Endemic or regionally limited bacterial and viral infections in haematopoietic stem-cell transplantation recipients: a Worldwide Network for Blood and Marrow Transplantation (WBMT) Review

Ibrahim N Muhsen, Sebastian Galeano, Dietger Niederwieser, Mickey B C Koh, Per Ljungman, Clarisse M Machado, Mohamed A Kharfan-Dabaja, Rafael de la Camara, Yoshihisa Kodera, Jeff Szer, Walid Rasheed, Simone Cesaro, Shahrukh K Hashmi, Adriana Seber, Yoshiko Atsuta, Mostafa F Mohammed Saleh, Alok Srivastava, Jan Styczynski, Abdulrahman Alrajhi, Reem Almaghrabi, Muhammad Bilal Abid, Roy F Chemaly, Usama Gergis, Eolia Brissot, Riad El Fakih, Marcie Riches, Malgorzata Mikulska, Nina Worel, Daniel Weisdorf, Hildegard Greinix, Catherine Cordonnier, Mahmoud Aljurf

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Section of Hematology and Oncology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA (I N Muhsen MD); **Hematology Department, British Hospital, Montevideo, Uruguay** (S Galeano MD); **Division of Hematology and Medical Oncology, University of Leipzig, Leipzig, Germany** (Prof D Niederwieser MD); **Lithuanian University of Health Sciences Kauno Klinikos, Lithuania** (Prof D Niederwieser); **Infection and Immunity Clinical Academic Group, University of London and Department of Haematology, St George's Hospital and Medical School, London, UK** (Prof M B C Koh MD); **Cell Therapy Facility, Blood Services Group, Health Sciences Authority, Singapore** (Prof M B C Koh); **Department of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska University Hospital Huddinge, Karolinska Comprehensive Cancer Center, Stockholm, Sweden** (Prof P Ljungman MD); **Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden** (Prof P Ljungman); **Virology Laboratory Institute of Tropical Medicine-University of São Paulo Medical School, São Paulo, Brazil** (Prof C M Machado MD); **HCT Program—Hospital Amaral Carvalho, Jahu, Brazil** (Prof C M Machado); **Division of Hematology-Oncology, Mayo Clinic, Jacksonville, FL, USA** (Prof M A Kharfan-Dabaja MD); **Department of Hematology, Hospital de la Princesa, Madrid,**

Literature discussing endemic and regionally limited infections in recipients of haematopoietic stem-cell transplantation (HSCT) outside western Europe and North America is scarce. This Worldwide Network for Blood and Marrow Transplantation (WBMT) article is part one of two papers aiming to provide guidance to transplantation centres around the globe regarding infection prevention and treatment, and considerations for transplantation based on current evidence and expert opinion. These recommendations were initially formulated by a core writing team from the WBMT and subsequently underwent multiple revisions by infectious disease experts and HSCT experts. In this paper, we summarise the data and provide recommendations on several endemic and regionally limited viral and bacterial infections, many of which are listed by WHO as neglected tropical diseases, including Dengue, Zika, yellow fever, chikungunya, rabies, brucellosis, melioidosis, and leptospirosis.

Introduction

People who receive haematopoietic stem-cell transplantation (HSCT), particularly allogeneic HSCT, are at an increased risk of infectious complications resulting from the immune suppression associated with the process.[1,2] Besides delayed immune reconstitution, people who receive allogeneic HSCT have a compromised immune system for an extended duration. The innate immunity could take months and the adaptive immune system could take several years before robust recovery.[3] Although there is substantial evidence related to a high risk of common infections after HSCT, there is a dearth of data regarding less common endemic diseases, particularly those infections that are endemic in countries other than western Europe, Australia, and North America.[4]

The aim of this paper is to inform transplantation physicians and those responsible for writing institutional guidelines, wherever applicable, on lesser reported, regionally endemic infections. We also provide practical recommendations to help transplantation physicians in the management of these patients. Because of the scarcity of good quality evidence for most of these infections in patients who receive HSCT, recommendations proposed herein were suggested on the basis of expert consensus, and not evidence grading. Although rare, the true incidence of these infections is probably not known, particularly in the cohort of immunocompromised patients, because they are prevalent in low-income and middle-income countries and can often be underreported due to scarce research. For all the listed infections, we recommend that transplantation physicians have a low threshold for diagnoses and travel history should be integral in clinical decision making. Additionally, although haematologists and HSCT physicians are familiar with most of the quintessential infections after HSCT (eg, cytomegalovirus [CMV], aspergillosis), the diagnosis and management of these rare infections require a multidisciplinary approach including timely consultations with infectious disease specialists, microbiologists, immunologists, and in some cases, with reference centres and laboratories.

Methods

The WBMT is a non-profit organisation, non-governmental organisation affiliate of WHO, and has the goal of education, practice, and scientific collaboration in HSCT at a global scale. It has 22 affiliated HSCT and cell therapy member organisations and one of its main focuses is the issues related to HSCT in low-income to middle-income countries.

The first phase of the project included the formation of a core group (MA, INM, CC, SG) with expertise in multiple areas who started the work early in 2019. Subsequently, a group of experts was formed in the second phase of the project and the panel was expanded to include HSCT and infectious diseases experts from the WBMT affiliate organisations, including both international and regional organisations with adequate representations from endemic areas. Infectious diseases experts included in the project writing come from the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research and experts from Latin America and Latin America Bone Marrow Transplantation Group, the Eastern Mediterranean Bone Marrow Transplantation group, and Asia Pacific Blood and Marrow Transplantation group. The group drafted the

