningitis) and disseminated tuberculosis are common, but tuberculosis is an enigma of a disease, in children the author witnessed all forms of tuberculosis in India. Surprisingly, the author successfully treated three cases of MDR tuberculosis, and the youngest is a female of 6 months of age with extra-pulmonary MDR. Tuberculosis spreads through inhalation route, via droplets. Each bout of cough can have as much as 3000 infectious droplets which contain 1000–10,000 bacili per microliter.

After ingestion, they are engulfed by the TH1 lymphocyte, which triggers an immune response which leads to the release of many mediators specifically the IFN-γ, which help minimum aggregation of more cells and formation of classic granuloma.

In children, the first response is often formation of a granuloma with draining lymph node called a primary complex. The allergic reaction to tubercular antigen causes pleural effusion whereas if body immune response is not adequate to contain the bacilli it spreads and causes dissemination of infection.

Diagnosis is often difficult in tuberculosis. In case of dissemination of tuberculosis, it is mainly clinical with chest radiograph showing military shadows or visibility of hepatosplenomegaly in abdominal ultrasonography. The meningeal tuberculosis is a severe form of tuberculosis in children. The child presents with high fever and signs of meningism. It is often complicated with stupor or coma and convulsions. TB meningitis is diagnosed by clinico-radiological methods. MRI of the brain is gold standard in diagnosis (Daniel et al. 2019). CSF examination is very helpful in establishing the diagnosis, which shows high protein, low sugar, lymphocytic predominance in cell type, and ADA more than 10 (Gupta et al. 2013).

Pulmonary tuberculosis is diagnosed radiologically by chest X ray and direct visualization of the bacilli by microscopy (always preferable). Now DNA study (GeneXpert/CBNAAT and truNAAT) helps in early diagnosis of drug-resistant tuberculosis mainly in case of Rifampicin-resistant tuberculosis.
Blood investigation may show a lymphocytic predominant response which lacks sensitivity. ESR has got no role in diagnosis.

8.8 Role of CRP in Lower Respiratory Tract Infections

Pneumonia is diagnosed by history, chest radiograph, and blood investigation, routine as well as culture. Blood count and CRP are quite high in bacterial pneumonias. CRP is also helpful in determining response and choices of antibiotics. Gonzalez et al. studied 557 subjects who are admitted with a diagnosis of pneumonia; the following microorganisms were found in 171 (30.7%): *Streptococcus pneumoniae* (highest percentage), *Pseudomonas aeruginosa* *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, influenza A, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis* and one for each of *Staphylococcus aureus*, *Moraxella catarrhalis*, *Escherichia coli*, and *Enterococcus faecium* (Ruiz-González et al. 2016).

Subjects with pneumonia had serum CRP concentrations (median 187 mg/L). In a study by Garcia et al., a cohort of 1222 patients with CAP was assessed. CRP levels were analyzed in 258 patients with a single etiological diagnosis. The mean CRP values in patients with pyogenic, atypical, viral, and *Legionella pneumophila pneumonia* were measured and noted as 16 mg/dL, 13 mg/dL, 14 mg/dL, and 25 mg/dL, respectively (Vázquez et al. 2003).

Serum CRP was not useful to distinguish between pneumococcal, chlamydial, and viral etiology in 193 pediatric patients with pneumonia in a prospective, population-based study (Heiskanen-Kosma and Korppi 2000).

Concerning the conclusion that higher CRP levels appear to predict severity of illness, Seppä et al. (2001) reported that a CRP level ≥ 100 mg/L is a marker independently associated with higher risk of death in patients with lower respiratory tract infections (Seppä et al. 2001).

Additionally, Hedlund observed the following: patients with higher CRP levels had longer duration of fever; patients had longer hospital stay; and fewer patients had recovered clinically or radiographically at 8 weeks of follow-up after discharge. These findings suggest that CRP could be used together with other clinical, radiographic, and laboratory findings for the risk stratification of patients with pneumonia (Hedlund 1995).

A study by Fujita et al. shows 109 patients with bronchial asthma, with or without attacks. Mean serum hs-CRP levels were significantly higher in patients without attacks (0.473 mg/L) and with attacks (0.908 mg/L) (*P < 0.001* for both) than in controls (0.262 mg/L) (Fujita et al. 2007).

