Global Distribution of Infectious Diseases Requiring Intensive Care

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Critical care and infectious disease specialists share the responsibility to treat a wide variety of patients with common and uncommon infections in the ICU in all areas where they exist. They exert synergistic expertise, one with special knowledge of the impact of overwhelming infections on the host and the way to counter life-threatening pathophysiologic alterations, the other with special understanding of the strategies and weaknesses used by the infecting microbe and how to help the host prevail by weakening or killing the infectious agent.

This article describes infectious diseases that are of special importance to intensivists. The emphasis on epidemiology notwithstanding, it also addresses clinical, diagnostic, and treatment issues related to each infection described. The discussion avoids terrorism-related aspects of these infections, because they were very well covered in the October 2005 issue of the *Critical Care Clinics*.

Severe bacterial and fungal infections

Acute, severe bacterial infections are cosmopolitan entities that comprise the most important infectious diseases causing ICU admission and treatment in all hospitals around the globe. The epidemiology of sepsis and severe sepsis has changed dramatically in the last decades but the absence

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of standardized definitions in different areas of the world, and the lack of large-scale studies based on significant cohorts, do not permit epidemiologic certainty [1]. Estimates of the epidemiology of sepsis published rely mostly on discharge diagnosis data. Annual incidence is high in the United States, around 300 per 100,000 population and mortality is also high, 18% to 28% [2,3]. Morbidity and mortality depend on the characteristics of the host and the infecting microbe. In terms of incidence and mortality, the situation regarding sepsis and severe sepsis in such areas as Latin America [4], Africa [5], and Asia [6] may be worse than in developed countries.

Although the average age of patients with the diagnosis of sepsis at the time of discharge is 60 years, the attack rate is very high in children (over 500 cases per 100,000 population per year), and low-weight newborns have the highest incidence. Both incidence and mortality decrease after age 1 year to increase gradually up to adulthood. Infection originates in the lungs, abdomen, urinary tract, and skin in most studies [7–10]. Ventilator-associated pneumonia is a leading cause of death from hospital-acquired infections in the ICU setting [11].

Bacteremic patients frequently evolve and develop sepsis, severe sepsis, and septic shock with correspondingly increasing mortality [12]. In adults, both in the United States and Europe, most (around 80%) patients admitted in ICUs with the diagnosis of sepsis have already been hospitalized for other causes and come from the hospital wards [13,14]. Severe bacteremia and sepsis caused by the classic pathogens *Neisseria meningitidis* and *Streptococcus pyogenes* is rarely found now, and has been replaced by sepsis caused by commensal microbes, which infect individuals with conditions that compromise their skin and mucosal barriers or their immune systems. Advances in surgical techniques including transplant medicine, and increased survival of patients with trauma, splenectomy, and neutropenias are, in part, caused by advances in the treatment of sepsis associated with these conditions. In 40% of the patients no responsible microorganism is isolated, in most the organism isolated from blood or the infection site was one that usually does not cause infection in healthy persons, and frequently the infection is polymicrobial [12,14]. Although for many years gram-negative bacteria were found in most bacteremic patients with severe sepsis, the percentage of cases associated with blood isolation of gram-positive pathogens has increased in the last decades and now *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci are responsible for 30% to 50% of the cases. Another recent tendency is to isolate fungi (5%–12%), notably species of *Candida* [14,15]. Difficult-to-treat pathogens include *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, *Enterobacter* species, resistant enterococci, and methicillin-resistant *S aureus*. A new syndrome of severe necrotizing pneumonia produced by infection by community-acquired methicillin-resistant *S aureus* led to ICU admissions because of the severe manifestations [16]. The organism is now also considered a hospital pathogen [17].

The cumulative economic impact of resistant bacteria is enormous [18]. Candidemia commonly originates from catheters in colonized patients. Species of *Candida*, some resistant to antifungals, can spread by hematogenous seeding to lungs, liver, spleen, cardiac structures, bone, skin, and eyes. Mortality is substantial. The introduction of new classes of antibiotics and antifungals, such as the oxazolidinones, the glycylglycines, and the equinocandins, has improved the ability to treat resistant pathogens.

Malaria

Malaria continues to represent a leading cause of disease burden, in terms of death and disability, in a substantial part of the world. About 40% of the world's population lives in countries of Africa, Asia, Central America, Oceania, and South America where the disease is endemic. Globally, 1.5 to 3.5 million malaria-related deaths occur annually. Children are the worst affected group, especially children aged 6 months to 5 years. It may cause as many as 10% of all deaths in children in some endemic regions of sub-Saharan Africa. Additionally, almost every country in the world experiences imported malaria.

