Acta Haematologica Polonica 2023
Number 5, Volume 54, pages 372–381
DOI: 10.5603/ahp.96092
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

VIA MEDICA

Emergencies in patients undergoing hematopoietic stem cell transplantation

Joanna Kujawska*, Magdalena Matuszak, Lidia Gil

Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznań, Poland

Abstract

Despite its high effectiveness, hematopoietic stem cell transplantation (HSCT) can sometimes be associated with multiple peri-transplant complications requiring urgent intervention. Life-threatening complications in the transplantation unit affect non-relapse mortality. This article sets out a practical approach to the essential peri-transplant clinical conditions, divided into infectious complications and complications related to immune response and endothelial damage. An early diagnosis of life-threatening conditions, and prompt implementation of the best therapy, can save patients' lives. This is especially the case regarding infectious complications in neutropenic patients and in the advanced stages of immunological complications such as graft-versus-host disease, veno-occlusive disease, graft failure, diffuse alveolar hemorrhage, and thrombotic microangiopathy associated with HSCT. These emergencies are discussed below, along with their risk factors and a summary of the management of patients in the early post-transplant period.

Key words: hematopoietic stem cell transplantation, HSCT, infectious complications after HSCT, immunological complications after HSCT

Acta Haematologica Polonica 2023; 54, 6: 372–381

Introduction

Hematopoietic stem cell transplantation (HSCT), both autologous (auto-HSCT) and allogeneic (allo-HSCT), is a complex medical procedure that is used to treat various malignant and non-malignant hematological disorders [1].

Despite advances in HSCT techniques, patients undergoing this procedure are at risk for varying complications, including emergencies that require prompt medical attention. The transplant committee qualifying a patient for treatment must consider indications for HSCT and risk factors of complications. During the qualification, various scales determining the stage of the disease and the general condition of the patient are helpful, including the Eastern Cooperative Oncology Group (ECOG) performance scale, and the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI), enabling the determination of the risk of HSCT procedure [2] and indications for HSCT [3].

A life-threatening condition is a sudden, or predictable in the short term, severe clinical deterioration following serious damage to the body's functions requiring immediate treatment [4]. Emergencies occurring in the early post-transplant period, such as infections and complications related to the immune response, affect non-relapse mortality (NRM), estimated at 30% in allo-HSCT recipients and 13% after autologous transplant [5]. An early diagnosis of a life-threatening condition in patients undergoing HSCT, and the prompt implementation of the most effective therapy, can save the patient's life.

This article discusses the practical approach to emergencies in patients undergoing HSCT, along with their risk factors (Tables I, II) and management. This approach is divided into infectious complications and complications

*Address for correspondence: Joanna Kujawska, Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, 84 Szamarzewskiego, 60–569 Poznań, Poland, e-mail: kujawska.joannam@gmail.com

Received: 18.06.2023 Accepted: 06.08.2023 Early publication date: 22.09.2023

Table I. Common risk factors for emergencies in hematopoietic stem cell transplantation (HSCT) recipients

Patient-related risk factors	Transplant-related factors
Advanced recipient age	Unrelated donor
General condition of patient: according to Karnofsky index <90 or ECOG >1	Major HLA disparity
Relapse/refractory disease	Myeloablative conditioning
Medical history of organ failure, comorbidities*	High doses of busulfan
Medical history of infections and co-existing infections in post-transplant period	Use of fludarabine in reduced-intensity conditioning
Previous alloimmunization (including pregnancy, multiple transfusions)	Total body irradiation (high-dose)
Iron overload	*Ex vivo* T-cell depletion
Previous therapy toxicity	Second HSCT

*According to the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI); ECOG — Eastern Cooperative Oncology Group performance scale; HLA — human leukocyte antigen

Table II. Risk factors and estimated incidence of selected complications in hematopoietic stem cell transplantation (HSCT) recipients

Complication	Estimated incidence	Risk factors
Graft-versus-host disease	~40%	Recipient seropositivity for cytomegalovirus
		Use of peripheral blood as opposed to bone marrow
		Use of female donor for male patient
Sinusoidal obstruction syndrome/veno-occlusive disease	10–15%	Prior liver radiation/hepatotoxic treatment
		Medical history of liver cirrhosis/fibrosis/thalassemia
		Prior treatment with gemtuzumab or inotuzumab ozagamicin
		Genetic factors (GSTM1-null genotype, MTHFR 677C/1298CC haplotype)
		Concomitant therapy with progestogens, azoles
		Increased aspartate transferase, bilirubin levels before HSCT
Diffuse alveolar hemorrhage	2–14%	Late granulopoiesis and platelet reconstitution
		Use of umbilical cord blood
Graft failure	<3–5%	Non-malignant underlying disease as indication for HSCT
	10%*	Extensive marrow fibrosis, extensive prior treatment
		Low count of CD34+ cell
		Cryopreservation
Thrombotic microangiopathy associated with HSCT	0.5–76%	Use of calcineurin inhibitors in immunosuppressive prophylaxis
		Administration of granulocyte-colony stimulating factor
		Genetic polymorphism
		Pre-transplant kidney dysfunction

*Cord blood and haploidentical HSCT

related to the immune response and endothelial damage. Moreover, we have devised figures that summarize practical algorithms for each complication (Figures 1–6).

