SARS and West Nile Virus

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Key Points

- Clinical presentation of SARS is nonspecific; the important clinical findings in West Nile virus infection are those associated with neurological complications.
- Rapid and accurate diagnosis of SARS and West Nile virus infection remains an important clinical challenge.
- Older adults are at higher risk of complications, including death from SARS and West Nile virus.
- At present, there is no effective therapy for these infections.
- Although efforts are under way, there are presently no effective vaccines for SARS or West Nile virus.

Introduction

In 1992, the Institute of Medicine defined emerging infections as “new, reemerging or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future” (1). Recently it has become evident that severe acute respiratory syndrome (SARS) and West Nile virus are emerging infections that can pose an important threat to the health of older adults. This chapter will focus on SARS and West Nile virus and will summarize available evidence of the impact of these infections on older adults.

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Severe Acute Respiratory Syndrome

Epidemiology and Clinical Relevance

SARS has been documented in over 8,400 persons globally, with cases in Asia, Europe, and North America. A novel coronavirus has been identified as the etiologic agent. In November 2002, the first cases of SARS arose from Guandong province, in the south of China. On February 13, 2003, based on initial reports from the Chinese government, the outbreak was officially recognized by the World Health Organization. Unfortunately, over the next 5 months, many more deaths ensued.

Both the global and local spread of SARS is related to so-called “super-spread ing” events. In late February 2003, a critical event for the global spread of SARS occurred at the Hotel Metropol in Hong Kong. A physician who had treated hospitalized patients in the city of Guangzhou, and who was symptomatic with SARS during his stay in Hong Kong, became the source of infection for 12 people, the majority of whom were staying on the same floor as him. These individuals, also tourists, eventually sought medical care in hospitals in Hong Kong, Vietnam, Singapore, Ireland, the United States, and Canada. There was secondary spread in all these countries with the exception of United States and Ireland.

Spread of SARS occurred primarily within the healthcare setting. The secondary spread that occurred, predominantly in acute care hospitals, was largely attributed to a failure to recognize a new respiratory syndrome along with the associated delay in assuming appropriate infection control precautions soon enough. Fortunately, the spread of SARS to elderly residents of long-term care facilities was limited. However, transfer of patients to a nursing home did lead to a secondary spread in Hong Kong (2). The incubation period of SARS, estimated to range from 2 to 10 days, with a mean incubation period of 6 days, is sufficiently long enough for some people to be pre-symptomatic on admission and later develop symptoms. Importantly, there is no evidence that individuals who are asymptomatic can transmit the virus. The incidence of asymptomatic infection appears to be very low. In fact, in the Toronto outbreak fewer than 2% of healthcare workers, who had multiple exposures to SARS patients, developed serological evidence of infection.

The reproductive number of the SARS coronavirus, that is the expected number of infectious secondary cases generated by an average infectious case in a completely susceptible population, has been estimated to range from 2.2 to 3.7 (3). This figure is not particularly high as compared with the reproductive numbers of other respiratory viruses spread by respiratory droplet aerosol such as influenza or measles. The clinical experience with SARS reflects this (i.e., once appropriate infection control precautions are instituted, the virus can promptly be contained and transmission stopped). The fact that SARS, unlike influenza for example, is not efficiently transmitted in the community supports this as well. The notable exceptions to the lack of community transmission was the spread at the Hotel Metropol, where it is hypothesized that the virus detected by polymerase chain reaction (PCR) in vomit near the index case’s room or elevator may have been the source of environmental transmission.
Community spread also occurred at Amoy garden, an apartment complex, in Hong Kong; the leading hypothesis in this case was that sewage contaminated with small virus-containing droplets entered the bathrooms of the apartment complex through dried-up U traps (4). A comprehensive review of all the cases of SARS in Hong Kong showed that the transmissibility of viral infection was low, with the exception of settings where intimate contact or where clinically significant contamination occurred (5).

The epidemiologic evidence suggests that within hospitals the transmission mode of SARS was by droplet, although limited aerosol transmission may have also played a role. Super-spreading events, defined as spread from one source patient to many others, played an important role in transmission of the disease. In one report of SARS transmission in a Beijing hospital, patients linked to super-spreading tended to be older, more ill, had more contacts, and were more efficient at spreading the virus as compared with other source patients who were not linked to super-spreading (6).

To date, there have been a number of studies that have addressed risk factors for acquiring SARS. There is no evidence to suggest that the elderly are prone to infection with SARS; however, there is ample evidence that outcomes are worse. A consistent finding is that exposure to aerosol generating procedures is high risk. For example, a retrospective cohort study in a Toronto hospital revealed that assisting with intubation as well as suctioning prior to intubation was associated with a fourfold risk of acquiring SARS among critical care nurses (7). Manipulation of an oxygen mask resulted in a ninefold increased risk to nursing staff. Studies to further define risk factors among household contacts and hospitalized patients are ongoing.