	Age in years; sex	Underlying disease (type of HSCT)	Country	Presentation (time after transplantation)	Infection management	Outcome
Dengue virus						
Figuero and Clavell, 2005[7]	6; female	ALL (allogeneic)*	Puerto Rico	Skin rash, mucositis, fever, severe and gross haematuria (5 days)	NR	Death on day 11 post-HSCT
Visuthranukul et al, 2009[8]	16; female	AML (allogeneic)	Thailand	Fever, headache, myalgia, and nausea (150 days)	NR	Clinical recovery after 14 days post-HSCT
Punzel et al, 2014[9]	51; male	AML (allogeneic)	Germany*	Undetermined (2 days)	IVIG; supportive care	Death†
Rigau-Perez et al, 2001[10]	6; male	NR (allogeneic)*	Puerto Rico	Fever (4 days)	NR	Death on day 11 post-HSCT
Sharma et al, 2011[11]	4 (NR)	CML (allogeneic)	India	Fever, headache, myalgia, and epistaxis (180 days)	Supportive care and platelets transfusion	Clinical recovery after 9 days post-HSCT
Sharma et al, 2011[11]	8 (NR)	Thalassaemia (allogeneic)	India	High grade fever (70 days)	NR	Clinical recovery after 12 days post-HSCT
Barroso et al, 2017[12]	65; male	MDS/MPN (allogeneic)	Brazil	Fever, altered mentation (34 days)	Supportive care	Developed acute GVHD while being treated and died a month post-HSCT
de Souza Pereira et al, 2017[13]	4; female	ALL (allogeneic)	Brazil	Fever, myalgia, GI bleed, and epistaxis (210 days)	Supportive care and platelets transfusion	Clinical recovery after 25 days post-HSCT; viraemia for 15 days
De Souza Pereira et al, 2017[13]	59; male	AML (allogeneic)	Brazil	Fever, rash, and myalgia (270 days)	Supportive care	Clinical recovery after 30 days post-HSCT
De Souza Pereira et al, 2017[13]	47; female	ALL (allogeneic)	Brazil	Fever, headache, photophobia, nausea, vomiting (105 days)	Supportive care and platelets transfusion	Clinical recovery after 30 days; viraemia for 80 days post-HSCT
Machado et al, 2009[14]	51; male	CML (allogeneic)	Brazil	Mild symptoms including fever (165 days)	Supportive care and decreased steroid dose	Recovered
Machado et al, 2009[14]	38; male	PNH (allogeneic)	Brazil	Mild symptoms including fever (575 days)	Supportive care	Recovered
Machado et al, 2009[14]	39; male	CML (allogeneic)	Brazil	Mild symptoms including fever (455 days)	Supportive care	Recovered
Zika virus						
Machado et al, 2017[15]	48; male	SS (autologous)	Brazil	Rash and fever (NR)	NR	Recovered; viraemia <7 days post-HSCT
Machado et al, 2017[15]	34; female	ALL (allogeneic)	Brazil	Rash, somnolence (NR)	NR	Recovered; viraemia <7 days post-HSCT
Raboni et al, 2017[16]	9; female	Fanconi anaemia (allogeneic)	Brazil	Guillain-Barré syndrome, respiratory failure (possible dengue virus old or concurrent infection) (95 days)	IVIG and plasmapheresis	Clinical recovery after 120 days post-HSCT
Chikungunya						
Machado et al, 2017[15]	30; male	AML (allogeneic)	Brazil	Fever, arthralgia, rash, GI symptoms (NR)	NR	Recovered; viraemia: <30 days post-HSCT
Brucellosis						
Al-Anazi et al 2009[17]	20; male	SAA (allogeneic)	Saudi Arabia	Fever, neutropenia, and thrombocytopenia (112 days)	Initial: streptomycin and ciprofloxacin; streptomycin switched to doxycycline after improvement	Recovered
Ertem et al, 2000[18]	8; male	Fanconi anemia (allogeneic)	Türkiye	Fever (NR)	Doxycycline and gentamicin	Recovered

Cases were selected as examples that reflect different clinical aspects. ALL=acute lymphocytic leukaemia. NR=not reported. AML=acute myeloid leukaemia. CML=chronic myeloid leukaemia. HSCT=haematopoietic stem-cell transplantation. MDS=myelodysplastic syndrome. MPN=myeloproliferative neoplasms. GVHD=graft-versus-host disease. IVIG=intravenous immune globulin. PNH=paroxysmal nocturnal haemoglobinuria. SS=Sézary syndrome. SAA=severe aplastic anaemia. *Possible transmission from the donor. In Punzel and colleagues' paper, the donor had a recent travel to Sri Lanka. †The patient had concurrent comorbidities including concurrent infections that might have led to outcome.

Table 1: **Selected cases of dengue virus, Zika virus, chikungunya, and brucellosis in recipients of HSCT**

initial outline and components, and started to identify relevant literature. Interim progress was discussed through multiple teleconferences until the completion of the first draft. Input was obtained from all authors on the initial draft and subsequent drafts were circulated for the whole group three times.

We did a comprehensive search; the network gathered data on selected reported cases and literature on multiple endemic or regionally limited infections that might confer an increased risk for poor outcomes among HSCT patients. We focused on infectious organisms and associated disease manifestations considered rare diseases that are endemic or prevalent in specific regions or continents,[5] and are listed as neglected tropical diseases by WHO, which includes 20 prevalent diseases in the tropical areas.[6]

The selected viral infections discussed in this paper consist of Dengue, Zika virus, yellow fever, chikungunya,

Spain (R de la Camara MD); **Center for Hematopoietic Stem Cell Transplantation, Aichi Medical University Hospital, Nagakute, Japan** (Prof Y Kodera MD); **Clinical Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, Victoria, Australia** (Prof J Szer MBBS); **Adult**

