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PEDIATRICS

SPECIAL VOLUME 26





Recent Advances in PEDIATRICS

Infectious Diseases I

The most up-to-date compendium of peer-reviewed, evidence-based and state-of-the-art topical issues of special relevance and applicability to the Indian subcontinent and other resource-limited countries, especially in the South-East Asian Region (SEAR)

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2 Seasonal Influenza: ABC and Beyond

Suraj Gupte, Utpal Kant Singh, R Kumar

ABSTRACT

As a rule, seasonal influenza, occurring year after year worldwide and having a huge annual global burden, is a mild illness that subsides in a week or so. Nevertheless, it can be debilitating and can cause complications that lead to hospitalization and even death in pediatric subjects. In fact, extremes of age, immunocompromised states and preexisting underlying chronic diseases like diabetes, cardiopulmonary conditions, obesity, renal insufficiency, chronic smoking, pregnancy, etc. or the established risk factors. Usually, influenza A and less often influenza B are responsible for it. Transmission of infection is via aerosol, direct contact or indirect contact. Diagnosis is clinical though rapid and other diagnostic tests are available if required in certain cases. Two groups of antiviral drugs, M2 inhibitors and neuraminidase inhibitors are available for treatment. They are most effective when given within first 48 hours of onset of illness. With the development of increasing resistance, use of M2 inhibitors is no longer recommended. Only neuraminidase inhibitors remain the option. Prevention may be in the form of nonpharmaceutical measures, antiviral drug (oseltamivir) therapy and vaccination. Highly effective and safe influenza vaccines are the "gold standard" in prophylaxis of influenza and its severe complications in vulnerable subjects. Antiviral drugs may come in handy when the vaccination has been willy-nilly skipped. The role of nonpharmaceutical measures is supportive. Often, these may be the only available course, especially in resource-poor communities.

Keywords: Clinical manifestations, Complications, Diagnosis, Epidemiology Hemagglutinin, Flu, Influenza tests, Neuraminidase, Pathophysiology, Prevention, Prognosis, Seasonal influenza, Seasonal vs pandemic influenza, Sialic acid, Spread, Transmission, Treatment, Viral shedding

INTRODUCTION

Seasonal influenza, a respiratory viral illness, is by and large benign in a majority of the cases. Nevertheless, it can be debilitating and cause complications that lead to hospitalization and even death, especially in certain situations.

Every year, the global burden of influenza epidemics is believed to be 3–5 million cases of severe illness and 300,000–500,000 deaths. The risk of serious illness and death is highest at the extremes of life, i.e. among

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persons aged >65 years and children aged <2 years, and persons who have medical conditions such as cardiopulmonary disease, diabetes, obesity, immunoincompetence/suppression, etc. that place them at increased risk of developing complications from influenza.[1-3]

ETIOLOGIC CONSIDERATIONS

Influenza viruses belong to the family, Orthomyxoviridae. Type A and type B are the principle influenza viruses that cause seasonal influenza.[2,4] Type C may cause an inapparent or asymptomatic illness. Since it usually remains unnoticed, it is vitually of no clinical significance.

Figure 2.1 represents the structure of the virus, highlighting the surface proteins, hemagglutinin and neuraminidase, and the nucleoprotein (RNA).

PATHOPHYSIOLOGY

After the influenza virus invades the host's cells, replication occurs in various steps. It terminates with maturity of the virus (Fig. 2.2).

The mature virus buds off from the cell in a sphere of host phospholipid membrane, acquiring hemagglutinin and neuraminidase with the membrane coat.[3] A noteworthy point is that the virus adheres to the host cell through hemagglutinin. Once the neuraminidase of the mature viruses has cleaved sialic acid residues from the host cell, the mature virus detaches. Following the release of the new influenza virus, the host cell undergoes death.

