Literature Review

Emerging Infectious Diseases and Transmission via Transfusion

Parichart Permpikul

Department of Transfusion Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University

Introduction

During last two decades, we have faced several new infectious diseases or infectious diseases which were never happened in our country but now posed threat to our patients and our community. The definition of emerging disease (EID) is "one that has appeared in a population for the first time, or that may have existed previously but is rapidly increasing in incidence or geographic range"[1]. There are so many emerging infectious diseases, they include all class of agents, more than half are zoonotic, several of these are derived from human activities and rapid transportation is one of important factors for rapid spread of these EIDs. When any community faced EIDs, there are concerned about transmission of these infectious agents via transfusion which need the following attribute: presence of infectious agent in asymptomatic blood donor, viable during processing and storage of blood product and finally the agents cause clinical problem in at least part of recipients[2]. This article will focus on Zika virus, Dengue virus, Chikungunya virus, and Hepatitis E virus which are EIDs that are relevance to Thailand and should be concerned about transmission via blood transfusion.

Zika Virus (ZIKV)

Zika virus is single stranded RNA, vector -borne virus in genus *Flavivirus*, family *Flaviviridae*. There are African and Asian lineages. This virus was first described in primate from Zika forest in Uganda in 1947 and later was isolated from *Ades* mosquito. The first three human infection cases was reported in 1954 from Nigeria[3]. Zika virus infections were reported from Africa and Asia including Thailand (7 cases of local resident were reported for Zika infection during 2012-2014 in Thailand)[4]. The first outbreak outside Africa and Asia started in 2007 from Yap Island across the Pacific. In 2015, Zika was spread to Brazil, Puerto Rico and many other countries. On February 1, 2016, WHO declared a public health emergency of international concern because there is increased microcephaly and neurological disorders occurred in area affected by Zika and in November 18, 2016, WHO declared of committed long term response to Zika infection[5].

Modes of transmission are mosquito *Aedes* spp. bite, maternal to fetal transmission (both intrauterine and perinatal), sexual transmission, laboratory exposure and theoretical -transfusion-transplant-fertility treatment and breast feeding. Incubation period ranges from 3-12 days. Viremia ranges from few days to 1 week and virus can remain in semen for longer period[6].

Symptoms are fever, skin rashes, muscle and joint pain, malaise, headache and conjunctivitis. Symptoms usually are mild and last for 2-7 days. Eighty percent of infection are asymptomatic.

Treatment: Because clinical symptoms are usually mild, last in days to weeks, hospitalization is uncommon and fatality is rare. There is no specific treatment, only symptomatic treatment is needed[6].

Clinical significance of Zika virus infection are

a. Microcephaly and CNS malformation: There was increased reported of microcephaly and CNS malformation in Brazil. Data confirmed that 17 microcephaly babies had Zika infection. ZIKV RNA was found in amniotic fluid (Zika virus can cross placenta) and was detected in brain of microcephaly baby.

b. Guillain Barre syndrome (GBS): During 2013 - 2014 outbreak in French Polynasia, there were 42 GBS which 98 percent had antibody to Zika virus. In 2016 outbreak

in Brazil, Columbia, El Salvadore, Suriname and Venezuela, there was increased cases of GBS[3,6].

Concern about blood transfusion: Zika virus can be transmitted via transfusion from asymptomatic infected blood donors. There were 2 reported cases of transfusion-transmitted Zika in Brazil[7].

Prevention: In endemic area, "accept risk" when transfusion is needed, encourage donor to report possible Zika infection symptoms to blood center. The donor testing (ZIKV NAT), pathogen inactivation and import of blood product from area without Zika are additional options for country with enough resources. In country with lower resource may select to provide Zika's safe blood for focus risk group e.g pregnant women or intrauterine transfusion[8]. Blood donor who had positive ZIKV NAT should be deferred for 120 days[9]. For non-endemic area, travel restriction and deferred donor who are at risk of Zika infection at least 28 days after resolution of symptoms[10].

Chikungunya Virus (CHIKV)

Chikungunya virus is a single-stranded RNA virus in genus *Alphavirus*, family *Togaviridae*. In 1952, Tanzania was first recorded endemic and spread to India, Southeast Asia including Thailand and Western Pacific. Large outbreak recently occurred in Indian Ocean Island, New Caledonia, Caribbean Island and Latin America[11].

Modes of transmission are vector borne by mosquito- *Aedes spp* and maternal-fetal transmission. Blood borne transmission was possible. Currently, there is no reported case of CHIKV transmission via transfusion but theoretical is possible because there is asymptomatic infection with high level of viremia[12,13].