	Dengue virus	Zika virus	Yellow fever	Chikungunya	Rabies
Most affected areas	Southeast Asia, the Americas, and Western Pacific regions	South America, southeast Asia, and Africa	Africa and South America	Asia, Africa, the Americas, and Europe	Present in all continents (highest mortality in Africa and Asia)
Incubation period	Up to 2 weeks	Up to 2 weeks	Up to 1 week	Up to 3 weeks	Up to months
Transmission	Commonly through mosquito bites (mainly *Aedes aegypti*), rarely: through blood products and vertical transmission	Commonly through mosquito bites (mainly *A aegypti*), rarely: through blood products, sexual transmission, and vertical transmission	Commonly through mosquito bites (mainly *A aegypti*)	Commonly through mosquito bites (mainly *A aegypti*), rarely: through blood products and vertical transmission	Commonly through animal bites (mainly dogs, rodents, bats, etc), rarely: through blood products and organ transplantation
Clinical symptoms	Fever, joint or muscle pain, breakbone fever, rash, retro-orbital pain, lymphadenopathy, bleeding	Fever, joint or muscle pain, rash, conjunctival injection, retro-orbital pain, lymphadenopathy, GBS, severe birth defects	Fever, joint or muscle pain, rash, jaundice, bleeding	Fever, polyarticular and migratory arthralgia, rash, red eye, retro-orbital pain, hepatomegaly, lymphadenopathy	Fever, encephalitis, aerophobia, hydrophobia, paralysis (ascending), coma
Diagnosis of acute infections	Detection of viral nucleic material using PCR and serological testing using ELISA	Detection of viral nucleic material using PCR and serological testing using ELISA	Detection of viral nucleic material using PCR and serological testing using ELISA	Detection of viral nucleic material using PCR and serological testing using ELISA	Intravitam diagnosis is based on PCR on multiple samples (saliva, cerebrospinal fluid, cornea) and serology on blood and cerebrospinal fluid

GBS=Guillain-Barré syndrome. ELISA=enzyme-linked immunosorbent assay.

Table 2: **Epidemiological, clinical, and preventive features of selected viruses**

Hematology and Stem Cell Transplant (W Rasheed MD, M F Mohammed Saleh MD, R El Fakih MD, Prof M Aljurf MD)**, Department of Medicine** (Prof A Alrajhi MD)**, and Organ Transplantation Center** (R Almaghrabi MD)**, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy** (Prof S Cesaro MD)**; Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA** (S K Hashmi MD)**; Department of Medicine, Sheikh Shakbout Medical City, Abu Dhabi, United Arab Emirates** (S K Hashmi)**; College of Medicine & Health Sciences, Khalifa University, Abu Dhabi, United Arab Emirates** (S K Hashmi)**; Hospital Samaritano Higienópolis and Graacc - Unifesp, São Paulo, Brazil** (Prof A Seber MD)**; Japanese Data Center for Hematopoietic Cell Transplantation, Nagakute, Japan** (Y Atsuta MD)**; Department of Registry Science for Transplant and Cellular Therapy** (Y Atsuta)**, Aichi Medical University School of Medicine** (Prof D Niederwieser)**, Nagakute, Japan; Department of Hematology, Christian Medical College, Vellore, India** (Prof A Srivastava MD)**; Department of Pediatric Hematology and Oncology,**

and rabies. Bacterial infections include brucellosis, melioidosis, and leptospirosis. Table 1 lists the cases that have been reported in the literature based on our literature search.

Viral infections

Viral infections such as cytomegalovirus, non-cytomegalovirus herpes viruses, and community respiratory viruses including SARS-CoV-2 are clinically significant causes of morbidity and mortality after HSCT.[19,20] In the next sections, we discuss less common endemic viral illnesses, including epidemiological, clinical, and preventive features (table 2). Additionally, we have provided general recommendations for HSCT physicians and transplantation centres regarding the donors and recipients at risk of these viral infections (panel 1).

Flaviviruses

Flaviviruses are RNA (positive single-stranded), tick-borne or mosquito-borne viruses that include dengue viruses, Zika virus, and yellow fever.[21] These viruses are endemic in different parts of the world. Per WHO classification, dengue viruses are considered a neglected tropical disease, and yellow fever and Zika virus are endemic diseases.[5] The diagnosis and management of these viruses are not well reported in the HSCT setting.

The Flaviviruses discussed here are mainly transmitted by mosquitoes; therefore, recipients of HSCT and potential donors should avoid travelling to endemic areas when possible. However, other modes of transmissions, including vertical transmissions and via blood transfusions have been reported. The WHO Global Outbreak Alert and Response Network is a useful resource to identify current endemic regions. Transplantation physicians are recommended to have a low threshold for prompt diagnosis of these viruses, particularly in recipients living in endemic regions or who have a history of recent travel to the endemic area. Potential recipients should use personal protective measures, such as using mosquito repellents and insecticidal nets and keeping skin covered.

Dengue virus

Dengue virus includes four genotypically distinct serotypes (DENV 1–4) and is transmitted to humans by infected female mosquitoes, *Aedes aegypti* and *Aedes albopictus*.[22] There are nearly 100 million new cases each year in more than 120 countries globally and epidemiological studies have shown a five-fold increase in the incidence of dengue in the past four decades.[22] Dengue is prevalent in many countries, with severe disease showing the highest incidence in some areas of southeast Asia, Western Pacific region and region of the Americas (mainly central and south). The disease transmits mainly via a mosquito to a human to mosquito cycle. Although rare, there are multiple reports of transfusion-related transmission of dengue,[23] suggesting that dengue could occur after HSCT because of a mosquito bite to the recipient, or as a result of a blood transfusion or stem cell infusion in case the donor is in the active phase of the disease at donation.

Dengue infection is commonly asymptomatic; however, dengue fever can present in various ways, including fever without warning signs, with warning signs, or as severe dengue fever, according to 2009 classification from WHO.[24] Dengue haemorrhagic fever and dengue shock syndrome are the main life-threatening complications of dengue virus and occur due to altered vascular permeability, plasma leakage, and lymphocytic infiltration of the liver, lungs, and kidneys, leading to a severe systemic inflammatory response. An imbalance between

coagulation and fibrinolysis is further postulated to cause haemorrhagic complications in dengue haemorrhagic fever and dengue shock syndrome.[25] Important to note is that dengue virus presentation shares some similarities with acute and chronic graft-versus-host disease (GVHD), including rash and thrombocytopenia.

