Chronic graft-*versus*-host-disease

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ABSTRACT

Chronic GvHD is a major cause of non-relapse morbidity and mortality after hematopoietic cell transplantation. Its incidence has increased due to more frequent use of unrelated and/or mismatched donors, reduced intensity conditioning regimens or intensified regimens and PBSC grafts. The first-line therapy for chronic GvHD is systemic corticosteroids associated with either CNI or sirolimus, as a steroid sparing agent. Since children are more susceptible to the long-term steroid side effects, development of steroid-free strategies for front-line therapy is crucial. Sirolimus seems to be an interesting choice due to its capacity of inhibiting T-cells preserving the Tregs cells and antifibrotic, antineoplastic and antiviral activities. FAM regimen (Fluticasone, Azitromycin and Montelucaste) is recommended in combination with systemic steroids for initial treatment of bronchiolitis obliterans. For steroid-refractory chronic GvHD, ruxolitinib is the standard of care, while extracorporeal photopheresis can be combined for better results, however treatment costs are limitations. Extracorporeal photopheresis, treatment that preserves graft-versus-leukemia effect due to its steroid sparing and immunomodulatory actions, and mesenchymal stem cells, another non-pharmacological strategy that can be combined with the options mentioned above in severe chronic GvHD. Since access to novel drugs and extracorporeal photopheresis or mesenchymal stem cells is tough, other options approved for the third line and beyond are ibrutinib, belumosudil and axatilimab. Conventional agents could be used such as imatinib, low dose-MTX, rituximab, however the expected response rates are lower. We reviewed clinical studies and published recommendations on pediatric chronic GVHD that were presented in debate rounds with GvHD experts of the Pediatric group of the Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea (SBTMO). The goal of this consensus is to standardize the prophylaxis, diagnosis, grading and treatment of chronic GvHD among Brazilian pediatric HCT centers, to improve post-transplant outcomes.

Keywords: Hematopoietic Cell Transplantation. Chronic Graft-*Versus*-Host-Disease. Risk Factors. Prophylaxis. Management.

INTRODUCTION

The incidence of pediatric chronic graft-*versus*-host disease (cGvHD) is variable (ranging from 6 to 65%), being higher for patients with risk factors such as: age ≥ 12, prior grade II–IV aGvHD, malignancies as indication, peripheral blood stem cell (PBSC) or mismatched donor transplants, reduced graft-*versus*-host disease (GvHD) prophylaxis (including off target calcineurin inhibitor blood level), older donor age (> 5), female donor for male recipient, and dysfunctional B-cell reconstitution post-transplant[1].

PATHOGENESIS

The cGvHD pathogenesis comprises three simultaneous phases:

- inflammatory: cytokines release recruit more immune cells to injury site;
- immune deregulation: inflammatory response, amplified by immune cells, damages tissues, leading to release of danger signals that perpetuates immune response stimulation;
- fibrotic/chronic inflammation phase: irreversible tissue fibrosis, organ function impairment and long-term damage.

To understand different involvement of disease phases, it is crucial to optimize treatment selection steps[2].

CLASSIFICATION

- Overlap: cGvHD manifestations concomitant with acute GvHD features;
- Classic: cGvHD manifestations meeting National Institutes of Health (NIH) 2014 diagnostic criteria: skin, nails, scalp and body hair; mouth; eyes; genitalia; esophagus; lungs; muscles and fascia.
  - De novo: cGvHD manifestations with no prior acute GvHD;
  - Quiescent: prior acute GvHD with complete response;
  - Progressive: prior active acute GvHD with progression to cGvHD.

DIAGNOSTIC CRITERIA: NATIONAL INSTITUTES OF HEALTH 2014

The diagnosis of cGvHD can be made solely based on diagnostic clinical signs and symptoms or in combination with laboratory, imaging, or anatomical-pathological tests.