Serum hs-CRP levels were inversely correlated with forced expiratory volume in 1 s/forced vital capacity in asthmatic patients (*r = −0.4915; P < 0.01*). So they conclude, serum hs-CRP levels may be related to the state of asthma exacerbation and allergic inflammation.
In another study by Monadi et al., a total of 120 patients and 115 controls were studied. They found that median serum hs-CRP in asthma was higher than control \((P = 0.001)\), so they conclude that serum hs-CRP in asthma is higher than healthy control (Monadi et al. 2016).

In a study by Kwas et al. (2015), 44 patients were treated for pulmonary tuberculosis. In this study, they saw patients with cavitary lung lesions more frequent with elevated CRP (16 cases vs. 3 cases) and often with an extensive and bilateral pulmonary involvement (15 cases vs. 3 cases). Sputum positive acid-fast bacilli found in sputum was more frequent in the group of patients with elevated CRP (22 cases vs. 6 cases) (Kwas et al. 2015).

Wilson et al. performed a study in an area of South Africa that has a very high prevalence of HIV infection (40%) and a very high annual incidence of active TB (1094 cases/100,000 population) (Wilson et al. 2011). Serum CRP levels were measured in 364 patients who were being evaluated in primary care clinics for possible TB; based on extensive clinical, imaging, and laboratory data collected over 8 weeks of follow-up, 37% of the patients were categorized as having confirmed TB, 31% as having possible TB, and 32% as not having TB. The proportion of patients with normal CRP levels in each group was 2%, 20%, and 59%, respectively. An elevated serum CRP level was found to have 98% sensitivity and 59% specificity for the diagnosis of TB; the positive predictive value was 74%, and the negative predictive value was 96%. Importantly, HIV status did not significantly influence median CRP levels in the three diagnostic categories, and among HIV-positive patients with confirmed TB, CRP levels were highest in those with advanced HIV disease.

The diagnostic value of CRP in a total of 207 cases was evaluated by different number of patients with exudative-fibrotic tuberculosis, tuberculous pneumonia, tuberculous effusion, cavitary tuberculosis, miliary tuberculosis, mycoplasmal pneumonia, bacterial pneumonia, bacterial pneumonia with effusion, lung abscess, \textit{Strongyloides stercoralis} pneumonia, aspergilloma, and \textit{Pneumocystis carinii} pneumonia. Depending on the type of pathogen and the severity of inflammation, CRP level varies in different disease state (Lin et al. 1990).

Patients at admission with CRP <100 mg/L level has reduced risk for 30-day mortality and complicated pneumonia (lung abscess, empyema, or complicated parapneumonic effusion). However, when the CRP level could not fall by 50% (or more) at day 4, then it leads to an increased risk of mortality (30-day), mechanical ventilation, and complicated pneumonia. Thus, CRP is an independent marker of severity in community-acquired pneumonia (Chalmers et al. 2008).

For community-acquired pneumonia and in ventilator-acquired pneumonia, the laboratory investigations include CRP tests. In asthma diagnosis, CRP is often low to normal even with viral infection as compared to the bacterial infection. However, hs-CRP is often found elevated in exacerbation as compared to non-infective stage.
In China, the Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection has tremendous health burden. The allergy status and clinical characteristic of patients infected with SARS-CoV-2 were investigated by the researchers. Significantly high level of CRP was recorded in 140 hospitalized COVID-19 patients (Zhang et al. 2020). Marked elevated levels of CRP were most frequently found in pneumonia patients. However, in most patients with acute exacerbation of chronic obstructive bronchitis, acute asthma, and acute bronchitis the values of CRP were within the normal range. CRP values reflected sensitivities and specificities in the diagnosis of these diseases (Ritland and Melbye 1991).

CRP and BMI are potential predictors of development of asthma in Egyptian polycystic ovary syndrome (PCOS) patients. Asthmatic female patients with PCOS had higher CRP levels and IL-6 representing inflammatory condition. As a predictor of asthma, CRP had a specificity of 66% (Nasser et al. 2019).

However in a large study population of 1955 adolescent participants, no association between hs-CRP levels and any allergic (asthma, eczema, allergic rhinitis, food sensitization, aeroallergen sensitization, and any sensitization) sensitization was found (Yang et al. 2019).

Serum hs-CRP was lower in 79 infants with recurrent physician-diagnosed wheezing with recurrent respiratory syndrome. In early childhood wheezing, hs-CRP-mediated low-grade systemic inflammation is very rare (Määttä et al. 2017).

