Viral Hemorrhagic Fever–Induced Acute Kidney Injury

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Summary: Viral hemorrhagic fevers (VHFs) are diseases caused by the RNA virus from 4 different families (*Flaviridiae, Arenaviridae, Bunyaviridae*, and *Filoviridae*) that are acquired through the bite of an infected arthropod or by the inhalation of particles of rodent excreta. Among the VHFs, dengue and yellow fever are the most prevalent in tropical regions worldwide. The clinical presentation is characterized by fever, malaise, increased vascular permeability, and coagulation defects that can result in bleeding. Acute kidney injury is an uncommon complication but renal dysfunction has been associated with various VHFs. In this article we review the renal manifestations of dengue and yellow fever infections.
Semin Nephrol 28:409-415
Keywords: *Acute kidney injury, viral hemorrhagic fever, dengue, yellow fever*

Viral hemorrhagic fevers (VHFs) are diseases caused by the RNA virus from 4 different families (*Flaviridiae, Arenaviridae, Bunyaviridae*, and *Filoviridae*) that are acquired through the bite of an infected arthropod (dengue, Rift Valley yellow fever, and the Crimean-Congo virus) or by the inhalation of particles of infected rodent excreta (Lassa, Junin, Machupo, and Hantaan virus) (Table 1). The natural host and the transmission route of the Marburg and Ebola virus are unknown. Although they have some differences, the clinical picture of VHF is characterized by fever, malaise, increased vascular permeability, and coagulation abnormalities that may lead to bleeding. Even though acute kidney injury (AKI) is an unusual complication of these diseases, renal dysfunction has been reported in association with several VHFs.[1-22] Of the VHFs, dengue and yellow fever have the greater incidence in tropical regions and are the objective of this review.

DENGUE

Dengue is currently the most important human viral mosquito-borne infection of public health significance. The main dengue vector is the female of the *Aedes aegypti* mosquito. There are 4 serotypes of the dengue virus (DEN-1 to DEN-4), a RNA flavivirus. They are closely related antigenically, but whereas infection with one serotype produces lifelong immunity to that serotype, immunity to other serotypes lasts only a few months.[23-26]

Approximately half of the world's population lives in areas potentially at risk for dengue—tropical and subtropical regions around the world—and up to 100 million cases are estimated to occur annually.[23-26] Because travelers to endemic areas are at risk of acquiring the disease, health professionals of regions not affected by dengue must be aware of its clinical picture, diagnosis, complications, and adequate treatment.

After the mosquito bite, there is an incubation period of 7 to 10 days, followed by a viremic phase, when the patient becomes febrile. The infection by the dengue virus may be asymptomatic or trigger an unspecific febrile disease, dengue fever, dengue hemorrhagic fe-

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Emerson Q. Lima was supported in part by a grant from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Brazil; and Mauricio L. Nogueira was supported by FAPESP and Conselho Nacional de Desenvolvimento Científico e Tecnológico grants.
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0270-9295/08/$ - see front matter
 doi:10.1016/j.semnephrol.2008.04.009

Table 1. Viral Hemorrhagic Fevers of Major Interest

Virus Family	Genus	Geographic Distribution
Flaviviridae	Dengue virus	All tropical regions
	YF virus	Africa, South America
Arenaviridae	Lassa virus	Western Africa
	Junin virus	Argentina
	Machupo virus	Bolivia
	Guaranito virus	Venezuela
Bunyaviridae	Rift Valley fever virus	Sub-Saharan Africa
	Crimean-Congo hemorrhagic fever virus	Africa, Asia, Middle East, Eastern Europe
	Hantaan virus	Eurasia
Filoviridae	Ebola virus	Central Africa
	Marburg virus	Central Africa

