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Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT

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Abstract

Non-graft-versus-host disease (non-GVHD) ocular complications are generally uncommon after hematopoietic cell transplantation (HCT), but can cause prolonged morbidity affecting activities of daily living and quality of life. Here we provide an expert review of non-GVHD ocular complications in a collaboration between transplant physicians and ophthalmologists through the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and the Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation. Complications discussed in this review include cataracts, glaucoma, ocular infections, ocular involvement with malignancy, ischemic microvascular retinopathy, central retinal vein occlusion, retinal hemorrhage, retinal detachment and ocular toxicities associated with medications. We have summarized incidence, risk factors, screening, prevention and treatment of individual complications and generated evidence-based recommendations. Baseline ocular evaluation before HCT should be considered in all patients who undergo HCT. Follow-up evaluations should be considered according to clinical symptoms, signs and risk factors. Better preventive strategies and treatments remain to be investigated for individual

ocular complications after HCT. Both transplant physicians and ophthalmologists should be knowledgeable of non-GVHD ocular complications and provide comprehensive collaborative team care.

Keywords

hematopoietic cell transplantation; complication; eye; review; prevention; treatment

Introduction

Hematopoietic cell transplantation (HCT) is a curative treatment for many hematologic malignancies and nonmalignant disorders, although a variety of complications and late effects may occur.[1-3] Non-graft-versus-host disease (non-GVHD) ocular complications are generally uncommon after HCT, but can cause prolonged morbidity affecting activities of daily living and quality of life. It is important for all health professionals taking care of HCT recipients to have adequate knowledge about ocular complications.

This review summarizes recent updates in non-GVHD ocular complications after HCT in a collaborative effort between transplant physicians and ophthalmologists through the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation (EBMT). We aim to provide an expert review of non-GVHD ocular complications after HCT with evidence-based recommendations for clinical practice and future research. The most frequent ocular complication after allogeneic HCT is ocular GVHD, which is addressed in a companion review.

Structures of the eye are shown in Figure 1. The anterior segment of the eye is formed by the cornea, aqueous humor, iris, ciliary body and crystalline lens. The posterior segment is formed by the vitreous body, retina, choroid and optic nerve.

Methods

We searched the Medline (PubMed) database using a broad search strategy to identify studies related to ocular complications after HCT. The primary search was conducted using the terms “hematopoietic transplantation AND (eye OR ocular),” and 552 articles were identified as of March 31, 2018. Relevant articles were also reviewed as needed. Recommendations are organized according to an evidence-based system described previously[4] to reflect the strength of recommendations and the quality of evidence supporting them (Table 1).

Cataracts

Incidence and risk factors

Cataracts, defined clinically as progressive opacification of the lens, are one of the most frequent late ocular complications after HCT. The reported incidence of cataracts in HCT

survivors varies among studies, ranging from 11% to 100% in adults[5,6] and from 4% to 76% in children (supplementary Table S1).[7,8] This large variability is attributable to heterogeneity in patient populations, conditioning regimens, supportive care, and length of follow-up.

Among patients who undergo allogeneic HCT, total body irradiation (TBI) as part of the conditioning regimen has been identified as a major risk factor for cataract formation. Posterior subcapsular cataracts are the most common subtype associated with exposure to ionizing radiation. The risk of cataracts is much higher after single dose TBI compared to hyper-fractionated TBI.[9] A higher dose rate (>0.04 Gy/min) has also been identified as a risk factor.[10] Lens-shielding in patients receiving TBI has been tested, mostly in pediatric patients, and has shown to reduce the incidence and severity of cataracts,[11] although controversy exists regarding a potentially increased risk of extramedullary disease relapse in the shielded area. One pediatric study showed that fractionated TBI was assocated with cataracts requiring surgery, while chemotherapy-based conditioning caused less severe cataracts usually not requiring surgery.[12]

In addition to TBI, prolonged steroid therapy, such as for treatment of GVHD, has been identified as an independent risk factor for cataracts after HCT.[13,14] A population-based study showed that even inhaled corticosteroids were associated with the development of posterior subcapsular and nuclear cataracts.[15] Survivors of allogeneic HCT are more likely to develop cataracts, when compared with those of autologous HCT.[10]

Screening, prevention and treatment

Comprehensive evaluation by ophthalmologists before HCT and then annually after HCT is warranted to diagnose and determine the appropriate timing for surgical intervention of cataracts (supplementary Table S2).[16] In adults, decreased visual acuity reported by the patients should initiate an eye examination. Pediatric patients require regular follow-up given that they may not complain of visual changes. Cataract prevention with use of fractionated TBI or use of non-TBI conditioning regimens and corticosteroids sparing, when clinically feasible, is the most important for minimizing cataract development.[9,12]

Surgery is the standard treatment for cataracts. Early diagnosis and appropriate timing for surgery are important in young children, especially those under 7 years old, in order to prevent irreversible amblyopia.[17] Cataract surgery is usually indicated for those with bilateral cataracts and best corrected visual acuity of 20/40 or worse, although the visual threshold for performing surgery should be tailored according to the needs of the patient. In both adult and pediatric patients, cataracts may present with dry eye and other manifestations of ocular GVHD. The concurrent ocular surface problems and postoperative complications should be controlled to obtain good surgical outcomes in these patients.[18]

Ocular infections

Ocular infections can be severe after HCT. The types of infectious organisms, involved ocular structures, symptoms and diagnostic tests are summarized in Table 2.

Incidence and risk factors

The incidence of ocular infections has decreased over time with advances in prophylaxis, screening guidelines and effective medications.[19,20] In a large series of 620 patients undergoing allogeneic HCT, 18 (3%) had serious ocular infections due to Gram-positive and negative bacteria (1.6%), fungi (0.16%), and virus (0.8%).[21] *Candida* and *Aspergillus* species are the most frequently isolated organisms in fungal keratitis and endophthalmitis.[22] The most common ocular protozoan infection is *Toxoplasma gondii,* although ocular toxoplasmosis is rare (0.3-0.5% of autologous and allogeneic HCT recipients).[23,24] Viruses that cause ocular infection after HCT include cytomegalovirus (CMV),[25-28] herpes simplex virus (HSV),[29] varicella zoster virus (VZV),[30,31] and adenovirus (ADV).[32] The most common virus that affects the eyes is CMV, with the incidence of retinitis ranging from <1% to 5% in all HCT recipients, and from 5% to 23% in patients with CMV viremia.[25-28] Ocular infections by HSV, VZV and ADV are rare.[29-31] In one study, ocular infection accounted for 2% of all VZV infections.[30]

Since ocular infections are uncommon, risk factors are often extrapolated from those for infections at other sites and include pre-HCT latent infections and post-HCT neutropenia, impaired cellular and humoral immunity and development of GVHD (Figure 2).[19,21] Patients with neutropenia or humoral deficiency are susceptible to developing bacterial infections, including corneal ulcers and periorbital cellulitis.[21] Risk factors for ocular fungal infection include fungemia and immunosuppression.[33] Risk factors for ocular toxoplasmosis include toxoplasma infection before HCT and impaired cellular immunity.[23] Risk factors for viral infections include positive serostatus before HCT, history of viremia before HCT, low lymphocyte counts, chronic GVHD, HLA mismatching, and unrelated donor.[25-27,30] Candidates for HCT should undergo serologic testing for latent viral infections and toxoplasmosis.[19,20]

Screening, prevention and treatment

Eye examination should be performed before HCT and at any time when patients have ocular symptoms after HCT. Early detection and prompt treatment are required to prevent visual loss. Prevention and treatment of ocular infections is similar to that of other systemic infections except where ocular penetration of the therapeutic agent is poor.