- Diagnostic: sufficient to diagnose cGvHD, do not need confirmatory biopsy.
  - Skin: poikiloderma, lichen planus-like eruption, deep sclerotic features, morphea-like superficial sclerotic features, or lichen sclerosus-like lesions;
  - Mouth: lichen planus-like changes;
  - Gastrointestinal tract: esophageal web, stricture, or concentric rings documented by endoscopy or barium contrast radiograph;
  - Genitalia: lichen planus-like, lichen sclerosus-like. Female: vaginal scarring or stenosis; clitoral or labial agglutination. Male: phimosis; urethral scarring or stenosis;
  - Lung: bronchiolitis obliterans syndrome (BOS) using pulmonary functions testing (PFT);
  - Muscle, fascia, joints: fasciitis; joints stiffness or contractures due to sclerosis.
- Distinctive: manifestations that by themselves are insufficient to diagnose cGvHD and require anatomical-pathological confirmation;

- Other: rare, controversial, or nonspecific characteristics that cannot be used alone to establish the diagnosis of cGvHD. Only be considered signs of cGvHD if the diagnosis is confirmed in another organ;
- Common: manifestations present in both acute and chronic GvHD.

The working group recommends that the diagnosis of cGvHD requires at least:

- One diagnostic manifestation of cGvHD;
- One distinctive manifestation plus a pertinent biopsy, laboratory;
- Other tests (e.g. PFTs, Schirmer's test), evaluation by a specialist (ophthalmologist, gynecologist);
- Radiographic imaging showing cGvHD in the same or another organ, unless stated otherwise[3].

HISTOPATHOLOGIC DIAGNOSIS

- Non-sclerotic cGvHD: apoptosis in the basilar layer, changes in the vacuoles, lichenoid inflammation with acanthosis and satellite lymphocytes;
- Lichen sclerosus: sclerosis of papillary dermal collagen with overlying interface changes including melanophages in the papillary dermis and sparse lymphocytic infiltrate;
- Lichen planus: combination of epidermal orthohyperkeratosis, hypergranulosis and acanthosis resembling lichen planus ± lichenoid inflammation and/or vacuolar changes of eccrine units[4] (Table 1).

Table 1. Differential diagnosis.

Organ	Differential diagnosis
Skin and appendages	Drug eruptions, allergic reactions, infections (*e.g.*, viruses, tinea corporis, secondary syphilis), neoplastic diseases (*e.g.*, mycosis fungoides), rheumatologic diseases (*e.g.*, scleroderma)[5]
Mouth	Candidiasis, herpes infection, drug reactions, mucosal trauma, neoplasms, drug-induced salivary dysfunction, vitamin deficiencies (A, B, C)[6]
Eyes	Post-radiation xerophthalmia, vitamin-A deficiency, infections (*e.g.*, CMV, herpes, toxoplasmosis), allergies, medications, autoimmune diseases (*e.g.*, Sjögren's syndrome)[7]
Liver	Viral hepatitis (HBV, HSV, ADV, VZV, HCV, EBV, CMV), drugs (azole antifungals, TKI, cyclosporine, tacrolimus, methotrexate), late-onset VOD, sepsis-related cholestasis, biliary lithiasis, iron overload, neoplastic infiltration (*e.g.*, lymphoma, PTLD)[8]
Genital	Viral hepatitis (HBV, HSV, ADV, VZV, HCV, EBV, CMV), drugs (azole antifungals, TKI, cyclosporine, tacrolimus, methotrexate), late-onset VOD, sepsis-related cholestasis, biliary lithiasis, iron overload, neoplastic infiltration (*e.g.*, lymphoma, PTLD)[9]
Lungs	Infections, idiopathic pneumonia, COP, pulmonary hypertension[10]
Gastrointestinal tract	Esophagitis (drug-induced, infectious), infections (*e.g.*, CMV, HSV, *Clostridium*, *Helicobacter pylori*, ADV, intestinal parasites), drug reactions, inflammatory bowel disease, malignant disorders (*e.g.*, PTLD)[11]
Muscles	Myositis (drug-induced, infectious, inflammatory)[12]

CMV: cytomegalovirus; HBV: hepatitis B virus; HSV: herpes virus; ADV: adenovirus; VZV: Varicella zoster virus; HCV: hepatitis C virus; EBV: Epstein-baar virus; TKI: tyrosine kinase inhibitor; VOD: veno-occlusive disease; PTLD: lymphoproliferative disease; COP: cryptogenic organizing pneumonia. Source: Elaborated by the authors.

