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RESEARCH ARTICLE

THERAPEUTIC APHERESIS IN TROPICAL MEDICINE

***Voinov, V.A. and Zumbana Lopez, G.G.**

[1]I.P.Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russia
[2]Clinica Baños de Agua Santa, Ecuador

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ABSTRACT

The article presents analysis of the most frequent diseases, characteristic for the tropical zone. The general factor defining diseases severity and even their outcome is endotoxemia associated with development of multiple organ insufficiency and drug therapy isn't always effective. It defines indications for extracorporeal detoxification and thus membrane plasma exchange is the most effective.

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INTRODUCTION

According to WHO reports up to 16 million people die every day from infectious diseases worldwide. Of these, 10-12% needs intensive care in the result of infectious toxic shock, toxic encephalopathy and lesions of other vital organs. Infectious diseases occur in 400-800 / 100,000 of the population and are responsible for morbidity and mortality in 40-70% of cases, especially in developing countries (Mbugi *et al.,* 2012; Gao JH, Huang RG, 2016; Rai, 2018). This is largely due to diversity and drug resistance of many pathogens, as well as their combinations and comorbidity (Nii-Trebi, 2017; Sokhna *et al.,* 2017; Osakunor *et al.,* 2018). In the countries of the tropical zone there is a group of diseases specific to this region. This mainly applies to various infectious diseases caused by a variety of pathogens such as viruses, bacteria, parasites, as well as poisoning, including those caused by snake and insect bites.

Infectious diseases: There are practically no infectious diseases not accompanied by significant intoxication, the latter usually determines the condition severity, being the main mechanism of tanatogenesis, significantly affecting the overall outcome of the disease. The structure of endotoxicosis consists of bacterial endo- and exotoxins, products of inflammation and tissue destruction from primary foci of inflammation entering the circulation, secondary metabolic disorders, the same as in septic complications (Voinov, 2013, 2016; Jeong *et al.,* 29018). Clinical manifestations of various infections are various, as well as the diverse affinity and selectivity of organ lesions in the result of endotoxicosis. In some cases, the most severe toxic lesions are of the myocardium (diphtheria), in others – of the liver (viral hepatitis, leptospirosis), kidneys (hemorrhagic fever with renal syndrome), brain (tick-borne encephalitis, botulism, typhoid-paratyphoid infections). Intestinal infections are often accompanied by dehydration syndrome with disorders of the central and peripheral hemodynamics. However, in most cases, there are combined lesions of many organs and systems.

Hepatitides: In particular, development of acute liver failure in viral hepatitis is facilitated not so much by the direct impact of viruses that damage hepatocytes as by a cascade of metabolic disorders with accumulation of highly toxic products. A special danger is the fulminant form of hepatitis with massive liver necrosis, which was previously called "acute yellow liver atrophy". Cytotoxic agents thus support active autolysis of hepatocytes with suppression of all regeneration processes. Developing "lysosomes explosion" and release of the active cyto- and proteolytic enzymes causes progressive autolysis and hepatocytes necrosis followed by conversion of the liver failure into hepato-cerebral one.

The endotoxins accumulation explains the naturally developing acute renal failure (hepato-renal syndrome), accelerating the onset of complete multiple organ failure. In acute hepatitis the genesis of neurological disorders is mostly affected by endotoxins, accumulating as the liver failure develops. However, we cannot exclude direct damaging effects of hepatitis viruses on the elements of the central nervous system,

especially since both antibodies against hepatitis C virus and the RNA of the virus itself were detected in the cerebrospinal fluid traced even during the following year (Jayakumar *et al.,* 2013; Haffar *et al.,* 2017; Tosone *et al.,* 2018). Severe endotoxicosis causes secondary toxic immunodeficiency, which further weakens the patient's resistance to infection, inhibits the production of specific antibodies. There are evidences that intensive therapy of acute hepatitis with intravenous infusions of high doses of immunoglobulins contributes to hypogammaglobulinemia development in the later period (up to two years), which is a predisposing factor in the chronization of the viral infection (Tateishi *et al.,* 2004). All this makes detoxification and apheresis therapy highly recommended at the height of endogenous intoxication syndrome manifestations, along with measures for immunostimulation by photo therapy, use of indirect electrochemical oxidation of the blood, which also has a bactericidal effect in addition to detoxification. Carrying out a massive membrane plasmapheresis with removal of up to 3500 ml of plasma in severe hepatitis B leads to clarification of consciousness, disappearance of euphoria, adynamia, headaches, drowsiness, tremor, tachycardia, the level of transaminases normalized. In the absence of positive dynamics repeated procedures of plasmapheresis were performed (Li *et al.,* 2005). At the onset of hepatic coma massive membrane plasmapheresis with removal of up to 5 liters of plasma proved most effective, which contributed to decrease of bilirubin levels by 40%, ammonia by 70%, methionine, phenylalanine and tyrosine by 60% and endotoxins by 20%. Unlike hemodialysis and hemofiltration, membrane plasmapheresis more fully removes high-molecular toxic products, including autoantibodies and immune complexes formed in the severe course of hepatitis B and exacerbating the damage of hepatocytes. It is also possible to combine the use of hemosorption and plasmapheresis in the treatment of fulminant liver failure complicated by hepatotoxic encephalopathy (Li *et al.,* 2014; Koch *et al.,* 2017).