Approximately 1300 cases and 10 deaths caused by malaria are diagnosed every year in the United States. Most of them (99%) are acquired outside the country. Over half the cases originate from Africa. *Plasmodia* metabolize hemoglobin and other red blood cell proteins to create a toxic pigment called "hemozoin." The parasites derive their energy solely from glucose, which they metabolize 70 times faster than the red blood cells they inhabit; hypoglycemia and lactic acidosis are common findings. Anemia is caused by lysis of both infected and uninfected red blood cells, suppression of hematopoiesis, and increased clearance of red blood cells by the spleen. Over time, malaria infection may induce thrombocytopenia and hepatosplenomegaly.

Of the four species of *Plasmodium* known to infect man, *P falciparum* is the most important. This is because the parasite is not only capable of infecting red cells of all ages and causing heavy parasite loads, but it also induces the production of proteinaceous knobs that bind to endothelial cells. These cytoadherent infected red blood cells tend to clump together within the small blood vessels in many organs and tissues, accounting for much of the damage incurred by the parasite.

To a large degree, the damage observed in malaria by *P falciparum* seems to be related to damage inflicted by the host against itself, in response to the parasite. This is thought to be related to release of tumor necrosis factor; up-regulation of tumor necrosis factor receptors (type 2); and consequent expression of adhesion molecules (intercellular adhesion molecule 1, especially). Infected cells stick to endothelium using a large malarial protein called PfEMP1, which binds CD36 or thrombospondin.

Because *P falciparum* malaria is a potentially life-threatening disease, close clinical and laboratorial monitoring of patients is necessary.

Moreover, reliable criteria for ICU admission should be defined and risk factors identified (Box 1).

In children, the complications of severe malaria include metabolic acidosis, often caused by hypovolemia; hypoglycemia; lactic acidosis; severe anemia; seizures; and increased intracranial pressure. In adults, renal failure and pulmonary edema are more common causes of death. In contrast, concomitant bacterial infections occur more frequently in children and are associated with mortality in them. Admission to critical care units or ICUs may help reduce the mortality, and the frequency and severity of sequelae related to severe malaria [19,20].

The mortality in acute renal failure without dialysis is 50% to 75%. Early diagnosis of established renal failure and institution of dialysis are important in preventing mortality. A rapidly rising creatinine level is the most sensitive indicator of the need for dialysis. Peritoneal dialysis reduces mortality, but hemofiltration is even more effective and is associated with an improved outcome [21].

Early ICU monitoring should be attempted, especially under the following conditions: lack of clinical response to antimalarial treatment within 48 hours or any signs of neurologic disturbance (hypoglycemia excluded). Prospective multicenter trials and guidelines for supportive intensive care are urgently needed [22].

The mortality can be reduced by early recognition of the features of severe malaria; prompt administration of appropriate antimalarials; and treatment of complications, preferably in an ICU setting. Clinicians must have a high index of suspicion, especially with travelers who have recently visited endemic areas. A high standard of nursing care and continued observation in the acute stage of the disease are important for reducing mortality [20].

Box 1. Criteria for admission of patients with severe malaria to ICU

Parasitemia
>20% in endemic areas
>10% in nonendemic areas
Acidosis: base excess <−8
Hypoglycemia: blood glucose level <2.2 mmol/L
Coma: Glasgow score ≤8; or Blantyre coma score ≤2
Pulmonary edema
Renal failure: urine output <0.5 mL/Kg/h

Modified from Njuguna PW, Newton CR. Management of severe falciparum malaria. J Postgrad Med 2004;50:45–50.

Leptospirosis

Leptospirosis is a widespread infection transmitted among animals and occasionally from animals to humans. Direct exposure to urine of infected animals or urine-contaminated water and soil, through recreational or occupational activities, represents the main source of infection for humans. In general, occupations with a greater risk include dairy farmers, sewer workers, and soldiers. The most common source of exposure in some developed countries is the dog or other household pets, followed by livestock, rodents, and other wild animals [23].

Although the distribution of leptospirosis is worldwide, tropical regions bear the brunt of its impact. Moreover, the environmental conditions prevalent in most tropical and subtropical regions, including abundant rainfalls, nonacidic soil, and high temperatures, along with numerous natural water courses and an abundant biodiversity, are particularly favorable for the transmission of *Leptospira* infection.

The icteric form or Weil's syndrome is associated with severe hepatic malfunction; marked jaundice; hemorrhages; and cardiac, hemodynamic, pulmonary, and neurologic alterations. Weil's syndrome has a high mortality rate. Frequently, serum bilirubin levels are above 15 mg per 100 cm^3. Although hepatic malfunction is not a major cause of death, it is associated with a higher incidence of complications and higher mortality.