Bacterial infections are treated with systemic antibiotics based on culture and sensitivity results. Topical antibiotics are also used for bacterial keratitis.[34] Systemic antifungal therapy is considered for patients with ocular fungal infection depending on the causative pathogen. Intravitreal administration can be performed with most antifungal agents, including amphotericin B, echinocandins and azoles, as penetration into eyes may not be sufficient with intravenous administration.[35] To treat fungal keratitis, antifungal agents such as voriconazole can be used topically.[36] There are no randomized trials comparing the efficacy of different prophylactic agents to prevent toxoplasmosis after HCT, although observational studies have demonstrated efficacy of trimethoprim-sulfamethoxazole from engraftment until immunosuppressive therapy is discontinued.[37] Treatment of active toxoplasmosis consists of antimicrobial agents such as trimethoprim-sulfamethoxazole, pyrimethamine/sulfadiazine, clindamycin, atovaquone, or azithromycin.[38]

Systemic therapy (e.g. ganciclovir and foscarnet) should be used for treatment of CMV ocular diseases.[28] When patients do not respond sufficiently to systemic therapy, intravitreous therapy is considered.[28] Third-party donor-derived CMV pp65-specific T-cells have resulted in resolution of refractory CMV retinitis.[39] Prophylactic acyclovir has reduced the risk of HSV infection.[40] A combination of systemic therapy and topical therapies is recommended for treatment of HSV ocular infection. Intravenous cidofovir is recommended for treatment of ADV infection.[41]

Ocular involvement by malignancy

Incidence and diagnosis

There is very limited information regarding ocular manifestations of malignancy after HCT. The incidence of ocular involvement by malignancy is rare. Relapsed disease after HCT may involve eyes, either *de novo* or in association with central nervous system or systemic relapse.[42,43]

Clinical presentations of intraocular neoplasms after HCT can include the anterior and posterior segments and orbital manifestations, amongst others. Despite the infrequent incidence of *de novo* or recurrent ocular neoplasms, a high index of suspicion necessitates proper clinical assessment and evaluation by an experienced ophthalmologist.[44] Computed tomography or magnetic resonance imaging may be helpful. Cytology, immunohistochemistry, flow cytometry, cytogenetics and molecular studies on aspirated fluid or tissue biopsy are necessary for definitive diagnosis.[44-46]

Screening, prevention and treatment

No evidence is available for screening and prevention of malignancies with ocular involvement. As a general recommendation, ocular evaluation may be necessary in patients with relapsed primary disease and ocular symptoms, in those with previous ocular involvement, and in those with new malignancy involving the central nervous system. Treatment approaches are extrapolated from literature on treatment of intraocular neoplasms in general and are not validated in HCT settings. These include intravitreal chemotherapy, radiation, photodynamic laser therapy, and disease-specific interventions based on site and histology of neoplasm.[47-49]

Ischemic microvascular retinopathy

Incidence and risk factors

Ischemic microvascular retinopathy (IMR) after HCT is a complication of the posterior segment that was first described in 1983.[50] IMR presents with retinal cotton-wool patches, vitreous hemorrhage and optic disc edema. The clinical presentation varies from asymptomatic to sight-threatening forms. Symptomatic patients often complain of blurred vision or color vision abnormality which can occur abruptly, gradually or progressively. One or both eyes can be affected.

There are at least 8 cohort studies examining complications of the posterior segment after HCT (supplementary Table S3).[21,22,51-56] IMR has been reported after both autologous and

allogeneic HCT, and the incidence of IMR ranges from 0% to 10%,[21,22,51-56] although the incidence is likely to be underestimated due to the asymptomatic presentation in many patients. IMR usually occurs within 6 months of allogeneic HCT,[52] although atypically late onset around 50 months after allogeneic HCT has been described in 4 patients.[54] Potential risk factors for IMR include TBI conditioning,[22,52,54] cyclosporine prophylaxis,[22,52] and conditioning regimens including busulfan or carmustine.[53,54]

Pathogenesis

Although the pathogenesis of HCT-associated IMR has not yet been elucidated, multifactorial processes are likely to cause capillary damage in the ocular fundus. IMR after HCT is morphologically similar to fundus changes associated with malignant hypertension in the general population,[57] but most HCT patients with IMR do not have malignant hypertension, suggesting a different pathogenesis. Although radiation has been associated with vascular retinopathy,[58] IMR also occurs among adult patients who have had autologous HCT using non-TBI conditioning regimens.[53] In an experimental rat model using retinal imaging, the combination of cyclosporine and dexamethasone led to progressive degenerative changes of the fundus with histologic thinning of the outer nuclear layer of the retina, suggesting that calcineurin inhibitors may contribute to ocular vascular endothelial injury.[59]

Screening, prevention and treatment

Data are lacking for the management of IMR after HCT. Based on the potential risk factors, it is important to avoid radiation to ocular areas, to monitor levels of calcineurin inhibitors, and to treat cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia. Importantly, spontaneous regression is frequent and permanent loss of visual acuity is rare. Withdrawal or reduction of immunosuppression can lead to resolution of the retinal lesions in many cases,[60] although proliferative retinopathy may have a poor visual prognosis.[61]

Future research should focus on the biology of IMR and identification of risk factors. Novel findings in retinopathy due to diabetes and sickle cell disease are worth investigating in HCT patients with IMR. For example, new sensitive technologies of ultra-wide field fluorescein angiography, spectral-domain optical coherence tomography and optical coherence tomography angiography may help diagnosis.[62,63] Vascular endothelial growth factor (VEGF) may serve as a diagnostic biomarker and a treatment target, since tissue ischemia increases VEGF that can promote abnormal neovascularization.[64]

Other ocular complications

Glaucoma

Glaucoma was diagnosed in 1.7% of HCT survivors, but this frequency was similar to 1.9% in their siblings.[65] In a study of 218 patients with chronic GVHD, 33 (15%) had increased intraocular pressure, 8 (3.6%) had suspicion of glaucoma, and 1 (0.4%) had glaucoma.[66] Classically, glaucoma is known as a late complication of irradiation used in conditioning regimens, with a median interval of 22 months to onset of glaucoma.[67] Long-term use of systemic corticosteroids for chronic GVHD can elevate intraocular pressure in susceptible

patients.[66,68,69] The risk of early intraocular pressure rise and amount of elevation are greater in children than adults.[70] Intraocular pressure may be elevated even after topical steroid use such as eye drops, ointment and inhalation. Other factors associated with open angle glaucoma are infectious keratitis and eye rubbing.[68] No correlation has been demonstrated between stem cell source and glaucoma.[21]

Patients who are receiving systemic or topical steroids should have periodic monitoring of intraocular pressure. A rise in intraocular pressure is often transient and resolves within 4 weeks of tapering or cessation of systemic steroid therapy.[66] If steroid use exceeds 18 months, the intraocular pressure may be permanently elevated. First-line treatment of glaucoma is topical aqueous humor suppressants, including beta-blockers, alpha 2 agonists, or carbonic anhydrase inhibitors.[71,72] For the 1-5% of patients with intractable glaucoma not adequately responsive to eye drop treatment, glaucoma surgery with trabeculectomy or other technique may be necessary to prevent vision loss.[73] Laser trabeculoplasty has shown efficacy in small retrospective studies.[74]