Infectious complications

Infections during neutropenia are life-threatening and remain among the leading early complications after HSCT [6, 7]. According to data from the Center for International Blood and Marrow Transplant Research (CIBMTR), within 100 days post-transplant, infectious complications account for significant percentages of the cause of death, estimated at 21% of patients undergoing auto-HSCT and 16–28% of allo-HSCT recipients, depending on the donor source [8]. It is essential to identify the population at high risk for infections and introduce effective standard prophylaxis [9]. The risk of infection results from the interaction of many factors related to the patient, the type of transplant, and the exposure to microorganisms. In the course of transplantation, the use of central venous catheters and

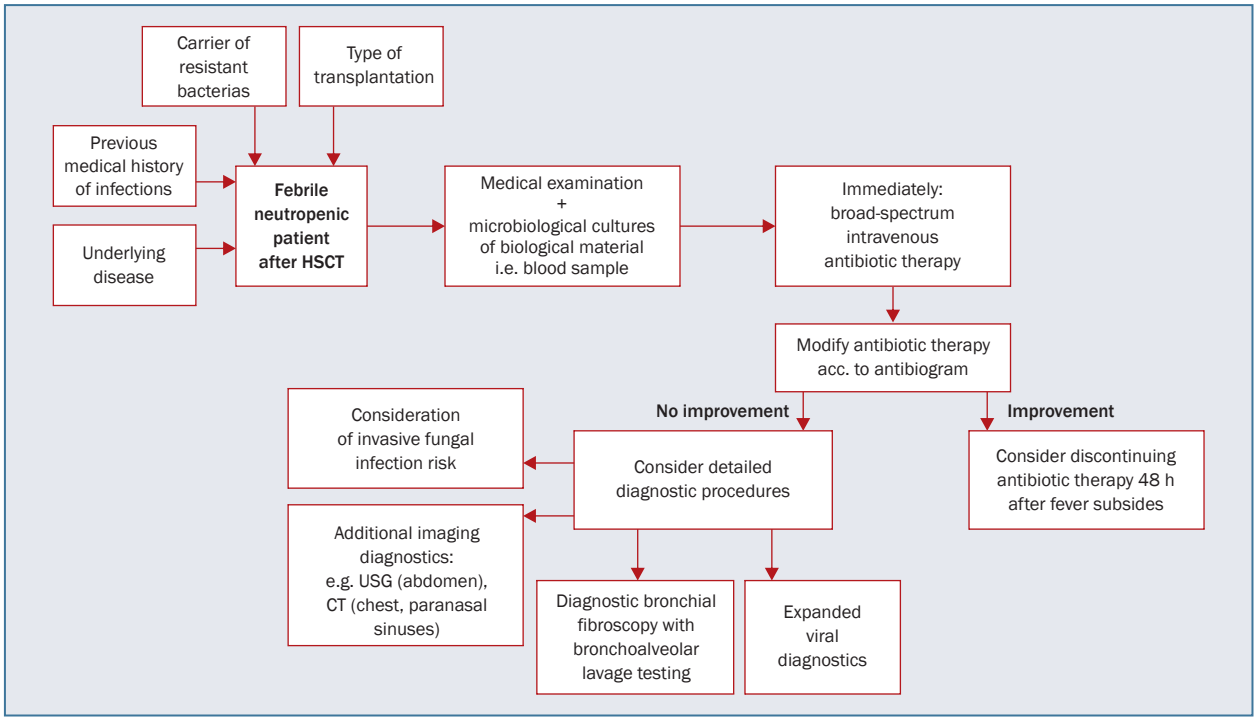

Figure 1. Practical algorithm of febrile neutropenic patient after hematopoietic stem cell transplantation (HSCT); USG — ultrasonography; CT — computed tomography