ATYPICAL MANIFESTATIONS

Alloreactive and autoimmune responses after hematopoietic cell transplantation can occur in tissues and organ systems non-classical for cGvHD or manifest in atypical ways in classical organs commonly affected by GvHD[13]. They represent 25% of all cGvHD cases, but only 2.2% present without classic manifestations. The most frequent ones are immune-mediated cytopenias (24.5%), renal cGvHD (13.7%), and serositis (13.7%). Several risk factors were proposed such as prior aGvHD, total body irradiation (TBI), and donor lymphocyte infusion (DLI), while gender and human leukocyte antigen (HLA) mismatches were less relevant than in classic cGvHD[14,15] (Table 2).

Table 2. Atypical manifestations.

1. Immune-mediated cytopenias	Immune-mediated neutropenia Hemolytic anemia Immune-mediated thrombocytopenia Evans syndrome Thrombotic microangiopathy
2. Gastrointestinal	Immune-mediated pancreatitis
3. Pulmonary	Organizing pneumonia Non-specific interstitial pneumonia Pulmonary fibroelastosis
4. Endocrine	Thyroiditis-Hashimoto's disease Thyroiditis- Grave's disease
5. Central nervous system	Neurocognitive deficits Meningoencephalitis Multiple sclerosis-like encephalitis Central nervous system vasculitis-like disorders
6. Peripheral nervous system	Chronic inflammatory polyneuropathy Guillain-Barre syndrome Small fiber polyneuropathy Myasthenia gravis Other peripheral neuropathies
7. Renal	Nephrotic proteinuria Renal thrombotic microangiopathy Glomerulonephritis and tubulointerstitial damage
8. Muscles, fascia, joints	Edema Muscle cramps Arthralgia Arthritis Myositis
9. Others	Cardiac conduction Cardiomyopathy/myocarditis Vasculitis Serositis Raynaud's phenomenon

Source: Adapted and modified from Kim DDH et al.[15].

NATIONAL INSTITUTES OF HEALTH CONSENSUS DIAGNOSIS CRITERIA FOR CHRONIC GRAFT-*VERSUS*-HOST-DISEASE

Eight organs or sites (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joint and fascia, and genital tract) are considered for calculating global score (Table 3).

Table 3. National Institutes of Health 2014: National Institutes of Health global severity of chronic graft-*versus*-host-disease.

	Criteria
Mild	One or two organs involved with no more than score 1 plus Lung score 0
Moderate	Three or more organs involved with no more than score 1 OR At least one organ (not lung) with a score of 2 OR Lung score 1
Severe	At least one organ with a score of 3 OR Lung score of 2 or 3

Source: adapted from Jagasia et al.[3].

QR code and link to access the National Institutes of Health-based chronic graft-*versus*-host-disease classification form: https://drive.google.com/file/d/1k93nBLVpP3jVbBb38DwD4_URNcISbmad/view?usp=sharing.