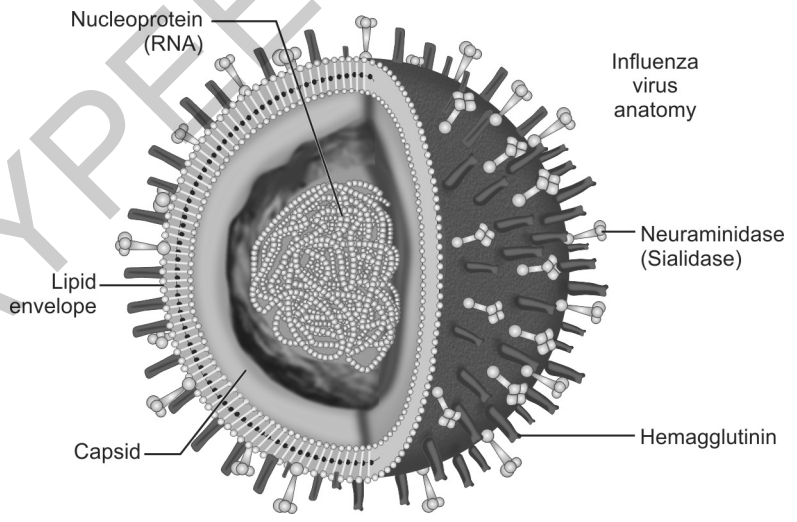

Fig. 2.1: Structure of the influenza virus: Note the surface proteins, hemagglutinin and neuraminidase (sialidase). Also highlighted are the lipid envelope and nucleoprotein (RNA) (*For color version, see Plate 1*)

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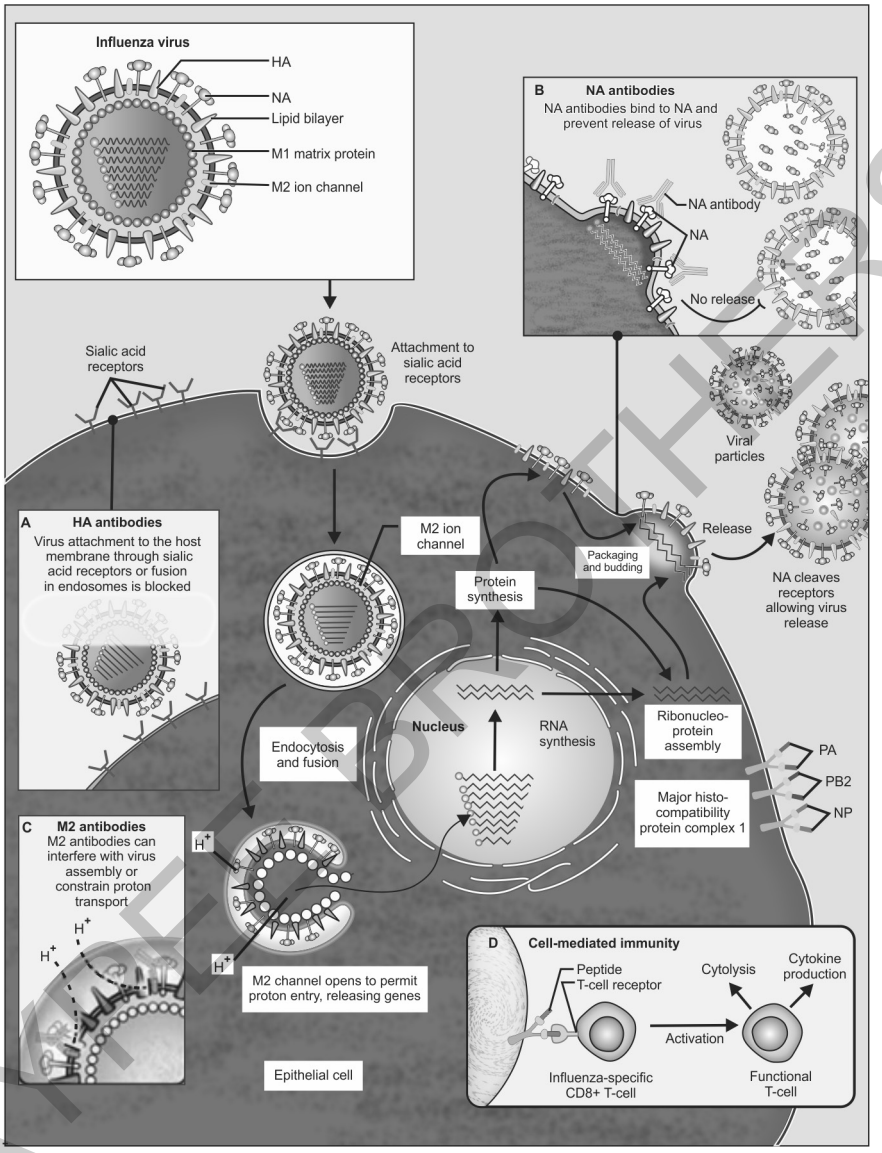