Leptospirosis: Severe forms of ictero-hemorrhagic leptospirosis are often accompanied by infectious-toxic shock with hemorrhagic syndrome on the 5th-6th day of the disease. With help of plasmapheresis it was possible to reduce the rates of intoxication; coagulogram improved, especially in DIC syndrome on the stage of hypocoagulation. Plasmapheresis also prevented development of multiple organ failure (Cerdas-Quesada, 2011). Valbonesi (1986) with help of massive plasmapheresis with the removal of up to 2.8 liters of plasma also managed to stop acute renal-hepatic insufficiency in 33 of 36 patients. Plasmapheresis was particularly effective in development of respiratory distress syndrome with pulmonary hemorrhage (Siriwanij *et al.,* 2005; Fonseka and Lekamwasam, 2018). Plasmapheresis was more effective than hemodiafiltration (Tse *et al.,* 2002).

West Nile fever: In recent years cases of virus-induced West Nile fever have increased, penetrating the hemato-encephalic barrier and causing severe meningitis, encephalitis, flaccid paralysis with frequent fatal consequences (Samaan *et al.,* 2016). Specific therapy has not yet been developed. However, not only direct viral damage to the nerve structures plays a role in the pathogenesis of the disease, but also general toxic effects (Lim *et al.,* 2011), which is already an indication for extracorporeal detoxification, especially since deaths are preceded by development of severe respiratory distress syndrome (Morrey *et al.,* 2012). But even after recovery there are quite severe neurological disorders such as systemic autoimmune demyelinating diseases with severe muscle weakness on the background of characteristic foci of the brain lesions (Cook *et al.,* 2010; Loeb *et al.,* 2011), which also raises the question of apheresis therapy use. Indeed, a course of plasmapheresis can achieve a significant improvement in neurological status (Leis and Stokic, 2012; Cooper and Said, 2014)

Hemorrhagic fever with renal syndrome: South-East Asia is the endemic area of this viral disease (Jang H *et al.,* 2016). Development of hemorrhagic syndrome on the background of infectious-toxic shock and acute renal failure is characteristic (Pal *et al.,* 2018). Using plasma exchange in the volume of 0.9 circulating plasma volume (CPV) with partial replacement of fresh frozen donor plasma leads to best results than isolated dialysis therapy (Clement J *et al.,* 2018). Positive results were also provided by plasmapheresis before hemodialysis.

Rickettsioses: In South-East Asia fever caused by rickettsiosis tsutsugamushi and close to it "Bush" fever (scrub typhus) are common and they are transmitted by tick bites. It is manifested by symptoms of nervous system involvement (encephalitis, meningitis), heart, kidneys, lungs, stomach and intestines with bleeding and severe endotoxemia until multiple organ failure. Untreated 35-45% of cases are fatal (Rahi *et al.,* 2015; Chakraborty and Sarma, 2017). Pregnant women often experience intrauterine growth retardation and preterm birth with high perinatal mortality (McGready R *et al.,* 2014).

Chagas disease: The South American continent is characterized by Chagas disease, a chronic heart disease affecting more than 16 million people and resulting from infection with the protozoan parasite Trypanosoma cruzi (Bahia MT *et al.,* 2104). It should be born in mind that the pathogen can be transmitted from mother to fetus, and with blood transfusions from infected donors. Moreover, even in non-endemic regions of Ecuador and Bolivia, about 1/4 of donors are positive to the presence of T. cruzi. For a long period this parasite can stay in the blood, regardless of the clinical condition, especially since most infected are asymptomatic and can be in the ranks of donors. The incubation period of the disease lasts up to 114 days. Tourists visiting countries located between 400 North latitude (Texas) and 430 South latitude (Argentina), as well as immigrants from these regions can get this disease.