Central retinal vein occlusion (CRVO)

CRVO is a vision-threatening retinal vascular disease, with an incidence of 0.2%-0.4% in the general population.[75] The pathophysiology of CRVO is not yet fully understood, but systemic diseases including hypertension, hyperlipidemia and diabetes mellitus, hypercoagulability and hyperviscosity may be associated with its pathophysiology. There are several reports of CRVO in patients with hematologic malignancies, but only two cases of CRVO have been reported at 2 and 5 months after HCT.[76]

The central retinal vein is compressed in patients with CRVO by the adjacent central retinal artery at the lamina cribrosa, leading to increased venous and capillary pressures, endothelial damage, permeability changes, and extravasation of blood and serous fluid in the retina. Capillary perfusion is reduced due to increased interstitial pressures, causing tissue ischemia. Interleukin-6 and VEGF are secreted in response to the ischemia, which promotes retinal edema, neovascularization and other complications including vitreous hemorrhage, tractional retinal detachment, iris neovascularization and neovascular glaucoma.[77]

Intravitreal injections of anti-VEGF agents are the first-line treatment for symptomatic macular edema due to CRVO, and have shown significant reduction in central retinal thickness from macular edema, significant improvement in best corrected visual acuity and a delay in development of neovascular complications in randomized studies.[78,79] Intravitreal steroid injections also have improved macular edema after CRVO in a randomized study.[80] A retrospective study showed that macular grid and panretinal laser photocoagulation are also effective for CRVO,[81] and these treatments are considered as second line or in cases with extensively ischemic retina.

Retinal hemorrhage and retinal detachment

Retinal hemorrhage and detachment usually occur as a consequence of other pathologies such as CMV retinitis and neovascularization due to ischemic retinopathy. A retrospective study of 635 patients who had allogeneic HCT showed that the most common posterior segment complication after allogeneic HCT was retinal hemorrhage (3.2%).[76] Standard

treatments include platelet transfusion to maintain the platelet count over 50,000/μl and correction of coagulopathy.

Retinal detachment is a rare posterior segment complication and accounts for <1% of ocular complications after HCT.[22,76] It can be seen in chronic GVHD, CMV retinitis, and rarely in acute GVHD. Most of the cases manifest as rhegmatogenous retinal detachment,[76,82] but 2 cases of vision-threatening exudative bullous retinal detachment have been reported in the literature.[83] Tractional retinal detachment due to proliferative retinopathy has also been reported after HCT.[84] In one study, retinal detachment occurred in 13% patients with CMV retinitis, and the visual prognosis was often poor.[76] Treatment depends on underlying disease and includes laser photocoagulation, cryotherapy, and various surgical techniques.

Medications with ocular toxicities

A variety of medications can cause ocular toxicities after HCT (Table 3). The most commonly reported ocular toxicity of anti-cancer drugs is keratoconjunctivitis. Systemic corticosteroids accelerate cataract formation[13,14,85] and glaucoma development.[66] Topical corticosteroids are commonly used for treatment of ocular GVHD, but their long-term use is associated with elevated intraocular pressure, decreased epithelial healing, infection and cataracts.[18] High-potency steroid eye drops should be avoided, and intraocular pressure should be monitored in patients who continue steroid eye drops for more than 2 weeks.[66] Topical use of tacrolimus and cyclosporine for treatment of ocular GVHD can cause conjunctival injection, burning and stinging sensation, which may be controlled with lubricating eye drops.[86-88] Voriconazole can cause blurred vision, changes in visual acuity and color perception, photophobia and visual hallucinations.[89] Other medications such as antihistamines[90] (e.g., diphenhydramine, loratadine) and anticholinergics[91] (e.g., sedatives, sleep aids, cold preparations, antidiarrheal and nasal decongestants) can inhibit lacrimal glandular secretions and cause dry eyes. Scopolamine patches used as antiemetic after high-dose chemotherapy can lead to anisocoria or mydriasis if the eye is contaminated with scopolamine.[92] Selective serotonin reuptake inhibitors can result in reduced accommodation.[93] Antipsychotics including phenothiazines such as haloperidol, chlorpromazine and thioridazine can cause mydriasis, cycloplegia,[93] and pigmentation of conjunctiva, cornea, eyelids and retina with their long-term use.[94] Sildenafil used for erectile dysfunction after HCT can cause a blue tinge to vision or an increased brightness of lights.[95] Topical nonsteroidal anti-inflammatory eye drops can cause stromal necrosis in dry eyes, and should be avoided in patients with ocular GVHD.[96]

Summary and future recommendations

The incidence, risk factors, screening and prevention recommendations for non-GVHD ocular complications after HCT are summarized in Table 4. Treatment recommendations are summarized in Table 5. Although non-GVHD ocular complications after HCT are rare, baseline ocular evaluation before HCT should be considered in all patients who undergo HCT. Follow-up ocular evaluations should be considered according to clinical findings and risk factors. Better preventive strategies and treatments remain to be investigated for individual ocular complications after HCT, particularly in high-risk patients. There is

significant overlap in the clinical presentation between infectious and non-infectious ocular complications and better diagnostic techniques need to be developed. There remains a paucity of data on the long-term visual outcomes, particularly in pediatric patients, as most studies have short follow up of less than 2 years. Better data collection is necessary to address these remaining questions. Both transplant physicians and ophthalmologists should be knowledgeable about non-GVHD ocular complications and provide a comprehensive collaborative team care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Socie G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A et al. Nonmalignant late effects after allogeneic stem cell transplantation. Blood 2003; 101: 3373–3385. [PubMed: 12511420]
2. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. Haematologica 2017; 102: 614–625. [PubMed: 28232372]
3. Battiwalla M, Hashmi S, Majhail N, Pavletic S, Savani BN, Shelburne N. National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Developing Recommendations to Improve Survivorship and Long-Term Outcomes. Biol Blood Marrow Transplant 2017; 23: 6–9. [PubMed: 27989931]
4. Couriel D, Carpenter PA, Cutler C, Bolanos-Meade J, Treister NS, Gea-Banacloche J et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant 2006; 12: 375–396. [PubMed: 16545722]
5. Dunn JP, Jabs DA, Wingard J, Enger C, Vogelsang G, Santos G. Bone marrow transplantation and cataract development. Arch Ophthalmol 1993; 111: 1367–1373. [PubMed: 8216017]
6. Tichelli A, Gratwohl A, Egger T, Roth J, Prunte A, Nissen C et al. Cataract formation after bone marrow transplantation. Ann Intern Med 1993; 119: 1175–1180. [PubMed: 8239248]