ver (DHF), or dengue shock syndrome (DSS) (Table 2). The clinical picture depends on the patient's age and, usually, young children have unspecific fever followed by maculopapular rash. Adolescents and adults usually present the classic dengue symptoms such as fever, headache, retroocular pain, myalgia, arthralgia, nausea, vomiting, and skin rash. Leukopenia, relative lymphocytosis, thrombocytopenia, and an increase of liver enzyme levels may be observed. DHF is a severe form of the disease characterized by a high fever lasting 2 to 7 days, hemorrhagic phenomena, thrombocytopenia, and evidence of plasma leakage (increased hematocrit level, pleural effusion, ascites, and hypoalbuminemia). DHF usually occurs in secondary dengue infections, although it may follow primary infections, particularly in infants.[25] In southeast Asia DHF affects predominantly children, whereas in North and South America all age groups are involved.[23,24,27] In the end stage of the febrile period, some patients present severe plasma leakage and shock (DSS). Patients with DSS have a high mortality rate (up to 40%) if not treated promptly and adequately.

The diagnosis of dengue may be confirmed by isolating the virus in serum; serology to detect antidengue antibodies; detection of the virus in the tissue, serum, or cerebrospinal fluid by immunohistochemistry; immunofluorescence; or enzyme-linked immunosorbent assay. The diagnosis also may be performed by the detection of viral RNA by reverse-transcription polymerase chain reaction (RT-PCR). When the patient is examined at the onset of fever, diagnosis may be performed only by the detection of the virus, RNA, or viral proteins in the blood. Serologic diagnosis will be positive only once there is no longer fever. On the other hand, patients with DHF/DSS, in whom symptoms of increased vascular permeability are observed only after there is no longer fever, the serology for dengue (IgM) will be positive whereas RT-PCR may be negative.

The differential diagnosis for dengue and DHF includes other virus diseases (human immunodeficiency virus, hantavirus, measles, rubella, enteroviruses, influenza, hepatitis, Chikungunya virus, yellow fever, and other viral hemorrhagic fevers), bacterial (leptospirosis, meningococcemia, scarlet fever, and typhoid fever), parasitic diseases (malaria), as well as autoimmune disorders (polymyositis, dermatomyositis, and vasculitis).[24,25] In particular, leptospirosis and Hantavirus infection may mimic DHF in almost all aspects, including renal injury and renal histology. However, infection by Hantavirus with hemorrhagic manifestations and/or renal abnormalities (hemorrhagic fever with renal syndrome and epidemic nephropathy) are very rare in tropical regions. In North and South America, Hantavirus infection is the cause of human pulmonary syndrome, a flu-like disease with pulmonary edema and hypotension. In this case, AKI is secondary to respiratory failure and shock.

Severe dengue infections, particularly DHF and DSS, may give rise to several organ dysfunc-

Table 2. World Health Organization Definition of Dengue Infection

Dengue fever
Acute febrile illness with 2 or more of the following:
Headache
Retro-orbital pain
Myalgia
Rash
Hemorrhagic manifestations
Leukopenia
Dengue hemorrhagic fever
All of the following must be present:
Fever, lasting 2 to 7 days, occasionally biphasic
Hemorrhagic manifestations with at least one of the following:
Positive tourniquet test,
Petechiae, ecchymoses, or purpura
Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations
Hematemesis or melena
Thrombocytopenia ($\leq$100,000/mm^3)
Evidence of plasma leakage manifested by at least one of the following:
Increase in the hematocrit level '20% for age, sex, and population
Decrease in the hematocrit after volume replacement $\geq$20% of baseline
Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia
Dengue shock syndrome
Criteria for DHF associated with:
Tachycardia
Pulse pressure $<$20 mm Hg
Hypotension for age
Cold skin and restlessness
Laboratory criteria confirmation
At least one of the following:
Isolation of the dengue virus from serum or autopsy samples
$\geq$4-fold change in IgG or IgM antibody specific to dengue virus
Detection of dengue virus in tissue, serum, or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or enzyme-linked immunosorbent assay

Data from World Health Organization.[55]

tions such as liver failure, encephalopathy, myocarditis, and AKI. AKI is an unusual complication of dengue, usually associated with hypotension, rhabdomyolysis, or hemolysis. Renal injury comprising creatinine increase, proteinuria, glomerulonephritis, AKI, and hemolytic uremic syndrome has been reported in dengue patients.[1-17]