Dengue should be clinically suspected in any febrile individual in the appropriate epidemiological setting or with relevant travel history. Laboratory diagnosis is done either by detecting viral components in serum (such as nucleic acid via RT-PCR or viral antigen) or by antibody testing. Serum testing is highly specific but more labour intensive, whereas antibody tests have lower specificity but are more accessible. The sensitivity of each test depends on the phase of the illness and if it is a primary or secondary infection. Although multiple tests can be used in the initial period of the infection (within 7 days of presentation), such as a nucleic acid amplification test (NAAT), viral antigen detection (mainly non-structural protein-NS1), and IgM testing, the diagnosis via direct detection of the virus nucleic material is favoured over indirect methods (table 2).[26]

Dengue virus is distinct in that antibodies developed after primary infection are paradoxically detrimental in terms of disease severity in second exposure to a dengue virus of a different serotype.[27–30] This paradoxical phenomenon is known as antibody-dependent enhancement. Primary dengue virus infections result in the development of both humoral and cellular immune responses, which protect the host from reinfection by the same serotype. However, primary infections do not confer long-term cross-protection to other serotypes. Non-neutralising serum antibodies from the previous exposure enhance access of the virion–antibody complex to Fc gamma receptor (FcγR)-bearing cells. Furthermore, cytotoxic (CD8+) T cells specific to the dengue virus serotype of a previous infection appear to be preferentially expanded during a secondary infection and thus further contribute to the severity of infection.[29,30]

Dengue infection has been reported in more than ten people who have received allogeneic HSCT,[7–10,11–14] mainly in either South America or Asia. In table 1 we list 13 cases selected on the basis of their clinical relevance and diversity. The most common presentation in patients was dengue fever with or without warning signs, and only three patients presented with severe dengue fever, of whom one survived. One case included a patient from Germany who received an HSCT from a donor who visited Sri Lanka before stem cell harvesting.[9] Of note, higher mortality was reported in patients who were diagnosed with dengue early after HSCT, which was possibly not just related to the dengue virus infection. Case reports suggest a possible transmission from donors to recipients, particularly in cases presenting early after transplantation.[7,9,10]

Because of the rarity of cases, inferring conclusions from these data is challenging, but the presented cases suggest that most patients who present after day 100 might recover clinically, with a small subset that might develop a state of prolonged viraemia.[13]

Treatment of dengue fever in a transplantation setting is generally similar to the general population with supportive measures and occasional use of platelet transfusion; however, there is not enough evidence to support practice. Because of the general scarcity of data on people who receive HSCT and had dengue, and because dengue vaccines are all live attenuated, no recommendation can be made on dengue vaccination in recipients of HSCT.

Multiple dengue vaccines have been developed or are under development. CYD-TDV (Dengvaxia), a live-attenuated vaccine, received regulatory approval in many countries; however, WHO recommends its use only in individuals who are seropositive, after pre-vaccination screening or in areas with recent documentation of seroprevalence rates of at least more than 80% by age 9 years. Other vaccines using virus-like particle delivery platforms are under development.[31–34] There is no antiviral agent for dengue virus and the treatment is merely supportive.[26]

Panel 1: Suggested recommendations on viral infections

Donor-related

- Travelling to endemic areas should be discouraged before stem cell harvest when planning a haematopoietic stem-cell transplantation (HSCT) from a known or identified donor
- Donors living in or with a history of recent travel to endemic areas should be screened for symptoms
- Low threshold for testing for donors with suggestive symptoms should be maintained
- Generally, no data support routine testing of asymptomatic donors
- Stem cell and blood product donations should generally be deferred, at least transiently; exceptions include time-sensitive transplantations, such as high-risk acute leukaemia
- The duration of deferral varies depending on the type of viral infection

Recipient-related

- Recipients of HSCT should be screened for symptoms and epidemiological risks before transplantation
- Recipients of HSCT living in or travelling to endemic or epidemic regions should be educated to take precautions, such as avoiding mosquito exposure
- A multidisciplinary approach, including the involvement of infectious disease specialists, is advised in patients presenting with symptoms suggestive of infections and epidemiological risk factors
- Whenever present, vaccination should be considered in recipients after transplantation; timing depends on type of the vaccine and the immunosuppression status; exceptions include post-exposure to rabies

Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland (Prof J Styczynski MD); **Divisions of Hematology/Oncology & Infectious Diseases, BMT & Cellular Therapy Program, Milwaukee, WI, USA** (M B Abid MD); **Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Prof R F Chemaly MD); **Sidney Kimmel Cancer Center, Philadelphia, PA, USA** (U Gergis MD); **Service d'Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Sorbonne Université, INSERM UMRs 938, Paris, France** (E Brissot MD); **Division of Hematology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA** (Prof M Riches MD); **Division of Infectious Diseases, DISSAL, University of Genova, Italy and IRCCS Ospedale Policlinico San Martino, Genova, Italy** (Prof M Mikulska MD); **Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna, Vienna, Austria** (Prof N Worel MD); **Division of Hematology, Oncology and Transplantation, University of Minnesota, MN, USA** (Prof D Weisdorf MD); **Medical University Graz, Division of Hematology, Graz, Austria** (Prof H Greinix MD); **Haematology Department, Henri Mondor Hospital and University Paris-Est-Créteil, Créteil, France** (Prof C Cordonnier MD)

Correspondence to:
Dr Ibrahim Muhsen, Section of Hematology and Oncology, Department of Medicine Baylor College of Medicine, Houston, TX, USA
ibrahim.muhsen@bcm.edu

For the **WHO Global Outbreak Alert and Response Network** see https://goarn.who.int/

For more on the **incidence of dengue worldwide** see https://www.healthmap.org/dengue/en/

For **a map on the distribution of dengue** see https://ntdhq.shinyapps.io/dengue5

There is not enough high-level evidence on dengue infection from endemic areas in recipients of HSCT. In addition to general preventive measures for flaviviruses, we have outlined the suggested recommendations for transplantation centres and recipients. Donors living in or with a history of recent travel to an endemic area should be screened for symptoms, and a lower threshold for testing should be maintained for donors with suggestive symptoms. Screening of individuals who are asymptomatic in epidemic or hyperendemic situations requires further studies. Stem cell and blood product donation with confirmed dengue virus infection should be avoided at least transiently. The duration of deferral is elusive. We recommend consultation with the centre's infectious disease and travel medicine experts. When possible, donors with a travel history should not donate blood or stem cells 3–4 weeks after travelling to the endemic areas (the reported incubation period is up to 2 weeks). Travel to endemic areas should be discouraged before stem cell harvest when planning a transplantation from a known donor (haploidentical or matched-related). The duration of deferral is unclear for potential recipients of HSCT from outbreak areas; no deferral is recommended for patients needing urgent transplantations, such as those with high-risk acute leukaemia. Recipients of HSCT in endemic countries are at risk of contracting dengue fever, particularly during epidemics and blood transfusions. Thus, low threshold for testing should be maintained.

