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Management of Severe Influenza Cases

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Abstract: ***The clinical spectrum of infection with influenza viruses (influenza A(H1N1) 2009, A(H3N2) and influenza B) can vary from mild to serious complicated illness, e.g. exacerbation of other underlying conditions, severe viral pneumonia with multi-organ failure, and invasive bacterial co-infection. The aim of the study was to highlight the approach considerations in management of influenza cases. In this systematic review, we searched MEDLINE/PubMed and the Cochrane Database for studies regarding management of severe influenza cases. Prevention is the most effective management strategy for influenza. Most patients with influenza recover in 3 days; however, malaise may persist for weeks. Patients who do not improve should return for further evaluation.***

Keywords: influenza, clinical spectrum, case management

1. Introduction

The clinical spectrum of infection with influenza viruses (influenza A(H1N1) 2009, A(H3N2) and influenza B) can vary from mild to serious complicated illness, e.g. exacerbation of other underlying conditions, severe viral pneumonia with multi-organ failure, and invasive bacterial co-infection (1,2). The incubation period is generally 2 to 3 days, but could range up to 7 days. Patients who present initially with uncomplicated influenza may progress to severe disease. In severe cases, patients generally begin to deteriorate around 3 to 5 days after symptom onset. In some cases, especially if the cause is a primary viral pneumonia, deterioration may be rapid, progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit for respiratory support. Clinical response is variable in such cases (3,4).

Case description: possible scenarios Uncomplicated influenza:
Influenza-like illness symptoms: fever, cough, sore throat, rhinorrhea, headache, muscle pain, malaise, *without shortness of breath or dyspnoea.* Gastrointestinal illness such as diarrhoea and/or vomiting, especially in children, but without evidence of dehydration.

Signs and symptoms of progressive disease:
Symptoms and signs suggesting cardiopulmonary insufficiency: shortness of breath, difficulty in breathing, hemoptysis or coloured sputum, chest pain and hypotension. In children fast or laboured breathing may indicate progressive disease. Hypoxia as indicated by pulse oximetry. Symptoms and signs suggesting central nervous system (CNS) complications: altered mental status, unconscious, drowsy, or difficult to awaken; recurring or persistent convulsions (seizures), severe weakness or paralysis. Evidence of sustained virus replication or invasive secondary bacterial infection is based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond three days, sepsis, rapid deterioration) (5,6). Severe dehydration: decreased activity, dizziness, decreased urine output, lethargy.

Complicated or severe influenza
May be indicated by shortness of breath, dyspnoea, tachypnea, hypoxia, cyanosis, CNS findings, radiological signs of pneumonia, severe dehydration or presenting secondary complications such as renal failure, multi-organ failure, septic shock. Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal failure, diabetes or other cardiovascular conditions can cause severe complications (7).

High Risk Groups for Complications:
Infants and young children, in particular those <2 years, pregnant women, and persons aged 65 years and older. Persons with the following medical conditions: chronic pulmonary disease (e.g. asthma, COPD), chronic cardiac disease (e.g. congestive cardiac failure), metabolic disorders (e.g. diabetes), chronic renal disease, chronic hepatic disease, chronic neurological impairment, hemoglobinopathies, immunocompromised or under immunosuppression therapy, children receiving chronic aspirin therapy, or morbidly obese (8-10). However, influenza virus infection in any patient can result in severe or complicated illness. WHO recommends that persons at risk for complications receive the seasonal influenza vaccine. The aim of the study was to highlight the approach considerations in management of influenza cases.

2. Material and Methods

In this systematic review, we searched MEDLINE/PubMed and the Cochrane Database for studies regarding management of severe influenza cases. We searched peer-reviewed journals on infectious diseases and viral infection including influenza, hand-searched selected articles and also looked at the websites of the leading health authorities (e.g. WHO, CDC, HPA). To minimise the introduction of bias, no

language or publication restrictions were applied. All results were downloaded in a Word document and duplicate citations were identified and removed.

3. Results

Diagnosis:
On an individual patient basis, uncomplicated influenza can be diagnosed based on signs and symptoms when influenza viruses are known to be circulating in a community. Reverse transcriptase polymerase chain reaction (RT-PCR) provides the most timely and sensitive detection of the infection (11-13). Rapid influenza diagnostic tests (Point-of-care test) can produce quick results in 15 minutes or less, however false negative results are common. Negative results from rapid tests cannot guide treatment and infection control decisions.

Overall recommendations
All patients should be instructed to return to the health care facility for follow-up, should they develop any signs or symptoms of progressive disease or fail to improve within 72 hours of the onset of symptoms. In patients with progressive or complicated illness, instigate continuous monitoring of vital signs (e.g. temperature, blood pressure, pulse, respiratory rate, level of consciousness, clinical signs of dehydration or shock) and oxygen saturation (pulse oximetry or blood gas analyses). Initial treatment decisions should be based on clinical presentation and epidemiological data and under no circumstances should treatment be delayed pending laboratory confirmation (14-16). Patients with severe, progressive or complicated illness
consistent with a diagnosis of influenza should be treated with neuraminidase inhibitors as soon as possible, irrespective of the presence of underlying comorbidities and even if the time elapsed between symptom onset and first opportunity to treat is >48hrs. If appropriate and available, begin therapy prior to hospital transfer.

