Chinese Guidelines for Diagnosis and Treatment of Influenza (2011)

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Introduction

Influenza, an acute respiratory infection caused by influenza virus, is one of public concerns to human health. Epidemiologically, influenza is characterized by a sudden outbreak and rapid transmission with varying epidemics, seasonality, and a high morbidity yet low case fatality (usually 0.003% to 0.03% except for human avian flu). The past 300 years has witnessed at least six global pandemics, including four in the 20th century -- three of them originated in China.

Seasonal influenza can typically give rise to rapid onset of acute respiratory disorders with febrile symptoms. Although self-limited in most of the times, influenza with severe infections or complications may necessitate hospital admission. The elderly, young children, pregnant women or those with underlying chronic diseases are at high risk of contracting severe influenza, and a few of them may die of respiratory or multiple organ failure. The human avian flu, on the other hand, is caused by highly-pathogenic avian influenza viruses (such as H5N1) with a case fatality up to 60%. While vaccination remains so far the mainstay for prevention and control of influenza, early use of antiviral agents may help relieve symptoms, shorten the course, reduce complications, attenuate viral shedding and even bring down the mortality. During an epidemic, prophylactic use of antiviral agents may also help reduce the incidence of influenza. Given the genetic variability of influenza viruses, effective prevention and treatment will continue to be a medical matter of top priority.

To further promote awareness and understanding of influenza among the public, government officials and patients, and to improve the clinical diagnosis and treatment, China has developed a series of medical documents, including the Draft Guidelines for Diagnosis and Treatment of Influenza (2002) (1), Interim Technical Guidance for Prevention and Control of Avian Influenza Epidemics (2004) (2) and four editions of Protocols for Diagnosis and Treatment of Influenza A (H1N1) (2009 and 2010) (3,4). Ever since, these documents have played a significant role in improving patient care, medical research and case fatality in relation to several types of influenza viruses in China.

However, reflection on the 2009 pandemic of influenza A (H1N1) virus demonstrated the dire need for a new set of guidelines that are well compatible with late-breaking advances and actually applicable for clinical practices, so as to improve understanding of and preparedness for prevention and control of influenza (including seasonal and avian flu). To this end, the Chinese Ministry of Health commissioned a panel of experts from fields of virology, epidemiology, laboratory diagnostics, clinical medicine, Chinese traditional medicine, and disease control and prevention related to influenza. The new guidelines for diagnosis and treatment of influenza were developed to adapt the bedside practice for vast majority of medical professionals in

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China, with reference to the previous editions, the latest studies worldwide, and local experience in management of influenza. The core of these guidelines has incorporated up-to-date information on virology, epidemiology, clinical manifestations, diagnosis and differential diagnosis, and treatment and prevention of influenza, hopefully to improve the medical care for this disease, and to reduce the huge threats it potentially imposes to human health and the society.

Virology

The influenza virus is a member of the Orthomyxoviridae family with a single-stranded segmented negative-sense RNA genome. In general, the viruses appear as spherical, enveloped particles 80-120 nm in diameter. Filamentous virions are usually seen in new isolates, and can measure up to several micrometers long. Influenza viruses are classified as types A, B and C, identified by antigenic differences in nucleocapside proteins (NP) and matrix proteins (MP). Influenza virus types A and B contain eight RNA segments, while type C contains only seven with the one that encodes neuraminidase missing (5). The genomes of influenza A and B strains encode at least 10 and 11 proteins, respectively. As these genomes are segmented rather than a single piece of nucleic acids, gene re-assortment among viral strains of a same species appears more likely to occur, and so does gene mutation in a higher frequency compared with other viruses, since RNA proofreading enzymes are absent in the process of influenza virus RNA replication (5,6). Influenza A viruses are further classified, based on structures and genetic properties of surface hemagglutinin (HA or H) and neuraminidase (NA or N). Currently, 16 HA subtypes (H 1 to 16) and 9 NA subtypes (N 1 to 9) of influenza A virus have been identified (7). For each new isolate of influenza A virus, the full nomenclature includes the type of virus, the host of origin (except for human), geographical site of isolation, number of isolate, and year of isolation followed by description of HA and NA subtypes in parentheses, eg. A/Brisbane/10/2006(H3N2). Types B and C viruses follow the similar nomenclature but without subtype classification. Influenza viruses are widespread in animals. All known subtypes of the type A virus, including the 16 HA and 9 NA subtypes, have been identified in avians, waterfowls in particular, and may also infect other animals such as pigs, horses, seals, whales, and minks. So far, humans are the only natural host for influenza B viruses. Influenza C viruses can infect both humans and pigs. All influenza viruses are readily inactivated by ultraviolet and heat (usually at 56 degree Celsius for 30 minutes). A pH of less than 5 or greater than 9 may quickly attenuate the communicability of the virus. Like other enveloped viruses, influenza viruses are susceptible to all membrane-perturbing reagents, including ionic and non-ionic detergents, chlorine-based disinfectants and organic solvents (7).

Epidemiology

A sudden outbreak and rapid transmission subsequently with varying epidemics typically features the epidemiology of influenza. Epidemics of influenza presents with certain seasonality, usually lasts 3 to 4 weeks before a spontaneous subsidence, and is associated with a high morbidity yet low case fatality. In northern China, a peak of influenza epidemics is common during the winter, whereas in the South, epidemic influenza can be perennial with one peak each in the summer and winter. China National Influenza Center provides weekly updates of epidemiological and virological surveillance on influenza at its website (www.cnic.org.cn).

Influenza may occur as sporadic cases, outbreaks, epidemics and pandemics. Sporadic cases occur during non-epidemic periods, with a low incidence, and in a scattered, isolated manner such that they are not interlinked chronologically or geographically. An outbreak occurs when influenza affect many individuals in a small, localized group or area over a short time. An epidemic is the occurrence of cases in obvious excess of what normally be expected in a larger geographical region. A pandemic, sometimes referred to as a global disease outbreak, occurs when influenza rapidly becomes widespread around the world, causing a high incidence and a certain death toll (8,9). Influenza pandemic often comes in two or three waves. The first wave generally last for a short time with a high incidence. The second one may last longer, which has a low incidence yet probably high mortality. In some cases, a third wave can follow. Influenza A viruses often occur in epidemics, and may evolve into a worldwide flu pandemic. Influenza B viruses often cause localized outbreaks and do not lead to pandemics. Type C viruses mostly give rise to sporadic cases, usually affect infants and young children, and rarely cause epidemics.

History of pandemic influenza

Over the past 300 years, there might have been at least six pandemics of influenza, including four with detailed records in the 20th century, and the one caused by reassortant H1N1 influenza A viruses in 2009. Of those events, the 1918 influenza pandemic known as Spanish flu (H1N1) probably originated in the United States; the 1957 Asian flu (H2N2) in China's Guizhou Province; the 1968 influenza pandemic (H3N2) in Hong Kong; the 1977 influenza pandemic, also called Russia influenza (H1N1), probably in Dandong, a north-eastern city of China; and the 2009 novel influenza A (H1N1) pandemic in Mexico and the United States (10). Previous pandemics of influenza encircled the globe in 6 to 9 months, with a speed apparently constrained by patterns of human travel and not accounting for seasonal factors. Given the amount and velocity of international traffics today, spread of influenza viruses can

conceivably be much faster.