There are no antiviral agents to treat dengue virus infection. Supportive care involves the management of intravascular volume, fever, bleeding, and plasma leakage. There is no role for intravenous immune globulin, pentoxifylline, or activated factor VII.[35–37] Blood transfusion and other blood products, including platelet concentrate, fresh frozen plasma, and cryoprecipitate, can be lifesaving in patients with severe bleeding and coagulation issues. The role of prophylactic platelet transfusions in dengue virus infections, even in cases of profound thrombocytopenia, has been controversial. Prophylactic platelet transfusions are not recommended.[38,39] No high-quality evidence currently supports the use of corticosteroids for the treatment of dengue shock syndrome, prevention of serious complications, or treatment of thrombocytopenia.[40–42]

Zika virus

For more on **the distribution of Zika virus** see https://wwwnc.cdc.gov/travel/files/zika-areas-of-risk.pdf/

For **frequent updates on Zika virus outbreaks** see https://wwwnc.cdc.gov/travel/page/zika-information

Zika virus is another mosquito-borne virus transmitted via *Aedes* mosquitoes, similar to dengue virus. Various outbreaks have been reported in many continents, including southeast Asia, Africa, and South America. Although mosquito-borne transmission is the primary mode of infection transmission, other methods of transmission include sexual, maternal-fetal, and transfusion of blood products.[43]

The incubation period of Zika virus is between 2 and 14 days. Typically, Zika virus causes asymptomatic or mild disease; however, some patients present with more severe symptoms with possible neurological complications, including Guillain-Barré syndrome (GBS). GBS, however, can also be a complication of chronic GVHD post-transplantation. The diagnosis of Zika virus in the initial period (first 7 days of symptoms) is typically PCR-based (via NAAT). In cases of late presentations (beyond 7 days of symptom onset) in patients with a high level of suspicion, serological testing for Zika virus IgM or plaque reduction neutralisation test, or both, could be employed (table 2).

Three cases were reported in the literature of Zika virus complicating allogeneic HSCT from Brazil (table 1). Two patients presented with mild and self-limiting disease and subsequently recovered after an extended duration of viraemia.[15] Machado and colleagues[15] presented an additional case of pre-transplantation Zika virus infection that was probably associated with delayed engraftment. In another case report,[16] a paediatric patient presented with GBS and was found to have a recent Zika virus infection; however, serological testing was also positive for dengue virus (although possible cross-reactivity and dengue virus past or concurrent infection could not be ruled out).[44] Treatment was generally supportive except in the patient with GBS, in whom intravenous immunoglobulins and plasmapheresis were used. So far, there is no specific antiviral therapy and no vaccine developed for Zika virus.

In 2017, the European Centre for Disease Prevention and Control categorised countries affected by Zika virus into four categories: category 1 includes countries with new introduction (reintroduction) and with ongoing transmission; category 2 includes countries with reintroduction and areas with endemic transmission; category 3 involves countries with interrupted transmission (with potential future ones); and category 4 includes areas with vectors but no documented transmission.[45] Additionally, WHO published a blood transfusion guideline in 2016.[46] Since 2021, the US Food and Drug Administration issued a new revision to its guidelines in 2016 and 2018, removing Zika virus from the list of the relevant transfusion-transmitted infections. This new recommendation was based on the low number of cases worldwide and the low number of outbreaks.[47]

The suggested treatment for Zika virus is mainly supportive (panel 1). Deferral of donors with Zika-virus-positive serology or suggestive clinical features with risk factors, such as recent travels, is advised. The duration of deferment varies between different guidelines from 28 days to 120 days.[48] WHO recommendations are to defer for 28 days after resolution of Zika virus symptoms. Additionally, WHO recommends deferral of transfusions for 28 days in donors with confirmed (after cessation of symptoms) or suspected Zika virus in the affected areas. It is further recommended not to use collected units for up to 14 days to allow monitoring of the donor for any symptoms. However, these recommendations are usually more challenging in the case of stem cell donations.

Yellow fever

Yellow fever is transmitted via mosquitoes and with an incubation period of around 3–6 days. The fever is endemic in areas in Africa, China, and central and South America, and presents a wide range of symptoms. A small proportion of patients will progress to the toxic phase with organ failure, jaundice, encephalopathy, and bleeding that can lead to death in 20–60% of the cases. The diagnosis of yellow fever involves serology by measuring IgM, PCR testing, or histopathological testing (table 2).

No yellow fever cases in allogeneic HSCT were reported in the literature. Compared with the other flaviviruses, a live-attenuated vaccine routinely given in some endemic countries is available. Yellow fever vaccine is generally not given to patients who underwent HSCT except 2 years after the procedure if the recipient is off immunosuppression. A couple of reports have shown that the vaccine is generally safe in recipients of HSCTs, providing the absence of GVHD and any immunosuppression use at the time of vaccination.[49,50] However, cases of vaccine transmitted disease have been reported in young, healthy adults.[51,52] Additionally, it should be noted that some recipients of HSCT who were vaccinated before transplantation or had donors who were vaccinated will have antibodies after the procedure and might be protected.[51]

In addition to following the general preventive measures for viral infections (panel 1), if the donor has recently been vaccinated for yellow fever, stem cell collection and harvesting are recommended to be deferred at least 2 weeks after vaccination.[34] Donors living in or with recent travel to an endemic or epidemic area should be screened for symptoms, and a lower threshold for testing should be maintained for donors with suggestive symptoms. Recipients living in or with recent travel to endemic or epidemic areas should undergo frequent symptom screening, and a lower threshold for testing should be maintained. Vaccination can be considered 24 months after allogeneic HSCT in recipients who are not receiving immunosuppressive agents, have no active GVHD, and are at high risk of possible exposure.[49] Treatment for yellow fever is mainly supportive.