Fig. 2.2: Influenza virus replication. Note the various steps of replication of the virus (*For color version, see Plate 2*)

EPIDEMIOLOGY

A viral zoonosis of birds and mammals, influenza has probably existed since antiquity. Attack rates of influenza are relatively high but mortality is relatively low. Influenza mortality is highest in the very young, the very old, and the immunosuppressed subjects.

A number of epidemiologic factors need elucidation.[4-6]

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Agent Factors

In case of influenza viruses A, animal hosts (pig, chicken) act as a reservoir for various strains. These viruses have a potential for infecting the human beings. Any of the 15 hemagglutinins (H) and 9 neuraminidases (N) harboring the animal reservoir may be passed into humans. When coinfection occurs, the segmental nature of the influenza genome facilitates occurrence of re-assortment through interaction between an animal virus and human virus.

Epidemiologically, influenza A viruses behave in a unique way as though there were several serotypes. Three types of antigenic variations (a unique feature) contribute to spread of the disease, namely:

- Antigenic drift, meaning minor changes within a serotype
- Antigenic shift, meaning major changes within a serotype
- Migratory avian host.

Globally, annual spread of influenza viruses occurs between the Northern and Southern hemispheres. The origin of new strains is frequently traced to Asia. Subsequent to entry of an influenza virus (identified by a distinct hemagglutinin or neuraminidase) into the population, chances of occurrence of a pandemic of influenza with high morbidity and mortality become significant in predominantly a nonimmune population. The infamous 1918 pandemic of influenza killing millions of people across the board is considered the worst ever.

By and large, yearly variation in the antigenic composition of the surface proteins, conferring a selective advantage to a new strain, causes localized epidemics of influenza. The mortality is largely confined to the elderly and those with pre-existing cardiopulmonary disease (asthma, cystic fibrosis, congenital or acquired heart disease) and immunodeficiency. Each year's strain is novel in case of infants who, understandably, are unlikely to have pre-existing antibodies (other than maternally-transferred ones) on account of absence of exposure.

Just a word about the reservoir of infection. Animals (swine, horse, dog, and cat) and birds (domestic poultry, wild birds) constitute the major reservoir of influenza infection. Recombination between influenza viruses of man, animals and birds eminently occurs in the animal reservoir, thereby providing new strains of the influenza viruses.

Source of influenza infection is usually a patient suffering from influenza. Even a patient in a subclinical form is good enough. This source plays an important role in spreading the infection. Usually, infective secretions from the airway play a major role in the spread of infection.

Period of infectivity of influenza viruses is short (1–2 days before and 1–2 days after the onset of symptoms) since the virus is present in the nasopharynx.

Host Factors

Age

Young children are known to have the highest attack rate of influenza. Moreover, they demonstrate the highest frequency of isolation of the virus.