7. Kinori M, Bielorai B, Souroujon D, Hutt D, Ben-Bassat Mizrachi I, Huna-Baron R. Ocular complications in children after hematopoietic stem cell transplantation without total body irradiation. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1397–1402. [PubMed: 25708560]
8. Frisk P, Hagberg H, Mandahl A, Soderberg P, Lonnerholm G. Cataracts after autologous bone marrow transplantation in children. Acta Paediatr 2000; 89: 814–819. [PubMed: 10943964]
9. Benyunes MC, Sullivan KM, Deeg HJ, Mori M, Meyer W, Fisher L et al. Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. Int J Radiat Oncol Biol Phys 1995; 32: 661–670. [PubMed: 7790252]
10. Belkacemi Y, Labopin M, Vernant JP, Prentice HG, Tichelli A, Schattenberg A et al. Cataracts after total body irradiation and bone marrow transplantation in patients with acute leukemia in complete remission: a study of the European Group for Blood and Marrow Transplantation. Int J Radiat Oncol Biol Phys 1998; 41: 659–668. [PubMed: 9635717]
11. van Kempen-Harteveld ML, van Weel-Sipman MH, Emmens C, Noordijk EM, van der Tweel I, Revesz T et al. Eye shielding during total body irradiation for bone marrow transplantation in children transplanted for a hematological disorder: risks and benefits. Bone Marrow Transplant 2003; 31: 1151–1156. [PubMed: 12796795]
12. Fahnehjelm KT, Tornquist AL, Olsson M, Winiarski J. Visual outcome and cataract development after allogeneic stem-cell transplantation in children. Acta Ophthalmol Scand 2007; 85: 724–733. [PubMed: 17725615]
13. van Kempen-Harteveld ML, Struikmans H, Kal HB, van der Tweel I, Mourits MP, Verdonck LF et al. Cataract-free interval and severity of cataract after total body irradiation and bone marrow transplantation: influence of treatment parameters. Int J Radiat Oncol Biol Phys 2000; 48: 807–815. [PubMed: 11020578]
14. Najima Y, Kakihana K, Ohashi K, Yamamoto N, Kobayashi T, Yamashita T et al. Incidence, risk factors, and clinical outcomes of cataracts following hematopoietic stem cell transplantation. Am J Hematol 2011; 86: 508–510. [PubMed: 21509794]
15. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med 1997; 337: 8–14. [PubMed: 9203425]
16. Bernard F, Auquier P, Herrmann I, Contet A, Poiree M, Demeocq F et al. Health status of childhood leukemia survivors who received hematopoietic cell transplantation after BU or TBI: an LEA study. Bone Marrow Transplant 2014; 49: 709–716. [PubMed: 24535128]
17. Tear Fahnehjelm K, Tornquist AL, Olsson M, Backstrom I, Andersson Gronlund M, Winiarski J. Cataract after allogeneic hematopoietic stem cell transplantation in childhood. Acta Paediatr 2016; 105: 82–89. [PubMed: 26331596]
18. de Melo Franco R, Kron-Gray MM, De la Parra-Colin P, He Y, Musch DC, Mian SI et al. Outcomes of cataract surgery in graft-versus-host disease. Cornea 2015; 34: 506–511. [PubMed: 25826324]
19. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009; 15: 1143–1238. [PubMed: 19747629]
20. Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Kruger W et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Ann Hematol 2016; 95: 1435–1455. [PubMed: 27339055]
21. Tabbara KF, Al-Ghamdi A, Al-Mohareb F, Ayas M, Chaudhri N, Al-Sharif F et al. Ocular findings after allogeneic hematopoietic stem cell transplantation. Ophthalmology 2009; 116: 1624–1629. [PubMed: 19729097]
22. Coskuncan NM, Jabs DA, Dunn JP, Haller JA, Green WR, Vogelsang GB et al. The eye in bone marrow transplantation. VI. Retinal complications. Arch Ophthalmol 1994; 112: 372–379. [PubMed: 8129664]
23. Sumi M, Aosai F, Norose K, Takeda W, Kirihara T, Sato K et al. Acute exacerbation of Toxoplasma gondii infection after hematopoietic stem cell transplantation: five case reports among 279 recipients. Int J Hematol 2013; 98: 214–222. [PubMed: 23749548]

24. Decembrino N, Comelli A, Genco F, Vitullo A, Recupero S, Zecca M et al. Toxoplasmosis disease in paediatric hematopoietic stem cell transplantation: do not forget it still exists. Bone Marrow Transplant 2017; 52: 1326–1329. [PubMed: 28604668]

25. Crippa F, Corey L, Chuang EL, Sale G, Boeckh M. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. Clin Infect Dis 2001; 32: 214–219. [PubMed: 11170910]

26. Jeon S, Lee WK, Lee Y, Lee DG, Lee JW. Risk factors for cytomegalovirus retinitis in patients with cytomegalovirus viremia after hematopoietic stem cell transplantation. Ophthalmology 2012; 119: 1892–1898. [PubMed: 22657564]

27. Hiwarkar P, Gajdosova E, Qasim W, Worth A, Breuer J, Chiesa R et al. Frequent occurrence of cytomegalovirus retinitis during immune reconstitution warrants regular ophthalmic screening in high-risk pediatric allogeneic hematopoietic stem cell transplant recipients. Clin Infect Dis 2014; 58: 1700–1706. [PubMed: 24700657]

28. Larochelle MB, Phan R, Craddock J, Abzug MJ, Curtis D, Robinson CC et al. Cytomegalovirus Retinitis in Pediatric Stem Cell Transplants: Report of a Recent Cluster and the Development of a Screening Protocol. Am J Ophthalmol 2017; 175: 8–15. [PubMed: 27746296]

29. Chen Y, Scieux C, Garrait V, Socie G, Rocha V, Molina JM et al. Resistant herpes simplex virus type 1 infection: an emerging concern after allogeneic stem cell transplantation. Clin Infect Dis 2000; 31: 927–935. [PubMed: 11049772]

30. Koc Y, Miller KB, Schenkein DP, Griffith J, Akhtar M, DesJardin J et al. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. Biol Blood Marrow Transplant 2000; 6: 44–49. [PubMed: 10707998]

31. Walton RC, Reed KL. Herpes zoster ophthalmicus following bone marrow transplantation in children. Bone Marrow Transplant 1999; 23: 1317–1320. [PubMed: 10414922]

32. Castleton A, Kottaridis PD. A case of ‘red eye’ post allogeneic stem cell transplantation. Bone Marrow Transplant 2007; 39: 241–242. [PubMed: 17211428]

33. Donahue SP, Greven CM, Zuravleff JJ, Eller AW, Nguyen MH, Peacock JE Jr. et al. Intraocular candidiasis in patients with candidemia. Clinical implications derived from a prospective multicenter study. Ophthalmology 1994; 101: 1302–1309. [PubMed: 8035995]

34. Shah VM, Tandon R, Satpathy G, Nayak N, Chawla B, Agarwal T et al. Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. Cornea 2010; 29: 751–757. [PubMed: 20489580]

35. Kramer M, Kramer MR, Blau H, Bishara J, Axer-Siegel R, Weinberger D. Intravitreal voriconazole for the treatment of endogenous Aspergillus endophthalmitis. Ophthalmology 2006; 113: 1184–1186. [PubMed: 16713628]

36. Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M et al. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol 2013; 131: 422–429. [PubMed: 23710492]

37. Martino R, Bretagne S, Einsele H, Maertens J, Ullmann AJ, Parody R et al. Early detection of Toxoplasma infection by molecular monitoring of Toxoplasma gondii in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis 2005; 40: 67–78. [PubMed: 15614694]

38. Bosch-Driessen LH, Verbraak FD, Suttorp-Schulten MS, van Ruyven RL, Klok AM, Hoyng CB et al. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. Am J Ophthalmol 2002; 134: 34–40. [PubMed: 12095805]