Reservoir

Subjects with clinical or subclinical infections are the major reservoir of influenza viruses, and remain contagious from late in the incubation period through the acute phase of the disease. Typically, the mean duration for sustained viral shedding from airway discharge is 3 to 6 days in adults and older children with uncomplicated seasonal influenza. Hospitalized adults may steadily transmit the infectious virus to others throughout one week or longer after onset. Long-term shedding (for 1 to 3 weeks) of viruses can be frequent in infants and young children with seasonal influenza or in patients with H5N1 avian influenza. Immunodeficient patients, including those with AIDS, may also show a prolonged period of viral shedding (10).

Transmission routes

Influenza is mainly spread through air droplets, or by direct or indirect contact with mucosa of the mouth, nose, eyes, and so on. Infection is also possible through contact with airway discharges and body fluids from patients, or with surfaces or materials that have been contaminated with the virus. The probable transmission through airborne aerosols from the airways is yet to be further confirmed.

Susceptible population

People are susceptible to influenza infection throughout their lives. Moreover, influenza viruses mutate frequently. For example, novel antigenic variants of influenza A viruses with epidemiological significance will emerge every two or three years as a result of immune pressure from the host population, and the highest infection rate is usually observed among young people.

Population at high risk of severe influenza

When flu-like symptoms are identified in the general population, specific population groups are prone to becoming severe cases of influenza and should therefore prompt medical alerts to early tests for influenza and other investigations as needed (4,11). These people may include:

A. Pregnant women;
B. those who have diseases or pertain to conditions as follows:
    a) Chronic airway diseases, cardiovascular diseases (not including hypertension), renal diseases, liver diseases, blood disorders, nervous system disorders or neuromuscular diseases, metabolic and endocrine diseases;
    b) Immune suppression (including immunocompromise caused by HIV infection or use of an immunosuppressant);
    c) Institutionalized in a nursing home or other chronic care facilities;
    d) Long-term aspirin users aged 19 years or younger;
C. Obese people [with a body mass index greater than 30, wherein BMI = weight (kg) / height $(m)^2$];
D. Children younger than 5 years old (those aged below 2 are more likely to have severe complications); and
E. People at the age of 65 years or older.

Pathogenesis and pathology

Pathogenesis

When airborne particles containing influenza virus are inhaled into the airway, viral neuraminidases begin to destroy neuraminic acids, so that mucins are hydrolyzed and glycoprotein receptors are exposed. Human influenza A and B virus absorb to receptors on the epithelial cells which contain sialic acid by HA protein (5). Human influenza viruses preferentially attach to sialic acid wih α-2, 6 receptors, which are present in the upper and lower respiratory tracts, mainly in the bronchial epithelium and alveolar type 1 cells, whereas avian influenza viruses prefer the α-2, 3 receptors which are found in the distal bronchioles, alveolar type 2 cells and alveolar macrophages. Influenza C virus binds to 9-O-acetyl-acetylneuraminic acid-bearing receptors.

After internalization into endosomes, the ion channel in the membrane comprised of M2 polypeptide is also activated by the acid pH in the endosomes. This process results in an influx of protons into the virion (uncoating). Following uncoating of virus and transportation of RNP into the nucleus, transcription and replication of viral genome take place in the nucleus. Viral nucleoproteins synthesized in the cytoplasm enter into the nucleus to form the nucleocapsid with viral RNA, which is released to the cytoplasm. Upon complete processing and modification, viral membrane proteins are embedded within the cell membrane. Following the export of the RNPs into the cytoplasm, the viral glycoprotieins assemble at the cytoplasmic membrane. Progeny virus particles are released by sialidase cleaving siliac acid receptors (budding). NA clears the virus and the cell membrane of sialic acids. Once the viral particle is outside the cell, the NA may further help to remove sialic acids from mucous substances in the respiratory tract, thus allowing the virus to reach other epithelial cells. Finally, HA is hydrolyzed by proteases of the host to form HA1 and HA2, which empower viral particles bearing infectivity. A small number of cells infected with influenza viruses will generate a large number of new progeny virions upon replication. These particles will spread through the respiratory tract to infect other cells (5).

Viremia or extrapulmonary infections were rarely found in cases of seasonal influenza. As for patients infected with H5N1 avian influenza viruses, higher viral load is observed in the lower respiratory tract than the upper end and throat than the nose; viremia, gastrointestinal infections and extrapulmonary spread may be seen sometimes, as well as occasional infection of the central nervous system. Viruses may be detected from the heart, liver, spleen, kidney, adrenal gland, muscle, and meninges, or cerebrospinal fluid in patients with central nervous system symptoms.

Bronchial inflammation and abnormal lung function may persist for weeks to months after infection. Lung function studies may also reveal restrictive and obstructive ventilatory dysfunction with alveolar gas exchange abnormalities, reduced carbon monoxide diffusing capacity and airway hyperresponsiveness.

The clinical symptoms of influenza may be associated with pro-inflammatory cytokines and chemokines (12-15). In vitro, following infection epithelial cells may generate IL-6, IL-8, IL-11, TNF-α, RANTES and other mediators. Elevated levels of a range of cytokines in nasal lavage fluids have been found in vivo, including IFN-α, IFN-γ, IL-6, TNF-α, IL-8, IL-1β, IL-10, MCP-10 and MIP-1α/MIP-1β, as well as blood IL-6 and TNF-α. Overexpression of cytokines such as MCP-1, IP-10 and MIG were often found in patients with fatal H5N1 avian flu, which may be partly response for severe pneumonia and multiple organ damage in these cases.

Pathology

Major pathological changes include degeneration of respiratory ciliated epithelial cells, epithelial cell metaplasia, and edema and congestion of mucosal lamina propria cells with mononuclear cell infiltrates in the lamina propria. In fatal influenza viral pneumonia, the gross pathological findings include bleeding, severe tracheal bronchitis and pneumonia, characterized by widespread bronchial and bronchiolar cell necrosis with ciliated epithelial cell loss, fibrin exudation, inflammatory cell infiltration, hyaline membrane formation, congestion of alveolar and bronchial epithelial cells, interstitial edema and mononuclear cell infiltration. Later changes include diffuse alveolar damage, lymphocytic alveolitis, metaplastic epithelial cell regeneration, or even extensive tissue fibrosis. Severe cases may be complicated with pneumonia as a result of secondary bacterial infection, mostly diffuse, and sometimes localized. In general, influenza patients will have a normal or slightly low peripheral complete blood cell count with increased lymphocytes, whereas total WBC and lymphocytes usually decrease in a few severe.In severe patients, chest x-ray may suggest unilateral or bilateral pneumonia, with pleural effusions in a few cases. The severity of pneumonitis relates to cell-mediated immune response, though its significance in the pathological process is still unclear. Patients with fatal cases of influenza often show pathological changes in other organs. In one autopsy study, diffuse brain tissue hyperemia, edema, and myocardial cell swelling, interstitial hemorrhage, lymphocytic infiltration, necrosis and other inflammatory reactions have been found in one-third autopsies (5).