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Following primary exposure to an influenza strain, they also become very powerful transmitters of infection because of higher levels and more shedding of the virus than by the adults.

Mobility

Human mobility in the form of fast travel, say in aircrafts, plays a considerable role in spreading the disease rapidly to different areas, even beyond the country limits.

Immunity

Three types of influenza viruses are antigenically unrelated. Therefore, no cross-protection is likely. Following infection, antibodies appear in around 7 days, reaching a peak level in around 14 days. After 8–12 months, there is a drop in the antibody level to pre-infection state. Resistance to initiation depends on antibody against HA that neutralizes the virus. Reduced severity of illness and reduced ability to transmit virus to contacts depend on antibody directed against NA.

Understandably, protection correlates with serum antibodies as well as secretory IgA antibodies in nasal secretions. The secretory IgA antibodies (with a short life of few months only) appear to be more important in protecting against infection than serum antibodies (with a long life of several months).

No doubt, antibodies are capable of modifying the course of the illness. If a subject with a low titer of antibodies gets infected, he is likely to suffer from only mild form of illness.

Understandably, incomplete immunity fails to provide protection against the same virus.

Environmental Factors

Seasonal Variations

Dry weather and less availability of ultraviolet radiation from sunlight cause peak prevalence in winter which is at vertically opposite times of the year in the Northern and Southern hemispheres. In other words, in actuality, there are two different influenza seasons each year, i.e. October–March in North Hemisphere and April–September in Southern Hemisphere. However, in tropics and subtropics, influenza can occur throughout the year. Box 2.1 lists the various factors contributing to seasonal occurrence of influenza.

Factors contributing to seasonal outbreaks of influenza include—

- Low air humidity causing dry weather that leads to drier air which may dehydrate mucus, preventing the body from effectively expelling virus particles.
- Reduced availability of sunshine and thus ultraviolet radiation.
- Reduced vitamin D levels since people tend to stay indoors in wintry and rainy seasons, leading to reduced immunity to the virus.

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- Close contact of people who tend to remain indoor, promoting person-to-person transmission.
- Increased travel due to winter holiday season, leading to quick spread.
- Overcrowding, as in close population groups (schools, theaters, institutions, etc.), enhances transmission and, thereby, attack rates of influenza in the community.

TRANSMISSION AND SPREAD

Influenza has the potential for rapid spread, often involving large populations. Influenza spreads in the following three main ways:

1. **Direct transmission:** Here, an infected subject sneezes mucus directly into the eyes, nose or mouth of another subject.
2. **Airborne (Aerosol) transmission:** Here an infected subject produces aerosols (by coughing, sneezing or spitting) that another subject inhales. Some droplets, being very small are easy to inhale. Though a single sneeze releases up to 40,000 droplets, a sheer one droplet is good enough to cause an infection. A close contact (up to 1–2 meters) is needed for transmission. The majority of the droplets, being quite large, quickly settle out of air. The low humidity and lack of ultraviolet radiation from sunlight in winter facilitates survival of the virus. Hence, seasonal influenza usually in November–April period of the year.
3. **Direct Contact:** Hand-to-eye, hand-to-nose or hand-to-mouth transmission either from the contaminated surfaces or direct personal contact such as a handshake.
4. **Fomites:** Here, transmission/spread occurs through handling of fomites such as toys, garments, handekrchiefs, door knobs, currency notes, etc.

VIRAL SHEDDING

The term, *viral shedding*, denotes the time during which a person may be infectious to the other person. It is an important feature at the onset of symptoms or just before the onset of illness (0–24 hours). Viral shedding continues for 5–10 days. Young children may shed virus longer, placing others at risk for contracting infection with the virus.

Classically, it begins a day prior to appearance of manifestations. Then, the virus is usually released over the next 5–7 days. A small proportion of subjects may shed the virus for a longer period. Children shed virus for as long as 2 weeks after infection. They are supposed to be more infectious than the adults. Between second day and third day after contracting infection, the subject is most infective (contagious). More the viral shedding, higher is the fever.