39. Leen AM, Bollard CM, Mendizabal AM, Shpall EJ, Szabolcs P, Antin JH et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. Blood 2013; 121: 5113–5123. [PubMed: 23610374]

40. Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS. Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med 1981; 305: 63–67. [PubMed: 6264292]

41. Matthes-Martin S, Feuchtinger T, Shaw PJ, Engelhard D, Hirsch HH, Cordonnier C et al. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell

transplantation: summary of ECIL-4 (2011). Transpl Infect Dis 2012; 14: 555–563. [PubMed: 23146063]

42. Green W, Rao PK, Harocopos GJ. Extramedullary Relapse of Acute Myelogenous Leukemia Presenting as a Large Serous Retinal Detachment. Ocul Oncol Pathol 2017; 3: 95–100. [PubMed: 28868277]
43. Matsuo T, Tanaka T, Ichimura K, Meguri Y. Intraocular Relapse with Hypopyon and Retinal Infiltrates after Chemotherapy and Peripheral Blood Stem Cell Transplantation for Extranodal NK/T-Cell Lymphoma. J Clin Exp Hematop 2015; 55: 157–161. [PubMed: 26763364]
44. Rothova A, Ooijman F, Kerkhoff F, Van Der Lelij A, Lokhorst HM. Uveitis masquerade syndromes. Ophthalmology 2001; 108: 386–399. [PubMed: 11158819]
45. Cohen VM, Dinakaran S, Parsons MA, Rennie IG. Transvitreal fine needle aspiration biopsy: the influence of intraocular lesion size on diagnostic biopsy result. Eye (Lond) 2001; 15: 143–147. [PubMed: 11339578]
46. Hormigo A, Abrey L, Heinemann MH, DeAngelis LM. Ocular presentation of primary central nervous system lymphoma: diagnosis and treatment. Br J Haematol 2004; 126: 202–208. [PubMed: 15238140]
47. Smith JR, Rosenbaum JT, Wilson DJ, Doolittle ND, Siegal T, Neuwelt EA et al. Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology 2002; 109: 1709–1716. [PubMed: 12208721]
48. Wiegel T, Bottke D, Kreusel KM, Schmidt S, Bornfeld N, Foerster MH et al. External beam radiotherapy of choroidal metastases--final results of a prospective study of the German Cancer Society (ARO 95-08). Radiother Oncol 2002; 64: 13–18. [PubMed: 12208569]
49. Kaliki S, Shields CL, Al-Dahmash SA, Mashayekhi A, Shields JA. Photodynamic therapy for choroidal metastasis in 8 cases. Ophthalmology 2012; 119: 1218–1222. [PubMed: 22386261]
50. Gratwohl A, Gloor B, Hahn H, Speck B. Retinal cotton-wool patches in bone-marrow-transplant recipients. N Engl J Med 1983; 308: 1101. [PubMed: 6339934]
51. Hirst LW, Jabs DA, Tutschka PJ, Green WR, Santos GW. The eye in bone marrow transplantation. I. Clinical study. Arch Ophthalmol 1983; 101: 580–584. [PubMed: 6340648]
52. Bernauer W, Gratwohl A, Keller A, Daicker B. Microvasculopathy in the ocular fundus after bone marrow transplantation. Ann Intern Med 1991; 115: 925–930. [PubMed: 1952488]
53. Johnson DW, Cagnoni PJ, Schossau TM, Stemmer SM, Grayeb DE, Baron AE et al. Optic disc and retinal microvasculopathy after high-dose chemotherapy and autologous hematopoietic progenitor cell support. Bone Marrow Transplant 1999; 24: 785–792. [PubMed: 10516683]
54. Bylsma GW, Hall AJ, Szer J, West R. Atypical retinal microvasculopathy after bone marrow transplantation. Clin Exp Ophthalmol 2001; 29: 225–229. [PubMed: 11545420]
55. Westeneng AC, Hettinga Y, Lokhorst H, Verdonck L, van Dorp S, Rothova A. Ocular graft-versus-host disease after allogeneic stem cell transplantation. Cornea 2010; 29: 758–763. [PubMed: 20489577]
56. Ivanir Y, Shimoni A, Ezra-Nimni O, Barequet IS. Prevalence of dry eye syndrome after allogeneic hematopoietic stem cell transplantation. Cornea 2013; 32: e97–101. [PubMed: 23187163]
57. Aissopou EK, Papathanassiou M, Nasothimiou EG, Konstantonis GD, Tentolouris N, Theodossiadis PG et al. The Keith-Wagener-Barker and Mitchell-Wong grading systems for hypertensive retinopathy: association with target organ damage in individuals below 55 years. J Hypertens 2015; 33: 2303–2309. [PubMed: 26335430]
58. Kaushik M, Pulido JS, Schild SE, Stafford S. Risk of radiation retinopathy in patients with orbital and ocular lymphoma. Int J Radiat Oncol Biol Phys 2012; 84: 1145–1150. [PubMed: 22592046]
59. Cooper AE, Cho JH, Menges S, Masood S, Xie J, Yang J et al. Immunosuppressive Treatment Can Alter Visual Performance in the Royal College of Surgeons Rat. J Ocul Pharmacol Ther 2016; 32: 296–303. [PubMed: 27008099]
60. Avery R, Jabs DA, Wingard JR, Vogelsang G, Saral R, Santos G. Optic disc edema after bone marrow transplantation. Possible role of cyclosporine toxicity. Ophthalmology 1991; 98: 1294–1301. [PubMed: 1923369]
61. Lopez PF, Sternberg P Jr., Dabbs CK, Vogler WR, Crocker I, Kalin NS. Bone marrow transplant retinopathy. Am J Ophthalmol 1991; 112: 635–646. [PubMed: 1957898]

62. Pahl DA, Green NS, Bhatia M, Lee MT, Chang JS, Licursi M et al. Optical Coherence Tomography Angiography and Ultra-widefield Fluorescein Angiography for Early Detection of Adolescent Sickle Retinopathy. Am J Ophthalmol 2017; 183: 91–98. [PubMed: 28860042]

63. Joltikov KA, de Castro VM, Davila JR, Anand R, Khan SM, Farbman N et al. Multidimensional Functional and Structural Evaluation Reveals Neuroretinal Impairment in Early Diabetic Retinopathy. Invest Ophthalmol Vis Sci 2017; 58: BIO277–BIO290. [PubMed: 28973314]

64. Hillier RJ, Ojaimi E, Wong DT, Mak MYK, Berger AR, Kohly RP et al. Aqueous Humor Cytokine Levels and Anatomic Response to Intravitreal Ranibizumab in Diabetic Macular Edema. JAMA Ophthalmol 2018; 136: 382–388. [PubMed: 29522144]

65. Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S et al. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. Leukemia 2010; 24: 2039–2047. [PubMed: 20861916]

66. Saboo US, Amparo F, Shikari H, Dana R. Prevalence of ocular hypertension and glaucoma in patients with chronic ocular graft-versus-host disease. Graefes Arch Clin Exp Ophthalmol 2016; 254: 923–928. [PubMed: 26968719]