Clinical manifestations and laboratory investigations

A typical incubation period of influenza is 1 to 7 days, 2 to 4 days in most of the times.

Symptoms and signs in general population (16)

Simple influenza

This is the most common type of influenza, manifested by a sudden onset, high fever (39-40 degree Celsius), chills or rigors, and in many cases, other systemic symptoms such as headache, muscle and joint pain, extreme fatigue, and loss of appetite. Sore throat, dry cough, nasal congestion, runny nose and retrosternal discomfort are commonly present. Typical patients may have facial flushing and mild conjunctival hyperemia at the lateral canthus. In uncomplicated and self-limited cases, the fever will resolve and general symptoms subside in 3 to 4 days after the onset, although disappearance of coughing and physical recovery usually takes 1 to 2 weeks. Mild cases of influenza may seem like common cold, often have fewer symptoms and can recover in 2 to 3 days.

Toxic influenza

An extremely rare type of influenza. Typical patients can have high fever, shock and disseminated intravascular coagulation (DIC) or other serious symptoms. The case fatality is high.

Stomach flu

Apart from fever, vomiting and diarrhea feature this type of influenza. More likely affects children rather than adults. Typical patients can recover in 2 to 3 days.

Symptoms and signs in specific population groups

Children

During flu seasons, more than 40% of preschool and 30% of school-age children can contract influenza. An average child infected with influenza viruses may present with mild symptoms like fever, cough, runny nose, nasal congestion, sore throat, headache, and less frequently, muscle pain, vomiting and diarrhea. Quite often, influenza in infants manifests in atypical symptoms, and sometimes may lead to febrile seizures.

Influenza in neonates is rare, but often gives rise to pneumonia and signs of sepsis, such as lethargy, milk refusal, and apnea. In children, influenza-induced viral laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia and gastrointestinal symptoms are more common than in adults.

The elderly

This group refers to patients at the age of 65 or above. As a result of respiratory and cardiovascular co-morbidities, influenza in the elderly may present with more severe conditions, faster progression, and higher incidence of pneumonia as compared with the younger. Damage to other organs may result in abnormalities due to influenza-related viral myocarditis in ECG, heart failure, acute myocardial infarction, and even encephalitis or poor blood sugar control.

Pregnant women

In addition to fever and cough, female patients in the second and third trimesters of pregnancy are prone to pneumonia with rapid onset of dyspnea, hypoxemia or even acute respiratory distress syndrome (ARDS), which may lead to miscarriage, premature birth, intrauterine fetal distress and death. Influenza infection during these periods may cause worsening of the underlying diseases, which is sometimes fatal. Failure to deliver a proper antiviral therapy within two days after onset is associated with a significant increase in the mortality for this population.

The immunocompromised

Immunodeficient individuals, including recipients of organ transplantation, HIV/AIDS patients and long-term users of immunosuppressant, are at a significantly higher risk of severe influenza once infected. Predisposed to influenza-related viral pneumonia, they may experience rapid onset of fever, cough, dyspnea and cyanosis, which contributes to a high mortality.

Clinical manifestations in severe cases of influenza (17,18)

Influenza-related viral pneumonia

Viral pneumonia associated with seasonal influenza A (H1N1, H2N2, H3N2, etc.) occurs mainly in infants, young children, the elderly, the immunocompromised group and those with chronic cardiopulmonary conditions. The 2009 influenza A (H1N1) even caused severe viral pneumonia in young adults, obese people, pregnant women and those with chronic underlying diseases, as well as refractory hypoxemia in a few (19). Infection with highly pathogenic avian influenza can often evolve into acute lung injury (ALI) or ARDS, which is potentially fatal (20,21).

Extrapulmonary manifestations (22)

Heart damages are unusual and may include myocarditis and pericarditis, as reflected commonly by elevated creatine kinase (CK) and abnormal electrocardiogram, and occasionally by high level of serum troponin. Complete recovery is often seen in majority of the cases, although in critical cases heart failure may occur.

Nervous system damages include encephalomyelitis, transverse myelitis, aseptic meningitis, focal neurological deficits, and Guillain-Barre syndrome.

Myositis and rhabdomyolysis rare in influenza. Main symptoms include muscle weakness, kidney failure and increased CK.

Critical case of influenza may result in multiple organ dysfunction (MODF), disseminated intravascular coagulation (DIC), or even death.

Complications (17)

Secondary bacterial pneumonia

Secondary bacterial pneumonia is reported in 5-15% of patients, usually manifested by deterioration of the general conditions in 2 to 4 days after onset of influenza or worsening of the illness even after the a period of convalescence, high fever, bouts of violent coughs, purulent sputum, dyspnea, moist rales and signs of pulmonary consolidation. There is a noticeable increase in peripheral white blood cells and neutrophils. Pathogens involved in this condition mainly includes Staphylococcus aureus [esp. methicillin-resistant Staphylococcus aureus (MRSA)], Streptococcus pneumoniae or Haemophilus influenzae.

Pneumonia caused by other pathogenic microbes

These may be associated with chlamydia, mycoplasma, Legionella pneumophila, fungi (Aspergillus), and so on. When influenza-related pneumonia does not respond to conventional anti-infective therapy, a fungal nature should be suspected.

Pneumonia caused by other species of virus

Common viruses include rhinovirus, coronavirus, respiratory syncytial virus and human parainfluenza viruses. This type of pneumonia often affects patients with chronic obstructive pulmonary disease (COPD) and may aggravate their conditions. Differentiation from influenza-induced pneumonia is clinically difficult and should depend on pathogenic and serological studies.

Reye syndrome

Occasionally seen in children aged 14 or younger, particularly those on aspirin or other analgesic and antipyretic agents that contain salicylic acid.

Radiological findings

Most patients have normal chest X-ray. Those with pneumonia may show patchy, multilobar infiltrates that can rapidly progress

into diffuse exudative lesions or consolidation of both lungs. Pleural effusion can be seen in individual cases.

Laboratory investigations

Routine tests

Peripheral hemogram: usually normal or lowered WBC count. Blood biochemistry: some patients may have hypokalemia, and a few have elevated levels of creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and creatinine.

Virological tests

These mainly involve virus isolation and detection of virus antigen, nucleic acids and antibodies. Virus isolation is the well-recognized gold standard for laboratory detection. Identification of virus antigen and nucleic acids can be used for early diagnosis, while detection of antibodies can be useful for retrospective surveys but not for early diagnosis. Instructions to the related detection methods are detailed in the Technical Guidance to Influenza Surveillance downloadable at the website of China National Influenza Center (www.cnic.org.cn). Please log in www.sfda.gov.cn for product descriptions of state FDA-approved reagents/kits used in the laboratory detection.