FIRST-LINE TREATMENT

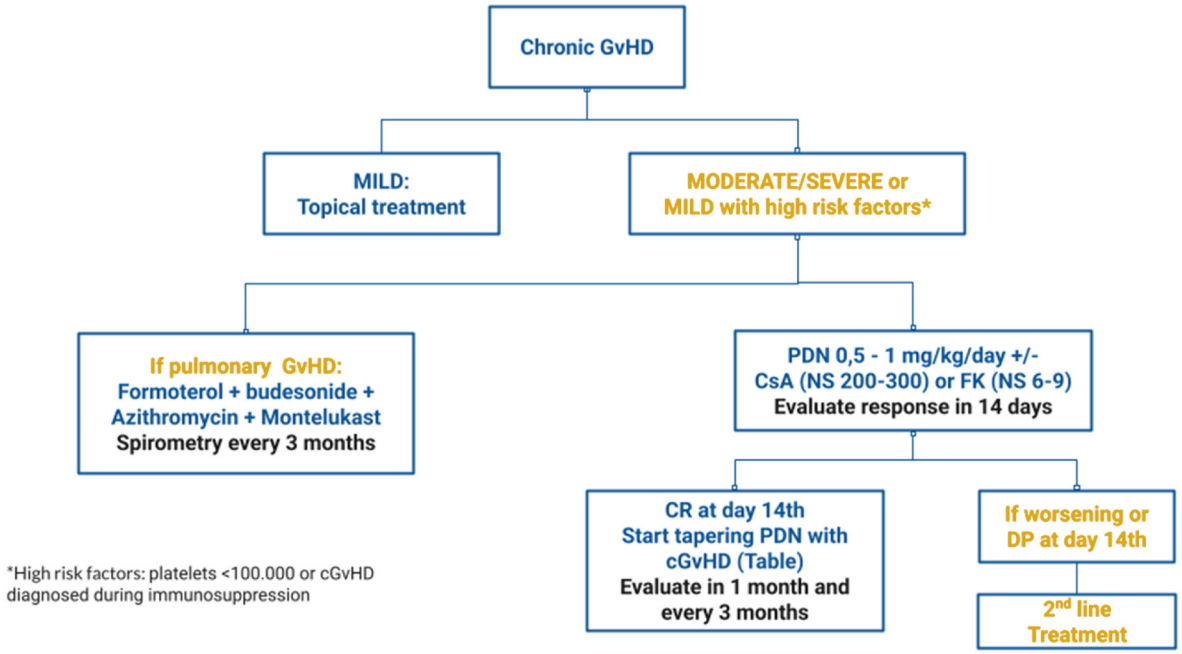
Steroids (1a-A)

- Indication: For the past 40 years, corticosteroids have remained the standard first-line treatment for moderate and severe cGvHD, while mild cGvHD is generally treated with topical treatment. In addition, mild cGvHD by the NIH criteria can be an indication for systemic treatment if prespecified high-risk features such as progressive onset or low platelet count are present (< 100,000 u/dL). None of the previous randomized trials has shown improved response rates by adding another agent to glucocorticoids for initial treatment of chronic GvHD, except calcineurin inhibitor (CNI) or sirolimus that can be worth considering as sparing steroid agents[16].
- Posology: methylprednisolone (MP) or prednisolone (PDN) 0.5–1 mg/kg/day. Systemic, treatment is usually prolonged (~one year). Remember to start osteoporosis prophylaxis.
- Expected response: The response rate is about 50% over two to three years, with greater than half of the patients requiring second-line therapy within 2 years[16].
  - Steroid-refractory: If manifestations progress while on PDN ≥ 1 mg/kg/day for one or two weeks or remain stable cGvHD while on PDN at 0.5 mg/kg/day (or 1 mg/kg every other day) for at least four weeks;
  - Steroid-dependence: If PDN > 0.25 mg/kg/day (or > 0.5 mg/kg every other day) is needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least two occasions, separated by at least eight weeks (Table 4; Fig. 1).

Table 4. Response definitions.

Response	Definition
Complete response	Resolution of all manifestations in each organ or site. The skin, mouth, liver, upper and lower gastrointestinal tract, esophagus, lung, eye, and joint/fascia are considered to evaluate response.
Partial response	Improvement in at least one organ or site without progression in any other organ or site.
Disease progression	For skin, eye, esophagus, upper and lower gastrointestinal tract: worsening of one point or more in a 0–3 scale. For joint/fascia: worsening of one point or more in a 0–7 scale (wrist, elbow or shoulder) or in 0–4 scale (ankle). For liver: increase of two or more times the upper limit of normal for the assay for alanine transaminase, alkaline phosphatase, or total bilirubin. For lung: absolute worsening of forced expiratory volume in 1 second by 10% predicted or more.
Mixed response	Defined as complete or partial response in at least one organ accompanied by progression in another organ.

Source: Adapted from Kim DDH et al. [15].



GvHD: graft-*versus*-host-disease; cGvHD: chronic graft-*versus*-host-disease; PDN: prednisolone; CsA: cyclosporine; FK: tacrolimus; CR: complete response; DP: disease progression. Source: Elaborated by the authors.