Renal involvement in severe leptospirosis is characterized by an increase in urea and creatinine levels, elevation of the sodium excretion fraction, and nonspecific abnormal findings in the urinalysis. These include leukocyturia, hematuria, proteinuria, and crystalluria. Oliguria occurs with variable frequency. Acute renal failure may be aggravated by hemodynamic alterations, such as dehydration and arterial hypotension. Notably, metabolic acidosis occurs more frequently in oliguric patients [24]. The use of dialysis methods to manage acute renal failure highly improves the survival of patients with severe leptospirosis [25].

Clinical cardiac involvement is frequent as a consequence of the concurrent myocarditis. Metabolic disturbances, such as hypokalemia, may aggravate this condition. The most common manifestations are EKG alterations and cardiac arrhythmia.

Hemorrhagic phenomena are relatively common, and may occur in the skin, mucosae, or internal organs. Over the past decade, pulmonary hemorrhage has been increasingly recognized throughout the world as a grave manifestation of leptospirosis. Pulmonary hemorrhages may vary from ordinary hemoptoic sputum to massive pulmonary hemorrhage. Gastrointestinal hemorrhages with variable degrees of severity may also occur, manifesting as melena, hematemesis, and enterorrhagia.

Pulmonary involvement is characterized by the presence of hemorrhagic interstitial pneumonia, with diffuse or localized pulmonary infiltrates. Respiratory failure with decreased arterial PaO$_2$ is attributed to impaired

oxygen diffusion at the alveolar-capillary membrane level as a result of edema and blood leakage into the pulmonary interstitium.

Leptospirosis associates with high lethality when complicated with organ dysfunction ($\geq 50\%$). Poor prognostic factors are male gender, alcohol dependence, age > 50 years, a high Multiple Organ Dysfunction Score, acute respiratory distress syndrome, presence of metabolic acidosis, and need for mechanical ventilation. Timely intervention and intensive therapy, however, may be lifesaving [26,27].

Complicated influenza including avium and severe acute respiratory syndrome

The excess morbidity and mortality associated with influenza epidemics and the increased hospitalization costs are secondary to severe cases of the disease [28]. Primary influenza pneumonia, secondary bacterial pneumonia, and mixed viral and bacterial pneumonia are critical human features of influenza virus infection. Although children are among the groups most at risk for developing influenza and its complications and are more likely to spread the infection to others, complications of seasonal influenza occur most frequently among patients older than 60 years and those with chronic comorbidities including diseases of the cardiovascular or pulmonary system, diabetes mellitus, hemoglobinopathies, renal insufficiency, and immunosuppression. Pregnancy may also pose an added risk. Recent information suggests that at least some avian influenza viruses may cause life-threatening and lethal disease in individuals without predisposing factors [29]. Other than differences in neuraminidase, the viral features that might make them more pathogenic for humans are unknown.

Despite the fact that influenza is in general worldwide in distribution, it tends to occur in partially confined outbreaks in communities of varying sizes with the prevalence of one viral strain. Primary influenza pneumonia, more commonly caused by influenza A virus, is not common, but no reliable information exists as to the exact prevalence of complicated disease [30]. Estimates vary, but studies of sequential epidemics suggest an overall complication rate of close to 10%.

Complicated respiratory influenza begins abruptly with typical features of seasonal disease but progresses rapidly and relentlessly to the adult respiratory distress syndrome. Diagnosis may be made aided by the epidemiology, rapid tests, viral isolation, culture, polymerase chain reaction, and serology, but in clinical practice is seldom documented on time for effective therapeutic measures to be taken. Sputum bacteriology is not helpful. Chest radiography typically shows bilateral infiltrates without consolidation, but localized pneumonia with segmental unilateral infiltrates occurs. There is no response to antibiotic treatment and mortality is high. Pathology shows diffuse pneumonia with hemorrhage, hyaline membranes but little inflammation.

The M2 ion channel inhibitors amantadine and rimantadine have activity against strains of influenza A but not B or C viruses. They are not active against the current H5 virus strain that threatens to become the precursor of the next pandemic. The neuraminidase inhibitors, extremely active against all influenza A strains, remain active against influenza B strains and the avian viruses of all neuraminidase subtypes, but resistant strains have been described. Clinical information supporting the efficacy of antiviral drugs in severe influenza pneumonia is not available, and recommendations are made based on case reports.

Secondary bacterial pneumonia is usually suspected when a patient experiences an exacerbation of fever and respiratory symptoms after a period of improvement from influenza like-illness. This biphasic evolution may not be present. Bacterial pneumonia may coincide with viral pneumonia in mixed viral and bacterial pneumonia. It may also be clinically indistinguishable from pneumonia in the absence of viral infection and separation is difficult during an influenza outbreak. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S aureus*, *Mycoplasma pneumoniae*, and other pathogens can be responsible.