Clinical significance: Viremia lasts 2-6 days, asymptomatic infection ranges from 3-28% of cases and incubation period varies from 3-7 days. Symptoms include high fever, joint pain, myalgia, arthritis, conjunctivitis, nausea, vomiting, maculopapular rash (involve trunk, extremities, palm sole and face). Fever can be biphasic, joint symptoms can be severe. Thrombocytopenia, lymphopenia, and elevated creatinine may be found. Serious complication is rare (myocarditis, ocular disease, hepatitis, neurologic disease - GBS, myelitis, cranial nerve palsies). Diagnosis is based on clinical features, laboratory detection of virus in serum and virus-specific antibodies with neutralization.

Treatment: In most cases, only symptomatic treatment is required[11].

Concern about transmission via blood transfusion: In La Union (2005), suspension of local blood donation, use of import red cells and use of pathogen inactivation are implemented[14] and in addition, CHIKV NAT is implemented in Saint Martin (2014)[15].

Dengue virus (DENV)

Dengue virus is single stranded RNA virus genus *Flavivirus* in the family *Flaviviridae*. There are 4 serotypes of dengue: *DENV-1, DENV-2, DENV-3, DENV-4*. Currently all 4 serotypes can be found in every endemic area. Dengue virus was first isolated in 1943 from blood sample collected during epidemic in Nagasagi[16]. In Thailand, after observation of first case of Dengue in 1949, there are cyclical epidemic activity of alternate year between low and high incidence[17].

Mode of transmission are vector borne by *Aedes* spp. Mosquitoes and blood borne transmission was reported[18].

Clinical significance: The incubation period is 4-7 days, symptoms last 3-10 days, mosquitoes can take infectious blood during 5 days of infection and be able to transmit to other, the virus will required additional 8-12 days to be able to infect another human. Symptoms include high fever, severe eye pain, joint and muscle pain, rash and bleeding. Clinicians in Thailand are familiar with Dengue infection. Some people may develop Dengue hemorrhagic fever which is immunepathologic disease. Dengue-virus immune complexes trigger release of vasoactive mediators causing vascular leakage, hemoconcentration, serous effusion, hemorrhagic manifestation and shock. Diagnosis was made from clinical symptoms plus detection of Dengue virus in patient blood and detection of IgM and IgG antibodies (4 folds rising).

Treatment: There is no specific treatment, Dengue vaccine become available recently. Treatment is supportive and symptomatic[17].

Concern about transmission via blood transfusion: There are several reported cases of transfusion-transmitted Dengue infection in Hong Kong, Singapore, Puerto Rico, and Brazil[18]. The RED III study (collaboration study between US and Brazil), during epidemic in Brazil in 2012 revealed that there was more than 0.5% of DENV RNA positive donation and transmission was occurred in one third. There is no clinical significant different between recipient of DENV RNA positive and DENV RNA negative blood transfusion. Estimation rate of Dengue viremia detection is about 1 donation DENV viremia per 800 clinical dengue cases[19]. Decision about screening of Dengue virus in endemic area need to be evaluated against the magnitude of threat in individual country[20].

Hepatitis E virus (HEV)

Hepatitis E virus is single stranded RNA virus, widespread in animal in many area both in developed and developing countries. HEV causes hepatitis with fatality rate of 0.2 - 4%. Asymptomatic infection is possible[21].

Transmission of HEV: In developing countries, by drinking contaminated water while in developed country, by consumption of uncooked infected animal (pork) or contact with infected animal. HEV can also be transmitted via blood transfusion, mother to child and organ transplantation.

Concern about transmission via blood transfusion: HEV were detected in blood donors from China, UK, Germany, Japan, The Netherlands and Scotland and there was documented transfusion transmission HEV in UK, France, Japan, Saudi Arabia and Germany[22]. In Japan report, Non-Hodgkin Lymphoma patient developed hepatitis 40-60 days after transfusion[23]. Hepatitis E infection can be serious in pregnancy and immunocompromised host. Chronic HEV was reported in immuno-compromised host. To manage for safety of blood supply, we have to "accept risk", donor management by deferral donor with active hepatitis E or hepatitis of unknown origin, their sexual partner, person who are closed contact with them for 12 months, donation testing (HEV NAT) and finally, pathogen inactivation process. Currently, Ireland and UK implement HEV NAT for donor screening[24].

Summary

Several emerging infectious diseases can be transmitted via blood transfusion. The above content is selected based on concern during 2016-2017 in our country but there are many more EIDs in our changing world. Additional screening for new infectious marker has considerable cost and pathogen inactivation in blood product which will be universal coverage for all infectious agents is currently expensive and may not be able to use for every blood component type. Hemovigilance system is very important tool to monitoring blood safety and possible problem in our transfused recipient. The National Blood Centre, Thai Red Cross Society established committee for Emerging Transfusion Transmitted Disease who will gather the relevant data and prepare consensus recommendation for proper practice in our country. More information about other EID and transmission through blood transfusion can be retrieved from excellent source at TRANSFUSION special issue for EID (August 2009)[25] or go to AABB website about EID.