SARS is caused by a novel strain of coronavirus (SARS-CoV) believed to have originated from an animal in southern China such as a masked palm civet. Coronaviruses are single-stranded RNA viruses known to cause illness in both animals and humans. The virus belongs to a new group within the coronavirus family. An important feature of the SARS-CoV is that, unlike other respiratory viruses, the viral load increases until about the tenth day of illness, and then it diminishes (4). This has implications for infection control precautions and also clinically ones. If a case is put into isolation before the viral load has peaked, then the chance of secondary transmission can be lessened. Clinically, after the first week of illness, one often sees a worsening of symptoms. Molecular epidemiologic studies reveal that the SARS-CoV from outbreaks in Hong Kong, Vietnam, Singapore, Toronto, and Taiwan are clonally related whereas those from Guangdong province are more diverse genetically (4). This may imply that some molecular lineages are more likely to be transmitted than others.

**Clinical Manifestations**

At presentation SARS is characterized by fever, myalgia, cough, chills, or rigors. Unfortunately, this syndrome is nonspecific, and the clinical features cannot be used to distinguish it from other viral or bacterial respiratory syndromes.
The most common symptom is fever, occurring in virtually all cases; shortness of breath occurs later in the illness. Some patients have diarrhea; others have nausea and vomiting. In the elderly, SARS may present as an afebrile illness, where malaise and decreased appetite are the main features. Alternatively, it can present with a low-grade fever with few respiratory symptoms (8). When compared with younger patients who have SARS, older patients are less likely to present with fever, chills, and diarrhea (9). This pattern is similar to community-acquired pneumonia, where symptoms and signs of pneumonia are less distinct in older adults.

There are a number of factors associated with a poor prognosis in SARS (see Table 1). An important factor is older age; studies have shown that older patients are at substantially higher risk of death. In a study from China, the mortality rate among patients aged 50 years and over was 13 times that for patients aged <50 years (10). In another study, every 10-year increase in age was associated with twofold increase in death (11). In a study from Hong Kong, multivariate analysis revealed that those who are older than 60 years (relative risk, 5.10; confidence interval (CI), 2.30–11.31); \( P < 0.001 \) and lactate dehydrogenase level greater than 3.8 \( \mu \)kat/L at presentation (relative risk, 2.20 [CI, 1.03–4.71]; \( P = 0.04 \) were independent predictors of mortality (12). Comorbidities, especially diabetes mellitus but heart disease as well, have also been repeatedly demonstrated to be risk factors for adverse outcomes in SARS (4). The aforementioned risk factors were noted in a Toronto study of 196 patients with SARS (13). Thirty-eight (19%) SARS patients became critically ill. The interquartile range age of the 38 patients was 57.4 (39.0–69.6) years. The median duration between initial symptoms and admission to the intensive care unit was 8 (5–10) days. Twenty-nine (76%) required mechanical ventilation. At 28 days, mortality was 13 (34%) of 38 patients, and for those requiring mechanical ventilation, mortality was 13 (45%) of 29. At 28 days, six patients (16%) remained mechanically ventilated. By 8 weeks’ follow-up, two of these patients had died. Patients who died were more often older, had preexisting diabetes mellitus, and on admission to the hospital were more likely to have bilateral radiographic infiltrates (13). High viral load at presentation can also be associated with poor outcomes. In a prospective study from Hong Kong, the following factors were independently associated with worse survival: older age (61–80 years) (adjusted hazard ratio (HR), 5.24, 95% CI 2.03–13.53), presence of an active comorbid condition (adjusted HR 3.36, 95% CI 1.44–7.82) and higher initial viral load of SARS coronavirus, according to quantitative PCR of nasopharyngeal specimens (adjusted HR 1.21 per log \( _{10} \) increase in number of RNA copies per milliliter, 95% CI 1.06–1.39) (14).

Along with increased lactate dehydrogenase, elevated serum creatinine kinase and alanine minotransferase are often seen in SARS. These laboratory indices, however, cannot discriminate SARS from other respiratory infections. In the majority

| Table 1 Risk factors for poor prognosis in severe acute respiratory syndrome (SARS) |
|-----------------------------------------------|
| Older age                                      |
| Co-morbidity                                   |
| High viral load                                |


of patients with SARS, the chest radiograph is abnormal; the most common abnormalities being ground-glass opacifications. Again, however, these findings are not specific for SARS.