Severe acute respiratory syndrome is a serious, infectious, pulmonary illness that jumped species from semidomesticated animals to humans, and spread from China and Hong Kong in late 2002. Most of the 8096 affected individuals were cared for in China (5327) and Hong Kong (1755). Cases were treated in 28 countries including Vietnam, Singapore, Thailand, Taiwan, and Canada, most in intensive care settings. Approximately 4 months after the first case, a coronavirus was identified as the causative organism [31]. Severe acute respiratory syndrome's main symptoms include high fever, myalgia, cough, and dyspnea progressing to the adult respiratory distress syndrome and multiple organ dysfunction [32]. Reverse-transcriptase polymerase chain reaction serology and culture are possible but have shortcomings making routine clinical use difficult. There is no specific anticoronavirus therapy and supportive care remains the principal therapeutic alternative. Rivabirin and corticosteroids have been used but their efficacy has not been established. Mortality is around 11%. Infection control practices are extremely important in halting the progression of an outbreak.

Tetanus and botulism

Generalized tetanus, a protein-toxin mediated neurologic disorder caused by *Clostridium tetani*, an obligate anaerobic, motile gram-positive rod with terminal spores has traditionally been, and continues to represent despite effective vaccine a common cause of intensive care admissions that are long and are associated with high mortality [33] and cost. The global incidence of tetanus has been estimated at about 1 million cases per year. In the United States the reported cases and deaths from tetanus have decreased

substantially since the 1940s because of successful vaccination efforts [34]. The risk of developing clinical tetanus after an acute puncture or laceration is higher in patients older than 60 years, a reflection of waning immunity, with a significant proportion of cases occurring in women [35], and a low mortality rate. Injection drug users are a growing population at risk [36]. In sharp contrast, the epidemiology of generalized tetanus in developing countries, where mortality figures may be up to 280 times higher, follows closely the problem of lack of immunization efforts. In some areas, neonatal tetanus, occurring in the offspring of unvaccinated women, causes approximately 50% of the cases and mortality. Even worse, mothers with a past history of babies suffering neonatal tetanus accounted for more than one third of all cases in one study [37].

The disease is seen predominantly in rural areas, in areas where soil is cultivated, and in tropical regions or in summer months in template regions. In developed countries, neonatal tetanus must still be suspected, especially in populations that avoid standard vaccination and prenatal care. Tetanus is one of the few diseases that are diagnosed only on clinical grounds (the only major differential diagnosis is strychnine poisoning), but in some difficult cases electromyography may assist the clinician. Treatment, details of which are beyond the scope of this article, includes supportive therapy, attention to several clinical manifestations, and passive immunization. The role of antibiotics against *C tetani* remains controversial. Mortality, even in experienced ICUs, may reach 60% in severe cases.

Tetanus is an inexcusable disease [38], because it is preventable with a three-dose series of an inexpensive and safe toxoid. The expanded program on immunization should be reinforced whatever the area of the world and age group.

Although the toxin produced by *Clostridium botulinum* is structurally and functionally similar to that of *C tetani,* its clinical effects are entirely different, and in a sense opposite. Whereas tetanus toxin produces muscular rigidity and spasms, botulinum toxins produce muscle weakness. Human botulism also has a worldwide distribution, and foodborne disease is usually present in outbreaks.

The epidemiology is different from that of tetanus and, at least in the United States, parallels the presence of the toxin type present in the spores of the environment [39]. In countries and societies around the world, such as Alaska, China, Egypt, and Mozambique, botulism may be linked to food preparation techniques [40–45], in others to religious practices [46]. Infant botulism, acquired through the consumption of spores rather than toxin and commonly attributed to consumption of honey and other sources [47], may present with constipation, feeding problems, hypotonia, and a weak cry. Respiratory assistance is necessary when upper airway obstruction ensues; this is commonly followed by respiratory insufficiency of long duration [48]. Relapses have been described. Clinically, and shortly after toxin ingestion, adult patients remain mentally intact but develop symmetric

descending weakness acutely in the absence of fever or sensory deficit outside of the eyes [49]. Nausea, dry mouth, and diarrhea may accompany the neuropathy. Several autonomic problems may also be present [50]. Patients requiring mechanical ventilation may necessitate long periods of treatment in the ICU setting [51] and prolonged intubation [52]. Toxin type may predict clinical manifestations [52]; disease caused by toxin A tends to be more severe than disease caused by toxin B.