The first line of therapy is the use of benznidasol and nifurtimox for 60-90 days. However, they have a sufficiently high hepatotoxicity and are accompanied by allergic reactions, eosinophilia, leukopenia, neurological and gastrointestinal disorders, anorexia, which often required treatment discontinuation (Bahia *et al.,* 2014; Pérez-Molina *et al.,* 2013; Urbina, 2015). After the acute phase of the disease, manifested by esophageal bleeding, often after 20-30 years there are signs of lesions of the esophagus (dilatation), colon (megacolon) and the heart with inflammatory cardiomyopathy and severe dilatation of the heart cavities, congestive heart failure, thromboembolism, stroke and lethal outcome (Vannucchi *et al.,* 2015). Histological examination revealed diffuse myocarditis with degeneration of cardiomyocytes, combined with fibrosis, mononuclear infiltration and damage to the elements of the cardiac conduction system in the absence of parasites themselves (Bocchi *et al.,* 2017; Pérez-Molina AND Molina, 2018). These data indicate a high probability of

autoimmune pathogenesis of this disease. Autoantibodies affect the G-protein receptors of the myocardium, such as β-adrenergic receptors and M2 acetylcholine receptor. There is evidence of structural (antigenic) proximity of the immunodominant ribosomal protein of this parasite and β1-adrenoreceptor, which indicates a possible cross-molecular mimicry of these two proteins, which makes antibodies, naturally developed against this parasite, react in the future with the structures of their own tissues of the heart muscle (Bonney and Engman, 2015; De Bona *et al.,* 2018). In addition to myocardium, antibodies produced against T. cruzi antigens cross-react with antigens of the endothelium, neurons of the brain and cerebellum, peripheral nerve trunks. This suggests that such "autoantibodies" are actually heterogeneous in nature, but react with autoantigens due to the proximity of the antigenic structure of the parasite and the host. In this case, the usual "triple" therapy (azathioprine, prednisolone and cyclosporine) can even reactivate this chronic parasitic infection. Given the autoimmune nature of endotoxemia background, plasmapheresis can also be used in treatment of this severe pathology. This is very important for patients who have undergone an acute phase of the disease and consider themselves recovered. However, the removal of such antibodies with help of plasmapheresis will be to some extent a guarantee to prevent later autoimmune lesions.

Ebola, Marburg hemorrhagic fever: In recent years, there have been reports of severe course of a number of hemorrhagic fevers caused by Ebola and Marburg viruses, accompanied by intoxication and severe shock with mortality up to 70-90%, since the treatment of these infectious diseases remains practically symptomatic (Rougerton *et al.,* 2015). The pathogenesis of these complications is based on release of a number of cytokines from leukocytes (tumor necrosis factor, interleukins 2, 6, 8) and other biologically active toxic compounds that damage the permeability of the vascular endothelium with development of toxic edema, which contributes to shock and multiple organ failure (Martines *et al.,* 2015). All these factors justify the use and methods of therapeutic apheresis, in particular using lectin-affine plasmapheresis (Büttner S *et al.,* 2014).

Dengue-viral infection: Dengue virus infection is the leading cause of morbidity and mortality in tropical countries (Dissanayake and Senevirantne, 2018). Over the past 50 years, its frequency has increased 30 times, affecting up to 100 million people and taking up to 22,000 lives (Byard, 2016). In its pathogenesis, autoimmune disorders with release of autoantibodies and toxic cytokines, including NS1-protein, which lead to cell death by apoptosis and pyroptosis, play an important role (Suwanmanee and Luplerlop, 2017). In case of the clinical signs of thrombotic thrombocytopenic purpura, neurological disorders such as Guillain-barré syndrome and glomerulonephritis, plasmapheresis is also used (Agarval *et al.,* 2017; Bastos *et al.,* 2018).

Zika-virus infection: Zika arbovirus is close to the Dengue virus from the Flaviviridae family and is also transmitted by mosquito bites. It causes lymphadenopathy and thrombocytopenia, conjunctivitis, fever, arthralgia and myalgia up to multi-organ failure, as well as acute neurological disorders up to development of Guillain-Barré syndrome and multiple organ failure (Calvet GA *et al.,* 2016; Boyer Chammard *et al.,* 2016). In pregnant women it leads to miscarriages and defects in fetal development such as microcephaly with intracranial calcification and sensory hearing loss (Leal MC *et al.,* 2016). The main foci of infection are in the tropical zone, but the first patients appear in the more Northern latitudes. There is no specific antiviral treatment and only supportive symptomatic therapy is used(Hamel R *et al.,* 2015). In severe cases, especially in case of Guillain-Barré syndrome plasmapheresis is also used, which is confirmed by our own clinical experience (Pinheiro *et al.,* 2016; Arias *et al.,* 2017].