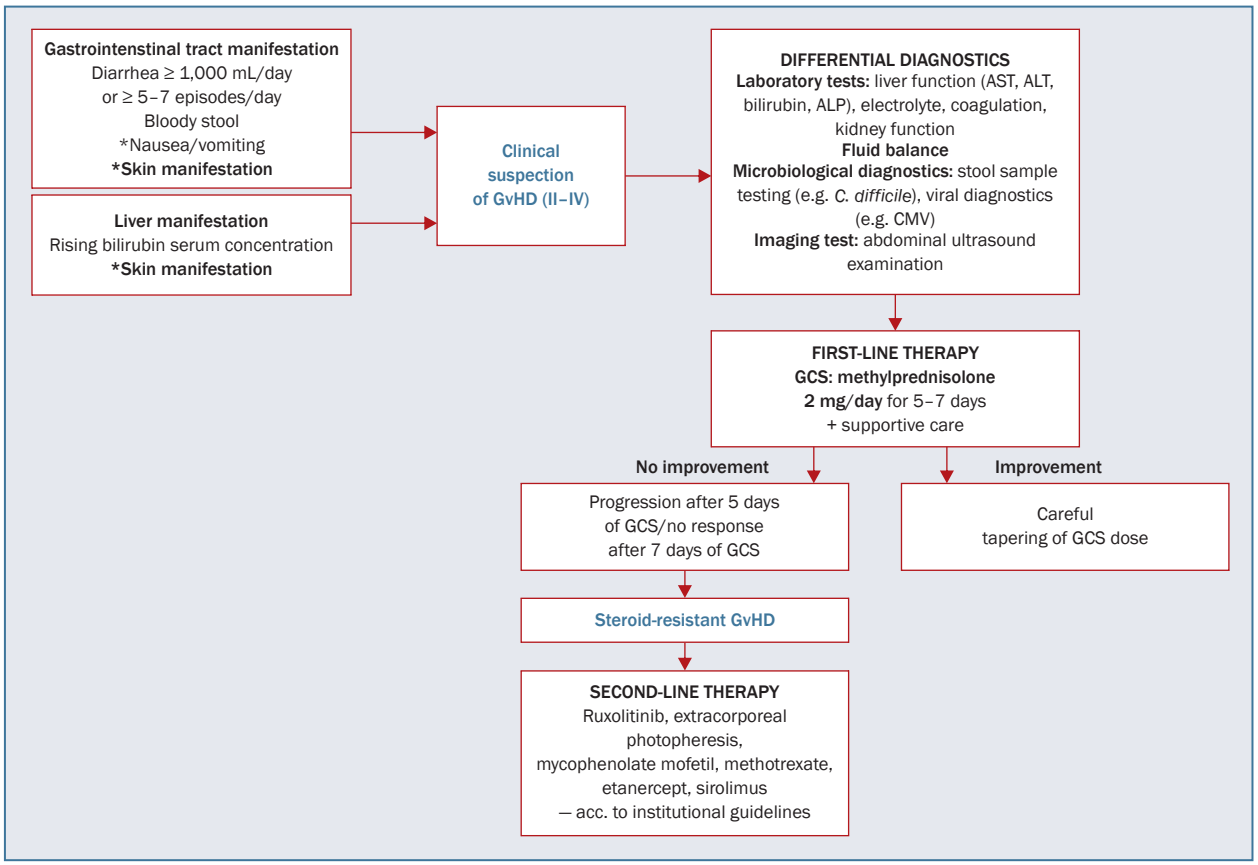

Figure 2. Practical algorithm of severe graft-versus-host disease (GvHD); AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase; CMV — cytomegalovirus; GSC —— glucocorticosteroids

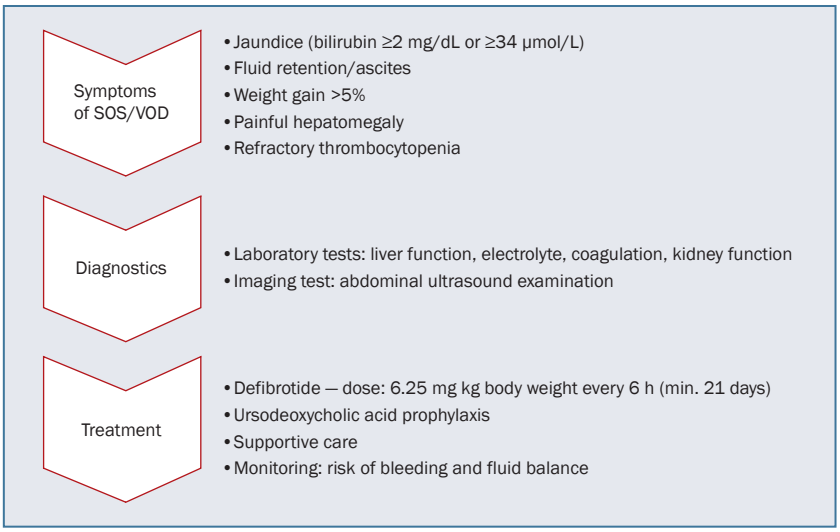

Figure 3. Practical algorithm of severe hepatic sinusoidal obstruction syndrome /veno-occlusive disease (SOS/VOD)

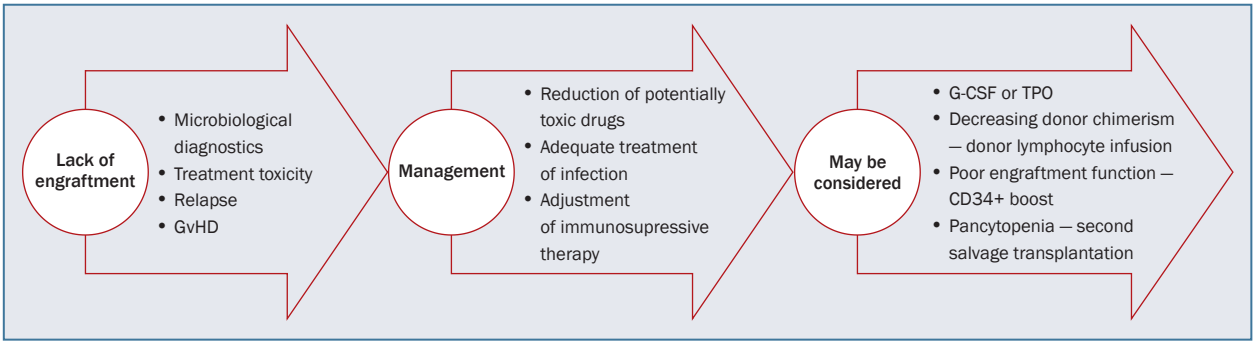

Figure 4. Practical algorithm of graft failure; GvHD — graft-versus-host disease; G-CSF — granulocyte-colony stimulating factor; TPO — thrombopoietin

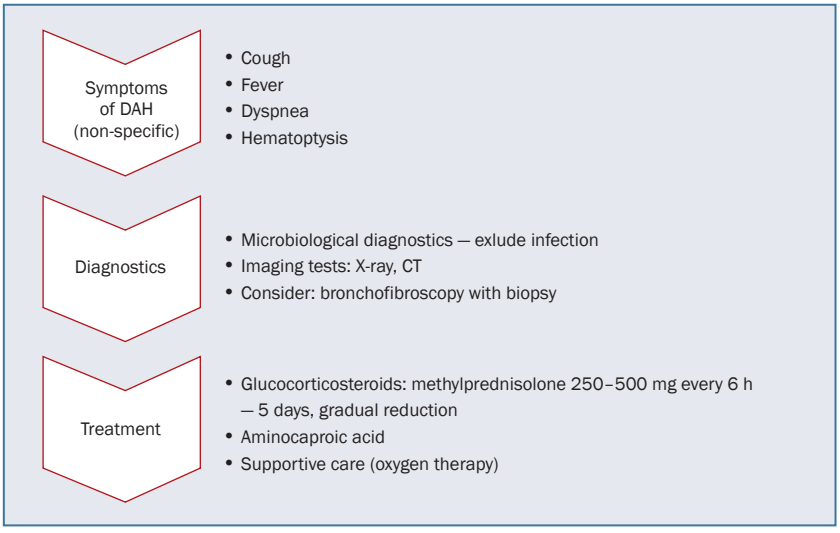

Figure 5. Practical algorithm of diffuse alveolar hemorrhage (DAH); CT — computed tomography