Tanphaichitr et al[6] found one case of "transient azotemia" and one case of "acute renal shutdown" among 17 patients with DHF and G-6-PD deficiency. Mendez and Gonzalez[8] found a 1.6% rate of acute renal failure (ARF) among 617 children with DHF in Colombia. More recently, Lee et al[11] reported a 4.9% rate of ARF in 81 Chinese patients suffering from DHF/DSS, and Abboud[12] reported a 5% rate of ARF in DHF. Wiwanitkit[13] revised the literature concerning fatal cases of DHF in Thailand, finding 51 fatalities in a total of 6,154 DHF cases. Among these patients 17 had AKI, yielding a rate of 33.3% of AKI in the patients who died and a rate of 0.3% of AKI for all DHF cases. Khan et al[18] described the outcome of 91 hospitalized patients with dengue in Saudi Arabia. Two patients (2.2%) presented with AKI at admission, with recovery of renal function during hospitalization. Besides these series of patients

there were 8 cases of AKI reported in patients with dengue fever[3,4,5,14,15] and 6 cases reported in patients with DHF or DSS.[7,9,10,16,17,19] The mortality rate was very high among these patients (38%).

Dengue virus also may cause a direct renal injury in the absence of hypotension, rhabdomyolysis, hemolysis, or the use of nephrotoxic drugs.[19] In a consistent way, Futrakul et al[1] reported a 71% rate of albuminuria, a 12.5% rate of hematuria, and an 82% rate of low C3 in DHF patients. The same group performed renal biopsies in 20 children with DHF and proteinuria, hematuria, or both (18 of them presented proteinuria, ranging from traces to 3+). All biopsy specimens showed glomerular changes characterized by hypertrophy and hyperplasia of mesangial and endothelial cells, the presence of monocyte-like cells in some of the glomerular capillary lumen, and focal thickening of the glomerular basement membrane. Immunocomplexes (IgG, IgM, or both, and C3) were found at glomeruli and arterioles in 10 patients undergoing a biopsy 2 weeks after the onset of symptoms. Dense, spheric particles were found in the 12 patients in whom electronic microscopy was performed. The investigators hypothesized that these particles might be nucleocapsid cores of dengue virions.[2] Actually, Jessie et al[28] showed the presence of viral antigens in the renal tubular cells of DHF and DSS patients. Horvath et al[29] also reported a 74% rate of proteinuria during a dengue-3 epidemic in Australia, including a patient with nephrotic syndrome (proteinuria, 10.8 g/24 h). More evidence that the dengue virus can induce glomerulopathy comes from 2 studies in which dengue virus type 2 was inoculated in mice. In the first study, diffuse proliferative glomerular injury was seen 14 days after the inoculation.[30] In the second study, there was enlarged glomerular volume, increased endocapillary and mesangial cellularity, and glomerular IgM deposition 48 hours after virus inoculation.[31]

The autoimmune-mediated mechanisms likely involved in the pathogenesis of DHF also might be related to the renal injury observed.[1,25-27,32,33]

The severity of dengue is related to immune activation markers (interleukin [IL]-6 and IL-8, tumor necrosis factor [TNF] α, interferon γ, and complement), platelet function, dendritic cells, monocytes, and T-lymphocyte abnormalities. IL-2, TNF-α, and interferon γ might increase vascular permeability in patients with DHF.[26] Endothelial dysfunction also could be induced by cross-reactivity between the antidengue nonstructural protein 1 and host proteins and endothelial cells.[34] Dengue nonstructural protein 1 activates the complement by the alternative route, a mechanism that could explain the complement consumption observed in patients with DHF and AKI.[35] Decreased T-cell response and immunosuppression-induced IL-2 generation in kidney transplant patients may explain the few reports of DHF in this population.[9,36]

Management of dengue is symptomatic because there is no specific drug to treat dengue virus. Maintenance of hydration is the major concern in the treatment of these patients. Acetaminophen might be used to treat fever. Aspirin should not be used because of the high risk of Reye's syndrome and bleeding. Patients with signs of dehydration or bleeding should be hospitalized to reduce the risks of complications and death related to the dengue virus.