Chikungunya

Chikungunya is a mosquito-borne viral disease that belongs to togaviruses, with reported outbreaks in Africa, Asia, Europe, and the Americas.[48] Chikungunya causes fever and systemic symptoms that include persistent arthralgias. Transmission through blood products and vertical transmission has been documented with chikungunya.[50,53] Although there is a theoretical risk of transmission through haematopoietic and solid organ transplantation, no cases are reported in the literature. Chikungunya could be diagnosed by PCR-based methods (via NAAT; table 2).[54]

Patients with solid organ transplantations have been reported to have a favourable outcome similar to the general population if they contract chikungunya.[48,55] Moreover, Machado and colleagues[15] reported a 30-year-old man with an allogeneic HSCT for acute myeloid leukaemia who presented 5 years after his HSCT with fever, arthralgia, rash, and gastrointestinal symptoms. The patient was not receiving immunosuppression treatment at that time, and after being tested for several endemic viruses including chikungunya by PCR, tested positive for chikungunya. The patient received supportive treatment and recovered fully in less than 10 days.

As recommended for other viral infections (panel 1), recipients of HSCTs and potential donors travelling or living in endemic areas should be educated to take adequate precautions to avoid mosquito exposure. Chikungunya viraemia precedes symptoms but can last up to around 7 days from the onset of symptoms. However, longer durations of viraemia have been reported, and genetic material (RNA) has reportedly been detected for up to 17 days.[56] Thus, deferring donors for at least 4 weeks if infected is advisable.[48] Not enough evidence supports the testing of asymptomatic donors. Recipients with risk factors should be screened for symptoms before transplantation; however, evidence to suggest routine screening is scarce. In the post-HSCT phase, recipients with risk factors should be frequently screened for symptoms, and low threshold for testing should be maintained. The treatment for chikungunya is mainly supportive.

Rabies

Rabies belongs to the Rhabdoviridae family and can be transmitted to humans through the saliva of different infected mammals (eg, dogs, bats, etc). No cases of rabies have been identified in the literature in the context of HSCT. Transmission from donors to recipients of HSCT has been documented in solid organ transplantation.[57] Rabies is prevalent worldwide with few exceptions, but is more prevalent in low-income and middle-income countries.

The incubation period of rabies varies but generally is weeks to months after the animal bite or saliva exposure (table 2). Rabies transmits via peripheral nerves to the CNS. The symptoms are usually neurological and mainly include fever, hydrophobia, a paralysis that progresses to coma, and death. Some patients will also present with a pattern similar to GBS and ascending paralysis. The diagnosis of rabies intra-vitam (during life) is based on PCR on multiple samples (saliva, cerebrospinal fluid, cornea) and serology on blood and cerebrospinal fluid.[58] These tests are usually performed in specialised laboratories.

Recipients of HSCT and potential donors travelling or living in endemic areas should avoid exposure to wildlife mammals and have up-to-date rabies vaccinations for their pets (eg, dogs, cats, and ferrets). Since the disease does not cause symptoms during the long incubation period, donors should be screened for recent exposure to

For **a map on the distribution of yellow fever** see https://www.cdc.gov/yellowfever/maps/index.html

For **data on the distribution of rabies** see https://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html

For more on **the distribution of chikungunya** see https://www.cdc.gov/chikungunya/geo/index.html

	Brucellosis	Melioidosis	Leptospirosis
Most affected areas	Middle East, the Indian subcontinent, sub-Saharan Africa, central Asia, and some parts of central and South America	Southeast Asia, China, and Northern states of Australia	Present in all continents (more common in temperate or tropical regions)
Incubation period	Up to 4 weeks but varies and up to a few months in some instances.	Up to 3 weeks	Up to 4 weeks
Transmission	Commonly through contact with infected animal or consumption of raw milk, very rarely: human to human transmission	Commonly through inhalation, percutaneous inoculation, or ingestion	Commonly through exposure to animal fluids or contaminated water
Clinical symptoms	Non-specific symptoms including fever, joint pain, weakness, weight loss	Non-specific and wide range of symptoms (could present as septic shock)	Fever, joint or muscle pain, rash, jaundice, conjunctival injection
Diagnosis of acute infections	Tissue (bone marrow), fluid or blood culture, in addition to serological testing using ELISA and PCR	Cultures of several samples (such as blood, urine, and sputum); serological and PCR testing is still of limited use	Serological and PCR testing

ELISA=enzyme-linked immunosorbent assay.

Table 3: **Epidemiological, clinical, and preventive features of included bacteria**

Panel 2: Suggested recommendations on bacterial infections

Donor-related

- Travelling to endemic areas should be discouraged before stem cell harvest when planning a haematopoietic stem-cell transplantation (HSCT) from a known donor
- Donors living in or with a history of recent travel to endemic areas should be screened for symptoms
- A low threshold for testing for donors with suggestive symptoms should be maintained; not enough data support routine testing of asymptomatic donors
- Stem cell and blood product donations should generally be deferred; duration of deferral varies depending on the type of infection but is generally unclear; a longer period of deferral is suggested for brucellosis

Recipient-related

- Recipients of HSCT should be screened for symptoms and epidemiological risks before transplantation
- Recipients of HSCT living in or travelling to endemic or epidemic regions or with occupational hazards should be educated on precautions, such as avoiding infected animals and consuming certain foods
- The involvement of infectious disease specialists is advised in patients presenting with symptoms suggestive of infections and epidemiological risks

bites or saliva from potentially infected animals. Low threshold for testing should be maintained. Recipients living in endemic regions should be evaluated before transplantation for previous exposure or risk factors. Rabies-inactivated vaccine has not been assessed after HSCT, but it might be considered 12–24 months after HSCT in individuals with a high risk of exposure. In the case of post-exposure prophylaxis, rabies vaccines and rabies immunoglobulin should be administered according to local or regional health-care guidelines, any time after transplantation.[59] No treatments are available for rabies.

