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Viruses in the Intensive Care Unit (ICU)

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INTRODUCTION

Infectious diseases in the developing world ICU usually involve bacterial sepsis resulting from community-acquired pneumonia, pelvic inflammatory disease, ruptured abdominal viscus (traumatic or spontaneous), necrotising fasciitis, or more exotic infections such as malaria. Despite their importance, viruses are rarely considered, except during outbreaks of hemorrhagic fever in which case they have short-lived notoriety.

Important viral infections in Africa often differ from those found in the United States of America (USA). This chapter will focus on viral hemorrhagic fevers, influenza, varicella, viral hepatitis, cytomegalovirus, measles and the respiratory syncitial virus.

Viral hemorrhagic fevers

The viral hemorrhagic fevers are generally characterized by a marked propensity for person-to-person spread and high mortality rates. This places them in the highest biohazard category (class 4) and renders them liable to control by the state in countries that have the relevant bio-safety regulations. The viruses themselves are numerous (1,2) (Table 1) and this chapter will confine discussion to those found in sub-Saharan Africa and some of those seen in South America and India. It is noteworthy that no cases of Hanta virus have been reported in Africa and in particular the Hanta virus pulmonary syndrome (3).

The viruses known or considered to be associated with hemorrhagic fever fall into three groups with respect to the primary means of transmission and reservoir hosts (Table 1). However, clinical manifestations are similar. They are febrile illnesses with an abrupt onset and usually with a

short incubation period. Headache, myalgia, lumbar pain, nausea, vomiting and diarrhea are frequent. Hematological and serological findings are leukopenia (or leukocytosis), thrombocytopenia and elevated transaminases (2,4,5). Coagulation profiles become progressively more abnormal and overt hemorrhagic features such as epistaxis; gingival bleeding and melena supervene from day 4 onward. In those most affected, multiple organ system failure and death ensue. Mortality is high, particularly with the filoviruses where Marburg has a fatality rate of 30%, Ebola Zaire 81-88%, with Ebola Ivory Coast intermediate between these two (4).

Table 1. Virus classification (HF, hemorrhagic fever)

Family	Diseases	Transmission
Arenaviridae	South American HF (Junin)	Rodent urine
	Lassa fever	Rodent urine
Bunyaviridae	Rift valley fever	Mosquitos / ticks
	Crimean Congo HF (CCHF)	Ticks
	HF with renal syndrome	Rodent
	Hantavirus (HV)	Rodent
Filoviridae	Filovirus HF	Unknown vectors
	Ebola, Marburg	
Flaviviridae	Yellow fever	Mosquito
	Dengue HF	Mosquito
	Kyasanur forest disease	Tick
	Omsk HF	Tick/rodent

The primary features of established illness are related to endothelial damage, hemorrhage and shock (1). Whereas direct cytopathogenesis appears to be a major mechanism of injury there is not extensive necrosis of endothelial cells (6). Endothelial dysfunction is more likely to be due to cytokine release as part of the systemic inflammatory response syndrome. Hemorrhage may be related to disseminated intravascular coagulopathy (DIC), but the presence of hepatic damage may confuse the picture. DIC is a regular feature of Marburg and Crimean-Congo HF but less frequent with arena-virus infections (5,7). Shock occurs as a consequence of hypovolemia. Only limited observations have been made in patients in whom shock persists after volume resuscitation and these have been contradictory with both an increased and a decreased systemic vascular resistance reported in association with a reduced cardiac index (3,8-10).

Therapy is supportive and directed toward ensuring adequate oxygen delivery. Hemorrhage is managed by replacement of appropriate clotting

factors, platelets and blood as required, with monitoring of cardiac output mandatory given the uncertainty as to the etiology of hypotension (10,11). Positive transfer of human antibodies has not been proven to be of benefit in filovirus infection but may be of value in CCHF, although there has been no controlled trial (5). It is of value in treatment of Junin virus, with a reduction of mortality to 1 – 2 % from 15-30% if initiated within the first 8 days of illness (12) and is also possibly of value in Lassa virus infection (13).