YELLOW FEVER

Yellow fever (YF) is a noncontagious infectious disease and it is endemic in tropical Africa, South America, and Panama. In Africa, the largest number of cases is observed in Nigeria. In South America, there are numerous cases in Brazil, Peru, and Bolivia. The YF virus is the prototype of the *Flavivirus* genus (*Flaviviridae* family), which includes approximately 70 viruses, most of them arboviruses.[37-39]

YF is transmitted to human beings by blood-eating insect bites of the *Culicidae* family, especially by the *Aedes* and *Haemagogus* genera.[39] There are 2 cycles, a sylvatic cycle and an urban cycle. The sylvatic cycle affects occasional visitors in economic or recreational activities who go into the forest and are in contact with the vectors. The urban cycle is carried by *Aedes aegypti* and involves the virus transmission to people in urban areas by the vector. In North and South America the urban cycle was extinguished in the 1940s and 1950s, although the resurgence of this cycle was documented recently in Bolivia.[40-44] The migration of in-

fected individuals during the viremic period from the jungle to cities with a high density of the vector can trigger explosive urban epidemics and affect thousands of people among the nonvaccinated population.[37,45]

There is no evidence of YF in Asia, despite an extensive spread of vectors. It is believed that the hyperendemicity of dengue in southwest Asia has protected this population by the cross-reaction of antibodies. This mechanism also might explain the lack of re-emergence of the urban YF in Brazil after the re-introduction of the *Aedes* vector and the occurrence of a large number of cases of dengue in the past 20 years.[38]

Clinically, YF virus infection might be asymptomatic, cause acute or moderate febrile disease, or be severe, causing hemorrhagic fever, liver and renal failure, and death.[38] The disease symptoms are characterized by high fever, malaise, headache, muscular pain, tiredness, and chills. After 3 to 4 days, most patients (85%) are fully recovered and permanently immunized against the disease. About 20% of the patients infected with the YF virus develop the severe form, with hemorrhagic fever, liver and renal failure, and death in 50% of patients.[37,38,46]

The disease incubation period ranges from 3 to 6 days. Its clinical picture starts abruptly with fever, chills, anorexia, myalgia, headache, vomiting, and bradycardia. There is concomitant viremia, and hemorrhagic manifestations, such as epistaxis, may occur. Then there is a remission period with symptom improvement. Mild cases do not have any further manifestation.[38,46] In the hemorrhagic form fever comes back, followed by vomiting, epigastralgia, and jaundice. This is called the *intoxication phase*. Laboratory tests show important transaminases and bilirubin increases (bilirubin levels may be >200 umol/L). Aspartate aminotransferase levels usually are greater than alanine aminotransferase levels, indicating damage of skeletal and cardiac musculature.[38] Hemorrhagic events such as hematemesis, melena, petechiae, bruises, mucosa bleeding, and metrorrhagia in women may occur. The genesis of coagulation disorders are multifactorial, caused by reduction of the synthesis of vitamin-K–dependent coagulation factors caused by hepatic damage and consumptive coagulopathy.[38] Microthrombosis, disseminated intravascular coagulation, tissue anoxia, oliguria, and shock may occur. These events are related to changes in TNF-α and other cytokine levels.[39,46] Leukopenia and S-T segment abnormalities also are found. The picture might evolve into dehydration, oliguria, and albuminuria. The worsening of jaundice, hypertension, hypothermia, tachycardia, azotemia, and coma precede death. The lethality of these cases reaches 50%.[37-39,46]

YF diagnosis is performed by serum IgM investigation, viral isolation in insect or mammal cells, and by molecular methods such as RT-PCR.[38,46,47] The most significant pathologic finding of YF is liver injury with formation of Councilman's corpuscles, which are typical markers of apoptosis and are different from the necrosis found in viral hepatitis. Both viral RNA and antigens are found in these cells, suggesting a direct action of the virus. Liver cells support YF replication in vitro and apoptosis is frequent in this system. In case of recovery there is no liver fibrosis.[38,46,48,49]