Research documentation revealed that hs-CRP can be a useful marker of airway inflammation in bronchial asthma in nonsmoking group without complications like hypertension heart disease, hyperlipidemia, infection or chronic obstructive pulmonary disease. Serum hs-CRP concentration significantly correlated with eosinophils and neutrophils count in the sputum. The serum hs-CRP level was higher in asthmatic patients as compared to healthy controls (Shimoda et al. 2015).

The mean serum hs-CRP levels were significantly higher in acute asthmatic patients as compared with healthy controls. Mean hs-CRP levels in patients were not correlated with indices of pulmonary function tests (forced expiratory volume in one second, forced vital capacity, and forced mid-expiratory flow). Thus, CRP is a useful diagnostic tool for detecting and monitoring inflammation in acute asthmatic patients (Razi et al. 2012).

Different studies were done to investigate the role of CRP in tuberculosis, it has been found that rise of CRP is different with different subset of patients as compared to mild localized disease, cavitary pulmonary disease, or bilateral diffuse infiltrative disease patients used to have higher CRP. In high CRP patients, chance of being sputum positive means chances of finding bacteria in sputum is also high.

High concentration of plasma CRP acts as an important predictor of pediatric active tuberculosis patients from healthy children in South Indian population (Albuquerque et al. 2019).
Children with active pulmonary tuberculosis and extra-pulmonary tuberculosis had significantly elevated levels of CRP, α-2 macroglobulin, hemoxygenase 1, and haptoglobin. CRP acts as a circulating biomarker (Kumar et al. 2013).

In a study by Bajaj et al., CRP levels were determined in 100 cases of tuberculosis and 30 age- and sex-matched children. Serial estimations, 1 and 3–6 months after initiation of therapy was done in 81 and 41 of these patients, respectively. Mean initial levels of CRP in tuberculosis group was 18.52μg/mL while in the control group it was 2.77μg/mL (P < 0.001). The elevated CRP levels fell significantly to 5.93μg/mL after 1 month of treatment (P < 0.001) and by 3–6 months of treatment had fallen to normal values. The fall in CRP levels correlated with clinical response. So they concluded that CRP is a sensitive indicator of activity of tuberculosis and the return to normal values of initially elevated CRP levels may indicate a good therapeutic response (Bajaj et al. 1989).

The antibiotic therapy of infants and children with pneumonia is based on the clinician’s diagnostic evaluations of the most common infecting pathogens, the susceptibilities of the host toward the infecting pathogens, and the gravity of the illness. Majority of the lower respiratory tract infections in children have a viral etiology, but bacterial etiology of pneumonia could not be ruled out. The causative pathogens are Streptococcus pneumoniae and Staphylococcus aureus. Pneumonia with viral etiology was not managed by antibiotic therapy. In replacement, protein-conjugated vaccines employing inflammatory biomarker like CRP could be employed. In case of invasive bacterial infection or viral etiology, new ancillary tests like blood culture, CRP level, and white blood cell count should be employed (Bradley 2002).

CRP and while blood cell counts have good negative predictive value and specificity in bacterial pneumonia where polymerase chain reaction technique remains too expensive (Le Roux 1998).

To withhold antimicrobial therapy, or its early discontinuance for subjects suspected of having neonatal sepsis, bacteremia, or pneumonia, CRP could be employed regardless of immune status. CRP was used in differential diagnosis of bacterial vs. viral diseases, acute otitis media, and lower respiratory tract infection (Jaye and Waites 1997).

8.9 Management of Acute Respiratory Tract Infections

Children become the future of the world after decades. According to their age, they are categorized as neonates, infants, children, etc. Acute respiratory tract infection carries a higher percentage in suffering, attending physician chamber, hospital admission, and overall a huge burden for the family in terms of money, anxiety, leave in workplace, etc. The signs and symptoms of acute respiratory tract infections are different in different age group. Neonates and infants, toddler, etc. can be
presented with crying, grunting, chest retraction, and little older age group can be presented with complain of earache, cough, throat pain, respiratory distress, or difficulty in sleeping or sitting in a particular posture (as explained by parents). According to anatomical position, we can divide the acute respiratory tract infections into two parts: upper respiratory tract infections which are above the vocal cord like sinusitis, pharyngitis, tonsillitis, epiglottitis, etc. and lower respiratory tract diseases which are below the vocal cord like pneumonia, bronchiolitis, tuberculosis, etc. and pneumonia is the major cause of under-five mortality in children.