Bacterial infections

Bacterial infections are a major cause of morbidity and mortality after HSCT. Whereas common bacterial infections are frequently reported, available literature on the epidemiological and clinical features and preventive measures, diagnosis, and treatment of less common endemic diseases are relatively limited. In this section, we discuss the evidence on brucellosis, melioidosis, and leptospirosis (table 3) and have suggested recommendations for transplantation centres (panel 2). The below described infections might present with non-specific symptoms, thus should be considered by experienced transplantation physicians in patients with risk factors. Additionally, recipients of HSCT and donors should follow recommendations for the general population regarding prevention, and education should be provided for patients residing or travelling to endemic regions (panel 2). Donors living in or with a history of recent travel to a hyperendemic area should be screened for symptoms, and a lower threshold for testing should be maintained for donors with suggestive symptoms. Not enough data support the screening of patients who are asymptomatic in endemic areas.

Brucellosis

Brucella spp is an intracellular gram-negative cocobacilli. The four species, *Brucella abortus*, *Brucella melitensis*, *Brucella canis*, and *Brucella suis* have been described to cause human disease. Brucellosis the most common zoonotic infection worldwide, which transmits to humans via infected animals or animal products, and is endemic in various regions, including but not limited to the Middle East, the Indian subcontinent, and sub-Saharan Africa.[60] In recipients of HSCT, brucellosis can be infrequently transmitted via the stem-cell graft or blood transfusions. Brucellosis could present with B symptoms (such as fever and weight loss) and arthralgias, and other organ involvement.[17] A definitive diagnosis of brucellosis is done with cultures; however, serological testing could be

considered in select cases.[17] Brucellosis is treated with antibiotics that generally include combination agents to prevent relapses and sequelae. Antibiotic choices preferably include doxycycline, in addition to rifampin, streptomycin, or gentamicin.[18] Trimethoprim-sulfamethoxazole can also be used instead of doxycyline in some populations, such as children younger than 8 years.[61] However, of note is that medications such as rifampin have extensive drug–drug interactions with medications commonly used in patients with GVHD.

Three cases of brucellosis have been reported in the literature, of which the full text was accessed in two of the three cases (table 1).[62,63] The first case highlights a 20-year-old man from Saudi Arabia who presented with fever, neutropenia, and thrombocytopenia approximately 4 months after receiving an allogeneic HSCT.[62] The patient was found to have brucellosis bacteraemia. He recovered fully after initial treatment with streptomycin and ciprofloxacin, and then ciprofloxacin and doxycycline. The second patient was an 8-year-old boy, who underwent allogeneic HSCT for Fanconi's anaemia in Türkiye,[63] and presented on day 32 post-HSCT (complicated with GVHD), with fever, and hepatosplenomegaly. The boy was successfully treated with doxycycline and gentamicin. Of note, the donor was positive for *Brucella* antibodies. Both cases shared similarities, including being in remission of their disease and having received HLA-matched, related donor grafts.

Specific preventive measures for brucellosis include avoiding the consumption of fresh (unprocessed) milk, unpasteurised dairy products, or undercooked meat. Additionally, workers handling potentially infected animals or animal products, such as farmers, veterinarians, or slaughterhouse workers, should avoid exposure during periods of severe immunosuppression and wear appropriate protective equipment. Screening of asymptomatic donors could be considered in hyperendemic areas. If clinically feasible, donors with recent travel to high-risk areas should be observed for a longer period before proceeding with stem cell apheresis or harvesting, because considerably long incubation periods have been reported in the literature. Recipients before and after transplantation with risk factors should be screened for symptoms and screening of asymptomatic recipients could be considered in hyperendemic areas.

Melioidosis

Melioidosis is an infection caused by *Burkholderia pseudomallei,* an intracellular gram-negative bacterium.[64] Melioidosis cases are predominantly reported from south and southeast Asia, China, and Australia.[65] However, outbreaks have been reported in other regions, for instance, a multi-state outbreak in the USA via the use of contaminated aromatherapy products was reported in 2021.[66] The disease is rare in other parts of the world, particularly in North America, but it should be noted that melioidosis is an underdiagnosed infection because symptoms are vague and mimic several other infectious and inflammatory diseases.

Transmission of melioidosis occurs via inhalation, percutaneous inoculation, and aspiration from dust, wet soil, and contaminated water. Cases of person-to-person transmission are rare and occur through contact with blood or bodily fluids.[64] The incubation period usually ranges from a few days to around 4 weeks. Clinical presentation varies, ranging from asymptomatic illness to septic shock,[64] although the most common presentations are pneumonia and skin manifestation. Microbiological cultures are the most useful method in diagnosing melioidosis, especially blood cultures, because a substantial number of patients have bacteraemia.[65] *Burkholderia pseudomallei* grows in most traditional cultures, but it could be missed due to scarcity of sensitive cultures and expertise. Other methods are being used and developed, including serology testing, but these tests have low sensitivity and specificity. Thus, the laboratory should be notified when clinically suspected, and appropriate samples should be collected (including blood, sputum, throat swab, etc).[64] To our knowledge, no cases were reported of melioidosis in HSCT; however, patients who are immunosuppressed are predisposed to infection.[64]

Specific preventive measures for melioidosis include avoiding bare skin exposure to wet surfaces and soils. Gloves and other protective equipment can be used along with staying indoors in rainy weather in epidemic regions. Thailand, for instance, publishes annual campaigns to help the public avoid melioidosis.[67] Donors living in areas of outbreaks should be screened for symptoms. No evidence supports donor deferral in patients with history of melioidosis. Recipients before and after HSCT with risk factors should be screened for symptoms.