Diagnosis must be suspected clinically, and is easier during an outbreak; the edrophonium test can be helpful to exclude myasthenia gravis and the absence of tick attachment helps rule out tick paralysis. The Guillain-Barré syndrome and the Miller Fisher variant, the Eaton-Lambert myasthenic syndrome, acute poliomyelitis, and magnesium intoxication are in the usual differential diagnosis. Anaerobic cultures and botulism toxin assays of serum, intestinal content, and suspect foodstuffs are useful when available as are electromyographic studies, especially the painful repetitive nerve stimulation.

Treatment consists of supportive care, including ventilator assistance, antitoxin treatment or human botulism immune globulin (for infant botulism), and surgical cleansing of wounds. Laxatives are important to eliminate active luminal toxin. Patient recovery is slow and muscular weakness and neuropsychiatric sequelae may remain. Application of all aspects of correct food handling protocols remains the best prophylactic measure against botulism. An effective vaccine for widespread use is sorely needed.

Rabies

The epidemiology of human rabies closely follows that of animal rabies and is only partially understood [53]. The degree of development of nations may predict the local transmission patterns. In general, in areas where dogs are not immunized, canine rabies exists, and most human cases result from dog bites. In contrast, in areas with successful immunization programs, most human cases derive from exposure to wild animal species. Globally, rabies virus has a broad host range. Dogs account for 54% of animal rabies and are the major reservoir, terrestrial mammals for 42%, and bats for 4%. Although canine rabies is now rare in Latin America, it remains uncontrolled in areas of Africa and Asia. Other wild animals, such as mongooses in Africa and Asia, skunks, gray and red foxes, raccoons (the principal reservoir in the United States), coyotes, and jackals in America, Europe, Africa, and Asia are reservoirs.

Ninety-nine countries reported animal rabies in 1999; 42 reported having no cases [54]. In the United States, the domesticated animal that causes more cases in humans is the cat, followed by the dog. Cattle, equines, sheep, goats, and pigs also transmit rabies variants. In a wide variety of species of insectivorous bats, rabies occurs in North America, Europe, Africa, Asia,

and Australia. No history of bite is obtained in a substantial proportion of bat-associated human rabies [53].

Worldwide, as many as 100,000 individuals die yearly and 4 million receive postexposure prophylaxis. Most of the doses of vaccine used for postexposure prophylaxis carry a risk of neurologic adverse effects.

Rabies virus is transmitted from salivary secretion through contact (usually bite) with an infected animal [55]. After a variable incubation period, the virus replicates locally and later reaches entry into the central nervous system through centripetal motion in peripheral nerves. It causes encephalitis, leading to an almost invariably lethal, progressive neurologic disease, characterized by agitation, upper neuron motor paralysis, impaired responses to external signals, and other abnormal neurologic signs. Infection of the salivary glands and possibly other tissues during the clinical stage leads to shedding of rabies virions and potential transmission. Corneal and other organ transplant has been responsible for rare human-to-human transmission [56].

The finding of rabies virus antibodies in the cerebrospinal fluid in a patient with encephalitis is diagnostic of rabies; reverse-transcriptase polymerase chain reaction in saliva and skin biopsy sample of the neck have high sensitivity for detection of genetic rabies virus material. Brain tissue is used for postmortem definitive diagnosis.

Once clinical rabies develops, there is no specific treatment and despite optimal intensive care, almost all patients gradually die. Even if intensive ventilatory support is applied, many complications develop. The survival, without the use of rabies vaccine, of a 15-year-old girl in whom clinical rabies developed 1 month after she was bitten by a bat made news in June 2005 [57]. She was treated by induction of coma and was supported in an ICU environment while receiving ketamine, midazolam, ribavirin, and amantadine. The patient was discharged after 76 days of hospital care. After 5 months, she exhibited choreoathetosis, dysarthria, and unsteady gait. The same treatment protocol, modified for specific complications, has been applied to at least two more rabies patients but survival has not been achieved.

The pre-exposure vaccination of high-risk individuals is strongly recommended, as is postexposure prophylaxis [58]. They are very effective and constitute specific measures.

Acute bacterial meningitis

Acute bacterial meningitis remains an important cause of morbidity, mortality, and neurologic sequelae in the world. Given the problems with reporting, it is unlikely that the world prevalence of the disease is less than the best United States estimates of approximately 3 cases per 100,000 population per year. In areas of Brazil, the attack rate might be as high as 45 cases per 100,000 population per year. Meningitis epidemics

have a strong environmental component in Africa, with the most severe epidemics occurring in the Sahelian region known as the Meningitis belt [59]. Mortality varies, but has been estimated between 25% and 35%. In countries where *H influenzae* vaccine coverage in children approaches that of developed societies, three major epidemiologic changes have occurred in regards to community-acquired bacterial meningitis: (1) there has been a dramatic decrease in meningitis caused by *H influenzae*, (2) bacterial meningitis has become a disease of adults, and (3) *S pneumoniae* is the leading cause of meningitis. Penicillin resistance may be very high [60].