Virus nucleic acid detection is to identify the nucleic acids of influenza viruses in airway specimens (throat swabs, nasal swabs, nasopharyngeal or tracheal aspirates, sputum) using RT-PCR (preferably real-time RT-PCR). The detection of virus nucleic acid may yield the highest specificity and sensitivity, and provide a quick identification of the virus types and subtypes, generally within 4-6 hours.

Virus isolation and culture is used to isolate the influenza viruses from airway specimens. This is also recommended for influenza-like patients who test negative for rapid antigen assay or immunofluorescence assay during the influenza season.

Virus antigen detection (with antigen rapid test kits) may be conducted on airway specimens (epithelial cells in throat swabs, nasal swabs and nasopharyngeal or tracheal aspirates) by immunofluoresence assay, in which monoclonal antibodies are employed for a clear distinction between influenza A and B viruses within hours (23). Alternatively, colloidal gold probe-based rapid immunochromatographic strip assay can be used, which normally yields a result in 10 to 30 minutes. The interpretation to rapid tests should be based on epidemiological history and clinical symptoms of the patient – a positive result of screening test in a non-epidemic period could be a false one, as could be a negative result in an epidemic period. In these scenarios, RT-PCR or virus isolation should be considered for further confirmation.

Serological test is used to determine the titers of influenza virus-specific IgM and IgG antibodies. A 4-fold or greater rise of IgG titer in paired acute and convalescent serum samples as indicated by serial measurements can be significant for a retrospective diagnosis.

Diagnosis

Clinical manifestations indicative of influenza (23)

During an epidemic period, any of the following manifestations may indicate influenza: Fever with cough and/or other acute respiratory symptoms, such as sore throat; Fever with acute exacerbation of underlying chronic lung disease; Fever in infants and children, without any other symptoms and signs; New onset of respiratory symptoms or aggravation of respiratory conditions in the elderly (aged ≥ 65 years), with or without fever; and fever or low body temperature in the critically-ill.

Regardless of whichever period (epidemic or non-epidemic), influenza should be suspected in a patient who presents with fever, cough and/or other acute respiratory symptoms (such as sore throat), and in whom influenza-related epidemiological history can be retrieved, such as visits within 7 days prior to onset of symptoms to any institution or community where an outbreak of influenza occurred, living together or having close contact with suspected influenza patients, or travel to any country or region where there was an on-going epidemic of influenza.

Clinical cases that need etiological investigations

Etiological investigations may be ordered, if available, for a definite diagnosis in the cases described hereinabove. Etiological investigations should be proactively accessed in those cases for which the clinical management depends substantially on a definite diagnosis. These cases may include: critical patients for whom timely initiation of antiviral therapy is to be decided on, patients in whom a confirmed diagnosis determines the use of subsequent investigations, patients for whom antibiotic treatment is pending, patients awaiting a definite diagnosis to justify subsequent infection control measures, and patients involved in an epidemiological sampling survey.

Diagnostic criteria for influenza (23,24)

Patients who are symptomatic and test positive for at least one of the following etiological investigations can be diagnosed with influenza: Nucleic acids of influenza viruses (using either real-time or classical RT-PCR); Rapid antigen test (using either immunofluorescence or colloidal gold assay), interpreted with reference to epidemiological history; Influenza virus isolation

Table 1. Defining differences between influenza and common cold

	Influenza	Common cold
Pathogen	Influenza virus	Rhinovirus, coronavirus, etc.
Influenza virusDetection	Positive	Negative
Communicability	Strong	Weak
Seasonality	Obvious (mostly prevalent from November to March in northern China)	Not obvious
Fever	Mostly high fever (39-40 °C), may be accompanied with chills	No fever or mild to moderate fever, no chills
Duration of fever	3 to 5 days	1 to 2 days
Systemic symptoms	Serious. Headache, aching muscles, fatigue	Mild or none
Course of disease	5 to 10 days	5 to 7 days
Complications	May be complicated by otitis media, pneumonia, myocarditis, meningitis, or encephalitis	Rare

and culture; and a four-fold or greater rise in virus-specific IgG antibody in paired acute and convalescent sera.

Clinical criteria for severe influenza (18,24)

Patients who meet diagnostic criteria for influenza and have at least one of the following are classified as severe cases: Altered states of consciousness: confused, somnolent, irritable or convulsive; Difficulty breathing and/or increased respiratory rate (> 30 times per minute in adults and children aged five or older; > 40 times per minute in young children aged between 1 and 5; > 50 times per minute in infants aged 2 to 12 months; > 60 times per minute in neonates or infants during the first two months of their life); Severe vomiting and diarrhea with signs of dehydration; Oliguria (urine output < 400 ml/24 hr in adults, < 0.8 ml/kg/h in children, or daily urine output < 200 ml/m^2 in infants, < 300 ml/m^2 in pre-school children, < 400 ml/m^2 in school-age children, < 17 ml/h in children aged 14 years or older) or acute renal failure; Arterial blood pressure < 90/60 mmHg; Arterial oxygen tension (PaO_2) < 60 mmHg (1 mmHg = 0.133 kPa), or oxygenation index (PaO_2/FiO_2) < 300; Bilateral or multilobar infiltrates on chest X-ray, or ≥ 50% extension of pulmonary infiltrates within 48 hours of admission; and a rapid elevation in levels of cardiac enzymes, including creatine kinase (CK) and MB-type isoenzyme of CK (CK-MB).

Differential diagnosis

Common cold

Influenza is non-specific by clinical symptoms and therefore can be readily mislabeled as common cold. Typically, influenza causes more systemic symptoms than does common cold. Retrieval of epidemiological history may be helpful in differential diagnosis. Patients with common cold are negative for influenza virus detection, or may show evidence of infection with other pathogens. Key points in the differential diagnosis (25-29) are listed in Table 1.

Other types of upper airway infection

These include acute pharyngitis, tonsillitis, rhinitis and sinusitis, usually with localized symptoms of the infection. Discharges from the affect site are negative for influenza viruses.

Lower airway infections

Influenza should be differentiated from acute tracheobronchitis when complicated by cough or tracheobronchitis, and from other types of pneumonia (bacterial, chlamydial, mycoplasmal, viral, fungal) and tuberculosis when complicated by influenza-related viral pneumonia. A preliminary diagnosis may be determined based on clinical manifestations, followed by confirmation with etiological investigations.

Other non-infectious diseases

Influenza should also be differentiated from non-infectious diseases which are complicated with fever and particularly lung shadows, such as in connective tissue diseases, pulmonary thromboembolism and lung cancer.

Treatment

Cardinal principles

Decide on where to treat according to severity assessment. Explicit criteria for hospital admission (patients who meet one

or more of the following should be hospitalized): Women in the second or third trimester of the pregnancy; Patients with apparently worsened co-morbidities, such as chronic obstructive pulmonary disease, diabetes, chronic heart failure, chronic renal insufficiency, or liver cirrhosis; Those who meet the diagnostic criteria for severe influenza; and those complicated with multiple organ dysfunction.