Renal manifestations of YF are common in the severe forms. Renal dysfunction usually is observed after 5 days of disease and manifests as urinary volume decrease. The presence of urinary volume less than 500 mL/24 hours is a frequent finding even with adequate hydration.[39] The patient might evolve with anuria and acute tubular necrosis. Mortality is increased in this period. In African patients AKI often is observed sooner and in the absence of jaundice or liver abnormalities. This group has higher and earlier mortality.[39,50] The mechanisms of kidney injury are poorly known. Experimental studies in Rhesus monkeys performed in the 1980s account for most of our understanding of the pathogenesis of YF.[38,48] In this model, renal disorder seems to be prerenal until the last 24 hours of life of the animal. In the terminal phase, marked oliguria occurs, followed by azotemia, proteinemia, acidosis, and cylindruria. Severe tubular necrosis is observed at necroscopy.[48,51]

In human beings, the microscopy of cases of YF indicates an eosinophilic degeneration of the epithelium without the presence of inflammatory tubular cells.[38,48,51] Viral antigens are identified in renal epithelium and the virus has

been also isolated from renal tissue in patients with viscerotropic disease caused by the vaccine.[52,53] These data, as well as the identification of viral antigens in the glomeruli 2 to 3 days after experimental infection in monkeys, suggest that the virus has a direct action on renal tissue.[48] In fact, in a murine model, renal tissue abnormalities are observed as early as the first day of infection.[54]

In summary, little is known about the role of the virus and its relationship with the host in the genesis of AKI secondary to YF. Although YF is one of the most common hemorrhagic fevers worldwide, scarce attention has been given to this disease. A better understanding of the systemic abnormalities induced by this viral disease is essential to provide a more effective approach to patient care.

Acknowledgment

The authors are grateful to Livia C. Burdmann for the excellent grammar review of the manuscript.