Malaria: Malaria is a real devastator for people, especially those living in tropical regions. This is mainly related to the tropical form of malaria caused by Plasmodium falciparum, which accounts for 98% of malaria deaths (Componovo *et al.,* 2017; Mutsigiri *et al.,* 2017; Soto-Calle *et al.,* 2017). Its crises are accompanied by severe endotoxemia with coma, acute renal and respiratory failure associated with infectious and toxic shock. Children and pregnant women are particularly affected (Dhingra *et al.,* 2010). All this makes extracorporeal detoxification methods indicated. Of course, the main method of treatment of infectious diseases remains etiotropic therapy – with antibiotics, but they are not always effective enough. Therefore, hemosorption can greatly help, which, in addition to effective detoxification, provides capture of pathogens from the flowing blood preventing them to return to the body. However, only decontamination and detoxification are not yet able to restore the patient's immune potential. If the body itself is unable to resist the infection, then no antibiotics will help. And here the plasma exchange comes to the fore, which, in addition to removing all pathological and toxic compounds effectively restores the immune system by replenishing the removed volume with donor fresh frozen plasma. Such tactics of primary detoxification and decontamination using hemosorption with subsequent plasma exchange appears to be the most justified (Voinov, 2016). An auxiliary role is played by methods of indirect electrochemical oxidation and ozonation of the blood, potentiating detoxification, and photo-hemotherapy (UV and laser irradiation of blood), having an immunostimulating effect. In general, antibiotics and other expensive drugs intake is significantly reduced as well as the period of patients stay in intensive care units, total duration of treatment, and mortality is reduced.

Poisonings: Various poisonings also pose a danger. They are very diverse both by the nature of exogenous toxic substances, the mechanisms of their effects on different tissues and organs, and by methods of their penetration into the body – inhalation, with water, food, through the skin. There may be various lesions of the entrance gate areas such as burns of the mucous membrane of the upper respiratory tract and respiratory parenchyma in case of inhalation lesions, chemical burns of the oral mucosa, esophagus and gastrointestinal tract in case of oral poisoning, chemical burns of the skin in case of percutaneous penetration of toxic substances (TS). Food poisoning is often caused by *Salmonella* (Toyofuku H, 2008). However, there are also significant general homeostasis disorders due to direct toxic effects of the penetrated TS, as well as secondary metabolic disorders, depending on the mechanisms of TS damaging effects.

Poisonous mushrooms: The greatest danger is posed by *Amanita phalloides*, secreting amatoxin poison, causing liver, kidney failure and coagulopathy with mortality up to 27% (Trakulsrichai *et al.,* 2017). With the onset of hemolysis caused by poisonous fungi, there is a sharp increase in the

concentration of free hemoglobin with renal function blockade. The most frequent is lipid peroxidation disorder with accumulation of toxic end-products and suppression of the antioxidant system, reducing the level of superoxide dismutase, α-tocopherol, and ceruloplasmin. Activity increase of proteolytic enzymes, in particular peptidases, is accompanied by an increase in the level of medium-molecular oligopeptides and molecules with the presence of free radicals in their structures. Appearance of circulating toxic products damages membrane potentials with excitation of platelet aggregation ability; it promotes the release of histamine and serotonin, which triggers a further cascade of reactions of DIC syndrome. Endotoxicosis is accompanied by secondary toxic immunosuppression. In some cases, there is a selective hepato, nephro- or neurotrophic effect, most often, especially in the terminal phase of disorders, multiple organ failure develops with a number of vicious circles, when the damaged hepatocytes further disrupt the processes of natural detoxification, and the lesion of glomerular or tubular renal apparatus slows the excretion of both the primary damaging agent and secondary products of impaired metabolism. In almost all cases of poisoning the use of apheresis therapy is pathogenetically justified, and plasmapheresis is in such cases the most universal method, even in cases where dialysis can be used to remove low-molecular weight TS (acetic acid, phenol), but rapidly advancing metabolic disorders with accumulation of medium and large-molecular toxic substances cannot be stopped by dialysis. Severe organ disorders thus contribute to the formation of "lethal synthesis" products even more toxic than the primary xenobiotics. With help of high-volume plasmapheresis performed with replacement of the removed volume with fresh frozen donor plasma in a ratio of 1: 1, it was possible to stop extremely severe *Amanita phalloides* poisoning and hepatic coma (Mydlik *et al.,* 2013; Lu *et al.,* 2018). Sometimes it is necessary to remove up to eight liters of plasma to adequately reduce the levels of ammonia, urea and amino acids and relieve hepatic coma (Clemmesen *et al.,* 2001).