Influenza virus is capable of survival outside the body and transmitted by contaminated surfaces like toys, currency notes, door-knobs, light switches and other household items.

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Duration of survival of influenza virus in various situations is as follows:

- *Hard, nonporous surfaces (plastic, metal)*: 1–2 days
- *Dry paper tissues*: 15 minutes
- *Skin*: 5 minutes
- *Mucus on currency notes*: Up to 17 days.

Avian influenza viruses, when frozen, can survive indefinitely. Heating to 56°C for a minimum of 60 minutes and acidic pH (<7) inactivate them.

Influenza is a disease of the relatively colder months (October–March) of the year. The portal of entry is the upper airway. Spread and transmission through the community, occurring by the small-particle aerosol, is rapid. In just 2–3 weeks, incidence of the illness reaches the peak. There is evidence that influenza contributes to hospital spread of infection. It is capable of complicating and worsening the primary illness with which the subject is hospitalized.

Influenza viruses are, as a rule, highly species-specific. This means that they usually do not spill over to cause infection in other species. This characteristic is ascribed to differences in the use of cellular receptors. Human influenza viruses bind to receptors that contain terminal 2–6-linked sialyl-galactosyl moieties. On the contrary, avian viruses bind to cell-surface glycoprotein containing sialyl-galactosyl residues linked by 2–3-linkage. For this reason, an avian virus has to acquire the ability to bind cells that display 2–6 receptors to facilitate its entry into the cell and replicate in it. Then and only then, it can transmit the illness to humans and between humans. At present we are aware of the potential routes whereby H5N1 can mutate and acquire human specificity. What we do not understand is as to which specific mutations are warranted for rendering H5N1 virus easily and sustainably transmissible among humans.

Out of the hundreds of strains of avian influenza, only four strains (H5N1, H7N3, H7N7 and H9N2) are on record to have caused infection in humans. The human infection as a result of transmission from avian reservoir has usually caused mild illness. Principal source of human infection with H5N1 is close contact with dead or sick birds (plucking, butchering, slaughtering, preparing) or exposure to feces of chickens on playgrounds.

Though, currently, H5N1 infection in humans is rare, there is evidence that the strains are becoming more virulent and pathogenic.

Since influenza is highly infective and modern travel is quite rapid, an epidemic stands good chance of developing pandemic proportions in a matter of weeks and a few months. This assertion is borne out by almost all past pandemics as well as the novel H1N1 pandemic of 2009–2010.

Invariably, one or two strains monopolize the seasonal influenza. Over the years, influenza type A strains with H1N1 and H1N2 serotypes are co-circulating. Since either type may be predominant in a given year, it becomes difficult to make predictions about the serotype and severity of the upcoming influenza season.

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CLINICAL MANIFESTATIONS[7-10]

The illness has a short incubation period of sheer 1–2 days.

Usually, onset of the illness is abrupt with typical systemic symptoms comprising high fever (ofen with chills and rigors), severe malaise, extreme fatigue and weakness, and bodily pains (headache, myalgia) in association with respiratory tract symptoms such as non-productive cough, sore throat, and rhinitis . Children often have additional acute otitis media (AOM) or croup. Nausea, and vomiting are frequent in them. Rarely, aypical presentation with febrile seizures or sepsis may be encountered.

The typical features of symptomatology of seasonal influenza without complications are listed in Box 2.1.

Severity of clinical presentation varies from afebrile respiratory symptoms resembling common cold to severe prostration without major respiratory signs and symptoms, especially in the elderly. Higher the fever, more severe are the symptoms.

Classically, fever and systemic symptoms last 3 days, occasionally up to 4–8 days, and gradually diminish. The cough and malaise may persist for more than 2 weeks. Second fever spikes are rare. The physical findings are summarized in Box 2.2. Full recovery may take 1–2 weeks. In the elderly people, it may take longer.