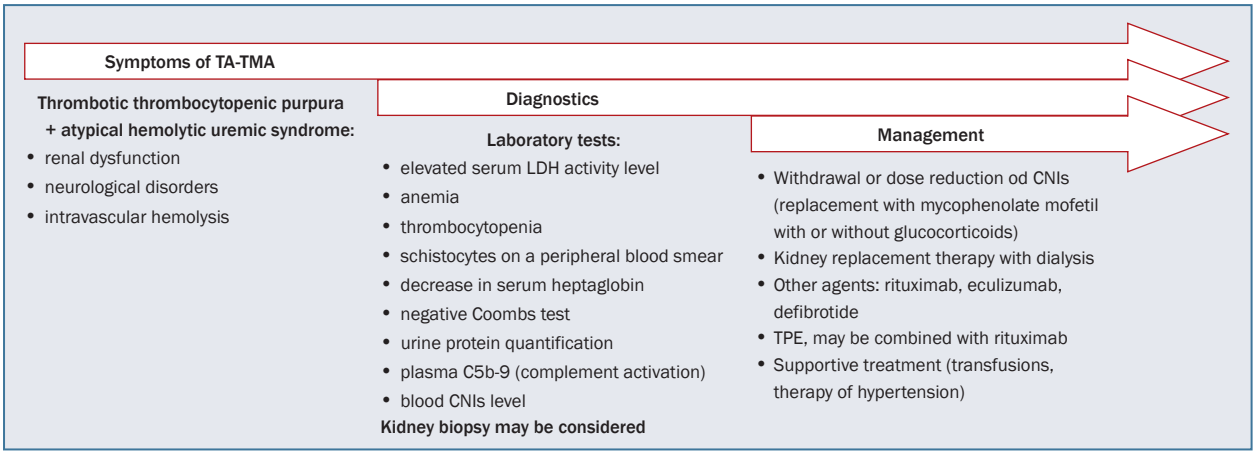

Figure 6. Practical algorithm of thrombotic microangiopathy associated with HSCT (TA-TMA); LDH — lactate dehydrogenase; CNIs — calcineurin inhibitors; TPE — therapeutic plasma exchange

mucocutaneous damage which might occur disrupt the natural barriers of the skin and mucous membranes, and may be a potential trigger point of infection. The previous microbiological history of the patient [i.e. a medical history of fungal infection, presence of pretransplant-specific immunity to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV)], as well as the viral status of the donor, should be taken into account. Moreover, the underlying disease in the setting of prior therapy and the type of HSCT (donor, source, conditioning, and immunosuppressive regimens) determine the risk of infection. Any other complication related to prolonged neutropenia, such as graft-versus-host disease and graft failure, increases the incidence of the infectious complication [10].

Bacterial infections are relatively common during neutropenia in both allo-HSCT recipients and patients undergoing auto-HSCT, while fungal and viral infections occur less frequently. For a proper diagnosis of patients with neutropenic fever (FN), detailed diagnostics are recommended, including microbiological cultures of biological material, i.e. venous blood, blood collected through a vascular catheter, urine, stool, and/or cerebrospinal fluid, depending on the accompanying symptoms [7, 10, 11].

Bacteremia is documented in 13–60% of patients with neutropenic fever, with a mortality rate reaching 12–42% [7, 11]. About half of the bacterial infections are caused by Gram-positive bacteria, particularly methicillin-resistant coagulase-negative *Staphylococci* and *Streptococcus spp.*, with a favorable prognosis. Recent years have seen a challenging increase in infections caused by resistant pathogens i.e. vancomycin-resistant *Enterococci* (VRE) and *Staphylococci* (vancomycin-intermediate *Staphylococcus aureus* (VISA), and hetero-resistant *Staphylococcus aureus* [hVISA]).

However, infections with resistant Gram-negative bacteria (MDR, multi-drug resistant), such as *Escherichia coli, Klebsiella sp., Pseudomonas aeruginosa*, and *Acinetobacter sp.*, are actually the most dangerous complications, as these are accompanied by a high mortality rate of c.50% [7, 12, 13].

In patients with FN, broad-spectrum intravenous antibiotic therapy should be implemented immediately even without identifying the pathogen and its susceptibility determination. The infection can spread quickly, causing a direct threat to life. The antibiotic therapy should cover the spectrum of Gram-positive and Gram-negative bacteria and then be modified depending on the patient's clinical condition, response to treatment, and potential microbiological identification. The choice of empirical therapy relies on the sensitivity of pathogens in the transplant center and the experience of the center's clinicians. Due to the potential toxicity and the development of bacterial resistance, there is a clear need to use narrowly-targeted therapy consistent with the antibiogram, and to consider discontinuing antibiotic therapy 48 h after the fever subsides, depending on the patient's general condition. In addition, if no clinical improvement is observed despite broad-spectrum empirical antibiotic therapy and the lack of microbiological identification, the imaging and microbiological diagnostics should be extended by the use of imaging diagnostics (ultrasonography of the abdominal cavity, computed tomography: high-resolution chest, paranasal sinuses) as well as invasive procedures, e.g. diagnostic bronchial fibroscopy with bronchoalveolar lavage testing [7, 10–14].

Recurrent or persistent FN, despite antibiotic therapy administration, might suggest invasive fungal infection (IFI), diagnosed mainly in allo-HSCT recipients with a high mortality rate. The incidence of IFI depends on the donor source and is estimated at 6–17%. The pathogens responsible for neutropenic infections are *Aspergillus sp., Mucorales*, and *Candida sp.* A medical history of IFI in transplant patients should always be considered. IFI is a significant clinical

problem, primarily in patients with graft-versus-host disease (GvHD) in the later post-transplant period. A strategy of antifungal therapy and prophylaxis during neutropenia has been described by the European Conference on Infections in Leukemia (ECIL) [7, 10, 15].