Scorpion bites: Severe intoxication associated with cardiogenic shock, pulmonary edema, brain disorders and multiple organ failure with fatal outcome occurs after scorpion bites (Cupo, 2015; Amr *et al.,* 2017). All this makes plasmapheresis indicated according to the ASFA recommendations (Schwartz *et al.,* 2013). Thus, with help of plasmapheresis 57% of patients were saved, while after standard drug therapy – only 14% survived (Mostafdazadeh, 2017]

Asian giant hornet bites: Severe renal-hepatic insufficiency develops after Asian giant hornet bites (the world's largest variety of wasps). It is possible to develop both acute toxic myocarditis and pulmonary edema with frequent fatal outcome (Kularatne *et al.,* 2014; Liu *et al.,* 2016). Only after intensive treatment with plasma exchange and hemofiltration it is possible to restore these organs functions (Zhang *et al.,* 2013; Yuan *et al.,* 2016). But sometimes in the later period neurological disorders (severe akinetic-rigid syndrome) may develop, for the relief of which plasmapheresis was also used (Leopold NA *et al.,* 1999).

Venomous snake bites: Every year from 1.2 to 5.5 million people suffer from bites of poisonous snakes, and in the tropical zone – at least 500,000, of which more than 100,000 die (Gutiérrez *et al.,* 2017). Indeed, in such cases, severe poisoning occurs due to development of microangiopathic hemolytic anemia, thrombocytopenia and multiple organ failure (Keyler, 2008; Ho *et al.,* 2010). With help of plasmapheresis it is possible to significantly reduce both general and local manifestations of such poisoning (Moujahid A *et al.,* 2009; Hatten BW *et al.,* 2013).

Conclusion

In the countries of the tropical zone, covering South America, Africa, Asia and Polynesia, there are a number of specific diseases that are still not fully understood, although many of them are accompanied by a high level of mortality. This is largely determined by the lack of etiotropic and pathogenetic treatment, limited to symptomatic therapy only. Nevertheless, the clinical picture of severe intoxication, up to multiple organ failure, dictates the need to perform extracorporeal detoxification and immune correction using plasmapheresis. It should be recognized that nowadays these issues do not raise significant questions and debates, and only the weakness of the material base and the lack of trained professionals, prevent the wider use of apheresis therapy and extracorporeal detoxification in the practice of infectious medical institutions. This task can be solved by simple and safe methods of membrane plasmapheresis using portable "Hemophenix" devices produced by Treckpor Technology Russian companies. This is facilitated by the small volume of filling, and their one-needle connection to any peripheral veins, including in infants (Voinov, 2013, 2016).

REFERENCES

Agarval, A., Vibha, D., Srivastava, AK., *et al.,* 2017. Guillain-Barré syndrome complicating chikungunya virus infection. *J Neurovirol.,* 23: 504-507.

Amr, ZS., Al Zou'bi, R., Abdo, N. and Bani Hani, R. 2017. Scorpion stings in Jordan: an update. *Wilderness Environ Med.,* 28: 207-212.

Arias, A., Torres-Tobar, L., Hernandez, G., *et al.,* 2017. Guillain-Barre syndrome in patients with a recent history of Zika in Cucuta, Colombia: a descriptive case series of 19 patients from December 2015 to March 2016. *J Crit Care.,* 37: 19-23.

Bahia, MT., Diniz, LF. and Mosqueira, VC. 2014. Therapeutical approaches under investigation for treatment of Chagas disease. *Expert Opin Investig Drugs.,* 23: 1225-1237.

Bastos, MLA., Araújo, RMO., Oliveira, DS., *et al.,* 2018. Thrombotic thrombocytopenic purpura associated with dengue and chikungunya virus coinfection: case report during an epidemic period. *Rev Inst Med Trop Sao Paulo*., 60: e48.

Bocchi, EA., Bestetti, RB., Scanavacca, MI., *et al.,* 2017. Chronic Chagas heart disease management: from etiology to cardiomyopathy treatment. *J Am Coll Cardiol.,* 70: 1510—1524.

Bonney, KM. and Engman, DM. 2015. Autoimmune pathogenesis of Chagas heart disease: looking back, looking ahead. *Am J Pathol.,* 185: 1537-1547.

Boyer Chammard, T., Schepers, K., Breures, S., *et al.,* 2017. Severe thrombocytopenia after Zika virus infection, Guadelupe, 2016. *Emerg Infect Dis.,* 23: 696-698.

Büttner, S., Koch, B., Dolnik, O., *et al.,* 2014. Extracorporeal virus elimination for the treatment of severe Ebola virus

disease – first experience with lectin affinity plasmapheresis. Blood Purif. 2014; 38: 286-291.

Byard, RW. 2016. Lethal Dengue virus infection: a forensic overview. *Am J Forensic Med Pathol.,* 37: 74-78.