Box 2.2 summarizes the classical clinical findings in uncomplicated influenza.

The patients are infectious 24 hours before the onset of symptoms and up to around seven days thereafter. Children are even more contagious. For instance, young children can shed virus for several days before the onset of their illness and can be infectious for >10 days. In case of severely

Box 2.1: Typical features of symptomatology of uncomplicated influenza

- Abrupt onset
- *Systemic*: feverishness, headaches, myalgias (extremities, long muscles of the back; eye muscles; in children: calf muscles), malaise, prostration
- *Respiratory*: dry cough, nasal discharge—may be absent in elderly people who may present with lassitude and confusion instead
- Hoarseness, dry or sore throat often appear as systemic symptoms diminish
- Croup (only in infants and children)

Box 2.2: Classical clinical findings in uncomplicated influenza

- *Fever*: Rapidly peaking temperature at 38–40°C (up to 41°C, especially in children), typically lasting 3 days (up to 4–8 days), gradually diminishing; second fever spikes are rare.
- *Face*: Flushed
- *Skin*: Hot and moist
- *Eyes*: Congested and watery
- *Nose*: Rhinorrhea
- *Ear*: Middle ear inflammation (acute otitis media)
- *Throat*: Pharyngitis; laryngeal edema (causing croup)
- *Mucous membranes*: Hyperemic
- *Cervical lymph nodes*: Enlarged (especially in children)

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immunocompromised persons, virus shedding may well be for weeks or months.

During nonepidemic periods, respiratory symptoms caused by influenza may be difficult to distinguish from symptoms caused by other respiratory pathogens (see Laboratory Findings). However, the sudden onset of the disease, fever and fatigue are characteristically different from the common cold (Table 2.1).

COMPLICATIONS[11-18]

Lower respiratory tract infection in the form of acute bronchitis and pneumonia (primary, secondary or mixed) are the most frequent complication of influenza. Influenza may exacerbate the underlying cardiopulmonary disease such as asthma, chronic bronchitis, cystic fibrosis, etc. Influenza infection may also be accompanied by neurologic complications (encephalopathy, transverse myelitis), myocarditis, pericarditis, myositis and Reye's syndrome.

Acute Bronchitis

Involvement of the lower airway passes in the form of bronchiolar inflammation with such symptoms as cough with expectoration (acute bronchitis) and, at times, tachypnea, is such a common accompaniment of influenza that it is taken as a part of its symptomatology. Following the influenza attack, it may occur in the patient as such or as an exacerbation of the pre-existing chronic bronchitis. A typical radiologic picture of acute bronchitis is presented in Figure 2.3.

Acute Bronchiolitis

In infants, influenza may be complicated by acute bronchiolitis characterized by superadded wheezing and dyspnea as a result of inflammation of the

Table 2.1: Comparison of salient features of influenza and common cold

Symptoms	*Influenza*	*Common cold*
Fever	Usually high, lasts 3–4 days	Unusual
Cough	Invariable present and significant	Unusual; slight
Headache	Usual	Unusual
Fatigue/or weakness	Significant (may last up to 2–3 weeks)	Only mild
Bodily pains/aches	Usual and often severe	Unusual
Stuffy nose	Sometimes	Usual
Sore throat	Sometimes	Usual
Chest discomfort	Common and sometimes severe	Uncommon; Mild
Complications	Bronchitis, pneumonia, acute respiratory distress syndrome (ARDS); in severe cases life-threatening	Sinusitis