References

1. *Morse SS. Factors in the emergence of infectious diseases. Emerg Inf Dis. 1995;1:7-15.*
2. *Stramer SL. Current perspectives in transfusion-transmitted infectious diseases: emerging and re-emerging infections. ISBT Sci Ser. 2014;9:30-6.*
3. *Plourde AR, Bloch EM. A literature review of Zika virus. Emerging infectious diseases. 2016;22:1185-92.*
4. *Buathong R, Hermann L, Thaisomboonsuk B, Rutvisuttinunt W, Klungthong C, Chinnawirotpisan P, et al. Detection of Zika virus infection in Thailand, 2012-2014. Am J Trop Med Hyg. 2015; 93:380-3.*
5. *World Health Organization. Fifth meeting of the emergency committee under the international health regulations regarding microcephaly, other neurological disorders and zika virus [Internet]. 2016 [Cited July 21, 2017]. Available from http://www.who.int/mediacentre/news/statements/2016/zika-fifth-ec/en/*

6. *Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016;374:1552-63.*
7. *Motta IJF, Spencer BR, Cordeiro da Silva SG, Arruda MB, Dobbin JA, Gonzaga YBM, et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. 2016;375:1101-3.*
8. *Musso D, Stramer SL, Busch MP. Zika virus: a new challenge for blood transfusion. Lancet. 2016;387:1993-4.*
9. *Food and Drug Administration Center for Biologics Evaluation and Research. Guide for industry: revised recommendations for reducing the risk of Zika virus transmission by blood and blood components [Internet]. 2016 [Cited July 22, 2017]. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm518213.pdf, accessed*
10. *World Health Organization. Zika virus and safe blood supply: questions and answers [Internet]. 2016 [Cited July 22, 2017] Available from: http://www.who.int/features/qa/zika-safe-blood/en/*
11. *Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med. 2015;372:1231-9.*
12. *Appassakij H, Khuntikij P, Kemapunmanus M, Wutthanarungsan R, Silpapojakul K. Viremic profiles in asymptomatic and symptomatic chikungunya fever: a blood transfusion threat? Transfusion. 2013;53:2567-74.*
13. *Chiu CY, Bres V, Yu G, Krysztof D, Naccache SN, Lee D, Genomic assays for identification ofchikungunya virus in blood donors, Puerto Rico, 2014. Emerg Infect Dis. 2015;21:1409-13.*
14. *Rasonglès P, France Angelini-Tibert M, Simon P, Currie C, Isola H, Kientz D, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La REunion. Transfusion. 2009;49:1083-91*
15. *Gallian P, de Lamballerie X, Salez N, Piorkowski G, Richard P, Paturel L, et al. Prospective detection of chikungunya virus in blood donors, Caribbean 2014. Blood. 2014;123:3679-81.*
16. *Takasaki T. Imported dengue fever/dengue hemorrhagic fever cases in Japan. Trop Med Health. 2011;39(Suppl 4):13-5.*
17. *Limkittikul K, Brett J, L'Azou M. Epidemiological trends of Dengue disease in Thailand (2000–2011): A Systematic literature review. PLoS Negl Trop Dis. 2014;8:e3241.*
18. *Tambyah PA, Koay ESC, Poon MLM, Lin RVTP, Ong BKC. Dengue hemorrhagic fever transmitted by blood transfusion. N Engl J Med. 2008;359:1526-7.*
19. *Sabino EC, Loureiro P, Lopes ME, Capuani L, McClure C, Chowdhury D, et al. Transfusion-transmitted dengue and associated clinical symptoms during the 2012 epidemic in Brazil. J Infect Dis. 2016;213:694-702.*
20. *Pozzetto B, Memmi M, Garraud O. Is transfusion-transmitted dengue fever a potential publichealth threat? World J Virol. 2015;4:113-23.*
21. *Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med. 2012;367:1237-44.*
22. *Zopet J, Lhomme S, Chapuy-Regaud S, Mansuy JM, Kamar N, Abravanel F. HEV and transfusion-recipient risk. Transfus Clin Biol. [Internet] 2017 Jul 6. (Epub ahead of print)*
23. *Matsubayashi K, Kang JH, Sakata H, Takahashi K, Shindo M, Kato M, et al. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. Transfusion. 2008;48:1368-75.*
24. *Domanovic D, Tedder R, Blümel J, Zaaijer H, Gallian P, Niederhauser C, et al. Hepatitis E and blood donation safety in selected European countries: a shift to screening? Euro Surveill. 2017;22:30514.*
25. *Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009;49(Suppl 2):s1-29.*