Promising results have been obtained with intravenous ribavirin in CCHF in South Africa and oral ribavirin in Pakistan but the discontinuation of the intravenous preparation has prevented proper evaluation (5,14). It is of particular value in Lassa fever with a reduction in mortality from 55% to 5% if begun within 6 days of onset of fever (15). In addition, ribavarin has some benefit in Argentine HF caused by Junin virus and reduces mortality in Hantan virus, which causes hemorrhagic fever renal syndrome in Asia (16).

Nursing and infection control are critical. It is possible that universal precautions may be sufficient to afford protection, however where a worry exists that airborne transmission is possible (this has been documented with the Reston and Zaire strains of Ebola virus in monkeys (4)), high level barrier nursing may be preferable utilizing isolation, protective clothing plus Hepa-filtered respirations. Infection control extends to the transport of specimens and their examination in the laboratory, where procedures should be in place to manage these materials.

Influenza

Influenza is increasingly being recognized as a cause of significant morbidity and mortality in the community, particularly among pediatric patients and the elderly (17,18). These viruses are subdivided into subtypes, which include host of origin, geographic location of first isolation, strain number and year of isolation (19). The antigenic description is of the hemaglutinin (HA) and neuraminidase (NA) and is given parenthetically.

Since 1933 major antigenic shifts have occurred in 1957 when the H_2N_2 subtype replaced the H_1N_1 subtype, in 1968 when the Hong Kong H_3N_2 virus appeared, in 1977 when the H_1N_1 virus reappeared and most recently in 1997 when the H_5N_1 Avian virus appeared (20,21). An epidemic was aborted in the latter case by eradication of the domestic bird population. Pneumonia is the most common complication, which occurs in high-risk

patients including those with comorbid illness such as cardiovascular or pulmonary disease, diabetes, renal failure, immunosuppression, the elderly, or residents of nursing homes. The pneumonia may be primary (of viral origin) or secondary (related to bacterial infection). Primary viral pneumonia is the most severe, although the least common of the pneumonic complications and may occur in patients that are otherwise normal (22). Whereas secondary bacterial pneumonia has been reported to be the most frequent cause of death in previous pandemics (23), this was not the case in the most recent outbreak in Hong Kong (24). Where secondary bacterial pneumonia occurs, the most common pathogens are S. *pneumoniae* (48%). S. *aureus* (19%) and *H. influenzae*. The incidence of S. *aureus* is significantly increased in influenza epidemic years (18).

Other complications that may result in ICU admission are rhabdomyolysis, encephalitis, transverse myelitis and less commonly Reyes syndrome. Management is supportive, though new antiviral agents may play a role, particularly if administered early. All currently available drugs should be started within 2 days of onset of symptoms to be effective (25). The practical effectiveness of drugs such as oseltamivir and rimantidine remains to be determined (26).

Respiratory syncitial virus (RSV)

RSV is a frequently encountered, potentially severe infection in childhood. Disease is less severe in adults but may be more severe in the elderly, and in those with comorbid disease or immunocompromise (27,28).

Presentation is non-specific with fever, myalgia, arthralgias, wheeze and non-purulent or bloody sputum. X-ray changes are also non-specific and not helpful in the etiologic diagnosis of pneumonia. In one study in South Africa, 1288 patients admitted to hospital with an acute lower respiratory tract infection were identified over a 15-month period (29). Of these, pneumonia was diagnosed in 62.2%, bronchiolitis in 20.6% and laryngotracheobronchitis in 8%. 48.9% and 13% had moderate or severe disease respectively, the latter requiring admission to ICU. RSV enzyme immunoassay was positive in 16.4% of cases in all groups of diagnoses. Viral culture performed in 162 of the cases (12.6%), grew RSV in 11.7%, adenovirus in 3.7%, parainfluenza in 2.5% and influenza B in 0.6%.