Adapted from: Gupte S. *Influenza*. Gurgaon (NCR): Macmillan 2010

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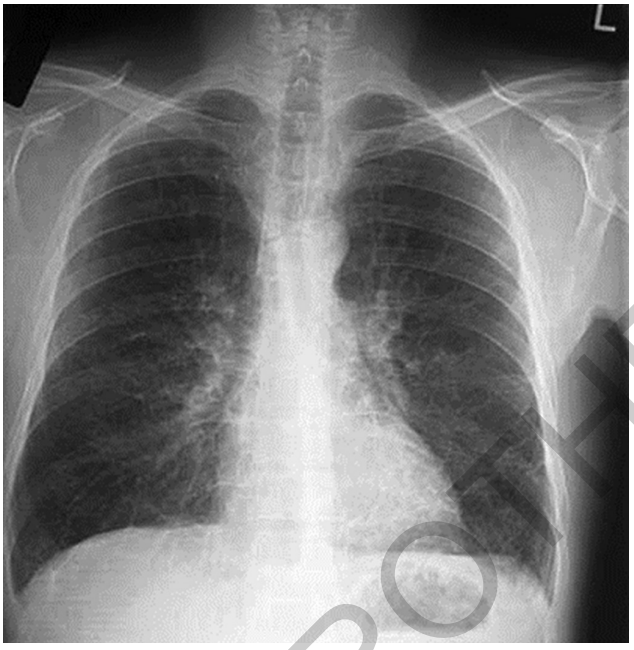

Fig. 2.3: Acute bronchitis. Note the inflammatory changes in the form of increased lung markings and bronchial wall thickening. Excessive mucus as such or with mucus plus leads to cough and, at times, tachypnea. Acute bronchitis is a common accompaniment of clinical spectrum influenza

small bronchioles. In the event of marked dyspnea, air hunger, flaring of cyanosis, alae nasi, chest retractions, hyper-resonant percussion note and widespread crepitations and wheeze. The child has a tendency to develop dehydration and respiratory acidosis. X-ray chest shows wide intercostal spaces, emphysema, prominent bronchovascular markings, small areas of collapse and low-lying diaphragm.

Pneumonia

- **Primary viral pneumonia:** Here, the clinical status shows progressive worsening with persistence of fever, dyspnea, and cyanosis. Initially, physical findings consistent with diagnosis of pneumonia may be missing. There may be evidence of acute respiratory distress syndrome (ARDS) with marked hypoxia. Figure 2.4 shows the microscopic picture of interstitial pneumonia. Classical X-ray findings include diffuse interstitial infiltrates (Fig. 2.5).
- **Secondary bacterial pneumonia:** *Streptococcus pneumoniae, Staphylococcus aureus,* and *Haemophilus influenza* are the most likely causes. The classical picture is that of a patient showing initially recovery from the acute influenza illness over 2–3 days followed by recurrence of

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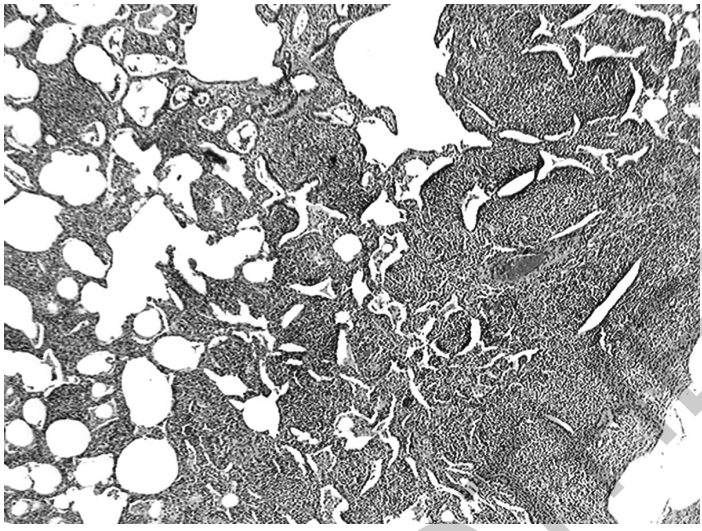