Infection control
Standard infection control measures and droplet precautions should be adhered to at all times. Vaccination of all health care workers is strongly recommended to protect from infection and to reduce risk of nosocomial infection of patients. Isolation precautions for hospitalized patients with influenza symptoms should be continued for 7 days after onset of illness or 24 hours after the resolution of fever and respiratory symptoms, whichever is longer, while a patient is in a health care facility (17-19).

Treatment options Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin
Paracetamol (acetaminophen) may be given orally or by Suppository. Avoid administration of salicylates (aspirin and aspirin containing products) in children and young adults (< 18 years old) due to the risk of Reye's syndrome.

Antiviral drug therapy
Patients in high risk groups with uncomplicated illness and hospitalized patients with suspected influenza should be treated with oseltamivir or zanamivir. ***Do not delay initiation of oseltamivir treatment while waiting for influenza testing results.***
Start treatment as soon as possible, as the benefits are greatest as close to illness onset as possible. ***Treatment should still be initiated >48hrs after symptom onset if the patient has severe disease or is deteriorating*** (20-22).

Amantadine and rimantadine are ineffective against all currently circulating virus strains.

- The conventional oseltamivir dose is 75mg twice per day (bid) for 5 days. See also table for notes on higher dosage. Combination antiviral therapy may have benefits in treating severe, complicated influenza cases and in decreasing the emergence of antiviral resistance (23,24)
- Immunosuppressed persons may demonstrate prolonged viral replication (weeks to months) and are at increased risk of developing oseltamivir resistant virus infections with
- oseltamivir treatment.
- Oseltamivir resistance remains low, but clinicians can consider the emergence of oseltamivir resistance in a treated patient who has not improved after 5 days or is worsening (25-28).

Oxygen therapy for severe disease

- Maintain oxygen saturation above 90%. When an oxygen saturation monitor is not available, provide oxygen if respiratory rate is elevated at rates indicated below:

Age Respiratory rate
<2 months ≥60/minute; 2–11 months ≥50/minute; 1–5 years ≥40/minute; >5–12 years ≥30/minute; ≥13 years ≥20/minute

- Consider increasing to 92–95% for some clinical conditions, e.g. during pregnancy.
- When treating severe hypoxaemia with an oxygen mask, the mask should be equipped with an oxygen reservoir bag and high-flow of oxygen should be used (up to 10-15 l/min in adults) to ensure sufficiently high inspired oxygen concentration (29).

Advanced respiratory support

- Lung protective mechanical ventilation strategies should be used.
- Early intubation seems to improve outcomes; current experience of intensive therapy unit staff suggests using noninvasive ventilation as an interim measure may worsen outcomes and possibly increase the potential for nosocomial transmission.
- Standard ventilation strategies (high positive end-expiratory pressure [PEEP], High Frequency Oscillation [HFO]) may cause alveolar over-distension or worsen
- oxygenation/haemodynamics (30-32).
- High sedative therapy may be needed to suppress ventilatory drive, anxiety, and delirium – requirement for neuromuscular blockade is common.
- Fluid expansion should be conservative as over-hydration has been associated with poorer outcomes.

Antibiotic treatment

- Primary viral pneumonia is the most common finding in severe cases and a frequent cause of death.
- Secondary bacterial infections have been found in approximately 30% of fatal cases.

- When pneumonia is present, co-infecting bacteria frequently reported include *Streptococcus pneumoniae*, *Streptococcus pyogenes, Haemophilus influenzae* and *Staphylococcus aureus (*which may include Methicillin sensitive Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus).
- Empirical treatment with antibiotics that will cover these pathogens, with consideration for local drug resistance patterns, is appropriate in the setting of severe influenza causing respiratory or multi-organ failure (33-36)

Corticosteroids

- Corticosteroids should not be used routinely for treatment of influenza virus infection but should not be withheld from patients with exacerbations of asthma if this forms a normal part of treating their exacerbation.
- Low doses of corticosteroids may be considered for patients in septic shock who require vasopressors and have suspected adrenal insufficiency.
- Prolonged use of or high dose corticosteroids can result in serious adverse events in influenza virus-infected patients, including opportunistic infection and possibly prolonged viral replication (37-39).

4. Conclusion

Prevention is the most effective management strategy for influenza. Most patients with influenza recover in 3 days; however, malaise may persist for weeks. Patients who do not improve should return for further evaluation. Patients diagnosed with influenza should be educated about potential complications and encouraged to return for evaluation if concerned. This is especially true of patients with underlying chronic disease or those who are immunocompromised.

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