Other bacterial pathogens responsible are *N meningitidis*, group B streptococci, and *Listeria monocytogenes*. Nosocomial bacterial meningitis also is a major problem, with case fatality ratio of approximately 35%. The case fatality rate for meningitis caused by Enterobacteriaceae is much higher, approaching 85%.

Factors involved in the pathogenesis of meningitis include the ability to colonize mucosal surfaces, intravascular survival, meningeal invasion, and survival in the subarachnoid space. Once replication is established in meningeal tissues, alterations in the blood-brain barrier, increased intracranial pressure, alterations in cerebral blood flow, and neuronal injury develops. Severe neurologic damage and mortality to the host are the consequences.

Patients present with headache, fever, nuchal rigidity, and signs of cerebral dysfunction. Kernig's or Brudzinski's signs might be present on physical examination. Prompt analysis of cerebrospinal fluid including cultures (and blood cultures) typically confirms the clinical diagnosis and guides empiric therapy. Gram stain and culture are positive in up to 90% of the cases.

Dexamethasone plus age and immune status–dependent bactericidal empiric or specific antimicrobial therapy with penetration into the cerebrospinal fluid must be started at appropriate doses immediately. In patients with increased intracranial pressure, several methods are available to intensivists effectively to reduce pressure. The timely use of pneumococcal, meningococcal, and *H influenzae* vaccines is advocated.

Hemorrhagic fevers

Viral hemorrhagic fevers are a heterogeneous group of severe, life-threatening viral diseases [61] that have as a common base a degree of vascular instability and permeability and decreased vascular integrity resulting in bleeding. Thrombocytopenia may be a feature that aggravates the bleeding tendency. With the exception of dengue and possibly yellow fever, travel to rural areas is a frequent epidemiologic clue to the diagnosis. The diseases are mentioned as they occur or threaten to occur in nature and some only briefly, highlighting the epidemiologic features that might make an intensive care specialist come in contact with them.

Dengue hemorrhagic fever and dengue shock syndrome

Dengue fever and dengue hemorrhagic fever (DHF) are increasingly important public health problems in the tropics and subtropics. Dengue has been called the most important mosquito-transmitted viral disease in terms of morbidity and mortality. About 2 to 5 billion people live in areas where dengue is endemic. The disease is now found in more than 100 countries throughout the Americas, Africa, the Eastern Mediterranean, Southeast Asia, and the western Pacific. An estimated 50 to 100 million cases of dengue fever and 250,000 to 500,000 cases of DHF are officially notified annually; however, the true incidence is not known. Case fatality rates vary from 3% to 5% in some Asian countries to 0.17% in the Americas [62,63].

In a small proportion of cases, the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation characteristic of DHF. Secondary infection by a different dengue virus serotype has been confirmed as an important risk factor for the development of DHF. In 20% to 30% of DHF cases, the patient develops shock, known as the "dengue shock syndrome." Worldwide, children younger than 15 years comprise 90% of DHF subjects; however, in the Americas, DHF occurs in both adults and children [63].

Patients with DHF who develop signs of dehydration, such as tachycardia, prolonged capillary refill time, cool or blotchy skin, diminished pulse amplitude, altered mental status, decreased urine output, rise in hematocrit, narrowed pulse pressure, or hypotension, require admission for intravenous fluid administration. Patients with shock may be classified into one of two groups according to the pulse pressure at admission. Those with pulse pressure >10 and ≤ 20 mm Hg are considered of moderate severity, whereas patients with pulse pressure ≤ 10 mm Hg are considered to have severe shock [64].

High-risk patients

The following types of patients are at risk, so attending staff must be particularly alert:

- Young infants <1 year old
- DHF grade IV or prolonged shock
- Overweight patients
- Patients with massive bleeding
- Patients with changes of consciousness (encephalopathy)
- Patients with underlying diseases (eg, thalassemia, G-6-PD deficiency, congenital heart disease, and so forth)
- Referred patients

These patients need special laboratory investigations because they may have complications, such as internal bleeding; severe hypoglycemia; electrolyte imbalance (hyponatremia, hypocalcemia); metabolic acidosis; liver

failure; and renal failure. To assess a patient's condition, the following laboratory tests are considered essential:

- Hematocrit
- Blood gases and serum electrolytes studies
- Liver function tests
- Platelet count, prothrombin and thrombin time, and partial thromboplastin time

Dengue shock syndrome, being a medical emergency, must be dealt with promptly by administering intravenous fluid to increase plasma volume. Patients, particularly children, may emerge in and out of shock during a 48-hour period. The patient must be monitored around the clock by medical staff.