Diagnosis is made most frequently by rapid antigen detection, but is not a routinely performed investigation outside of research studies. Enzyme

immunoassays have sensitivities of 71-100% and specificities of 74-90% (30).

Treatment of RSV is supportive although nebulized ribavirin has proven effective in infants (31). This agent is not readily available in developing countries and it would be impractical to recommend routine enzyme testing for children or adults admitted to the ICU.

Varicella pneumonia

Varicella pneumonia represents a severe complication of varicella and most frequently occurs in adults. Estimates as to the incidence vary, with the highest being 50% of all adult cases and the overall incidence in the region of 14% (32-34). Varicella pneumonia has been reported to carry an overall mortality of between 10 and 30%. However, where mechanical ventilation is necessary, mortality is as high as 50% (35-37). Risk factors include cigarette smoking, pregnancy, immunocompromise and male gender (38-40). Whereas chickenpox is primarily a disease of childhood and less than 5% of reported cases occur in adults, more than 75% of all deaths take place in this group. Recent evidence indicates that there is an upward shift in the age at which chicken pox is contracted and as a consequence it is possible that more critically ill patients with varicella may be seen (41).

Varicella pneumonia causes an interstitial pneumonia with severe impairment of gas exchange. Pathologically this manifests as a florid immune reaction characterized by an interstitial pneumonitis with mononuclear cell infiltrates, capillary endothelial cell destruction, intra-alveolar exudates and hemorrhage, septal wall invasion by mononuclear cells and inflammatory changes in the bronchioles (38). The pneumonitis appears to be due to the host response rather than to specific virally mediated tissue injury.

Whereas usual therapy involves support and acyclovir, the benefit of the latter is uncertain (39). It is possible that acyclovir may hasten improvement in those that are less ill and do not require ventilation (35,38) but despite the recognition of limited efficacy it is still widely recommended as early primary therapy (39,41). A study performed in our ICU indicates that corticosteroids may dramatically alter the course of the most severe disease and should be considered in addition to antiviral therapy along with appropriate supportive care in any previously well patient with life threatening varicella pneumonia (42).

Little is known about the incidence and clinical cause of varicella pneumonia in HIV (human immunodeficiency virus) infected individuals (43,44). Patients with HIV or AIDS (acquired immunodeficiency syndrome) who are hospitalized with chickenpox appear to be at high risk for developing varicella pneumonia, which manifests in a similar clinical fashion to that in immunocompetent individuals. In a recent review conducted in a regional infectious diseases hospital affiliated to our institution, 58% of the patients who were hospitalized with chickenpox developed pneumonia (45). This incidence is significantly greater than in any previously reported study in immunocompetent patients.

Immunocompromised patients with varicella pneumonia have previously been reported to do poorly, with mortality as high as 50%, despite prompt initiation of antiviral therapy and supportive care (45). Our experience suggests that response to adjunctive corticosteroid therapy in patients with HIV/AIDS is as favorable as in immunocompetent patients.

Interestingly, recurrent varicella pneumonia requiring acute treatment followed by secondary antiviral prophylaxis in an HIV-infected adult patient has been described, analogous to other AIDS complicating opportunistic infections (43).

Hepatitis

The proportion of viral hepatitis infections that progress to acute liver failure caused by viruses is very low, occurring in less than 1% of patients with acute A or B hepatitis. However, viruses account for between 30-60% of all cases of liver failure (46,47). Most of these are related to hepatitis B (HBV) and a relatively smaller proportion to A (HAV) or other newly identified viruses. Fulminant hepatic failure is defined either as acute liver disease, occurring in the absence of pre-existing liver disease, which leads to encephalopathy within 8 weeks of onset of symptoms, or as liver disease, which leads to encephalopathy within 2 weeks of onset of jaundice (47). Clinical features are often non-specific, such as nausea and vomiting with progression to encephalopathy and coma. The prognosis is inversely proportional to the degree of encephalopathy.