We have to diagnose whether the infections are viral, bacterial, or allergic or other factors. The lines of management are different according to etiologies and stage of suffering. In medical science, to make a diagnosis, contribution of patients’ history is about 60–70%, clinical examination about 20–30%, and nearly 15–20% from laboratory investigations. In Infants, toddlers, preschool children and little older children getting proper history is often difficult as they do not express themselves properly. Furthermore, to clinically examine a child is also difficult as they turn restless. To prepare a patients’ history out of this and diagnose accurately is very challenging. The whole process of diagnosis should be made with great care. In case of infants, the total WBC count is usually high. CRP estimation has high importance in correct diagnosis as serial measurement of CRP level helps the clinicians to determine the children’s responsiveness in treatment. Gradual decrease in CRP level reflects therapeutic responsiveness and an increase in CRP concentration showed the worsening health status of the child.

For effective management (Florman et al. 1987), it is recommended that

1. The suffering patient with acute respiratory infections who is to be treated as an outpatient may need routine laboratory (if any) investigations.

2. If a child is admitted to hospital, then serum CRP test, cold agglutinin test (according to appropriate age), urine bacterial antigen tests will help to identify (type/strain) the etiology of the infection (or allergic infection also). Apart from viral, bacterial, or allergic infections, parasitic infections are also considered.

3. If antibiotic therapy is to be given, blood culture should be done before starting to check the culture positivity and sensitivity of the strain (toward the antibiotic). Diagnostic (bacterial or viral cause) or prognostic (self-limiting or life-threatening infection) ambiguity makes it complicated for clinicians to know when to prescribe and when to hold back antibiotic treatment.

4. For the child admitted to the hospital with viral lower respiratory infection or possible chlamydial infection, specific therapy is needed. Nasopharyngeal secretions should be studied for antigens of respiratory viruses like RSV, H1N1, Influenza, Parainfluenza and also chlamydia and other common pathogens, which helps us to move toward targeted therapy. Serum IgM level of different pathogen may also helpful for acute infections. For chlamydia infections and other viral infections, it should be diagnosed and move toward targeted therapy. Serum for IgM level may also be helpful.
5. For the child who has been intubated for additional respiratory support, a specimen of bronchoalveolar lavage is to be collected for Gram stain, fungal stain, Ziehl-Neelsen staining (ZN stain) and culture sensitivity of the lavage, viral markers (antigen) determination for more accurate diagnosis that will help for specific management.

8.10 Clinical Study Design

Dr. Das ascertains a correlation between CRP value in children with upper respiratory tract infection and lower respiratory tract infection including tuberculosis. The aim of this study is to find the contributory role of CRP in URTI and LRTI patients in positive diagnosis. The level of CRP is correlated with the administration of antibiotic among patients in three hospitals, namely Daffodil Polyclinic, Rajarhat, Kolkata; Astha Polyclinic, Ghusuri, Howrah; and Nibedita Polyclinic, Bally, Howrah, West Bengal.

The study of population includes 25 patients suffering from URTI (Group I) and 20 patients suffering from LRTI (Group II) who went for medical check-up in OPD with subsequent follow-up. Some patients were admitted under Dr. Das in nursing homes of Kolkata over a period of 1 year from 2017 till the end of the year.

The age of the children is strictly to be taken below 14 years and neonatal and infant cases were excluded.

8.10.1 Materials and Methods

Pediatric population of more than 1–14 years were considered for the study over a period of 1 year from January 2017 to December 2017 taken into consideration with the standard protocols for diagnosis. For URTI, only fever with common cold that is rhinorrhea, sinusitis, acute pharyngitis, tonsillitis, adenoids, croup is considered, whereas in LRTI only radiography proved pneumonia and acute exacerbation of asthma is considered. Patients’ blood samples were sent for laboratory investigations including CRP test. The levels of CRP of the patients were taken for this study (Table 8.1). Disease remission is taken into account by follow-up visits or telephonic conversation with the patients. Remission is taken based on the absence of the three symptoms, fever, cough, and breathing difficulty (if present), at the time of diagnosis. Generalized symptoms at the time of presentation include headache and chest pain.