Monitoring of patients in shock

- Blood pressure, pulse, and respiration must be recorded every 30 minutes (or more frequently, if required) until shock is overcome.
- Hematocrit or hemoglobin levels have to be checked every 2 hours for the first 6 hours, and then every 4 hours until stable.
- A fluid balance sheet must be maintained. It should contain details of the type of fluid and rate and volume of its administration. The volume and frequency of urine output must also be recorded here.

Most children with dengue shock syndrome respond well to cautious treatment with isotonic crystalloid solutions. Early intervention with colloid solutions is not generally indicated. The fluid regimen of Ringer's lactate at 25 mL/kg over a period of 2 hours is now supported by strong prospective evidence and should be recommended for children with moderately severe shock. For those with severe shock, the situation is less straightforward, and clinicians must continue to rely on personal experience, local availability of particular products, and cost. Minor advantages in initial recovery has been observed with starch, and significantly more adverse reactions were associated with dextran, so if the use of a colloid is considered necessary, starch may be the preferred option [65,66].

Yellow fever

Yellow fever follows different transmission patterns in areas of Sub-Saharan Africa and South America. In Africa the epidemiology of yellow fever has been from outbreak to epidemic in nature. Some studies have estimated that epidemics of the last two decades have been large [67]. In South America, in sharp contrast, a low-grade endemic situation exists, with few cases reported per year, usually in young men, from rural forest areas in a jungle cycle. The potential for urbanization by migration of infected

individuals to cities and for large-scale epidemics caused by the presence of vectors in those cities in both areas of the world exists.

Yellow fever varies greatly in clinical presentation and severity, from an asymptomatic infection; to undifferentiated febrile illness; to a typical biphasic (infection plus intoxication) illness; to a severe hemorrhagic fever with high mortality. The abrupt onset of fever, headache, myalgia, and hepatitis accompanied by leucopenia and albuminuria is typical but may not be present in all patients. Prostration is common in severe disease and may progress to stupor and coma. Patients must be treated in an intensive care facility and isolated from mosquitoes. Hypotension and shock, renal failure, and metabolic acidosis are poor prognostic signs. Severe yellow fever is a very serious disease, with case fatality ratios of 20% to 50%. Secondary bacterial infections worsen the prognosis of many patients but are amenable to treatment. Laboratory confirmation of yellow fever, serologically or from tissue samples, is very important epidemiologically and must be pursued. Supportive measures are used as needed, but no treatment protocols or affective antiviral drugs have been developed. Survival is associated with lifelong immunity.

Lassa fever

An arenavirus, Lassa virus causes endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, Liberia, and possibly other areas of West Africa [68]. The virus reaches humans endemically year round and epidemically during dry seasons from rodents by aerosolized small particles. It can also be transmitted by close interhuman contact and by nosocomial exposure. The number of cases in Africa is unknown, but in endemic countries, Lassa fever is a common cause of admission. Estimates place in tens of thousands of cases annually in Africa. A febrile disease contrasts with dengue fever in its gradual onset, followed by severe fatigue and prostration. A maculopapular rash might be present or noted. Bleeding is seen in 15% to 30% of the cases. Elevated transaminase levels predict adverse outcomes, and are considered an indication for ribavirin treatment. Convalescence is slow and associated with bilateral deafness in a significant number of cases. Progress has been made toward a vaccine [69].

Argentine, Bolivian, Brazilian, and Venezuelan hemorrhagic fevers

Diseases seen in rural areas of South America [70] caused by Junin, Machupo, Sabia, and Guanarito arenaviruses have so far been local public health problems. Clinically, they are similar to Lassa fever but thrombocytopenia and central nervous system dysfunction are more common and severe. Intensive care specialists outside of these areas are unlikely to see patients, but should suspect the diagnosis of the South American hemorrhagic fevers given the right epidemiologic exposures, which with the

exception of Sabia virus occur after contact with wild rodents in rural agricultural areas.