REFERENCES

1. Futrakul P, Poshyachinda V, Mitrakul C, Kun-Anake C, Boonpucknavig V, Boonpucknavig V, et al. Renal involvement and reticulo-endothelial-system clearance in dengue hemorrhagic fever. J Med Assoc Thai. 1973; 56:33-9.
2. Boonpucknavig V, Bhamarapravati N, Boonpucknavig S, Futrakul P, Tanpaichitr P. Glomerular changes in dengue hemorrhagic fever. Arch Pathol Lab Med. 1976;100:206-12.
3. George R, Liam CK, Chua CT, Lam SK, Pang T, Geethan R, et al. Unusual clinical manifestations of dengue virus infection. Southeast Asian J Trop Med Public Health. 1988;19:585-90.
4. Hommel D, Talarmin A, Reynes JM, Hulin A. Acute renal failure associated with dengue fever in French Guiana. Nephron. 1999;83:183.
5. Gunasekera HH, Adikaram AV, Herath CA, Samarasinghe HH. Myoglobinuric acute renal failure following dengue viral infection. Ceylon Med J. 2000;45: 181.
6. Tanphaichitr VS, Chonlasin R, Suwantol L, Pung-Amritt P, Tachavanik K, Yogsan S, et al. Effect of red blood cell glucose-6-phosphate dehydrogenase deficiency on patients with dengue hemorrhagic fever. J Med Assoc Thai. 2002;85 Suppl 2:S522-9.
7. Radakovic-Fijan S, Graninger W, Muller C, Honigsmann H, Tanew A. Dengue hemorrhagic fever in a British travel guide. J Am Acad Dermatol. 2002;46: 430-3.
8. Mendez A, Gonzalez G. Dengue haemorrhagic fever in children: ten years of clinical experience. Biomedica. 2003;23:180-93.
9. Chacko B, John GT, Jacob CK, Vijayakumar TS. Dengue shock syndrome in a renal transplant recipient. Transplantation. 2004;77:634-5.
10. Davis JS, Bourke P. Rhabdomyolysis associated with dengue virus infection. Clin Infect Dis. 2004;38: e109-11.
11. Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005;72:221-6.
12. Abboud O. Tropical acute renal failure. Third Congress of Nephrology in Internet. Available from: http:/www.uninet.edu/cin2003/conf/aboud/aboud.html.
13. Wiwanitkit V. Acute renal failure in the fatal cases of dengue hemorrhagic fever, a summary in Thai death cases. Ren Fail. 2005;27:647.
14. Nair VR, Unnikrishnan D, Satish B, Sahadulla MI. Acute renal failure in dengue fever in the absence of bleeding manifestations or shock. Infec Dis Clin Pract. 2005;13:142-3.
15. Wiersinga WJ, Scheepstra CG, Kasanardjo JS, de Vries PJ, Zaaijer H, Geerlings SE. Dengue fever-induced hemolytic uremic syndrome. Clin Infect Dis. 2006;43: 800-1.
16. Garcia JH, Rocha TD, Viana CF, et al. Dengue shock syndrome in a liver transplant recipient. Transplantation. 2006;82:850-1.
17. Karakus A, Banga N, Voorn GP, Meinders AJ. Dengue shock syndrome and rhabdomyolysis. Neth J Med. 2007;65:78-81.
18. Khan NA, Azhar EI, El-Fiky S, Madani HH, Abduljadial MA, Ashshi AM, et al. Clinical profile and outcome of hospitalized patients during first outbreak of dengue in Makkah, Saudi Arabia. Acta Trop. 2008;105:39-44.
19. Lima EQ, Gorayeb FS, Zanon JR, Nogueira ML, Ramalho HJ, Burdmann EA. Dengue haemorrhagic fever-induced acute kidney injury without hypotension, haemolysis or rhabdomyolysis. Nephrol Dial Transplant. 2007;22:3322-6.
20. Muranyi W, Bahr U, Zeier M, van der Woude FJ. Hantavirus infection. J Am Soc Nephrol. 2005;16: 3669-79.
21. Ardalan MR, Tubs RS, Chinikar S, Shoja MM. Crimean-Congo haemorrhagic fever presenting as thrombotic microangiopathy and acute renal failure. Nephrol Dial Transplant. 2006;21:2304-7.
22. AlHazmi M, Ayoola EA, Abdurahman M, Banzal S, Ashraf J, El-Busra A, et al. Viral hemorrhagic fever hazards for travelers in Africa. Clin Infect Dis. 2003; 36:245-52.
23. Guzman MG, Kouri G. Dengue: an update. Lancet Infect Dis. 2002;2:33-42.
24. Gibbons RV, Vaughn DW. Dengue: an escalating problem. BMJ. 2002;324:1563-6.
25. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Postgrad Med J. 2004;80: 588-601.