67. Takeda A, Shigematsu N, Suzuki S, Fujii M, Kawata T, Kawaguchi O et al. Late retinal complications of radiation therapy for nasal and paranasal malignancies: relationship between irradiated-dose area and severity. Int J Radiat Oncol Biol Phys 1999; 44: 599–605. [PubMed: 10348290]

68. Tatematsu Y, Ogawa Y, Abe T, Kamoi M, Uchino M, Saijo-Ban Y et al. Grading criteria for chronic ocular graft-versus-host disease: comparing the NIH eye score, Japanese dry eye score, and DEWS 2007 score. Sci Rep 2014; 4: 6680. [PubMed: 25338290]

69. Tripathi RC, Parapuram SK, Tripathi BJ, Zhong Y, Chalam KV. Corticosteroids and glaucoma risk. Drugs Aging 1999; 15: 439–450. [PubMed: 10641955]

70. Kwok AK, Lam DS, Ng JS, Fan DS, Chew SJ, Tso MO. Ocular-hypertensive response to topical steroids in children. Ophthalmology 1997; 104: 2112–2116. [PubMed: 9400772]

71. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. JAMA Ophthalmol 2013; 131: 724–730. [PubMed: 23579344]

72. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S, Low-Pressure Glaucoma Study G. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol 2011; 151: 671–681. [PubMed: 21257146]

73. Im L, Allingham RR, Singh I, Stinnett S, Fekrat S. A prospective study of early intraocular pressure changes after a single intravitreal triamcinolone injection. J Glaucoma 2008; 17: 128–132. [PubMed: 18344759]

74. Rubin B, Taglienti A, Rothman RF, Marcus CH, Serle JB. The effect of selective laser trabeculoplasty on intraocular pressure in patients with intravitreal steroid-induced elevated intraocular pressure. J Glaucoma 2008; 17: 287–292. [PubMed: 18552614]

75. Zhou JQ, Xu L, Wang S, Wang YX, You QS, Tu Y et al. The 10-year incidence and risk factors of retinal vein occlusion: the Beijing eye study. Ophthalmology 2013; 120: 803–808. [PubMed: 23352194]

76. Yoo YS, Na KS, Shin JA, Park YH, Lee JW. Posterior Eye Segment Complications Related to Allogeneic Hematopoietic Stem Cell Transplantation. Retina 2017; 37: 135–143. [PubMed: 27380428]

77. Campa C, Alivernini G, Bolletta E, Parodi MB, Perri P. Anti-VEGF Therapy for Retinal Vein Occlusions. Curr Drug Targets 2016; 17: 328–336. [PubMed: 26073857]

78. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology 2012; 119: 2587–2591. [PubMed: 22902212]

79. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology 2012; 119: 802–809. [PubMed: 22301066]

80. Haller JA, Bandello F, Belfort R Jr., Blumenkranz MS, Gillies M, Heier J et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein

occlusion twelve-month study results. Ophthalmology 2011; 118: 2453–2460. [PubMed: 21764136]

81. Pikkel YY, Sharabi-Nov A, Beiran I, Pikkel J. Comparison of anti-vascular endothelial growth factors, laser treatments and a combination of the both for treatment of central retinal vein occlusion. Int J Ophthalmol 2016; 9: 431–433. [PubMed: 27158615]
82. Eid AJ, Bakri SJ, Kijpittayarit S, Razonable RR. Clinical features and outcomes of cytomegalovirus retinitis after transplantation. Transpl Infect Dis 2008; 10: 13–18. [PubMed: 17511815]
83. Peng KL, Chen SJ, Lin PY, Hsu WM, Yang MH, Tzeng CH et al. Exudative bullous retinal detachment after peripheral blood stem cell transplantation. Eye (Lond) 2005; 19: 603–606. [PubMed: 15332110]
84. Wiznia RA, Rose A, Levy AL. Occlusive microvascular retinopathy with optic disc and retinal neovascularization in acute lymphocytic leukemia. Retina 1994; 14: 253–255. [PubMed: 7973121]
85. Alloin AL, Barlogis V, Auquier P, Contet A, Poiree M, Demeocq F et al. Prevalence and risk factors of cataract after chemotherapy with or without central nervous system irradiation for childhood acute lymphoblastic leukaemia: an LEA study. Br J Haematol 2014; 164: 94–100. [PubMed: 24116693]
86. Abud TB, Amparo F, Saboo US, Di Zazzo A, Dohlman TH, Ciolino JB et al. A Clinical Trial Comparing the Safety and Efficacy of Topical Tacrolimus versus Methylprednisolone in Ocular Graft-versus-Host Disease. Ophthalmology 2016; 123: 1449–1457. [PubMed: 27086024]
87. Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. Cornea 2009; 28: 1091–1096. [PubMed: 19770713]
88. Dietrich-Ntoukas T, Cursiefen C, Westekemper H, Eberwein P, Reinhard T, Bertz H et al. Diagnosis and treatment of ocular chronic graft-versus-host disease: report from the German-Austrian-Swiss Consensus Conference on Clinical Practice in chronic GVHD. Cornea 2012; 31: 299–310. [PubMed: 22157574]
89. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents : pharmacokinetics, safety and efficacy. Drugs 2004; 64: 1997–2020. [PubMed: 15341494]
90. Slattery A, Liebelt E, Gaines LA. Common ocular effects reported to a poison control center after systemic absorption of drugs in therapeutic and toxic doses. Curr Opin Ophthalmol 2014; 25: 519–523. [PubMed: 25226509]
91. Santaella RM, Fraunfelder FW. Ocular adverse effects associated with systemic medications : recognition and management. Drugs 2007; 67: 75–93. [PubMed: 17209665]
92. Jaanus SD. Ocular side effects of selected systemic drugs. Optom Clin 1992; 2: 73–96. [PubMed: 1363080]
93. Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. CNS Drugs 2010; 24: 501–526. [PubMed: 20443647]
94. Li J, Tripathi RC, Tripathi BJ. Drug-induced ocular disorders. Drug Saf 2008; 31: 127–141. [PubMed: 18217789]
95. Laties AM, Fraunfelder FT. Ocular safety of Viagra, (sildenafil citrate). Trans Am Ophthalmol Soc 1999; 97: 115–125; discussion 125-118. [PubMed: 10703120]
96. Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. Drug Saf 2002; 25: 233–250. [PubMed: 11994027]
97. Mynarek M, Ganzenmueller T, Mueller-Heine A, Mielke C, Gonnermann A, Beier R et al. Patient, virus, and treatment-related risk factors in pediatric adenovirus infection after stem cell transplantation: results of a routine monitoring program. Biol Blood Marrow Transplant 2014; 20: 250–256. [PubMed: 24269896]
98. Lass JH, Lazarus HM, Reed MD, Herzig RH. Topical corticosteroid therapy for corneal toxicity from systemically administered cytarabine. Am J Ophthalmol 1982; 94: 617–621. [PubMed: 6756155]
99. Fraunfelder FW, Solomon J, Druker BJ, Esmaeli B, Kuyl J. Ocular side-effects associated with imatinib mesylate (Gleevec). J Ocul Pharmacol Ther 2003; 19: 371–375. [PubMed: 12964961]