Calvet, GA., Santos, FB. and Sequeira, PC. 2016. Zika virus infection: epidemiology, clinical manifestations and diagnosis. *Curr. Opin. Infect Dis.,* 29: 459-466.

Cerdas-Quesada, C. 2011. Potential benefits of plasma exchange by apheresis on the treatment of severe icteric Leptospirosis: case report and literature review. *Transfus Apher Sci.*, 45: 191-194.

Chakraborty, S. and Sarma, N. 2017. Scub typhus: an emerging threat. *Indian J Dermatol.,* 62: 478-485.

Clement, J., Lee, APK., Verpooten, GA., *et al.,* 2018. Acute hantavirus infection presenting as haemolytic-uraemic syndrome (HUS): the importance of early clinical diagnosis. Eur J Clin Microbio. *Infect Dis.,* 37: 135-140.

Clemmesen, JO., Kondrup, J., Nielsen, LB., *et al.,* 2001. Effects of high-volume plasmapheresis on ammonia, urea, and amino acids in patients with acute liver failure. *Am J Gastroenterol,* 96: 1217-1223.

Componovo, F., Bever, CA., Galactionova, K., *et al.,* 2017. Incidence and admission rates for severe malaria and their impact on mortality in Africa. *Malar J.,* 16: 1.

Cook, RL., Xu, X., Yablonsky, EJ., *et al.,* 2010. Demographic and clinical factors associated with persistent symptoms after West Nile virus infection. *Am J Trop Med Hyg.,* 83: 1133-1136.

Cooper, CJ. and Said, S. 2014. West Nile virus encephalitis induced opsoclonus-myoclonus syndrome. *Neurol Int.,* 6: 5359.

Cupo, P. 2015. Clinical update on scorpion envenoming. *Rev Soc Bras Med Trop.,* 48: 642-646.

De Bona, E., Lidani, KCF., Bavia, L., *et al.,* 2018. Autoimmunity in chronic Chagas disease: a road of multiple pathways to cardiomyopathy? *Front Immunol.,* 9: 1842.

Dhingra, N., Jha, P., Sharma, VP., *et al.,* 2010. Adult and child malaria mortality in India. *Lancet*, 20 (376): 9754.

Dissanayake, HA. and Senevirantne, SL. 2018. Liver involvement in dengue viral infection. *Rev Med Virol.,* 28: 10.1002/rmw.

Fonseka, CL. and Lekamwasam, S. 2018. Role of plasmapheresis and extracorporeal membrane oxygenation in the treatment of leptospirosis complicated with pulmonary hemorrhages. *J Trop Med.,* 2018: 4520185.

Gao, JH. and Huang, RG. 2016.(Epidemic trend on notifiable communicable diseases from 2010 to 2015 in Beijing). 37: 836-840.

Gutiérrez, JM., Calvete, JJ., Habib, AG., *et al.,* 2017. Snakebite envenoming. *Nat Rev Dis Primers.,* 3: 17063.

Haffar, S., Bazerbachi, F., Prokop, L., *et al.,* 2017. Frequency and prognosis of acute pancreatitis associated with fulminant or non-fulminant acute hepatitis A: a systematic review. *Pancreatology,* 17: 166-175.

Hamel, R., Deajrnac, O., Wichit, S., *et al.,* 2015. Biology of Zika virus infection in human skin cells. *J Virol.,* 89: 8880-8896.

Hatten, BW., Bueso, A., French, LK., *et al.,* 2013. Envenomation by the Great Lakes Bush Viper (Atheis nitschei). Clin Toxicol (Phila). 51: 114-116.

Ho, WK., Verner, E., Dauer, R. and Duggan, J. 2010. ADAMTS-13 activity, microangiopathic haemolytic anaemia and thrombocytopenia following snake bite envenomation. *Pathology,* 42: 200-202.

Jang, H., Du, H., Wang, LM., *et al.,* 2016. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. *Front Cell Infect Microbiol.,* 6: 1.

Jayakumar, S., Chowdhury, R., Ye, C. and Karvellas, CJ. 2013. Fulminant viral hepatitis. *Crit Care Clin.,* 29: 677-697.

Jeong, YJ., Park, SK., Yoon, SJ., *et al.,* 2018. Experimental in vivo models of bacterial Shiga toxin-associated hemolytic syndrome. *J Microbiol Biotechnol.,* 28: 1413-1425.

Keyler, DE. 2008. Envenomation by the lowland viper (Proatheris superciliaris): severe case profile documentation. *Toxocon,* 52: 836-841.

Koch, A., Trautwein, C. and Tacke, F. 2017.(Acute liver failure). Med Klin Intensivmed Notfmed. 112: 371-381.