Fig. 2.4: Interstitial pneumonia (viral) in influenza. The classical interstitial changes in the photomicrograph form a hallmark of the disease
(*For color version, see Plate 3*)

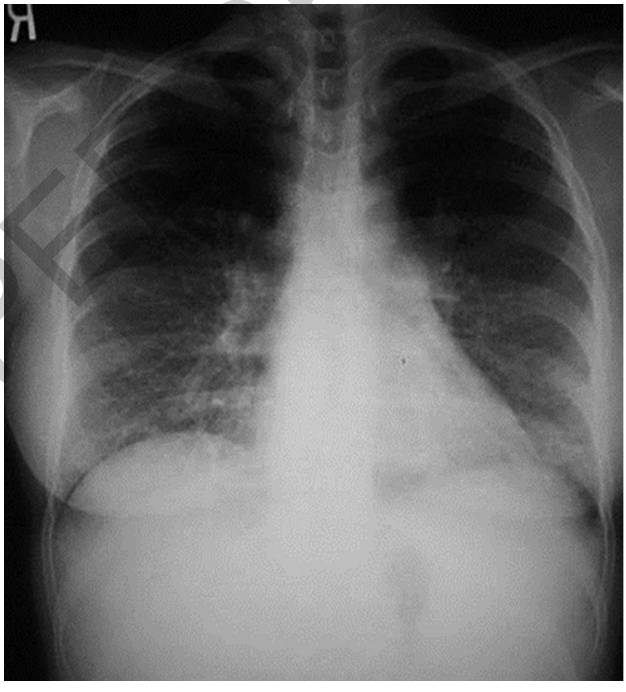

Fig. 2.5: Primary viral pneumonia. Note the classical interstitial changes in both lungs. Such a pneumonia as a result of influenza virus per se takes longer time top resolve. There is also additional risk of superadded bacterial infection, causing secondary pneumonia

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fever. Clinical signs and symptoms (cough, purulent sputum, and physical findings) are consistent with classical bacterial pneumonia. Chest X-ray shows signs of lobar pneumonia (consolidation) (Fig. 2.6). Predisposing factors for superadded bacterial pneumonia in influenza include chronic cardiapulmonary disease and olde age (>65 years). Institution of an appropriate antimicrobial regimen, depending on the probable etiologic bacteria, usually leads to recovery.

- **Mixed viral and bacterial pneumonia:** Mixed influenza pneumonia occurs in patients with underlying chronic cardiopulmonary or immunocompromised state (Fig. 2.7).

Exacerbation of Chronic Pulmonary Disease

Infectious pathogens play an important role in the pathogenesis of chronic respiratory disease. In chronic bronchitis, clinical influenza infection may lead to a permanent loss of pulmonary function. In infants and children, influenza-induced asthma may continuously deteriorate during the first two days of illness. Reconvalescence is typically longer, most subjects having it for at least seven days. There is evidence that influenza virus may have a role in the pathogenesis of asthma attacks in adults.

Croup

A proportion of children suffering from influenza may develop croup. It is likely to be of severe type compared to other viruses, say parainfluenza viruses.

Failure of Recovery

Severely compromised elderly people (>65 years) and infants and young children, especially with a cardiopulmonary disease, are at particular risk of morbidity and mortality. What is remarkable is the risk of morbidity may extend beyond the first week, fortnight or more after influenza complications. A small proportion of patients may simply never recover from influenza complications—and eventually succumb to deterioration of underlying pulmonary, cardiovascular, or renal function.

Myositis

Myositis, usually involving calf muscles, may infrequently occur as a complication of influenza B virus infection, and to a lesser extent influenza A around 3 days after the onset of the influenza infection). Resolution of symptoms occurs within 3 days or so. Rarely, it may persist for a week or two. Serum creatine phosphokinase (CPK) level is generally high.

Cardiac Complications

Though skeletal muscle insult is common in influenza, myocarditis, once considered a frequent complication, is a rare event during influenza infection.

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