**Diagnostic Tests**

Making the diagnosis has been one the most important challenges of SARS. The lack of an accurate real-time diagnostic test allowed SARS to be spread in hospitals around the world. SARS can be diagnosed very accurately retrospectively using serology. That is, antibodies to the virus will appear in over 95% of infected patients at least 21 days (but preferably 28 days) or longer after onset of symptoms. Although this is of important epidemiologic value, it is not helpful to the front-line clinician who must decide if a patient has SARS. A number of groups are working on developing nucleic acid amplification tests such as reverse transcription-PCR; however, none of these tests has proven to have a sufficiently high positive or negative predictive value to date. For example, in one recent report the highest detection rate was 75% between days 5 and 7 of illness (15). Although SARS-CoV is readily cultured, the infection control risks to laboratory workers do not make routine culturing of the virus an attractive option. Other types of assays being studied, including immunoblot assays and radioimmunoassays, are still in a development phase. The utility of individual clinical symptoms in diagnosing SARS is limited. However, clinical prediction rules, where constellation of symptoms and signs are used to diagnose, can be of benefit to clinicians in the setting of a SARS outbreak. For example, in a study from Hong Kong, the sensitivity of a clinical prediction rule was 90%; however, specificity was lower at 62% (16).

**Treatment**

There are a number of agents that have been proposed as therapy for SARS. However, there have not been any randomized controlled trials of therapy to document efficacy. Ribavirin, a synthetic nucleoside antiviral agent with inhibitory activity against both DNA and RNA viruses, was commonly used during the SARS outbreak. Usually in an aerosolized form, it has been used, in both adults and children, for the treatment of respiratory syncytial virus pneumonitis. The combination of oral ribavirin and interferon has also been shown to be efficacious in the treatment of chronic hepatitis C. High-dose intravenous ribavirin has been used in the treatment of Lassa fever and hemorrhagic fever with renal syndrome. The theoretical rationale for using this agent was that it was known to have in vitro activity against other respiratory viruses, including respiratory syncytial virus and influenza; also its use began before the agent of SARS was fully defined. There are no systematic evaluations of efficacy of ribavirin for SARS. However, there are reports of toxicity.
In Toronto, 61% of patients with SARS who were treated with ribavirin developed hemolytic anemia. Hypocalcemia and hypomagnesemia were reported in 58 and 46% of patients, respectively (17).

There have been reports of benefit with treatment from high-dose corticosteroids; however, there have been no randomized controlled trials to substantiate efficacy (18). One concern about these regimens is long-lasting adverse reactions such as avascular necrosis and neuromuscular sequelae. One study has confirmed that in patients with SARS, who were treated with corticosteroids, cumulative dose of prednisone is an important risk factor for developing osteonecrosis of the hip and knee.

There is theoretical and limited clinical data suggesting a role for interferon-alpha in the treatment of SARS. Evidence exists that prophylactic treatment of SARS coronavirus-infected macaques with the pegylated interferon-alpha significantly reduces viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage compared with untreated macaques. In a study of 22 patients with probable SARS, interferon treatment was associated with a shorter time to resolution of radiologic infiltrates, better oxygen saturation, less of an increase in creatine kinase, and more rapid resolution of lactate dehydrogenase.

**Prevention**

There are many groups that are presently working on a vaccine against the SARS coronavirus. One of the obstacles they have faced has been the inability to find an animal model where the disease manifestations are reliably reproduced when the animal is challenged with the virus. Once an animal model can be found, then testing where these animals are vaccinated then challenged with the SARS Co-V can begin. Research groups are currently working on vaccines using inactivated virus, recombinant virus, and plasmid DNA vaccines.

In the absence of a vaccine, surveillance measures are an important strategy for preventing the spread of SARS. Use of personal protective equipment is also important. Evidence exists suggesting that use of a mask can reduce the relative risk of SARS by 80% in critical care units (7).

**West Nile Virus**

**Epidemiology and Clinical Relevance**

In North America, West Nile virus (WNV) has emerged as an important human pathogen. In 1937, the virus, a type of flavivirus, was first isolated from the blood of a febrile patient in northern Uganda. Outbreaks of West Nile fever and meningoencephalitis have since been described in many parts of the world, including...
Africa, Europe, the Middle East, and Asia (19). The first North American outbreak was in 1999 in New York City (20), where 62 cases of WNv meningoencephalitis were reported. In late August 1999, a physician in Queens, New York, recognized an unusual cluster of elderly patients with viral encephalitis. These cases were initially thought to be St. Louis encephalitis; however, follow-up serologic and virologic investigation revealed that the cases were caused by WNv. Subsequent epidemiologic studies, however, suggested widespread transmission in New York City, with thousands of infections in the city. Sequence data from the infecting virus suggested that it was imported from the Middle East. Since then, there have been annual outbreaks of WNv across the United States and Canada.