Kularatne, K., Kannangare, T., Jayasena, A., *et al.,* 2014. Fatal acute pulmonary oedema and acute renal failure following multiple wasp/hornet (Vespa affinis) stings in Shri Lanka: two case report. *J Med Case Rep.,* 8: 188.

Leal, MC., Muniz, LF., Ferreira, TS., *et al.,* 2016. Hearing loss in infants with microcephaly and evidence of congenital Zila virus infection – Brazil, November 2015 - May 2016. *MMWR Morb Mortal Wkly Rep.,* 65: 917-919.

Leis, AA. and Stokic, DS. 2012. Neuromuscular manifestations of West Nile virus infection. *Front Neurol*., 3: 37.

Leopold, NA., Bara-Jimenez, W. and Hallett, M. 1999. Parkinsonism after a wasp sting. *Mov Disord.,* 14: 122-127.

Li, LJ., Liu, XL., Xu, XW., *et al.,* 2005. Comparison of plasma exchange with different membrane pore sizes in the treatment of severe viral hepatitis. *Ther Apher Dial.,* 9: 396-401.

Li, MQ., Ti, JX., Zhu, YH., *et al.,* 2014. Combined use of non-biological artificial liver treatments for patients with acute liver failure complicated by multiple organ dysfunction syndrome. *World J Emerg Med.,* 5: 214-217.

Lim, SM., Koraka, P., Osterhaus, A. and Martina, B. 2011. West Nile virus: immunity and pathogenesis. *Viruses,* 3: 811-828.

Liu, Z., Li, XD., Gou, BH., *et al.,* 2016. Acute interstitial nephritis, toxic hepatitis and toxic myocarditis following multiple Asian giant hornet stings in Shaanxi Province, China. *Environ Health Prev Med.,* 21: 231-236.

Loeb, M., Eskandarian, S., Rupp, M., *et al.,* 2011. Genetic variants and susceptibility to neurological complications following West Nile virus infection. *J Infect Dis*., 204: 1031-1037.

Lu, Z., Chen,YB., Huang, B., *et al.,* 2018.(Mixed amantia phalloides poisoning with rhabdomyolysis: analysis of 4 cases). Nan Fang Yi Ke Da Xue Xue Bao. 38: 635-638.

Martines, RB., Ng, DL., Greer, PW., *et al.,* 2015. Tissue and cellular tropism, pathology and pethogenesis of Ebola and Marburg viruses. *J Pathol.,* 235:153-157.

Mbugi, EV., Kayunze, KA., Katale, BZ., *et al.,* 2012. 'One Health' infectious diseases surveillance in Tanzania: are we all on board the same flight? *Onderstepoort J Vet Res.,* 79: 500.

McGready, R., Prakash, JA., Benjamin, SJ., *et al.,* 2014. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. *PLoS Negl Trop Dis.,* 8: e3327.

Morrey, JD., Siddharthan, V., Wang, H., *et al.,* 2012. Respiratory insufficiency correlated strongly with mortality of rodents infected with West Nile virus. *PLoS One,* 7: e38672.

Mostafdazadeh, B. 2017. The effect of plasmapheresis on treating disseminated intravascular coagulation (DIC) caused by a Hemiscorpius lepturus (Gadim) sting. Clin Toxicol (Phila). 55: 902-907.

Moujahid, A., Laoutid, J., Hajbi, H., *et al.,* 2009. Plasma exchange therapy in a severe snake bite victim. *Ann Fr Anesth Reanim.,* 28: 258-260.

Mutsigiri, F., Mafaune, PT., Mungati, M., *et al.,* 2017. Malaria morbidity and mortality trends in Manicaland province, Zimbabwe, 2005-2014. *Pan Afr Med J.,* 27: 30.

Mydlik, M., Derzsiová, K. and Frank, K. 2013. Renal replacement therapy in acute poisonings – one center experience. Przegl Lek. 70: 381-385.

Nii-Trebi, NI. 2017. Emerging and neglected infectious diseases: Insights, advances, and challenges. Biomed Res Int. 2017; 5245021.

Osakunor, DNM., Sengeh, DM. and Mutapi, F. 2018. Coinfections and comorbidities in African health systems: at the interface of infectious and noninfectious diseases. *PLoS Negl Trop Dis.,* 12: e0006711.

Pal, E., Korva, M., Resman Rus, K., *et al.,* 2018. Sequential assessment of clinical and laboratory parameters in patients with hemorrhagic fever with renal syndrome. *PLoS One,* 13: e0197661.

Pérez-Molina, JA. and Molina, I. 2018. Chagas disease. *Lancet,* 391 (10115): 82-94.