Figure 1. Algorithm first line treatment.

Adjuvant cutaneous treatment

The goals for adequate support are: control of itching and pain; prevention of changes in joint mobility; and topical treatment of erosions, ulcerations, and superinfection[17–19].

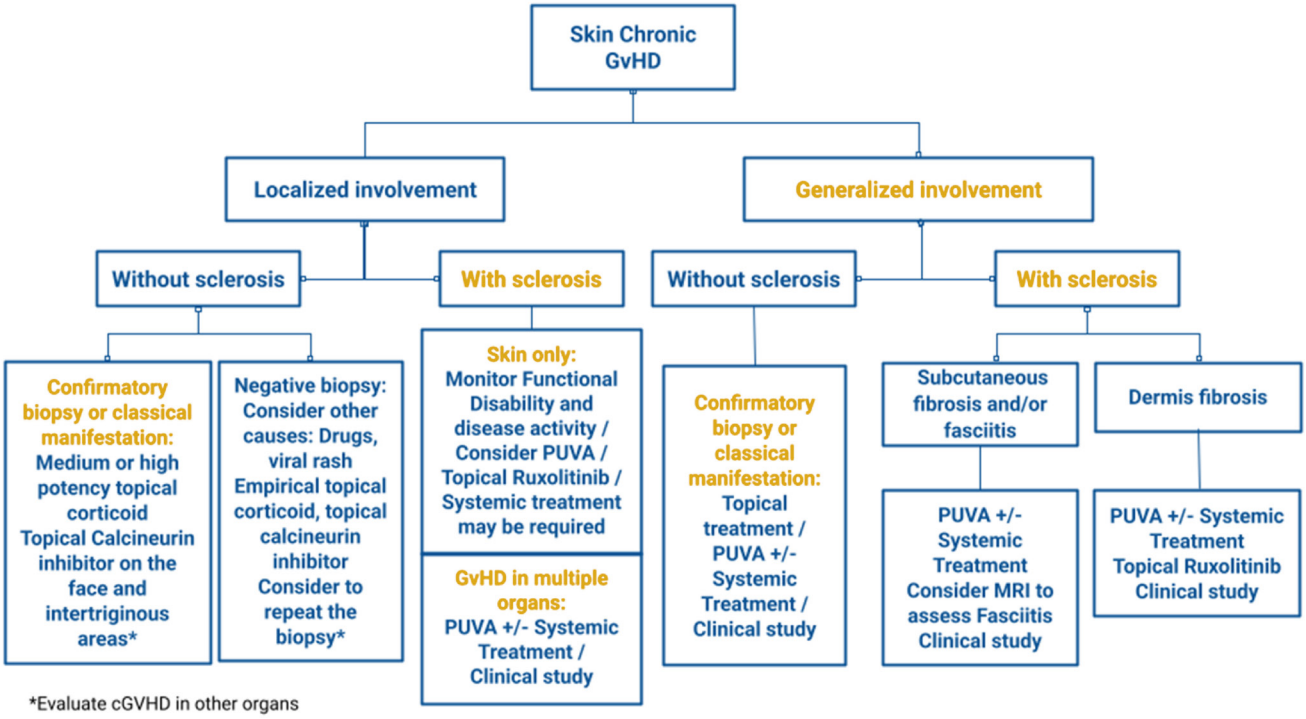
INTACT SKIN

- Topical corticosteroids or CNI (see scheme in aGvHD chapter): for isolated mild skin disease and select moderate GvHD cases, when graft-*versus*-leukemia (GvL) effect is prioritized and/or immunosuppression cannot be tolerated. Also used for symptomatic relief and faster tapering of immunosuppression[20];
- Topical ruxolitinib 1.5%: GvHD global and lesions severity improvement in a randomized trial[21];
- Dupilumab: inhibits interleukin (IL)-4 / IL-13 signaling seems to have greater efficacy than conventional steroid-sparing agents for atopic dermatitis-like[22];
- Sun protection: essential to prevent cGvHD, since ultraviolet radiation induce or exacerbate cutaneous GvHD[21,23,24];
- Prevent photosensitivity: avoid sun exposure and the combination of photosensitizing agents, such as: trimethoprim/sulfamethoxazole, sirolimus, and voriconazole[24,25].
- Non-intact skin: skin infections demand microbiological cultures. In the naked area, topical antimicrobials (mupirocin and fusidic acid), products containing 1% silver sulfadiazine, alginate hydrogel and protective films based on petrolatum can be used to improve healing. Recalcitrant wounds should be conducted by plastic surgeon and dermatologist and may need hyperbaric oxygen therapy and products with hyaluronic acid, collagen, fibroblasts or keratinocytes. Compressive therapy may be indicated in wounds with surrounding edema[26].