Among the viral infections in patients after allo-HSCT, the most important clinical problem is CMV reactivation [10, 16]. Both CMV viremia and CMV disease are associated with higher mortality. Historically, CMV reactivation occurred in 20–30% of HSCT recipients without adequate treatment, with a mortality rate exceeding 70%, as the first cause of treatment-related mortality (TRM). Pneumonia and enteritis are the most significant clinical manifestations associated with CMV disease, which can be fatal. The major risk factors for CMV reactivation and disease are GvHD, high-dose glucocorticoids (GCS), and prior CMV viremia. Nowadays, in the era of primary prophylaxis with letermovir, the occurrence of CMV disease has decreased to c.5%, as has the rate of deaths related to CMV disease, which is 2–3%.

However, CMV reactivation is related to an increased incidence of cytopenia and other infectious complications, and worsens survival rates of seropositive allo-HSCT recipients. Therefore, monitoring for CMV viremia to detect early CMV reactivation and, when it occurs, promptly implementing the use of pre-emptive therapy with anti-viral agents such as gancyclovir, valgancyclovir, foscarnet, cidofovir, and maribavir is essential [10, 16, 17].

Another potentially life-threatening complication is post-transplant lymphoproliferative disorder (PTLD), occurring in allo-HSCT recipients, in which B cells transformed by EBV proliferate uncontrollably. EBV infection occurs in 30% of HSCT recipients, and the incidence of PTLD is estimated at 1.1–1.7%, with a mortality rate exceeding 80% before the introduction of today's treatment methods. The development of EBV-PTLD is closely related to the use of anti-thymocyte globulin (ATG) and the type of transplant. Immediate therapy of established EBV-PTLD, due to the risk of the rapid growth of high-grade lymphoid tumors and its life-threatening consequences, should be introduced. This includes using rituximab (RTX) and the reduction of immunosuppression for first-line therapy, with an efficacy of over 80%. In the case of RTX failure, chemotherapy or the use of cellular therapy with cytotoxic T lymphocytes (EBV-CTL), well-tolerated and effective, is indicated [10, 18–20].

Complications related to immune response and endothelial damage after HSCT

Acute graft-versus-host disease

Acute GvHD (aGvHD) is a common complication of allo-HSCT, which occurs when immune cells from the graft recognize the host as foreign, thereby initiating a complex immune reaction that causes disease in c.40% of allo-HSCT recipients in the early post-transplantation period — around the white blood cell reconstitution, classically before day +100. Clinical manifestations of severe or life-threatening aGvHD include grade II or higher. Regarding the gastrointestinal tract and liver, the patient may present symptoms such as persistent nausea, vomiting, abdominal cramps with or without ileus, and, most importantly, diarrhea with a volume >1,000 mL/day or >5–7 episodes/day or bloody stool (regardless of stool volume) and liver dysfunction — with rising bilirubin serum concentration (>3.1 mg/dL). Skin-limited manifestation is a mild condition, but when a rash coexists with other forms of aGvHD and includes >50% of the body surface area, it affects the severity of the disease. The gastrointestinal form of aGvHD (GI-aGvhD) occurs in varying degrees in about half of patients with aGvHD. The watery mucous diarrhea in stages III/IV of GI-GvHD leads to water, electrolyte, and functional disorders that can lead to paralytic obstruction of the gastrointestinal tract and rapid decompensation of the patient. Abnormal liver function tests, most commonly bilirubin and alkaline phosphatase, reflect the pathology associated with hepatic GvHD: damage to the bile canaliculi, leading to cholestasis. Coagulopathy and hyperammonemia occur rarely, and mostly in severe cases. Patients may present painful hepatomegaly, dark urine, pale stool, fluid retention, and pruritus. The advanced stages of liver and GI-aGvhD can be fatal and require urgent intervention [10, 21].

The first-line therapy of grades II–IV aGvHD includes using systemic GCS in high doses — methylprednisolone at an initial dose of 2 mg/kg/day for 7–14 days (or equivalent). In cases of upper GI involvement, non-absorbable oral steroids are given, along with systemic GCS, e.g. budesonide (9 mg/day). During the treatment, individualized symptomatic and supportive therapy should be used to maintain vigilance in every single case of severe aGvHD. Long-term use of high doses of corticosteroids increases the risk of infection, including CMV reactivation, which is clinically significant in transplant recipients, as well as electrolyte disturbances and therapy-induced diabetes [21, 22].

Steroid-resistant aGvHD (SR-aGvHD) occurs in about half of the patients and is associated with mortality rates of up to 90%. When there is clear progression after five days of GCS, or when there is no response after seven days of GCS, it is recommended to introduce second-line therapy. Until now, there has been no standard second-line treatment for acute GvHD, and prospective clinical trials are still being conducted to examine the effectiveness of components. Ruxolitinib was approved by the US Food and Drug Administration and the European Medicines Agency for SR-aGVHD treatment in patients ≥12 years, with efficacy exceeding 70% and a favorable toxicity profile [23]. Moreover, in SR-aGvHD patients, depending on the institutional guidelines of transplant centers, the following agents may be used: extracorporeal photopheresis, mycophenolate

mofetil, methotrexate, etanercept, sirolimus, anti-thymocyte globulin, alemtuzumab, and vedolizumab; efficacies are 40-70%. There has been research into using fecal microbiota transplantation in second-line therapy, but this is yet to be approved [22, 24, 25].

Hepatic sinusoidal obstruction syndrome; veno-occlusive disease

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a life-threatening systemic complication of HSCT caused by injury to sinusoidal endothelial, hepatic cells that usually appears in the first 35–40 days after HSCT. The syndrome is characterized by hepatomegaly, fluid retention, jaundice, and refractory thrombocytopenia, and it can rapidly progress to multiorgan dysfunction and death. The incidence is estimated at 10–15% after myeloablative conditioning, while in the case of reduced intensity conditioning (RIC), it is c.5%. Before the patient's conditioning, the risk of SOS/VOD should be determined each time, as reducing the modifiable risk factors plays an important role in preventing this complication. The mild stage of SOS symptoms is self-limiting; however, the subsequent stages, especially taking into account the criteria of weight gain (>5%, <10%) and developing multiple organ failure, should be considered as a severe life-threatening condition. The mortality rate with severe hepatic SOS/VOD without adequate treatment exceeds 80% [10, 26].