West Nile virus is transmitted to humans through the bite of infected mosquitoes, primarily the *Culex* species. West Nile virus is maintained in nature in a transmission cycle that involves primarily birds and mosquitoes. Mosquitoes become infected when they feed on infected birds, where the virus is amplified (e.g., in robins and sparrows, in which a high degree of viremia is seen). Humans and other mammals are “dead-end” or incidental hosts. In late August and early September, the peak incidence of human disease in North America occurs. Predicting the temporal characteristics of future WNv transmission seasons, based on limited reports available to date, is not possible.

Recently, in North America, there has been a dramatic increase in the incidence of human cases of WNv (21). In 2007, there were 3,576 human cases of WNv infection reported to the Centers for Disease Control Prevention, and 353 cases reported in Canada, the highest number reported annually since WNv was first detected in 2002.

### Clinical Manifestations

The pathological changes within the central nervous system due to WNv, an enveloped RNA virus, appear to be due to several factors, including the direct result of viral proliferation within neuronal and glial cells, cytotoxic immune response to infected cells, diffuse perivascular inflammation, and microglial nodule formation (22–23). The range of clinical manifestations of WNv infection is, however, highly variable (Table 2). Fever, headache, and fatigue are common while skin rash on the trunk, swollen lymph glands, and eye pain occasionally are seen. The incubation period is thought to range from 3 to 14 days.

| Table 2  | Clinical presentations of West Nile virus infection |
|----------|-----------------------------------------------------|
| West Nile fever |
| Meningitis |
| Encephalitis |
| Acute flaccid paralysis |
| West Nile poliomyelitis |
Of infected persons, approximately 20% experienced mild symptoms (“West Nile Fever”), and about 1% develop meningitis, encephalitis, or acute flaccid paralysis (24). The incidence of such severe neurological syndromes increases with age. Thus, older adults are at increased risk for developing neuroinvasive disease. Although less common, other syndromes include peripheral neuropathy, polyradiculopathy, and optic neuritis.

When the central nervous system is affected, clinical syndromes ranging from febrile headache to aseptic meningitis to encephalitis may occur, and these are usually indistinguishable from similar syndromes caused by other viruses.

About 60–75% of people with neuroinvasive WNv infection, reportedly have encephalitis or meningoencephalitis, which is characterized by altered mental status or focal neurologic findings.

West Nile encephalitis, the most severe form of neuroinvasive West Nile viral disease, manifests as fever and headache, but there are more global symptoms. Usually, there is an alteration of consciousness, which may be mild and result in lethargy but may progress to confusion or coma. Focal neurologic deficits, including limb paralysis and cranial nerve palsies, may be observed; also noted have been tremors and movement disorders.

West Nile poliomyelitis, a flaccid paralysis syndrome associated with WNv infection, is less common than meningitis or encephalitis. This syndrome is generally characterized by the acute onset of asymmetric limb weakness or paralysis in the absence of sensory loss. Pain sometimes precedes the paralysis. The paralysis can occur in the absence of fever, headache, or other common symptoms associated with WNv infection. Involvement of respiratory muscles, leading to acute respiratory failure, can sometimes occur.

Recent studies of persons infected with WNv report that symptoms and signs such as fatigue, psychological dysfunction, and motor abnormalities, can persist for months after the onset of symptoms (25, 26). Existing reports provide valuable information on self-reported outcomes but have limitations, including single follow-up assessments, follow-up at ≤12 months after symptom onset, and lack of validated instruments to measure physical and mental functioning. Moreover, factors associated with slower recovery are unknown.

**Diagnostic Tests**

The diagnosis of WNv is typically made by an IgM antibody capture enzyme-linked immunosorbent assay (ELISA). The diagnosis can also be made if IgM is detected in the spinal fluid. One limitation of the ELISA test is that the antigen can cross-react with other flaviviruses such as dengue. Because serum IgM antibody may persist for more than a year, it is important to determine whether the antibody is the result of a WNv infection in the previous year and unrelated to the current clinical presentation. To confirm the diagnosis of WNv infection, a plaque reduction neutralization assay can be performed, although this is typically used for research purposes.
Treatment

There is no proven therapy for WNv infection. Management is mainly supportive for those persons with neuroinvasive disease, often involving hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections for patients with severe disease.

Ribavirin in high doses and interferon alpha-2b were found to have some activity against WNv in vitro, but no controlled studies have been completed on the use of these or other medications, including corticosteroids, antiseizure drugs, or osmotic agents, in the management of WNv encephalitis.

Prevention

Although clinical trials of human vaccines are in various stages of development, at present there is no available human vaccine. Use of personal protective behavior, including mosquito repellent, wearing shirts with long sleeves, long pants, and avoidance of mosquitoes can substantially reduce risk. Source reduction such as removing standing water around the home, may also reduce risk.

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