26. Halstead S. Dengue. Lancet. 2007;370:1644-52.
27. da Fonseca BA, Fonseca SN. Dengue virus infections. Curr Opin Pediatr. 2002;14:67-71.
28. Jessie K, Fong MY, Devi S, Lam SK, Wong KT. Localization of dengue virus in naturally infected human tissues, by immunohistochemistry and in situ hybridization. J Infect Dis. 2004;189:1411-8.
29. Horvath R, McBride WJH, Hanna JN. Clinical features of hospitalized patients during Dengue-3 epidemic in Far North Queensland, 1997-1999. Dengue Bull. 1999;23:20-4.
30. Boonpucknavig S, Vuttiviroj O, Boonpucknavig V. Infection of young adult mice with dengue virus type 2. Trans R Soc Trop Med Hyg. 1981;75:647-53.
31. Barreto DF, Takiya CM, Paes MV, et al. Histopathological aspects of Dengue-2 virus infected mice tissues and complementary virus isolation. J Submicrosc Cytol Pathol. 2004;36:121-30.
32. Lin CF, Wan SW, Cheng HJ, Lei HY, Lin YS. Autoimmune pathogenesis in dengue virus infection. Viral Immunol. 2006;19:127-32.
33. Bray M. Pathogenesis of viral hemorrhagic fever. Curr Opin Immunol. 2005;17:399-403.
34. Lin CF, Ley HF, Shiau AL, Liu CC, Liu HS, Yeh TM, et al. Antibodies from dengue patient sera cross-react with endothelial cells and induce damage. J Med Virol. 2003;69:82-90.
35. Avirutnan P, Punyadee N, Noisakran S, Komoltri C, Thiemmeca S, Auethavornanan K, et al. Vascular leakage in severe dengue virus infections: a potential role for the nonstructural viral protein NS1 and complement. J Infect Dis. 2006;193:1078-88.
36. Azevedo LS, Carvalho DBM, Matuck T, Alvarenga MF, Morgado L, Magalhaes I, et al. Dengue in renal transplant patients: a retrospective analysis. Transplantation. 2007;84:792-4.
37. Figueiredo LT. The Brazilian flaviviruses. Microbes Infect. 2000;2:1643-9.
38. Monath TP. Yellow fever: an update. Lancet Infect Dis. 2001;1:11-20.
39. Vasconcelos PF. Yellow fever. Rev Soc Bras Med Trop. 2003;36:275-93.
40. Benchimol JL. Febre amarela: a doença e a vacina, uma história inacabada. ed. FIOCRUZ; 2001.
41. Filippis AM, Nogueira RM, Jabor AV, Schatzmayr HG, Oliveira JC, Dinis SC, et al. Isolation and characterization of wild type yellow fever virus in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vaccine. 2004;22:1073-8.
42. Tesh RB. Viral hemorrhagic fevers of South America. Biomedica. 2002;22:287-95.
43. Van der Stuyft P, Gianella A, Pirard M, Cespedes J, Lora J, Peredo C, et al. Urbanisation of yellow fever in Santa Cruz, Bolivia. Lancet. 1999;353:1558-62.
44. Vasconcelos PF, Costa ZG, Travassos Da Rosa ES, Luna E, Rodrigues SG, Barros VL, et al. Epidemic of jungle yellow fever in Brazil, 2000: implications of climatic alterations in disease spread. J Med Virol. 2001;65:598-604.
45. Massad E, Burattini MN, Coutinho FA, Lopez LF. Dengue and the risk of urban yellow fever reintroduction in Sao Paulo State, Brazil. Rev Saude Publica. 2003;37:477-84.
46. Figueiredo LT. Viral hemorrhagic fevers in Brazil. Rev Soc Bras Med Trop. 2006;39:203-10.
47. de Morais Bronzoni RV, Baleotti FG, Ribeiro Nogueira RM, Nunes M, Moraes Figueiredo LT. Duplex reverse transcription-PCR followed by nested PCR assays for detection and identification of Brazilian alphaviruses and flaviviruses. J Clin Microbiol. 2005;43:696-702.
48. Monath TP, Barrett AD. Pathogenesis and pathophysiology of yellow fever. Adv Virus Res. 2003;60:343-95.
49. Quaresma JA, Barros VL, Pagliari C, Fernandes ER, Andrade HF Jr, Vasconcelos PF, et al. Hepatocyte lesions and cellular immune response in yellow fever infection. Trans R Soc Trop Med Hyg. 2007;101:161-8.
50. Serie C, Lindrec A, Poirier A, Andral L, Neri P. Studies on yellow fever in Ethiopia. I. Introduction—clinical symptoms of yellow fever. Bull World Health Organ. 1968;38:835-41.
51. Monath TP, Brinker KR, Chandler FW, Kemp GE, Cropp CB. Pathophysiologic correlations in a rhesus monkey model of yellow fever with special observations on the acute necrosis of B cell areas of lymphoid tissues. Am J Trop Med Hyg. 1981;30:431-3.
52. De Brito T, Siqueira SA, Santos RT, Nassar ES, Coimbra TL, Alves VA. Human fatal yellow fever. Immunohistochemical detection of viral antigens in the liver, kidney and heart. Pathol Res Pract. 1992;188:177-81.
53. Vasconcelos PFC, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VLRS, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet. 2001;358:91-7.
54. Gershy-Damet GM. Ultrastructural changes caused by yellow fever virus at the level of the kidneys in newborn mice. Arch Inst Pasteur Tunis. 1984;61:97-106.
55. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control, ed 2. Geneva, Switzerland, World Health Organization, 1997.