The diagnosis of SOS/VOD should be made using the European Society for Blood and Marrow Transplantation (EBMT) revised diagnostic criteria for adults or alternative models (e.g. Seattle, Baltimore) which include: serum bilirubin (≥2 mg/dL; ≥34 μmol/L) plus two of the following three: painful hepatomegaly, weight gain >5%, and ascites. Abdominal ultrasound examination and laboratory findings defining liver and kidney functions help determine the severity of SOS/VOD [10, 26].

Defibrotide is indicated for managing severe SOS/VOD in HSCT recipients at a dose of 6.25 mg/kg every six hours, administered for a minimum of 21 days depending on the response [6, 26]. In patients who have developed severe SOS/VOD while receiving ursodeoxycholic acid (UDCA) prophylaxis, UDCA can be continued while they are treated with defibrotide [28]. Moreover, during the treatment, we should implement supportive care, and oversee vital signs, organ function parameters, fluid balance, and bleeding risk, because hemorrhage and hypersensitivity can be rare but life-threatening adverse effects. Early diagnosis of SOS/VOD and the introduction of defibrotide therapy significantly improve survival, as the percentage of complete remissions goes up to 50% [29–30].

Graft failure

Graft failure (GF) is a severe complication of allo-HSCT, characterized by the failure of donor hematopoietic cell reconstitution (at +28 days in bone marrow (BM) or peripheral blood (PB) and +42 days in umbilical cord blood (UCB). Primary GF is defined as a lack of initial donor engraftment; in contrast, secondary GF is characterized by losing donor cells after initial hematological recovery. In differential diagnosis, infectious causes (especially CMV reactivation and HHV-6 infection), treatment toxicity, relapse of the underlying disease, and GvHD should all be considered. The incidence of GF is estimated at 3–5% in allo-HSCT from a matched donor. This reaches up to 10% when using an alternative donor, i.e. a haploidentical donor (haplo-HSCT) or UCB. The mortality rate of GF is high due to the implications of cytopenia, such as severe infections and hemorrhagic complications [10, 31–33].

The critical aspects in managing GF are taking preventive measures and the early identification and withdrawal of potential causes if they might be reverted, i.e. reduction of drug toxicity, adequate infectious treatment, and adjustment of immunosuppressive therapy. Moreover, a trial of using granulocyte-colony stimulating factor (G-CSF) or thrombopoietin analogs (TPO) may be justified. In patients with an observed decrease in donor chimerism, the use of donor lymphocyte infusion (DLI) should be considered, although a high risk of aGvHD development is to be expected. The infusion of a CD34+ boost of the donor can be taken into account in patients with poor engraftment function. A second salvage transplantation from the same donor or an alternative donor remains the treatment of choice, promising for selected patients with primary GF or acute graft rejection related to trilinear cytopenia. New therapeutic and preventive approaches, such as mammalian target of rapamycin inhibitors, mesenchymal stromal cells, Tregs, or statins, could be an option for GF in the future [10, 31–34].

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is associated with blood leakage from the pulmonary capillaries into the alveoli, diagnosed in 2–14% of patients, most often in the first month after HSCT (median +23 days). The onset of DAH is usually abrupt. Symptoms are non-specific, including cough, fever, dyspnea, and hemoptysis (occurring in one in three patients). DAH can have both an infectious and a non-infectious etiology, and microbiological and imaging diagnostics may be insufficient to make a proper differential diagnosis. In selected clinical situations, bronchial fibroscopy should be considered, where blood is usually visualized in the orifices of segmental bronchi and bronchoalveolar. The diagnosis is confirmed by the presence of >20% of macrophages loaded with hemosiderin (though note that the absence of macrophages does not exclude the diagnosis of DAH, and their presence may occur after 72 h). The prognosis in DAH is very unfavorable, and mortality reaches 70–100% [10, 35–39].

The management of DAH without infectious evidence includes the prompt use of high doses of GCs — methylprednisolone at a dose of 250–500 mg every six hours for five days, followed by a gradual reduction of dose for 2–4 weeks and aminocaproic acid [10, 36]. A study has shown the validity of using GCs in lower doses (methylprednisolone <250 mg/d); however, further randomized prospective studies are indicated [37]. The addition of VIIa factor does not seem to improve the course of DAH. For patients with infection-associated DAH, treatment of the infection is crucial. Supportive care, including platelet transfusions and oxygen therapy, should be given. It is recommended to avoid mechanical ventilation, if possible. Patients with DAH may require intensification of therapy in the ICU due to its dynamic clinical course and frequently coexisting multi-organ failure [36–39].

Thrombotic microangiopathy associated with HSCT

Thrombotic microangiopathy associated with HSCT (TA-TMA) is a potentially life-threatening complication of HSCT caused by endothelial injury. The clinical manifestation of TA-TMA includes renal dysfunction and/or unexplained neurological dysfunction co-existing with evidence of intravascular hemolysis. The symptoms are associated with thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS), which typically occur up to 100 days after transplantation (median time +32 to +40 days). TA-TMA incidence differs widely due to various diagnostic criteria — 0.5–76%, according to a multicenter study — 3% [7, 40]. TA-TMA frequently has a poor prognosis with a mortality rate of up to 60%, mainly when the patient develops multiple organ failure. TA-TMA is not associated with calcineurin inhibitors (CNIs) [40, 41].