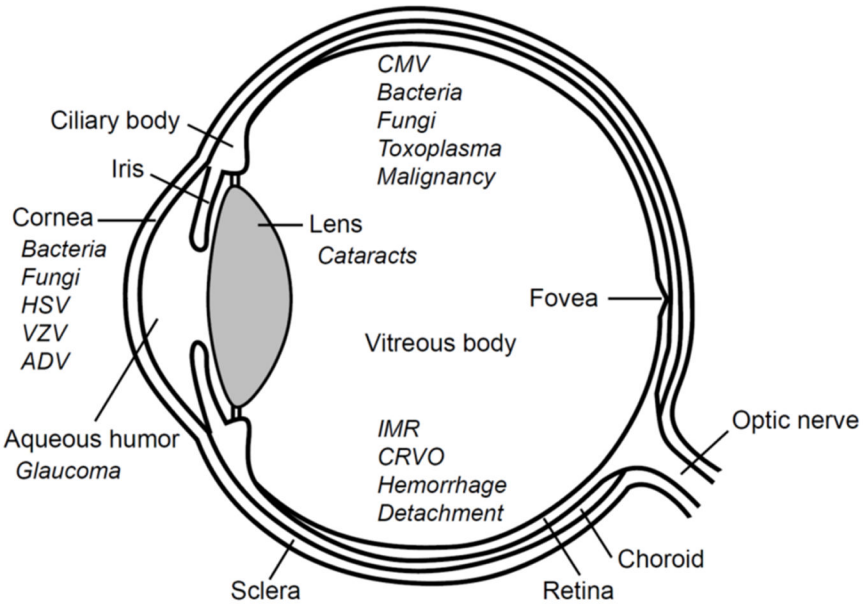

Figure 1.
Structures of the eye

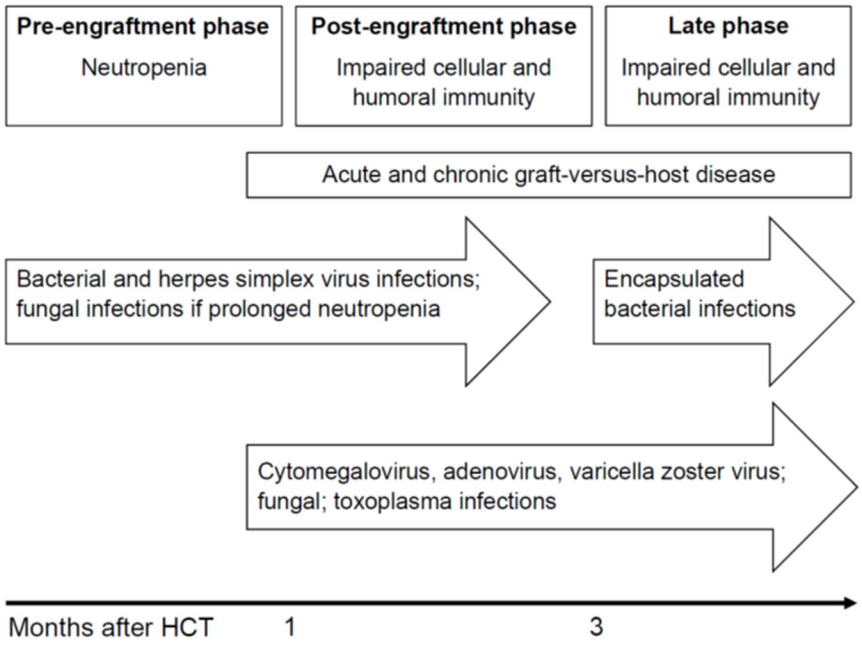

Figure 2.
Ocular infections after allogeneic hematopoietic cell transplantation

Table 1.

Evidence-based rating system used in this review

Category	Definition
Strength of the Recommendation:	
A	Should always be offered.
B	Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against, or evidence for efficacy might not outweigh adverse consequences, or cost of the approach. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Quality of Evidence Supporting the Recommendation:	
I	Evidence from at least one properly randomized, controlled trial.
II	Evidence for at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from more than one center) or from multiple time-series or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive.

Table 2.

Involved structures, symptoms and diagnostic tests of ocular infections following HCT

Organism	Involved structures	Symptoms and clinical findings	Diagnostic tests
Bacteria[21] *Staphylococci, Haemophilus, Streptococci, Pseudomonas, and others*	Lids, conjunctiva, cornea, intraocular	Pain or irritation, erythema, discharge, photophobia, impaired vision	Conjunctival culture, culture of corneal scrapings or vitreal fluid
Fungi[21]	Cornea, intraocular	Pain, erythema, photophobia, excessive tearing or discharge, blurred vision, vision loss	Corneal infiltrates with feathery edges, culture of corneal scrapings or vitreal fluid
Toxoplasma[23,24]	Retina	Pain, photophobia, scotoma, blurred vision, vision loss	Raised, yellow/white, cottony retinal lesions in a non-vascular distribution and vitreal inflammation, serum PCR or serology, PCR of aqueous humor, vitreal fluid and tissue
Virus			
Cytomegalovirus[25-28]	Retina	May be asymptomatic early, visual loss, floaters, progressive visual loss	Dilated pupil examination showing cream-colored lesions with hemorrhage and perivascular cuffing of retinal vessels, PCR of vitreous fluid
Herpes simplex virus[29] Varicella zoster virus[30,31]	Conjunctiva, cornea	May be asymptomatic, periorbital pain or rash, conjunctival erythema, blurred vision, vision loss	Swelling and cloudiness of cornea on ophthalmologic exam, PCR, DFA from base of skin lesion scrapings, viral culture
Adenovirus[32,41,97]	Conjunctiva, cornea	Erythema, chemosis, discharge	Culture, PCR

PCR, polymerase chain reaction; DFA, direct fluorescent assay.

Table 3.

Medications with ocular toxicities

Drug	Ocular toxicity	Frequency	Management and prevention recommendation	Strength
Cytosine arabinoside	Keratoconjunctivitis[98]	Common	Prophylactic glucocorticoid eye drops,[98] 2-deoxycytidine eye drops applied prior to therapy[98]	A-II
	Ocular pain, tearing, foreign body sensation, photophobia, epiphora, blurred vision with evidence of bilateral conjunctival hyperemia and fine corneal punctate opacities[98]	Occasional	Eye washing with physiologic saline, 0.1% sodium betamethasone eye drops applied prior to therapy	B-III
Imatinib	Peri-orbital edema, sometimes leading to visual obstruction[99]	Common	Warm compress	A-III
Corticosteroids (systemic)	Cataracts,[13,14,85] increased IOP, glaucoma[66,68,69]	Common	Limit use	A-III
			Screening for cataracts and glaucoma	C-III
Corticosteroids (topical)	Increased IOP, glaucomatous optic atrophy, visual field defects, cataracts, infectious keratitis	Occasional to rare	Monitor IOP within 1 month of initiating treatment, restrict extended use of high potency steroids	A-III
			Regular screening for cataracts, surgery as needed[18]	B-III
			Discontinue steroids,[66] topical aqueous humor suppressants,[71,72] trabeculectomy[73]	A-I
Cyclosporine (systemic)	Microvascular retinopathy[60]	Rare	Improve with drug discontinuation[60]	A-II
Cyclosporine (topical)	Redness, stinging, burning	Occasional	Lubricating drops,[88] chill bottle[87] before instilling cyclosporine	A-II
Tacrolimus (topical)	Burning sensation	Common	Symptoms typically improve in 1 month after drug discontinuation.[86]	A-II
Phenothiazines (chlorpromazine, thioridazine)	Abnormal pigmentation of the eyelids, interpalpebral conjunctiva and cornea with long-term use[94]	Common	Improve with drug discontinuation	B-III
	Decreased accommodation and deposits in the lens	Common	Topical cholinergic agent (pilocarpine)	B-III
Tricyclic antidepressants (amitriptyline)	Mydriasis, cycloplegia, blurred vision, presbyopia, mild and transient visual disturbances[93]	Common	Improve with time as tolerance develops.[93] Topical cholinergic agents (bethanechol or pilocarpine)	B-II
	Decreased lacrimation, dry eyes, glaucoma attacks (anticholinergic)	Rare to common	Artificial tears, avoid in patients with narrow angles[93]	B-II
Selective serotonin reuptake inhibitors (sertraline, paroxetine, fluoxetine, citalopram)	Mydriasis, reduced accommodation, increased IOP, glaucoma,[93] blurred vision	Common	Improve with drug discontinuation	B-III
Antihistamines (chlorpheniramine, meclizine, promethazine, diphenhydramine)	Mydriasis (anticholinergic)[90], dry eyes, decreased accommodation	Common	Transient, reversible	B-III
	Angle closure glaucoma (anticholinergic)	Rare	Avoid in patients with angle closure glaucoma	B-III