The relationship between CRP values of two groups is calculated and relationship with remission is also calculated.

Study Design

Prospective observational study (cohort) taking only the values of CRP, age of patient, and antibiotic treatment.
Study Setting and Timeline
Pediatric population from more than 1 year to 14 years of age group come on OPD basis, they then may be admitted depending upon the disease severity by the clinician.

Place of Study
In three hospitals, namely Daffodil Polyclinic, Rajarhat, Kolkata; Astha Polyclinic, Ghusuri, Howrah; and Nibedita Polyclinic, Bally, Howrah.

Period of Study
Timeline is for 1 year from first January 2017 to 23 Dec 2017.

Study Population
Pediatric population from more than 1 year to 14 years of age group.

Sample Size
Sample size in this study includes the URTI group ($n = 25$) and LRTI group ($n = 20$). Both groups contain OPD patients; however, patients may be admitted after first OPD visit.

Inclusion Criteria
1. Pediatric population from more than 1 year to 14 years of age group.
2. All patients in this age group who visited the OPD of Dr. Das.
3. Patients having symptoms of respiratory tract infection were grouped based on the symptoms of URTI or LRTI. The most frequent medical symptom observed was acute cough. Wheezing, shortness of breath, and chest tightness were also recorded.

Exclusion Criteria
1. Subjects with severe form of disease needing ICU admission like acute epiglottitis were excluded.
2. Associated congenital diseases were excluded.
3. Any comorbidities like type 1 diabetes mellitus, Addison’s disease, and hypothyroidism were excluded.
4. Patient already on antibiotics dose prior to first OPD visit. That could modify the study result.

Study Variables
Age, sex, days at presentation, CRP test given to each subject, antibiotics required or not was noted (Table 8.1), days of remission which is defined in this study as the absence of at least fever, cough, and respiratory difficulty (if present) at onset.
| Sl no | Sex | Age | Disease | Days at presentation | CRP mg/dL | Antibiotics | Admission | Remission (days) |
|-------|-----|-----|---------|---------------------|-----------|-------------|-----------|-----------------|
| 1     | M   | 8   | URTI    | 8                   | 12        | No          | No        | 14              |
| 2     | M   | 13  | URTI    | 4                   | 8         | No          | No        | 11              |
| 3     | F   | 11  | LRTI    | 3                   | 86        | Y           | Y         | 16              |
| 4     | M   | 7   | LRTI    | 5                   | 112       | Y           | Y         | 17              |
| 5     | F   | 14  | LRTI    | 2                   | 45        | Y           | No        | 14              |
| 6     | F   | 8   | URTI    | 3                   | 23        | Y           | No        | 9               |
| 7     | M   | 14  | LRTI    | 3                   | 75        | Y           | Y         | 14              |
| 8     | M   | 9   | URTI    | 2                   | 8         | No          | No        | 12              |
| 9     | F   | 10  | LRTI    | 3                   | 86        | Y           | Y         | 16              |
| 10    | F   | 14  | LRTI    | 5                   | 102       | Y           | Y         | 13              |
| 11    | M   | 7   | URTI    | 2                   | 0.8       | No          | No        | 9               |
| 12    | F   | 12  | URTI    | 2                   | 18        | Y           | No        | 10              |
| 13    | M   | 11  | LRTI    | 3                   | 98        | Y           | Y         | 14              |
| 14    | F   | 8   | URTI    | 4                   | 9         | No          | No        | 8               |
| 15    | M   | 5   | URTI    | 3                   | 7         | No          | No        | 10              |
| 16    | M   | 3   | URTI    | 1                   | 11        | No          | No        | 14              |
| 17    | F   | 7   | LRTI    | 2                   | 7         | Y           | No        | 16              |
| 18    | M   | 12  | URTI    | 2                   | 8         | Y           | No        | 8               |
| 19    | F   | 11  | LRTI    | 2                   | 54        | Y           | No        | 13              |
| 20    | F   | 9   | URTI    | 2                   | 3         | No          | No        | 8               |
| 21    | F   | 5   | LRTI    | 4                   | 55        | Y           | No        | 14              |
| 22    | M   | 9   | LRTI    | 2                   | 38        | Y           | No        | 11              |
| 23    | F   | 10  | LRTI    | 1                   | 86        | Y           | Y         | 15              |
| 24    | F   | 4   | URTI    | 1                   | 3         | No          | No        | 9               |
| 25    | M   | 8   | URTI    | 3                   | 4         | No          | No        | 9               |
| No | Gender | Age | Diagnosis | Symptoms | Fever | Cough | Nasal Obstruction | CRP | Diagnosed | CRP | Diagnosed |
|----|--------|-----|-----------|----------|-------|-------|-------------------|-----|------------|-----|------------|
| 26 | F      | 14  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 27 | F      | 11  | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 28 | F      | 9   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 29 | M      | 11  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 30 | M      | 13  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 31 | F      | 4   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 32 | M      | 8   | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 33 | M      | 10  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 34 | F      | 10  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 35 | F      | 14  | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 36 | M      | 7   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 37 | M      | 3   | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 38 | F      | 4   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 39 | M      | 14  | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 40 | M      | 12  | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 41 | F      | 8   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 42 | M      | 9   | LRTI      | No       | Y     |       |                   | No  | No         |     |            |
| 43 | M      | 11  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 44 | F      | 12  | URTI      | No       | Y     |       |                   | No  | No         |     |            |
| 45 | F      | 7   | URTI      | No       | Y     |       |                   | No  | No         |     |            |
8.10.2 Results and Interpretation