Home quarantine: Non-hospitalized individuals suspected to have influenza should stay at home for quarantine in a well-ventilated room. They should rest and be given plenty of fluids and nutrient-rich, easily digested foods. Keep a close watch on their conditions, especially for the elderly and children.

Start anti-influenza medications within 36-48 h from the onset as early as possible (30): Although the use of neuraminidase inhibitors beyond 48 h after onset was shown to be as effective, most studies have demonstrated that earlier treatment with these agents may result in better outcomes.

Avoid unnecessary or inappropriate use of antimicrobial drugs (31,32): Antibiotics are indicated only when the influenza is complicated with secondary bacterial pneumonia, otitis media and sinusitis. A series of studies on the 1918 Spanish flu and the 2009 H1N1 influenza pandemics have shown that secondary bacterial pneumonia in patients with influenza is mostly caused by Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae, as similarly seen in community-acquired pneumonia. And accordingly, amoxicillin, amoxicillin/clavulanic acid, second- or third-generation cephalosporins (ceftriaxone and cefotaxime), or quinolones may be used for the treatment. If there is a high isolation rate of methicillin-resistant Staphylococcus aureus (MRSA) in the area, particularly the community-associated MRSA (CA-MRSA), glycopeptide antibiotics or linezolid should be considered. In mild cases, less expensive therapy with compound sulfamethoxazole (SMZco) or clindamycin may be as well selected according to drug susceptibility test. It should be noted that in victims of the 2009 pandemic of H1N1 influenza, primary viral pneumonia was more common than secondary bacterial pneumonia, which should prompt careful differential diagnosis between the both. Generally, pneumonia that appears at the mid- to late-stage (≥ 5 d) of influenza will show infiltrates or consolidation localized or concentrated within certain pulmonary lobes or segments on chest X-ray (rather than diffuse interstitial lesions). Clinically, persistent fever and cough with yellow purulent sputum may suggest bacterial pneumonia that requires antibiotics as mentioned above. If the pneumonia occurs in hospitalized patients with severe flu (including those on mechanical ventilation), antibiotics can be given based on the treatment protocols for hospital-acquired pneumonia (or ventilator-associated pneumonia) (33).

Unlike the common cold, specific anti-viral agents have now been available for use in influenza. In most of influenza patients with early use of antiviral drugs, symptomatic medications (such as antipyretics, analgesics, decongestants, anti-allergics, and anti-tussives) are hardly needed. Otherwise, the use of composite agents for symptomatic treatment should be minimized and preferably be replaced with more specifically targeting drugs. For pediatric cases, aspirin or aspirin-containing medications, and other derivatives of salicylic acids are contraindicated owing to their association with Reye syndrome – an occasionally fatal complication that affects the liver and nervous system in patients with influenza.

Antiviral drugs for influenza

Indications (34-36)

Recommended use: For adults and children who are with laboratory confirmed or highly suspected influenza, and at high risk of complications, antiviral treatment should be initiated within 48 h of onset regardless of the underlying diseases, previous vaccination and severity of influenza; For adults and children who are with laboratory confirmed or highly suspected influenza that necessitates hospitalization, antiviral drugs should also be administered if they test positive for influenza viruses in 48h of onset, regardless of the underlying diseases and previous vaccination for influenza.

Considered use: Adults and children who are suspected for influenza at the clinic, with high risk for complications, no improvements at 48h and positive outcomes of specimen test for influenza virus beyond 48 h of onset; Those who visit the clinic with laboratory confirmed or highly suspected influenza within 48h of onset, and although at no risk of complications, attempt to shorten the course of illness and thus further eliminate the potential for complications, or have had close contact with influenza patients at high risk of complications. Patients with evident symptoms that persist for more than 48 h can also benefit from antiviral therapy, although the safety and efficacy are yet to be assessed in prospective studies.

Drugs (5)

Neuraminidase inhibitors work by blocking virus release from infected cells and invasion of adjacent cells, thus reducing viral replication in the body. These agents are effective against both types A and B viruses. Two products of this category, Oseltamivir and Zanamivir, have become commercially available in China; yet Peramivir and Laninamivir have not, although recently approved for intravenous use in Japan and some other countries. A great number of clinical trials have shown that neuraminidase inhibitors can benefit influenza patients with ameliorated symptoms, shortened duration of illness and length of hospital stay, fewer complications, reduced medical costs, and in certain populations, lowered death rate (particularly when used within 48 h of onset). Oseltamivir is an oral neuraminidase

inhibitor approved for use in children older than 1 year and in adults; adequate data are now pending in relation to its safety and efficacy for children younger than 1 year. The adverse reactions of Oseltamivir may include gastrointestinal symptoms, cough, bronchitis, dizziness, fatigue, and neurological symptoms (headache, insomnia, and vertigo). Seizures and neuropsychiatric disorders have been reported mainly in children and teenagers, although causal relationship to the drug is uncertain. Occasional cases of skin rashes, allergic reactions and hepatobiliary disorders have also been noted. Zanamivir is another neuraminidase inhibitor available as an inhalation powder, and has been approved for used in children older than 5 years (UK) or 7 years (US) and in adults, with similar efficacy to Oseltamivir as shown in comparative studies. Occasionally, Zanamivir may cause bronchospasm and allergic reactions, and therefore should be used with caution in patients with asthma or similar underlying diseases. Other adverse reactions are rare.

M_2 ion channel blockers work by blocking the M2 protein ion channel of influenza viruses and thus inhibit viral replication, but they are only effective against influenza A viruses. Commercially available products of this category include Amantadine and Rimantadine. Neural adverse reactions include nervousness, anxiety, difficulty concentrating and mild headache, which are more common with Amantadine. Gastrointestinal adverse reactions include nausea and vomiting, which are generally mild and can disappear quickly after discontinuation.

For medications, the dosage differs but the duration is the same between children and adults. In case of emergency, Oseltamivir can be given to infants aged older than 3 months. Antiviral therapy should be initiated in children even when the time of referral has exceeded 48 h from onset.

Drug resistance, treatment options and clinical usage

Antiviral therapy is an essential and vital component in the treatment of influenza. However, the readiness for emergence of drug-resistant influenza virus strains has been much of a concern. Influenza viruses have long been resistant to M2 ion channel blockers. According to currently available data on influenza surveillance within and outside China, nearly 100% of seasonal influenza A viruses (H1N1 and H3N2) and the 2009 (H1N1) influenza viruses are resistant to alkylamines. As reported, more than 80% of seasonal influenza viruses (H1N1) are resistant to Oseltamivir though still sensitive to Zanamivir (37); other species of seasonal influenza viruses (H3N2) and the 2009 influenza A (H1N1) viruses are susceptible to Oseltamivir and Zanamivir; and H5N1 avian influenza viruses have low resistance to both agents. Unfortunately, influenza viruses are prone to experience genetic mutations that underlie their resistance to antiviral medications. In recent years, an increasing proportion of seasonal influenza viruses (H1N1) have gained dual resistance to Amantadine and Oseltamivir, and these drug-resistant strains can spread by human to human transmission. Hence, options of clinical medication should be based on local prevalence of virus types/subtypes and data from regional drug resistance surveillance. The National Influenza Center provides a weekly update of drug surveillance in China at its website (www.cnic.org.cn). Because the virus subtyping and drug resistance surveillance are not widely available, the impacts of drug resistance on clinical treatment so far remain under-evaluated. As a rule of thumb, Zanamivir, Oseltamivir, Rimantadine or Amantadine can be used against influenza A viruses, and Oseltamivir or Zanamivir can be used against influenza B viruses, pending the current situation of drug resistance in clinical settings to be clarified.