Leptospirosis

Leptospirosis is a bacterial zoonotic infection caused by the spirochete, *leptospira*, which is common in tropical regions; however, cases of leptospirosis also occur in the temperate regions.[68] Leptospirosis in humans usually results from contaminated water or infected animals' tissues or urine, especially from rodents.[69] The infection is generally not transmitted from person to person, but rare transmission cases via sexual intercourse or breastfeeding have been reported.[70] Transmission via blood products has not been described in the literature, to our knowledge. Patients with leptospirosis have a wide range of presentations, including asymptomatic, mild symptoms, and some patients with severe disease.

Symptoms are usually non-specific, predominantly with fever, headache, and muscle tenderness. A more common, specific sign is a conjunctival injection in patients who are infected. Other symptoms and signs could include hepatosplenomegaly, jaundice, skin rash, aseptic meningitis, haemorrhages, and acute renal failure.[71] The incubation period is usually around 10 days but can last up to 4 weeks.[71] Patients with leptospirosis are usually

Search strategy and selection criteria

This Review was not done systematically, and the articles identified were limited to the English language. We identified the literature used in the preparation of this manuscript using MEDLINE from inception to December, 2021. We used Boolean logic with terms including "Bone Marrow Transplantation" and "Hematopoietic Cell Transplantation" in combination with infections-related terms, including "Dengue", "Zika", and "Brucellosis" to ensure a comprehensive search. Additionally, manual searching of guidelines (ie, reference lists, etc) and review articles was done and we identified additional resources from the authors' own files. Because of the rarity of these infections, we included published peer-reviewed articles regardless of their type, since the majority of identified articles were case reports or case series. When possible, we reviewed and referenced transplantation-specific guidelines or general guidelines of the included infections.

diagnosed by PCR during the first weeks of symptoms or serology later on. A high clinical suspicion is needed to diagnose leptospirosis. The treatment usually includes antibiotics with oral doxycycline for mild and intravenous penicillin for severe disease. Based on our search, no cases of leptospirosis were reported in HSCT.[72] However, one 43-year-old patient with a kidney transplantation presented with fever, severe jaundice, and pruritus that responded to antibiotics and dose reduction of immunosuppressive medications.[73] Several univalent or multivalent inactivated vaccines are recommended for highly exposed individuals (eg, river divers). There is no contraindication of such vaccines after HSCT, thus it should be considered, but at the same time, there are not enough data in the literature to support their efficacy.

Recipients of HSCTs and donors should follow recommendations for the general population regarding leptospirosis in endemic areas, particularly minimising occupational exposure (farm workers, veterinarians) and avoiding recreational (eg, swimming in freshwater, kayaking, etc) or household exposures (eg, pets, including birds). Vaccination of animals could be considered a community effort to reduce transmission in certain situations. No data support routine screening of asymptomatic donors or donor deferral. Recipients with risk factors should be screened for symptoms. Antibiotic prophylaxis in recipients at risk with doxycycline might be used in select cases; however, no data support its routine use.

Conclusions

Data on endemic and regionally limited viral and bacterial infections after HSCT are scarce. These infections are generally rare and their incidence is probably underreported. In this paper, we used current literature and expert opinion to provide insight and guidance into the diagnosis, treatment, and prognosis of such infections in patients after HSCT. Additionally, we highlighted the limitations of the current literature providing a framework for future researchers. This paper highlights the importance of obtaining travel history and surveys from donors and recipients and considering these infections in patients presenting with signs of infection. However, this Review has multiple limitations. Firstly, there are no published cohort or epidemiological studies to ascertain the prevalence and incidence of these infections in HSCT donors and recipients. Secondly, the prognosis of these infections cannot be clearly identified because of the publication bias, since published cases are probably cases in which the infection was correctly diagnosed and treated. Thirdly, the references were limited to the English language, which might mean that some references were missed because of the high prevalence of these infections in non-English speaking countries. Finally, we did not conduct a systematic search of literature and focused on selected cases.

Future research should investigate the prevalence and incidence of such infections in donors and recipients with epidemiological and cohort studies. The role of international and regional institutions and databases is important in data collection and coordinating with regional transplantation centres in endemic regions.

Contributors

INM, SG, DN, MBCK, PL, AdS, MM, HG, DW, CC, and MA conceptualised the paper. INM, SG, CMM, MFMS, MBA, and RFC contributed to data curation. INM, SG, DN, MBCK, PL, AdS, MM, HG, DW, MFMS, MBA, RFC, REF, CC, and MA contributed to the methods. INM, SG, CMM, MAK-D, YK, SC, YA, JaS, REF, CC, and MA contributed to the resources. INM, SG, and MA wrote the original draft. CC and MA supervised the writing of the paper. All authors reviewed and edited the paper.

Declaration of interests

MBK declares honoraria from Gilead and an advisory board role at Gilead. RDLC declares honoraria from Gilead. NW declares honoraria and consultancy fees from Novartis; travel and honoraria from Kite Gilead; honoraria and research funding from Sanofi Genzyme; honoraria and speaker fees from Therakos Mallinckrodt; and travel fees from BMS Celgene. EB declares honoraria Novartis, Astellas, Alexion, Gilead, MSD, Keocyt, Jazz Pharmaceuticals, and Amgen; and travel fees from Jazz Pharmaceuticals, Novartis, and Amgen. JeS declares honoraria from Alexion, Sobi, and Takeda; consultancy fees from Alexion, Sobi, and Takeda; travel fees from Sobi; and an advisory board role at Prevail Therapeutics. JaS declares honoraria from MSD, Glead, TEVA, Atara, and Takeda. DW declares research funding from FATE therapeutics: Research Funding and Incyte. SKH declares honoraria from Pfizer, Novartis, Janssen, Therakos Mallinckrodt, Sanofi, and Roche. YA declares lecture fees from Novartis, AbbVie GK, and Astellas and consultancy honoraria from Meiji Seika, JCR Pharmaceuticals, and Kyowa Kirin. PL declares honoraria from Takeda, OctaPharma, and MSD. All other authors declare no competing interests.

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