Hepatitis A is an RNA virus transmitted by the fecal-oral route. Hepatitis B is a DNA virus and accounts for 40% to 75% of virally caused fulminant hepatitis. Transmission is via sexual contact, transplacentally, parenterally and in particular occupationally. Hepatitis D is an incomplete RNA virus that requires the presence of hepatitis B virus in order to infect an individual. It is an important cause of fulminant hepatitis and

aggressive chronic hepatitis in HBV carriers (48). Hepatitis E virus is an RNA virus transmitted by the fecal-oral route and possibly parenterally which for unknown reasons carries a high mortality from fulminant hepatitis in pregnant women and is also the commonest cause of fulminant hepatitis in India (49,50). Hepatitis C virus is an RNA virus of the flaviviridae family and is responsible for 20% of acute hepatitis, 70% of chronic hepatitis and 40% of end-stage cirrhosis in Europe. 80% of patients infected with hepatitis C develop chronic infection consisting of either chronic hepatitis, fibrosis or cirrhosis. It is also not usual for it to cause a fulminant hepatic failure (51) but this occurs only in areas with high hepatitis C serum prevalence (47).

The diagnosis of HAV is made on the basis of the detection of high levels of IgM antibodies in the serum. In fulminant hepatitic failure caused by HBV, the widespread hepatic necrosis that occurs as a consequence of immune mediated lysis of infected hepatocytes may result in IgM anti-hepatitis B core (anti-HBc) being the only marker of hepatitis B, as hepatitis B surface antigen and hepatitis B DNA may be absent from serum (46).

Other viruses in the herpes group (cytomegalovirus, herpes simplex and Ebstein Barr virus), adenovirus and influenza virus may rarely cause fulminant hepatic failure.

Treatment involves identification of the cause and if possible, specific therapy. If facilities are available, patients with grade 2 encephalopathy or greater should be transferred to a liver transplant center (52). Supportive therapy, involves hemodynamic management, ventilation, prevention and treatment of hemorrhage, dialysis, therapy of co-existent sepsis and electrolyte disturbance, and management of intracranial pressure (47). Orthoptic liver transplantation is not frequently available in developing countries, but in appropriate patients has been shown to improve survival significantly (52).

Measles

Measles is a frequently encountered disease in the ICU in developing countries. The presence of malnutrition and often the lack of an effective vaccination programme combine to convert this “harmless” childhood infection into a major killer. In one case series of 15 patients admitted to an ICU during a measles epidemic, 11 were malnourished and none had been vaccinated. All 15 required mechanical ventilation for pneumonia and ARDS, 4 died and 4 developed long-term sequelae, i.e. chronic lung

disease, subacute sclerosing panencephalitis, hemiplegia or partial amputation of a limb (53). Young adults are not exempt from the ravages of this disease. In a study from Greece, 424 previously healthy young males were hospitalized with measles. 41 had bacterial pneumonia on admission and 71 developed pneumonia in hospital or post discharge (54). In another study of 68 adult patients admitted with measles diagnosed on clinical and serological grounds, 9 required intensive care, six mechanical ventilation for approximately 15 days, and two deaths occurred. Prior vaccination history was not available (55).

It would be best to avoid measles entirely by means of vaccination, however once contracted a study conducted in South Africa indicated that Vitamin A supplements reduce morbidity and mortality significantly and concluded that these should be given regardless of the presence or absence of clinical evidence of Vitamin A deficiency (56).

Herpes simplex virus type 1 encephalitis

Herpes encephalitis is the most common cause of fatal sporadic encephalitis in the United States, accounting for 10-20% of the annual 20 000 cases of viral encephalitis. No accurate figures are available as to the incidence of this disease in the developing world, however we see sporadic cases in our ICU. This disease occurs in all age groups with the development of focal encephalitis with progressive oedema and necrosis. The syndrome is characterized by rapid onset of fever, seizures, focal neurological signs and impaired level of consciousness (57-59).