Recommended dosage and usage for anti-influenza drugs are listed in Table 2. For the critically-ill, an extended course (up to 10 days) of double-dose Oseltamivir has been proposed (23); and whenever possible, intravenous Zanamivir may be considered in these patients. Moreover, clinical medication should advisably be guided by the latest information on antiviral drugs for influenza available at the website of State Food and Drug Administration (www.sfda.gov.cn).

Treatment of severe cases

The principles of treatment of severe cases are aggressive management of primary diseases, prevention of complications, and delivery of effective organ support.

Respiratory support therapy (33)

Severe pneumonia is the most common of serious, sometimes fatal, complications in influenza. About 30% of deaths from severe pneumonia are associated with secondary bacterial infections. Common causes of death include respiratory failure, refractory shock and multiple organ failure.

Oxygen therapy

Oxygen therapy should be given immediately to patients with hypoxemia, to maintain a level of pulse oxygen saturation (SpO_2) above 90% (when possible, a level of 93% or above may provide greater safety margin). In special cases, such as pregnant women, the SpO_2 level should be maintained at 92% to 95%. On highlands, the goal for SpO_2 level should be modified according to specific diagnostic criteria for hypoxia at higher elevation.

Serial observation should be performed on the patient's conditions. In the cases where oxygenation is not improved as expected with oxygen therapy, or dyspnea becomes worsened, or pulmonary disease progresses rapidly, a timely assessment and decision on the need for mechanical ventilation, either non-invasive or invasive, should be made.

Mechanical ventilation

Severe cases of influenza can deteriorate rapidly. The time from

Table 2. Recommended dosage and usage of anti-influenza drugs for adults and children

Drug	Age group	Treatment	Prevention
Neuraminidase inhibitors			
Oseltamivir			
	Adults	75 mg, twice daily, for 5 days	75 mg, once daily, Refer to Chapter 8 for the treatment course
	Children ≥ 1 years old, weight		
	≤ 15 kg	60 mg/d, twice daily	30mg, once daily,
	15-23 kg	90 mg/d, twice daily	45mg, once daily,
	24-40 kg	120 mg/d, twice daily	60mg, once daily,
	> 40 kg	150mg/d, twice daily	75 mg, once daily,
	6 to 11 months	50mg/d, twice daily	25mg, once daily,
	3 to 5 months	40mg/d, twice daily	20mg, once daily,
	< 3 months	24mg/d, twice daily	No recommended dose
Zanamivir	Adults	10 mg (5 mg/tablet) inhaled, twice daily	10 mg (5 mg/tablet) inhaled, once daily
	Children	10 mg (5 mg/tablet) inhaled, twice daily (> 7 years old)	10 mg (5 mg/tablet) inhaled, once daily (> 5 years old)
M_2 ion channel blockers			
Rimantadine	Adults	200 mg/d, once or twice half-dose	Same as treatment dose
	Children, age		
	1 to 9 years old	5 mg/kg.d, (6.6 mg/kg.d) once or twice half-doseNo more than 150 mg/d	5 mg/kg.d, (6.6 mg/kg.d), onceNo more than 150 mg/d
	≥ 10 years old	200 mg/d, once or twice half-dose	Same as treatment dose
Amantadine	Adults	200 mg/d, once or twice half-dose	Same as treatment dose
	Children, age		
	1 to 9 years old	5-8 mg/kg.d, once or twice half-dose (no more than 150 mg/d) Used until 24-48 h after the symptoms disappeared	5-8 mg/kg.d once or twice half-dose (No more than 150 mg/d)
	≥ 10 years old	200 mg/d, once or twice half-dose	Same as treatment dose

symptom onset to hospital admission is usually 2-7 days, and 10-30% of hospitalized patients need referral to an intensive care unit (ICU) on the same day of or in 1-2 days after admission. In these severe cases, disorders of the lung as one of the most frequently involved organs are usually manifested by rapidly progressive severe pneumonia which may develop into acute lung injury occurs (ALI) or even acute respiratory distress syndrome (ARDS) (40,41). For patients in need of mechanical ventilation, relevant guideline recommendations for ventilation in the ARDS can be followed (42-44).

Non-invasive positive pressure ventilation (NIPPV)

Due to a lack of evidence, it remains uncertain as to whether

non-invasive positive pressure ventilation should be a first-line choice in patients with severe respiratory failure, ALI/ARDS in particular. Nevertheless, early application of NIPPV has been shown to reduce the need for endotracheal intubation and improve the outcomes in patients who are concomitantly with acute exacerbation of COPD (AECOPD), acute cardiogenic pulmonary edema or immunocompromised status.

Preliminary studies by several Chinese medical centers have demonstrated and recognized the benefits of NIPPV among patients with respiratory failure who contracted the 2009 influenza A (H1N1) viruses. Early use of non-invasive ventilatory support is recommended for critically ill patients with SpO_2≤93%, arterial oxygen tension (PaO_2) ≤65 mmHg, oxygenation index [PaO_2/inspired oxygen concentration (FiO_2)] <300 mmHg, or respiratory rate > 30 times per min, despite breathing oxygen with a face mask (>5 L/min); or for those with perceived respiratory distress. NIPPV should also be attempted early in patients who are diagnosed with influenza and respiratory failure, and are concomitantly with acute exacerbation of COPD, acute cardiogenic pulmonary edema or immunocompromised status. A full-face mask is preferred for non-invasive ventilation. Throughout the entire procedure, the patients should be kept on close watch so that a conversion to invasive approaches may be started early when they do not appear to benefit from the on-going NIPPV, or may suffer adverse consequences from a delayed decision on use of invasive ventilation. Such a conversion is typically considered for patients with poor conditions despite 2-4 hours of standard non-invasive ventilation, e.g. no improvement in PaO_2 even when FiO_2≥60%, PaO_2/FiO_2≤200 mmHg or progressively decreasing, or sustained respiratory distress.

Invasive mechanical ventilation

The indications of it are respiratory distress, hypoxemia, and specific criteria of failed oxygen therapy or non-invasive ventilation.

