Pathogenesis and Immunity

Influenza initially establishes a local upper respiratory tract infection. To do so, the virus first targets and kills mucus-secreting, ciliated, and other epithelial cells, causing the loss of this primary defense system. NA facilitates the development of the infection by cleaving sialic acid residues of the mucus, thereby providing access to tissue. Preferential release of the virus at the apical surface of epithelial cells and into the lung promotes cell-to-cell spread and transmission to other hosts. If the virus spreads to the lower respiratory tract, the infection can cause severe desquamation (shedding) of bronchial or alveolar epithelium down to a single-cell basal layer or to the basement membrane.

In addition to compromising the natural defenses of the respiratory tract, influenza infection promotes bacterial adhesion to the epithelial cells. Pneumonia may result from a viral pathogenesis or from a secondary bacterial infection. Influenza may also cause a transient or low-level viremia but rarely involves tissues other than the lung.

Histologically, influenza infection leads to an inflammatory cell response of the mucosal membrane, which consists primarily of monocytes and lymphocytes and few neutrophils. Submucosal edema is present. Lung tissue may reveal hyaline membrane disease, alveolar emphysema, and necrosis of the alveolar walls (See Figure 1).

Interferon and cytokine responses peak at almost the same time as virus in nasal washes and are concomitant with the febrile phase of disease. T-cell responses are important for effecting recovery and immunopathogenesis. However, influenza infection depresses macrophage and T-cell function, hindering immune resolution. Interestingly, recovery often precedes detection of antibody in serum or secretions.

Protection against reinfection is primarily associated with the development of antibodies to HA, but antibodies to NA are also protective. The antibody response is specific for each strain of influenza, but the cell-mediated immune response is more general and is capable of reacting to influenza strains of the same type (influenza A or B virus). Antigenic targets for T-cell responses include peptides from HA but also from the nucleocapsid proteins (NP, PB2) and M1 protein. The NP, PB2, and M1 proteins differ considerably for influenza A and B.
but not between strains of these viruses; hence T-cell memory may provide future protection against infection by different strains of either influenza A or B.

The symptoms and time course of the disease are determined by interferon and T-cell responses and the extent of epithelial tissue loss. Influenza is normally a self-limited disease that rarely involves organs other than the lung. Many of the classic “flu” symptoms (e.g., fever, malaise, headache, and myalgia) are associated with interferon induction. Repair of the compromised tissue is initiated within 3 to 5 days of the start of symptoms but may take as long as a month or more, especially for elderly people. The time course of influenza virus infection is illustrated in Figure 2.

### Epidemiology

Strains of influenza A virus are classified by the following four characteristics:

1. Type (A, B, and C)
2. Place of original isolation
3. Date of original isolation
4. Antigen (HA and NA)

For example, a current strain of influenza virus might be designated A/Bangkok/1/79 (H3N2), meaning that it is an influenza A virus that was first isolated in Bangkok in January 1979 and contains HA (H3) and NA (N2) antigens.

Strains of influenza B are designated by (1) type, (2) geography, and (3) date of isolation (e.g., B/Singapore/3/64), but without specific mention of HA or NA antigens, because influenza B does not undergo antigenic shift or pandemics like influenza A does.

New influenza A strains are generated through mutation and reassortment. The genetic diversity of influenza A is fostered by its segmented genomic structure and ability to infect and replicate in humans and many animal species (zoonose), including birds and pigs. Hybrid viruses are created by coinfection of a cell with different strains of influenza A virus, allowing the genomic segments to randomly associate into new virions. An exchange of the HA glycoproteins may generate a new virus that can infect an immunologically naïve human population. For example, an H5N1 duck virus and an H3N2 human virus infected pigs, reassortants were isolated from the pig, and the resulting virus was able to infect humans (Figure 59-5). This type of reassortment is postulated to be the source of pathogenic human strains. Because of its high population density and proximity of humans, pigs, chickens, and ducks, China is thought to be a breeding ground for new reassortant viruses and the source of many of the pandemic strains of influenza.

In 1997, a highly pathogenic avian influenza virus (HPAIV) (H5N1) strain was isolated from at least 18 humans and caused six deaths in Hong Kong. Wild water fowl have become a reservoir for this virus.
and spread the virus around the world. Outbreaks of infection of poultry and isolated human cases continue to be reported in Africa, Europe, and Asia. Although relatively few humans were infected, this H5N1 virus is unusual because it is not a reassortant, it is very virulent, and it can pass directly from bird to man. A tropism for the lower lung requires inhalation of larger amounts of virus, and the virus and target tissue make human infection very lethal. Avian influenza is transmitted in bird feces, not by human-to-human transmission. Outbreaks of avian influenza require the destruction of all potentially infected birds, such as for the 1.6 million chickens in Hong Kong, to destroy the potential source of the virus. Concern that a reassortant with a human influenza virus might generate a pandemic has spearheaded an international drive for development and stockpiling of vaccines.

**Minor antigenic changes** resulting from mutation of the HA and NA genes are called **antigenic drift**. This process occurs every 2 to 3 years, causing local outbreaks of influenza A and B infection. **Major antigenic changes** (**antigenic shift**) result from the reassortment of genomes among different strains, including animal strains. This process occurs only with the influenza A virus. Such changes are often associated with the occurrence of pandemics.

Antigenic shifts occur infrequently but can be devastating. For example, the prevalent influenza A virus in 1947 was the H1N1 subtype. In 1957, there was a shift in both antigens, resulting in an H2N2 subtype. H3N2 appeared in 1968, and H1N1 reappeared in 1977. The reappearance of H1N1 put the population younger than age 30 at risk to disease. Prior exposure and an anamnestic antibody response protected the members of the population older than 30 years. In contrast to influenza A, influenza B is predominantly a human virus and does not undergo antigenic shift.

The changing antigenic nature of influenza ensures a large proportion of immunologically naïve, susceptible people (especially children) in the population. An influenza outbreak can be readily detected from the increased absenteeism in schools and work and the number of emergency department visits. During the winter, influenza outbreaks occur annually in temperate climates. Fortunately, influenza virus is present in a community for only a short time (4 to 6 weeks).

Influenza infection is spread readily via small airborne droplets expelled during talking, breathing, and coughing. The virus can also survive on countertops for as long as a day.

The most susceptible population is children, and school-age children are most likely to spread the infection. Contagion precedes symptoms and lasts for a long time, especially in children. Children, immunosuppressed people (including pregnant women), the elderly, and people with heart and lung ailments (including smokers) are at highest risk for more serious disease, pneumonia, or other complications of infection. More than 90% of mortalities occur in patients who are older than 65 years.

Extensive surveillance of influenza A and B outbreaks is conducted to identify new strains that should be incorporated into new vaccines. The prevalence of a particular strain of influenza A or B virus changes each year and reflects the particular immunologic naïveté of the population at that time. Surveillance also extends into the animal populations because of the possible presence of recombinant animal influenza A strains that can cause human pandemics.

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