Hantavirus pulmonary syndrome

Hantavirus pulmonary syndrome is a disease that predominates in South (Andes virus) and North America (Sin Nombre virus), in China, and in Russia (Seoul virus) [71]. Laboratory rats may be infected and transmit disease to humans. Hantavirus epidemics have been associated with seasons or years of increased rodent populations. The viruses, basically parasites of wild rodents, produce severe pulmonary edema (secondary to increased vascular permeability), hemoconcentration, and shock in humans. The disease commonly starts with severe myalgia and abdominal pain. Severe hypoxia and shock are managed in the ICU and, if the patient survives, reversion of the vascular leak permits complete recovery. Diagnosis is based on the fact that IgM and IgG antibodies are present very early in the illness and can be measured by ELISA on admission. Reverse-transcriptase polymerase chain reaction in blood samples and immunohistochemical staining of tissues may detect hantavirus. Treatment consists of judicious administration of fluids, cardiotonic drugs, and other supportive measures.

Other viral hemorrhagic fevers of interest, but unlikely to be treated in ICUs outside of discrete areas of the world are Crimean-Congo fever, Ebola and Marburg virus hemorrhagic fevers, Kyasanur, and Omsk. Laboratory confirmation is very important.

Fulminant viral hepatitis

Approximately 1% of patients who develop symptoms of acute hepatitis without pre-existing liver disease progress to severe acute, so-called "fulminant liver failure" (FLF) with hepatic failure (defined as the presence of encephalopathy) within 8 weeks of the onset of symptoms. The term "acute liver failure" is used to describe the onset of encephalopathy within 12 weeks of the onset of jaundice.

There are considerable geographic variations in the etiology of acute and FLF. The most common causes in Japan and Asia are related to viral hepatitis. Hepatitis E is the leading cause in India, whereas hepatitis B virus infections are the leading cause in France and Japan [72]. Temporal changes in the etiology of FLF are evident. Drug-induced (acetaminophen toxicity) fulminant hepatic failure is currently a leading cause of liver failure in Western developed countries [73].

Many viruses other than hepatitis also are recognized causes of FLF in childhood, including Epstein-Barr virus; cytomegalovirus; paramyxovirus; varicella-zoster virus; herpesvirus types 1, 2, and 6; parvovirus; and adenovirus [74,75]. Hepatitis B virus is the most common cause of FLF in endemic

areas. Recognized sources of infection include women with positive anti–hepatitis B antigen who give birth, and carriers of subdeterminants of hepatitis B surface antigen who donate blood.

Hepatitis A virus infection is a well-known cause of FLF in individuals of all ages, with an estimated prevalence rate of 1.5% to 31%. Diagnosis of hepatitis A virus infection is made by the presence of anti–hepatitis A virus IgM in the patient's serum [76]. The risk of developing FLF is generally low but there are groups with higher risks. Pregnant women with acute hepatitis E virus infection have a risk of FLF of around 15%, with a mortality of 5%. The risk of developing FLF in hepatitis A virus infection increases with age and with pre-existing liver disease. Fulminant hepatitis B is seen in adult infection but it is relatively rare [74,76].

The pathogenesis of FLF usually initiates with the exposure of a susceptible person to an agent capable of inducing severe hepatic injury, even though the exact etiology remains undisclosed in most cases of FLF. Similarly, the pathophysiologic mechanism involved in the occurrence of hepatic encephalopathy in children with FLF has not been fully defined [77]. Viral agents may cause damage to hepatocytes either by direct cytotoxic effect or as a result of hyperimmune response. Apparently, the interaction between the infectious agent and the host determines the incidence of FLF. Fulminant hepatic failure is an uncommon but devastating illness in which the liver fails in a short period of time (<8 weeks in the initial definition [1]) in the absence of chronic liver disease. It must be distinguished from the much more common acute decompensation that develops abruptly and without warning in patients with chronic liver disease. In fulminant hepatic failure, mortality rate is higher and significant morbidity results from cerebral edema and intracranial hypertension, which are rare in patients with chronic disease. Fulminant hepatic failure is defined by the development of coagulopathy and encephalopathy and is associated with rapid progression of multiple organ system failure. Acetaminophen has surpassed viral hepatitis as the leading cause of fulminant hepatic failure in the United States and accounts for 39% and perhaps as much as 50% of the cases [2,3]. Mortality rate is high but recovery is possible in 20% to 50% of patients with supportive care. The decision to proceed to liver transplantation is complicated. Although the course may be protracted, recovery is usually complete. Liver transplantation remains the sole lifesaving option for many patients. Patients who have fulminant hepatitis have a mortality of up to 50% and should be transferred immediately to a facility that offers liver transplantation [78]. Nevertheless, with an improved understanding and recognition of the syndrome, more aggressive medical therapy, intensive monitoring, and the advent of orthotopic liver transplantation as a treatment option, survival rates have improved considerably [79]. FLF constitutes a medical emergency with a tendency to evolve rapidly and the prompt response of experienced clinicians is imperative for a successful outcome to be achieved.

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