In adults the etiology is herpes simplex type 1 whereas in neonates type 2 may also be involved and confers a worse outcome. Brain biopsy is no longer a routine diagnostic test and polymerase chain reaction assays are considered the best non-invasive technique (60,61). This test is positive early in the disease and remains so during the first week. Early aggressive antiviral therapy with acyclovir improves mortality and reduces subsequent cognitive impairment. Acyclovir provides better outcome than vidaribine.

Cytomegalovirus (CMV)

Whereas CMV is usually asymptomatic, severe morbidity may occur in the premature neonate and organ and bone marrow transplant recipients (62). Seronegative patients receiving a seropositive organ transplant will develop a primary infection in 70-90% of cases (63,64). Seropositive patients will develop CMV infection by superinfection or reinfection in 60-100% of cases. Primary infection is the most likely type and is also

usually more severe. Those who receive anti-thymocyte or anti-lymphocyte globulins and those who have bone marrow transplants also have more severe disease and a mortality of 75-90% (65,66). CMV infection occurs most frequently 3-16 weeks after transplantation. Manifestations include, fever, hepatitis, leukopenia and thrombocytopenia. The most important condition resulting in admission to ICU is interstitial pneumonitis. This is associated with variable changes in the chest radiograph, most commonly showing diffuse bilateral infiltrates, but focal consolidation or nodules may occur. In the developing world CMV is more frequently seen in association with HIV. Despite the clear association with mortality in organ transplant recipients, in particular bone marrow transplants, the significance of CMV as a pathogen in patients with AIDS is unclear. Autopsy studies demonstrate that although CMV pneumonitis is frequently present it is not commonly found as the sole pathogen (67,68). In addition bronchoalveolar lavage specimens are also positive for CMV in more than 60% of patients (69). CMV has also been reported to be a potential cause of ventilator associated pneumonia in immunocompetent patients (70) and it is suggested that CMV should be considered as a possibility in patients not responding to antimicrobials or if there is evidence of other hospital outbreaks of viral infection particularly in the pediatric wards (71).

Diagnosis is made most frequently with an antigenemic assay incorporating antibodies directed at the pp65 matrix protein of the CMV virus (72). This test has gained acceptance particularly in immunocompromised hosts and correlates with viremia (72,73). The polymerase chain reaction has an even higher sensitivity, but is not always widely available (74).

The mainstay of therapy for solid organ transplant is Ganciclovir, which appears to reduce morbidity (63, 75,76). In contrast, Ganciclovir is not effective in bone marrow transplant recipients. It should not therefore be used as a single agent therapy in these patients (77, 79). It is possible that combinations with immunoglobulin or cytomegalovirus immunoglobulin may be of value (80,81).

Severe Acute Respiratory Syndrome (SARS)

On November 16th 2002 an unusual respiratory illness was reported in Guangdong Province, Southern China, which was designated the severe acute respiratory syndrome (SARS)(82). Subsequent world -wide transmission was initiated by a doctor who traveled to Hong Kong, where he infected 10 guests in the same hotel (83).

A global alert was issued by the WHO on 12/3/03, an unprecedented step, which nevertheless was proven to be appropriate when 3 days later, as a consequence of this alert, similar cases were identified in Singapore and Canada. Early international recognition of an impending crisis was precipitated in part by the detailed report by WHO clinician Carlo Urbani, who subsequently himself demised from SARS (84). Local spread of this disease occurred in Vietnam, Canada, Hong Kong, Singapore, China and Taiwan.

The Organism. Tissue culture isolation and electron microscopy resulted in rapid identification of the culprit virus as a novel coronavirus only distantly related to any that had previously infected humans (85,86). It is likely that it originated in animals, but it differs from all previously known coronaviruses in that most cause disease in only one host species whereas this virus appears also to have acquired the ability to infect humans.