Most definitions of TA-TMA include a combination of characteristic clinical symptoms and the following laboratory findings: elevated serum lactate dehydrogenase (LDH) activity level, anemia, thrombocytopenia, presence of schistocytes on a peripheral blood smear, decrease in serum haptoglobin, negative Coombs test, urine protein quantification, and plasma C5b-9 (a product of complement activation). Moreover, in cases where the diagnosis is uncertain based on clinical findings, a kidney biopsy may be helpful to establish the diagnosis of TA-TMA.

The treatment of TA-TMA withdrawal or dose reduction of CNIs should be considered, especially when the blood CNI level is higher than expected. Replacement with mycophenolate mofetil, with or without GCS, may be reasonable. In patients with severe TA-TMA that progresses despite supportive measures, kidney replacement therapy with dialysis and additional treatments such as rituximab, eculizumab, and defibrotide may be needed. The efficiency of therapeutic plasma exchange (TPE), which can be combined with rituximab, reaches 60% CR, whereas the effectiveness of therapy with defibrotide or eculizumab is up to 70%. Moreover, supportive treatment with transfusions, and the appropriate management of hypertension, are indicated [10, 40–43].

Article information and declarations

Acknowledgements

Not applicable.

Author contributions

JK — concept, manuscript writing. MM — data check, critical revision. LG — idea for manuscript, critical revision. All authors — final approval of manuscript.

Conflict of interests

The authors declare no conflict of interests.

Funding

None.

Supplementary material

None.

References

1. Appelbaum FR. Hematopoietic-cell transplantation at 50. N Engl J Med. 2007; 357(15): 1472–1475, doi: 10.1056/NEJMp078166, indexed in Pubmed: 17928594.
2. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005; 106(8): 2912–2919, doi: 10.1182/blood-2005-05-2004, indexed in Pubmed: 15994282.
3. Snowden JA, Sánchez-Ortega I, Corbacioglu S, et al. European Society for Blood and Marrow Transplantation (EBMT). Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022; 57(8): 1217–1239, doi: 10.1038/s41409-022-01691-w, indexed in Pubmed: 35589997.
4. Ustawa z dnia 8 września 2006 r. o Państwowym Ratownictwie Medycznym. Dz.U. 2006 nr 191 poz. 1410. https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=wdu20061911410 (January 28, 2023).
5. Gratwohl A, Sureda A, Baldomero H, et al. Joint Accreditation Committee (JACIE) of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) and the European Leukemia Net (ELN). Economics and outcome after hematopoietic stem cell transplantation: a retrospective cohort study. EBioMedicine. 2015; 2(12): 2101–2109, doi: 10.1016/j.ebiom.2015.11.021, indexed in Pubmed: 26844291.
6. Styczyński J, Tridello G, Koster L, et al. Infectious Diseases Working Party EBMT. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplant. 2020; 55(1): 126–136, doi: 10.1038/s41409-019-0624-z, indexed in Pubmed: 31455899.
7. Rupa-Matysek J, Gil L, Mozer-Lisewska I, et al. Neutropenia — there are always two sides to a story. Acta Haematol Pol. 2020; 51(3): 133–141, doi: 10.2478/ahp-2020-0025.