Pérez-Molina, JA., Sojo-Diradon, J., Norman, F., *et al.,* 2013. Nifurtimox therapy for Chagas disease does not cause hypersensitivity reactions in patients with such previous adverse reactions during benznidazole treatment. *Acta Trop.,* 127: 101-104.

Pinheiro, TJ., Guimarães, LF,. Silva, MT. and Soares, CN. 2016. Neurological manifestations of Chikungunya and Zika Infections. *Arq Neuropsiquiatr.,* 74: 937-943.

Rahi, M., Gupte, MD., Bhargava, A., *et al.,* 2015. DHR-ICMR Guidelines for diagnosis and management of Rickettsial diseases in India. *Indian J Med Res.,* 141: 417-422.

Rai, SK. 2018. Changing trend of infectious diseases in Nepal. *Adv Exp Med Biol.,* 1052 : 19-38.

Rougerton, V., Feldman, H., Drard, G., *et al.,* 2015. Ebola and Marburg haemorrhagic fever. *J Clin Virol.,* 64:111-119.

Samaan, Z., McDermid, VS., Bawor, M., *et al.,* 2016. Neuropsychological impact of West Nile virus infection: an extensive neuropsychiatric assessment of 49 cases in Canada. *PLoS One,* 11: e0158364.

Schwartz, J., Winters, JL., Padmanabhan, A., *et al.,* 2013. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the writing committee of the American Society for Apheresis: the Sixth Special Issue. *J Clin Apher.,* 28: 145-284.

Siriwanij, T., Suttinont, C., Tantawichien, T., *et al.,* 2005. Haemodinamics in leptospirosis: effects of plasmapheresis and continuous venovenous haemofiltration. Nephrology, (Carlton). 10: 1-6.

Sokhna, C., Gaye, O. and Doumbo, O. 2017. Developing research in infectious and tropical diseases in Africa: the paradigm of Senegal. *Clin Infect Dis.,* 65 (Suppl. 1): S64-69.

Soto-Calle, V., Rosas-Aguirre, A., Llanos-Cuentas, A., *et al.,* 2017. Spatio-temporal analysis of malaria incidence in the Peruvian Amazon Region between 2002 and 2013. *Sci Rep.,* 7: 40350.

Suwanmanee, S. and Luplerlop, N. 2017. Immunopathogenesis of Dengue virus-induced redundant cell death: apoptosis and pyroptosis. *Viral Immunol.,* 30: 13-19.

Tateishi, Y., Hirasawa, H. and Nitta, M. 2004.(Apheresis treatment for fulminant hepatitis). 62 (Suppl. 5): 462-466.

Tosone, G., Simeone, D., Spera, AM., *et al*, 2018. Epidemiology and pathogenesis of fulminant viral hepatitis in pregnant women. *Minerva Ginecol.,* 70: 480-486.

Toyofuku, H. 2008. Epidemiological data on food poisonings in Japan focused on Salmonella, 1998-2004. Rood Addit Contam Part a Chem Anal control Expo Risk Assess. 25: 1058-1066.

Trakulsrichai, S., Sriapha, C., Tongpoo, A., *et al.,* 2017. Clinical characteristics and outcome of toxicity from Amanita mushroom poisoning. *Int J Gen Med.,* 10: 395-400.

Tse, K-C., Yip, P-S., Hui, K-M., *et al.,* 2002. Potential benefit of plasma exchange in treatment of severe Icteric Leptospirosis complicated by acute renal failure. *Clin Diagn Lab Immunol.,* 9: 482-484.

Urbina, JA. 2015. Recent clinical trials for the etiological treatment of chronic chagas disease: advances, challenges and perspectives. *J Eukaryot Microbiol.,* 62: 149-156.

Vannucchi, V., Tomberli, B., Zammarchi, L., *et al.,* 2015. Chagas disease as a cause of heart failure and ventricular arrhythmias in patients long removed from endemic areas: an emerging problem in Europe. *J Cardiovasc*., Med (Hagerstown). 16: 817-823.

Voinov, VA. 2013. Tactics of apheresis therapy in sepsis. *Vestnik Chirurgii* (Rus). 172 (2): 74-77.

Voinov, V.A. 2016. Therapeutic apheresis. Constanţa: Celebris.

Yuan, H., Chen, S., Hu, F. and Zhang, Q. 2016. Efficacy of two combinations of blood purification techniques for the treatment of multiple organ failure induced by Wasp stings. *Blood Purif.,* 42: 49-55.

Zhang, L., Yang, Y., Tang, Y., *et al.,* 2013. Recovery from AKI following multiple wasp stings: a case series. *Clin J Am Soc Nephrol.,* 8: 1850-1856.

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