Ventilator modes and settings for invasive mechanical ventilation: Patients with ALI/ARDS induced by severe influenza can be treated on invasive mechanical ventilation according to relevant guidelines for ARDS management, which usually should follow the lung protective ventilation strategies below: (i) Small tidal volume ventilation (≤ 6 ml/kg actual body weight) is given with volume- or pressure-control mode; (ii) high-concentration oxygen can be used initially to ameliorate hypoxemia as soon as possible, followed by gradual decrement according to oxygen saturation measured with pulse oximetry or blood gas analysis; (iii) the level of positive end-expiratory pressure (PEEP) is often set at 5-12 cmH_2O (usually no greater than 15 cmH_2O). For use in patients with severe oxygenation impairment, the level of PEEP can be configured somewhere between 15 and 20 cmH_2O, or adjusted according to the pressure-volume diagram and hemodynamic parameters, or set by using the ARDSnet FiO_2/PEEP table; (iv) the plateau pressure should be maintained below 30 cmH_2O; and (v) for refractory hypoxic patients, lung recruitment maneuvers and prone position ventilation may be considered.

Special considerations during invasive mechanical ventilation: Keep a close watch on changes in vital signs and ventilation parameters during ventilation to prevent barotrauma or pneumothorax; Provide adequate sedation to reduce ventilator-associated lung injury; Start with high-concentration oxygen, followed by gradual decrement in fractional concentration of inspired oxygen as appropriate; Avoid unnecessary airway suction so as not to interfere with the PEEP level; Prevent ventilator-associated pneumonia; and attach the importance to fluid management. Current evidences on the treatment of ARDS suggest that conservative fluid management is beneficial for patients with stable hemodynamics. Meanwhile, low fluid volume should be corrected in patients with severe influenza to ensure hemodynamic stability.

Extracorporeal membrane oxygenation (ECMO) (45-49)

There is much controversy surrounding the use of ECMO in adult patients with ARDS. However, ECMO may be useful as a life-saving or life-sustaining measure in patients with severe ARDS resulting from influenza-induced pneumonia where mechanical ventilation has failed to improve the oxygenation; in particular, ECMO can be more valuable as an alternative for patients in whom acute respiratory failure is caused by correctable causes. There have been domestic and international reports on successful rescue of critical cases of severe oxygenation dysfunction with ECMO during the pandemic of 2009 influenza A (H1N1).

Circulatory support therapy (44)

Refractory shock is one of the most common causes of death in influenza patients. While the shock in influenza is frequently of a septic nature, cardiogenic shock may sometimes be noted. Influenza viruses rarely cause direct damages to the heart, but they have been linked to myocarditis and pericarditis. Moreover, the viruses may activate release of proinflammatory cytokines which in turn impose indirect damages to the heart and lead to deterioration of the underlying heart disorders. In cases of severe influenza, both direct and indirect factors may contribute to the development of a cardiogenic shock.

Treatment of septic shock

Early aggressive fluid resuscitation strategies: Upon confirmed diagnosis of a secondary infection or septic shock, aggressive fluid resuscitation should be initiated as soon as possible to ensure that the following goals are achieved within 6 hours: a.

central venous pressure (CVP) 8-12 mmHg; b. mean arterial pressure >65 mmHg; c. urine output >0.5 ml/kg/h; and d. central venous oxygen saturation ($ScvO_2$) or venous oxygen saturation (SvO_2) >70%. In cases where CVP returns to 8-12 mmHg but $ScvO_2$ or $ScvO_2$ sustains below 70% after fluid resuscitation, consider packed red blood cell transfusion (until hematocrit > 30%) or intravenous use of dobutamine in order to achieve these goals.

Proper use of vasoactive and inotropic drugs: Norepinephrine and dopamine are first-line vasoactive agents in the treatment of septic shock. However, evidences do not show that low-dose dopamine can improve visceral organ blood flow or protect the kidneys. Dobutamine is generally used in septic shock when the cardiac function does not improve with adequate fluid resuscitation.

3) Low-dose glucocorticoids can be used for patients with vasopressor-dependent septic shock.

4) The key to treatment of ARDS and concomitant shock is a combination of active anti-shock therapy and careful fluid management. A modest negative fluid balance can be beneficial for patients with stable hemodynamics.

Treatments of cardiogenic shock

The strategies include maintenance of the airway, breathing and circulation (ABC principles) (50), fluid replacement, use of vasoactive and inotropic agents, and mechanical circulatory support (such as intraaortic balloon pump counterpulsation).

Renal support therapy

Kidney involvement as reflected by acute renal failure is also common in severe cases of influenza. In most of the cases, acute renal failure arises from prerenal and/or renal factors, and may increase the fatality rate by 10-60%.

ARDS patients with acute renal failure can be treated with continuous veno-venous hemofiltration or intermittent hemodialysis. Renal replacement therapy is helpful for fluid management in ARDS patients with acute renal insufficiency. Patients with hemodynamic instability may benefit more from continuous renal replacement therapy.

Treatment with glucocorticoids

The use of glucocorticoids in patients with severe influenza is not evidence-based by far. Low-dose glucocorticoids may be considered for patients with septic shock who need administration of vasopressors (51). High doses of systemic glucocorticoids may be associated with serious side effects (such as secondary infection or increased viral replication) in patients infected with influenza viruses, and are thus used only when hemodynamic instability is complicated. Dosage: hydrocortisone 200-300 mg/d (for adults) or 5-10 mg/kg.d (for children) i.v.; methylprednisolone 80-120 mg/d (for adults) or 1-2 mg/kg.d (for children), i.v.

Other supportive care options

Apart from the lungs, heart and kidneys, influenza viruses may also affect other organs such as meninges, nerves and muscles. In addition, the systemic inflammation induced by influenza viruses can lead to multiple organ dysfunction syndrome (MODS), which is one of the leading causes of death. Signs of probable damages to other organs should be handled with proper supportive treatments. Pay attention to nutritional support, prevent and treat gastrointestinal failure in patients with severe influenza. Restore the homostasis, particularly, correct electrolyte imbalance and metabolic acidosis.

Treatment with Chinese traditional medicine

Non-severe cases

Wind heat invading the Defensive Qi. Main symptoms: sore throat, mild cough with little sputum, mildly sweating at the early stage; Tongue and pulse: red tongue with thin or greasy coating, floating and rapid pulse; Regimen: dispersing heat.

Basic prescription: honeysuckle flower, forsythia fruit, mulberry leaf, chrysanthemum, fried bitter apricot seeds, fritillaria bulb, Fineleaf Schizonepeta Herb, Great Burdock Fruit, reed rhizome, Wild Mint Herb mint (decocted later), and unprocessed licorice.

Decoction method: decoct with water down to 400 ml, 200 ml administered orally twice daily per oral 200ml. If necessary, dose can be doubled by oral administration of 200 ml four times a day at an interval of 6 hours.

Modification: if tongue coating is thick and greasy: add Agastache and Fortune Eupatorium Herb; if diarrhea: add Berberine and Costus root.

Commonly used Chinese medicine: Shufengjiedu capsules (52,53); Yinqiaojiedu tablets; Shuanghuanglian oral agents.

Pathogenic cold hampering the exterior

Main symptoms: chills with or without fever, body pain, headache, runny nose but no sweat at the early stage.

Tongue and pulse: Pink tongue with thin and moist coating.

Regimen: relieving exterior syndrome with herbs pungent in taste and warm in nature.