The high concentration of viral DNA in the sputum suggested that droplet spread was the main mode of transmission. Lack of antibody in the general community indicated that this virus had not circulated widely in humans.

Diagnosis. The rapid sequencing of the genome allowed early development of diagnostic tests. A number of PCR protocols have been developed (87). These tests have high sensitivity, but a negative test cannot rule out infection. SARS follows an unusual pattern in that during the initial phases of the illness, virus shedding is relatively low. Because shedding peaks in respiratory specimens and stool only at around 10 days after onset of clinical illness, tests of very high sensitivity, which do not yet exist, are necessary (88).

Virus culture is extremely demanding and not useful for rapid diagnosis, however ELISA, immunofluorescence and neutralization tests will soon be available commercially. Detectable immune responses begin at day 5 or 6 but reliable antibody tests are available only after about day 10 following onset of symptoms. Seroconversion or a fourfold rise in titre indicates recent infection.

Diagnostic tests currently have severe limitations and extreme caution should be used before excluding the possibility of SARS on the basis of a test alone. Suspicious laboratory features include lymphopenia, thrombocytopenia and elevated lactate dehydrogenase levels (82).

Clinical Definition. From the perspective of clinicians, where local transmission has occurred, all cases of community-acquired pneumonia are suspect. Otherwise a travel history to an affected country or contact with an infected patient is essential. The WHO case definition as of 1/5/03 for a suspected or probable case of SARS is a useful resource (88).

Clinical Features. In a recent study by Peiris (89), all patients became apyrexial within 48 hours, but fever recurred in 85% (64 patients) at a mean of 8.9 days (± 3.1). In only 10 of these was nosocomial bacterial sepsis the cause. Between days 13 and 15, 23% of patients had another episode of fever. Radiological worsening occurred in 80% of patients at a mean of 7.4 (± 2.2 days), 61% subsequently improved, 15% had remained unchanged at the time of writing and 24% had progressed further to a diffuse ground glass appearance at a mean of 12.0 (± 4.4) days. 44% developed desaturation of less than 90% in room air at 9.1 (± 4.2) days after onset of symptoms. 32% (24) required ICU at a mean of 11.0 (± 6.4) days of whom 19 were intubated and 15 required mechanical ventilation for ARDS. The development of ARDS had a bimodal pattern with a peak at 11 days and another at 20 days. On univariate analysis, the risk factors for development of ARDS were age, male sex, chronic hepatitis B carriage, raised creatinine and recurrence of fever. IgG seroconversion had a 93% sensitivity at day 28 even with corticosteroid therapy; however, nasopharyngeal viral RNA detection was present in only 32% at presentation

In the study by Lee (82) 23.2% were admitted to ICU, all for respiratory failure. Mechanical ventilation was required in 19 (13.8%). 5 died (3.6%) all of whom had co-existing conditions. Multivariate analysis defined age [Odds Ratio (OR)/per decade of life 1.80 (1.16-2.81), p = 0.009; high peak LDH, O.R. per 100 units 2.09 (1.28-3.42) p = 0.003 and a neutrophil count that exceeded the upper limit of normal at presentation, O.R. 1.60 (1.03-2.50) p=0.04] as predictors of mortality. In those admitted to ICU, dramatic increases in lung opacity, shortness of breath and hypoxia occurred at a median of 6.5 days (range 3 to 12).

In a further study by Booth (90), 20% were admitted to ICU and of these 8 died i.e. there was a 6.5% 28-day mortality. Diabetes, relative risk (RR) 3.1 (95% CI 1.4-7.2) p=0.01, and other comorbid conditions, RR 2.5 (1.1-5.8) p=0.03, were independently associated with outcome.

Treatment. Viral amplification may be associated with cellular damage by cytolysis or immunopathological mechanisms (91). Once an immune

response is mounted auto-immune tissue injury may occur. This has been the rationale for corticosteroid therapy in this condition (92).