Drug	Ocular toxicity	Frequency	Management and prevention recommendation	Strength
Scopolamine patch	Anisocoria, mydriasis, dry eyes[92]	Common	Avoid rubbing eyes with fingers after application of the patch[92]	A-II
Voriconazole	Blurred vision, changes in visual acuity, color perception, photophobia, visual hallucinations[89]	Common	Consider alternative drugs	A-III
Erectile dysfunction drugs (e.g., sildenafil)	Blue vision[95]	Common	Improve with drug discontinuation	B-II
Non-steroidal anti-inflammatory drugs (topical)	Redness, stinging, corneal epithelial toxicity, stromal necrosis (corneal melts) especially in dry eyes	Occasional	Limit use for dry eye or GVHD, drug discontinuation[96]	B-II

IOP, intraocular pressure; GVHD, graft-versus-host disease.

Table 4.

Incidence, risk factor, screening and prevention recommendations of non-GVHD ocular complications after HCT

Complication	Incidence	Risk factor	Prevention and screening recommendation (strength)
Cataracts	11%-100% in adults,[5,6] 4%-76% in children[7,8]	TBI (particularly single dose or dose rate>0.04 Gy/min),[9,10] corticosteroids,[13-15] allogeneic HCT[10]	Hyper-fractionated TBI instead of single-dose TBI[9] (A-I), non-TBI conditioning[12] (B-II), lens shielding[11] (C-II)
Bacterial infection	<2%[21]	Neutropenia,[21] impaired humoral immunity[21]	By clinical presentation (A-II)
Fungal infection	<2%[21,22]	Fungemia[33], immunosuppression[33]	By clinical presentation or fungemia[33] (A-III)
Toxoplasma infection	0.3-0.5%[23,24]	Pre-HCT infection,[23] impaired cellular immunity[23]	Pre-HCT screening examination for retina scar and serologic testing[37] (B-III), by clinical presentation
Viral infection			
Cytomegalovirus (CMV)	Retinitis <1%-5% in all HCT patients, 5%-23% in patients with CMV viremia[25-28]	Positive serostatus,[25] viremia pre-HCT,[27] reactivation by day +100,[25] high peak DNA levels,[26] delayed lymphocyte engraftment,[25] chronic GVHD,[25,27] HLA mismatching,[26,27] unrelated donor[26]	Screening fundiscopic examination in patients at risk every 6-8 weeks (B-III)
Herpes simplex virus (HSV), Varicella zoster virus (VZV)	Rare,[29,31] 2% of VZV infection[30]	Extensive chronic GVHD[30]	By clinical presentation (A-III), prophylactic acyclovir[40] (A-I)
Adenovirus	Rare	No data	PCR surveillance for systemic reactivation in high risk patients (B-III)
Involvement with malignancy	Rare	No data	Evaluation of ocular involvement in patients with relapsed primary disease and ocular symptoms[42,43] (C-III), and in asymptomatic high-risk patients (previous ocular involvement, new malignancy involving central nervous system)[44] (C-III)
Ischemic microvascular retinopathy	0-10%[21,22,51-56]	TBI, [22,52,54] cyclosporine,[22,52] conditioning regimens including busulfan or carmustine[53,54]	Avoid radiation to ocular areas, monitor levels of calcineurin inhibitors (B-III)
Glaucoma	0.4-1.7%[65,66]	Irradiation,[67] topical or systemic corticosteroids[66,68,69]	Monitor intraocular pressure in patients with risk factors (A-II)
Central retinal vein occlusion	Rare	Hypertension, hyperlipidemia, diabetes mellitus, hypercoagulability, hyperviscosity	Funduscopic testing if visual acuity impairment (A-III)
Retinal hemorrhage	3.2%[76]	Cytopenia, particularly thrombocytopenia	Funduscopic testing if visual acuity impairment (A-III)
Retinal detachment	<1%.[22,76]	CMV retinitis[76]	Funduscopic testing if visual acuity impairment (A-III)

TBI, total body irradiation; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease.

Table 5.

Treatment recommendations of non-GVHD ocular complications after HCT

Complication	Treatment recommendation	Strength
Cataracts	Surgery[17]	A-II
Bacterial infection	Antibiotic eye drops,[34] oral or intravenous antibiotic agents, intravitreal injections	A-I
Fungal infection	Antifungal eye drops,[36] oral or intravenous antifungal agents, intravitreal injections[35]	A-I
Toxoplasma infection	Trimethoprim-sulfamethoxazole-pyrimethamine, clindamycin, atovaquone, azithromycin[38]	A-I
Viral infection		
Cytomegalovirus	Intravenous ganciclovir, oral valganciclovir, intravenous foscarnet[28]	A-II
	Intravitreal ganciclovir or foscarnet for resistant infections[28]	B-II
	Virus-specific T-cell infusion[39]	C-II
Herpes simplex virus	Oral acyclovir/valacyclovir/famciclovir, intravenous acyclovir	A-II
Varicella zoster virus	Oral acyclovir/valacyclovir/famciclovir, intravenous acyclovir for opthalmicus	A-II
Adenovirus	Decrease immunosuppression, intravenous cidofovir[41]	A-II
Involvement with malignancy	Intravitreal chemotherapy, radiation therapy, photodynamic laser therapy, disease-specific interventions based on site and histology of neoplasm[47-49]	C-III
Ischemic microvascular retinopathy	Reduction or withdrawal of calcineurin inhibitors,[60] treatment for hypertension, GVHD and transplant-associated microangiopathy	B-III
Glaucoma	Discontinue steroids,[66] topical aqueous humor suppressants,[71,72] trabeculectomy[73]	A-I
Central retinal vein occlusion	Intravitreal anti-VEGF injections[78,79]	A-I
	Intravitreal glucocorticoids[80]	B-I
	Macular grid and panretinal laser photocoagulation[81]	C-II
Retinal hemorrhage	Maintain the platelet count over 50,000/μl	B-III
Retinal detachment	Photocoagulation, cryotherapy and surgical techniques	B-III

VEGF, vascular endothelial growth factor.