Age and Sex

A. URTI cohort—there were 25 patients in this cohort, of them 13 boys and 12 girls, the age distribution is as follows:

| Age    | Number of patient |
|--------|-------------------|
| 0–4    | 2                 |
| 4–8    | 5                 |
| 8–12   | 11                |
| 12–14  | 7                 |

The mean age was 8.96 years with SD of 3.039

B. LRTI cohort—there were 20 patients in this cohort, of which 7 boys and 13 girls, the age distribution are as follows:

| Age    | Number of patients |
|--------|--------------------|
| 0–4    | 0                  |
| 4–8    | 5                  |
| 8–12   | 9                  |
| 12–14  | 6                  |

The mean age was 10.05 years with SD 3.119

CRP

A. URTI cohort—there were 25 patients in this cohort, the CRP distribution is as follows:

| CRP value (mg/L) | Number of patients |
|------------------|--------------------|
| 0–7              | 11                 |
| 8–15             | 11                 |
| 16–23            | 2                  |
| 24–30+           | 1                  |

The mean CRP value was 8.632 and the Standard Deviation was $\sigma$: 6.115 the variance is 37.3941

B. LRTI cohort—there were 20 patients in this cohort, there were 7 boys and 13 girls, the age distribution is as follows:

| CRP value (mg/L) | Number of patients |
|------------------|--------------------|
| 0–30             | 2                  |
| 30–60            | 6                  |
| 60–90            | 8                  |
| 90–120+          | 4                  |

The mean CRP value was 66.95, the Standard Deviation was $\sigma$: 25.935, the variance was 672.6475
The difference of mean of CRP in two groups is $\bar{\Delta} = -58.268$, with standard error $5.351$, value of $t$ statistics is $-10.890$ with $P$ value $<0.0001$, which is significant.

8.11 Discussion on the Clinical Study

As in authors’ study, the significance of CRP determination is high in LRTI compared to URTI patients. It also can be seen that patient with high CRP needs antibiotics as treatment measures.

ARTIs are among the most frequent reasons to consult in primary care for children and a common reason to prescribe antibiotics. Most of these prescriptions increase only the emerging problem of bacterial resistance. The use of so many antibiotics over the past few years has made almost all disease-causing bacteria resistant to antibiotics, which were commonly used to treat them. Studies showed that indiscriminate use of antibiotics is more pronounced in ARTIs (Little et al. 2013; Butler et al. 2009).

The blow of antibiotic resistance on human health are most commonly highest in countries with the lowest income because the spread of resistant bacterial strains is accompanied by poor hygienic condition, contaminated food, overcrowding, polluted water, and increased susceptibility to infection consequential from malnutrition or HIV. Diagnostic uncertainty makes it complicated for clinicians to know when to prescribe and when to withhold antibiotic treatment.

CRP is a diagnostic marker that helps to distinguish grave infections like pneumonia and sepsis from other self-limiting illnesses (Hopstaken et al. 2003; van der Meer et al. 2005). The effect of CRP in reducing antibiotic therapy for LRTI prescribing for lower respiratory tract infections has been studied in developed countries (Cals et al. 2010).

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