Interestingly SARS behaves similarly to varicella, in that the disease is more severe in adults, pneumonic manifestations may occur some days after the onset of clinical symptoms and dramatic responses have been apparent after the use of corticosteroids (see varicella). Whereas there has been concern regarding the use of corticosteroids there have also been many proponents, particularly from those at the coalface in Hong Kong.

Rivabirin was initially the antiviral of choice since it is an effective treatment of fulminant hepatitis in mice infected with the mouse hepatitis coronavirus (93). However, no anti-viral has been reported to be clinically effective in humans. This drug is extremely expensive in its intravenous form and Health Canada recently stated that it would no longer provide access to ribavirin because of side effects and lack of clear efficacy (94).

So et al (91) have described a standard protocol for the management of SARS which involves the administration of a combination of ribavirin and corticosteroids for those patients with:

- extensive or bilateral chest radiographic involvement,
- persistent chest radiographic involvement and high fever for 2 days
- or worsening clinical, radiographic or laboratory findings, or oxygen saturation less than 95% in room air.

Late administration of corticosteroids appears to be less effective, correction of dose according to body weight results in more rapid improvement of symptoms in obese patients, and step-down within 2-3 days resulted in re-bound in some patients. Steroids in this protocol were administered in high doses beginning with methylprednisone (1 mg/kg 8 mg x 5 days) and weaning over 21 days. There was no mortality and only 4 required short periods of non-invasive ventilation.

Mortality. The WHO has revised its initial estimates of the case fatality rates on the basis of more complete data from China, Hong Kong, Singapore and Vietnam (95). Mortality varies according to age; being less than 1% aged 24 years or younger, 6% aged 25-44, 15% aged 45-64 and greater than 50% aged 65 and older

Infection Control. SARS is highly contagious, specifically to health care workers and in particular where the index case is not immediately identified as having the disease. At the Prince of Wales Hospital, a patient was admitted on the 4/3/03 with "pneumonia" and was discharged well on the 11/3/03. On the 10/3/03 however, 18 health care workers became ill and a further 50 potential cases were identified on that day. By March 25th, 156 patients had been admitted to Prince of Wales Hospital with SARS, all traceable to this index patient (96). In Singapore similarly, initial transmission occurred from an index case to 12 patients, 10 of whom were primary contacts and 5 of whom were health care workers (97). In this latter case, Singaporean media labeled this patient a super-spreader, a concept that, although as yet inadequately defined may possibly be correct (98,99). Some patients do appear to spread the disease more readily and this may be related to the rate of shedding of viral particles. In Toronto amongst 144 cases 73 (51%) were health care workers and the subsequent outbreak of at least 90 patients occurred as a consequence of a cluster of unrecognized patients that had been admitted to North York Hospital in Toronto (90).

Infection control measures should include negative pressure wards, the use of N95 masks, gloves at all times, disposable impermeable gowns and eye protection. Hand washing after removal of gloves and avoidance of touching nose, eyes and mouth if at all possible are the most important practical measures (96).HCWS should be cohorted to decrease the number of people exposed and visiting should be strictly limited. Alcohol, phenol and quaternary ammonium based disinfectants are highly active against coronavirus. Certain features appear to enhance spread, in particular overcrowding of hospital wards, outdated ventilation systems and the use of nebulizers in the ward environment (96). Endotracheal intubation, open suctioning of respiratory secretions, the use of Bi-PAP and high frequency oscillatory ventilation in which air is forced around the face mask appear to be some of the most high- risk procedures

Numerous sources describing adequate infection control procedures are available, as well as those on the CDC website (99-101). The primary factor responsible for transmission seems to be inadequate training in or compliance with infection control procedures (102).

CONCLUSION

Whereas viruses are not usually considered to be important causes of ICU admission this review has demonstrated this perception to be incorrect.

Viruses and their manifestations differ from continent to continent and hemisphere to hemisphere and it is essential that the intensivist be familiar with diagnosis and management of these ubiquitous organisms.

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