Basic prescription: baked ephedra, fried bitter apricot seeds, cassia twig, pueraria root, prepared licorice, notopterygium root and Herba Periliae.

Decoction method: decoct with water down to 400 ml, 200 ml administered orally twice daily per oral 200ml. If necessary, dose can be doubled by oral administration of 200 ml four times a day at an interval of 6 hours.

Commonly used Chinese medicine: Jiuwei Notopterygium particles and Oral Liquid of Dispelling Cold and Reducing Fever.

Pathogenic heat invading the lungs

Main symptoms: high fever, cough, sticky sputum, difficulty expectoration, thirsty, sore throat, and red eyes.

Tongue and pulse: red tongue with yellow or greasy coating, slippery and rapid pulse.

Regimen: clearing away the lung heat.

Basic prescription: baked ephedra, bitter apricot seed, gypsum (decocted earlier), common anemarrhena, reed rhizome, Great Burdock Fruit, fritillaria bulb, honeysuckle, artemisia annua, Wild Mint Herb, Pericarpium Trichosanthis, and unprocessed licorice.

Decoction method: decoct with water down to 400 ml, 200 ml administered orally twice daily per oral 200ml. If necessary, dose can be doubled by oral administration of 200 ml four times a day at an interval of 6 hours.

Modification: if constipation: add unprocessed rhubarb.

Commonly used Chinese medicine (54,55): Lianhua-qingwen capsules, Lianhuaqingre effervescent tablets, Children Chiqiaoqingre granules and so on.

Note: The above prescription and dosage are for reference only. The dose for children should be reduced accordingly and treatment for patients with complications or chronic underlying diseases should be built on the specifc conditions.

Severe cases

Pathogenic heat obstructing in the lung

Main symptoms: high fever, cough, expectoration, shortness of breath; or heart palpitations, anxiety and irritation, cyanotic lips, dark red tongue, yellow greasy or gray coating, slippery pulse.

Regimen: clearing away the heat and eliminating stasis.

Basic prescription: baked ephedra, gypsum, fried bitter apricot seed, common anemarrhena, trichosanthes, skullcap, fritillaria bulb, unprocessed rhubarb, cortex mori radicis, Salvia miltiorrhiza, and European verbena.

Decoction method: decoct with water down to 400 ml, administered 200ml orally four times a day. Colon dripping may be used for severe cases with the same dosage and frequency.

Modification: for high fever, coma and delirium: add Angongniuhuang Wan; for seizures: add antelope horn, silkworm, pheretima etc.; for abdominal distension and constipation: add citrus aurantium and sodium sulphate.

Deficiency of healthy energy and sthemia of evil

Main symptoms: shortness of breath or faint, or assisted ventilation, conscious indifference or even dizziness; pale or flushing face, cold sweat or dry skin; cold limbs, dry mouth and throat, dark tongue, white coating, or purple-red tongue with weak but frequent pules.

Regimen: strengthening healthy energy.

Basic prescription: for deficiency of Yang Qi: ginseng, radix aconiti praeparata, dried ginger, fructus cornus, etc.; for deficiency of Yin Qi: red ginseng, radix ophiopogon, schisandra chinensis, fructus cornus, rehmannia root and prepared licorice.

Decoction method: decoct with water down to 400 ml, administered 200ml orally four times a day. Colon dripping may be used for severe cases with the same dosage and frequency.

Modification: Angongniuhuang Wan if still high fever.

Prevention with traditional Chinese medicine

People having definite contact with influenza patients: Prescription for children, young adults, and other healthy people: honeysuckle 6g, folium isatidis 6g, Wild Mint Herb 3g, unprocessed licorice 3g, decocted with water and administered once per day for 5 consecutive days; Prescription for the frail elderly: codonopsis pilosula 6g, Herba Periliae 6g, Fineleaf Schizonepeta Herb 6g, decocted with water and administered once per day for 5 consecutive days.

Prevention

Seasonal influenza spreads very fast from person to person, making proactive prevention and control more necessary than effective yet limited treatment measures.

Personal hygiene and health education

Maintain good indoor ventilation, and avoid gathering places during influenza epidemic; Cover coughing and sneezing with a tissue to avoid spraying droplets; Wash hands frequently and keep dirty hands away from the mouth, eyes and nose; and go to the doctor's office as soon as possible when influenza-like symptoms are present during epidemic period, stay home and minimize contact with others.

Intra-facility outbreak prevention and control

When there is an influenza epidemic in the community and two or more people in one facility have presented with influenza-like symptoms within 72 hours, pathogen detection should be performed as soon as possible to identify the cause. Once diagnosed, patients are required to be hospitalized or staying at home while maintaining good personal hygiene and minimizing contact with others. Once an intra-facility outbreak is identified, the Infectious Diseases Prevention Law and the Public Health Emergency Response Guide shall be observed. In the case of a nosocomial outbreak, protective isolation measures shall be performed in accordance with the National Influenza Surveillance Technology Guide (56).

Influenza immunization

Influenza vaccination is an indispensable and most effective way of preventing and controlling influenza as well as its complications. To obtain fully effective protection, annual inoculation will be required, and the replacement of vaccine strains will rely on the WHO decision based on global monitoring results. China's relevant technical guidance on vaccination is listed on the website of National Influenza Center (www.cnic.org.cn)

Vaccine priority groups: Six to 59 month-old infants; The elderly who are ≥ 60 years old; Adults and children suffering from chronic respiratory disease, cardiovascular disease, kidney disease, liver disease, blood disease, metabolic disorders and other diseases; Immunosuppressed adults and children; The disabled and those at risk of aspiration of upper respiratory tract secretions due to nervous system disorders; People living in nursing homes and other long-term care facilities for other chronic diseases; and women who have planned to become pregnant during influenza seasons.

Recommended groups: Health care providers; Providers at nursing homes and other care centers for chronic diseases; and family members and care providers for patients with influenza who are at risk of complications (such as infants, the elderly, chronically ill, and immunosuppressed).

Contraindications: People allergic to egg protein or any vaccine; People with severe acute fever; People who have suffered from Guillain-Barre syndrome; and those not eligible for receiving influenza vaccination as deemed by their doctors.

When and where to get inoculation: Children aged 6 months to 9 years who have never been vaccinated against influenza or have received only one shot in the last year should be shot twice at an interval of 4 weeks, followed by one inoculation before the influenza season each year from then on. Other people should be inoculated once a year. Intramuscular or deep subcutaneous injection is used for vaccination. Intramuscular injection at the lateral thigh is recommended for infants. For most regions in China, the vaccination shall be initiated before October every year.

Antiviral prophylaxis

Drug prevention is no substitute for vaccination. It serves only as an temporary preventive measure under emergency for high-risk groups who have not been immunized or have not established full immunity after inoculation. Antiviral drugs to which pandemic strains are sensitive should be the choice of preventive agents. Depending on the physician, the course of administration may generally be 1 to 2 weeks. A decision should also be made by the physician as to whether, when, and how long an additional administration will be needed and at what dose for those in whom effective immunity is not likely to establish due to immunosuppression despite vaccination.

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