8. Auletta JJ, Kou J, Chen M, Shaw BE. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021.
9. Styczynski J, Piekarska A, Zaucha-Prażmo A, et al. Antimicrobial prophylaxis in adults and children undergoing hematopoietic cell transplantation: 2021 Polish recommendations. Acta Haematol Pol. 2021; 52(6): 528–542, doi: 10.5603/ahp.a2021.0097.
10. Carreras E, Dufour C, Mohty M, Kröger N. eds. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. 7th ed. Springer, Cham 2019.
11. Mikulska M, Del Bono V, Viscoli C. Bacterial infections in hematopoietic stem cell transplantation recipients. Curr Opin Hematol. 2014; 21(6): 451–458, doi: 10.1097/MOH.0000000000000088, indexed in Pubmed: 25295742.
12. Averbuch D, Orasch C, Cordonnier C, et al. ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013; 98(12): 1826–1835, doi: 10.3324/haematol.2013.091025, indexed in Pubmed: 24323983.
13. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017; 65(11): 1819–1828, doi: 10.1093/cid/cix646, indexed in Pubmed: 29020364.
14. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011; 52(4): e56–e93, doi: 10.1093/cid/cir073, indexed in Pubmed: 21258094.
15. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020; 71(6): 1367–1376, doi: 10.1093/cid/ciz1008, indexed in Pubmed: 31802125.
16. Annaloro C, Serpenti F, Saporiti G, et al. Viral Infections in HSCT: detection, monitoring, clinical management, and immunologic implications. Front Immunol. 2020; 11: 569381, doi: 10.3389/fimmu.2020.569381, indexed in Pubmed: 33552044.
17. Ljungman P, de la Camara R, Robin C, et al. 2017 European Conference on Infections in Leukaemia group. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019; 19(8): e260–e272, doi: 10.1016/S1473-3099(19)30107-0, indexed in Pubmed: 31153807.
18. Styczynski J, Einsele H, Gil L, et al. Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. Transpl Infect Dis. 2009; 11(5): 383–392, doi: 10.1111/j.1399-3062.2009.00411.x, indexed in Pubmed: 19558376.
19. Styczynski J, Reusser P, Einsele H, et al. Second European Conference on Infections in Leukemia. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant. 2009; 43(10): 757–770, doi: 10.1038/bmt.2008.386, indexed in Pubmed: 19043458.
20. Marjanska A, Styczynski J. Who is the patient at risk for EBV reactivation and disease: expert opinion focused on post-transplant lymphoproliferative disorders following hematopoietic stem cell transplantation. Expert Opin Biol Ther. 2023; 23(6): 539–552, doi: 10.1080/14712598.2023.2196366, indexed in Pubmed: 36971380.
21. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020; 7(2): e157–e167, doi: 10.1016/S2352-3026(19)30256-X, indexed in Pubmed: 32004485.
22. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia. 2015; 29(10): 2062–2068, doi: 10.1038/leu.2015.212, indexed in Pubmed: 26228813.
23. Martini DJ, Chen YB, DeFilipp Z. Recent FDA approvals in the treatment of graft-versus-host disease. Oncologist. 2022; 27(8): 685–693, doi: 10.1093/oncolo/oyac076, indexed in Pubmed: 35443042.
24. Zhang H, Chen R, Cheng J, et al. Systematic review and meta-analysis of prospective studies for ECP treatment in patients with steroid-refractory acute GVHD. Patient Prefer Adherence. 2015; 9: 105–111, doi: 10.2147/PPA.S76563, indexed in Pubmed: 25653504.
25. Malard F, Huang XJ, Sim JPY. Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia. 2020; 34(5): 1229–1240, doi: 10.1038/s41375-020-0804-2, indexed in Pubmed: 32242050.
26. Bonifazi F, Barbato F, Ravaioli F, et al. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. Front Immunol. 2020; 11: 489, doi: 10.3389/fimmu.2020.00489, indexed in Pubmed: 32318059.
27. Mohty M, Malard F, Abecasis M, et al. Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a position statement from an international expert group. Bone Marrow Transplant. 2020; 55(3): 485–495, doi: 10.1038/s41409-019-0705-z, indexed in Pubmed: 31576023.
28. Stutz L, Halter JP, Heim D, et al. Low Incidence of hepatic sinusoidal obstruction syndrome/veno-occlusive disease in adults undergoing allogenic stem cell transplantation with prophylactic ursodiol and low-dose heparin. Bone Marrow Transplant. 2022; 57(3): 391–398, doi: 10.1038/s41409-021-01546-w, indexed in Pubmed: 34980902.
29. Nauffal M, Kim HT, Richardson PG, et al. Defibrotide: real-world management of veno-occlusive disease/sinusoidal obstructive syndrome after stem cell transplant. Blood Adv. 2022; 6(1): 181–188, doi: 10.1182/bloodadvances.2021005410, indexed in Pubmed: 34666352.
30. Mohty M, Blaise D, Peffault de Latour R, et al. Real-world use of defibrotide for veno-occlusive disease/sinusoidal obstruction syndrome: the DEFI-France Registry Study. Bone Marrow Transplant. 2023; 58(4): 367–376, doi: 10.1038/s41409-022-01900-6, indexed in Pubmed: 36564486.
31. McCann S. Graft failure. Bone Marrow Transplant. 2020; 55(10): 1888–1889, doi: 10.1038/s41409-020-0860-2, indexed in Pubmed: 32161320.
32. Olsson RF, Logan BR, Chaudhury S, et al. Primary graft failure after myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancies. Leukemia. 2015; 29(8): 1754–1762, doi: 10.1038/leu.2015.75, indexed in Pubmed: 25772027.
33. Ozdemir ZN, Civriz Bozdağ S. Graft failure after allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci. 2018; 57(2): 163–167, doi: 10.1016/j.transci.2018.04.014, indexed in Pubmed: 29724627.

34. Locatelli F, Lucarelli B, Merli P. Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. Expert Opin Pharmacother. 2014; 15(1): 23–36, doi: 10.1517/14656566.2014.852537, indexed in Pubmed: 24156789.
35. Diab M, ZazaDitYafawi J, Soubani AO. Major pulmonary complications after hematopoietic stem cell transplant. Exp Clin Transplant. 2016; 14(3): 259–270, doi: 10.6002/ect.2015.0275, indexed in Pubmed: 27040986.
36. Keklik F, Alrawi EB, Cao Q, et al. Diffuse alveolar hemorrhage is most often fatal and is affected by graft source, conditioning regimen toxicity, and engraftment kinetics. Haematologica. 2018; 103(12): 2109–2115, doi: 10.3324/haematol.2018.189134, indexed in Pubmed: 30076172.
37. Rathi NK, Tanner AR, Dinh A, et al. Low-, medium- and high-dose steroids with or without aminocaproic acid in adult hematopoietic SCT patients with diffuse alveolar hemorrhage. Bone Marrow Transplant. 2015; 50(3): 420–426, doi: 10.1038/bmt.2014.287, indexed in Pubmed: 25531284.
38. Afessa B, Tefferi A, Litzow MR, et al. Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med. 2002; 166(10): 1364–1368, doi: 10.1164/rccm.200208-792OC, indexed in Pubmed: 12406834.
39. Majhail NS, Parks K, Defor TE, et al. Diffuse alveolar hemorrhage and infection-associated alveolar hemorrhage following hematopoietic stem cell transplantation: related and high-risk clinical syndromes. Biol Blood Marrow Transplant. 2006; 12(10): 1038–1046, doi: 10.1016/j.bbmt.2006.06.002, indexed in Pubmed: 17067910.
40. Epperla N, Li A, Logan B, et al. Incidence, risk factors for and outcomes of transplant-associated thrombotic microangiopathy. Br J Haematol. 2020; 189(6): 1171–1181, doi: 10.1111/bjh.16457, indexed in Pubmed: 32124435.
41. Scully M, Cataland S, Coppo P, et al. International Working Group for Thrombotic Thrombocytopenic Purpura. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017; 15(2): 312–322, doi: 10.1111/jth.13571, indexed in Pubmed: 27868334.
42. Lazana I. Transplant-associated thrombotic microangiopathy in the context of allogenic hematopoietic stem cell transplantation: where we stand. Int J Mol Sci. 2023; 24(2), doi: 10.3390/ijms24021159, indexed in Pubmed: 36674666.
43. George JN, Li X, McMinn JR, et al. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. Transfusion. 2004; 44(2): 294–304, doi: 10.1111/j.1537-2995.2004.00700.x, indexed in Pubmed: 14962323.