Ultraviolet radiation therapy (2b-C)

Phototherapy is a useful therapy to avoid additional immunosuppression or for mild cGvHD. Subtypes: psoralen + ultraviolet A (PUVA), with 320–400 nm spectrum; ultraviolet A1 (340–400 nm) and narrow-band ultraviolet

B (311–313 nm), according to the light wavelength utilized and in the depth of cutaneous penetration[27–29]. PUVA is recommended for dermal lesions, mainly sclerosis, while narrow-band ultraviolet B for children, low skin phototypes, vitiligo, lichen planus-like, follicular keratosis, localized morphea and its use is increasing for scleroderma[30,31]. Narrow-band ultraviolet B phototherapy reduces the risk of long-term carcinogenesis, photoaging and phototoxic reactions to drugs[32] (Fig. 2).



PUVA: psoralen + ultraviolet A. Source: Elaborated by the authors.

Figure 2. Algorithm for therapeutic treatment of cutaneous graft-*versus*-host-disease (GvHD).

SECOND-LINE TREATMENT

Second-line therapy should include agents with high efficacy and good safety profile. European Society for Blood and Marrow Transplantation (EBMT) consensus recommends ruxolitinib as standard care for steroid-refractory GvHD. In acute lymphoblastic leukemia patients, it is crucial to spare the GvL effect, which can be achieved with extracorporeal fotoferesesis, since it preserves the antiviral immune response and anti-leukemic effect. Tyrosine kinase inhibitors also enhance the antileukemic effect and are very effective in steroid-refractory cGvHD, but high incidence of infectious complications must be considered. When choosing second and later lines of therapy, it must be considered that some agents are more effective for specific affected sites, for instance: imatinib and rituximab for skin, musculoskeletal and lungs; sirolimus and mycophenolate mofetil for gastrointestinal tract and skin; methotrexate for musculoskeletal/joints and liver; and ibrutinib and belumosudil for fibrotic manifestation (Table 5).

Extracorporeal fotoferesesis (1b-A)

Advantages: immunomodulatory treatment; reported incidence of infectious and adverse events in cGvHD was lower on extracorporeal fotoferesesis (ECP) compared with pharmaceutical management, because it preserves the antiviral and anti-leukemic effects[68].

Continuation.

Table 5. Main treatment second-line therapy or beyond options for steroid-refractory chronic graft-*versus*-host-disease (cGvHD).

Therapy	Type	Recommendation	Overall response and overall survival	Toxicities	Study type
Ruxolitinib	Janus kinase 1/2 inhibitor	≥ Second line	Best overall response = 76% (complete response = 12%; partial response = 64%) in 165 patients with steroid-refractory cGvHD[2]; 85% (complete response = 7%; partial response = 78%) in 41 patients with steroid-refractory cGvHD[35–37] Overall survival: 97% at six months[34]	Viral reactivation/infection, peripheral neuropathy; anemia, thrombocytopenia and neutropenia[34,37], viral reactivation, cytopenia, and malignancy relapse[36]	Phase 3 randomized trial
Ibrutinib	Bruton's tyrosine kinase inhibitor	≥ Third line	Best overall response = 67% (complete response = 21%; partial response = 45%) in 42 patients with cGvHD with median follow up of 13,9 months[38] Overall survival: 71% at two years in cGvHD[39]	Pneumonia and impaired platelet function[40]	Phase 2a trial
Extracorporeal photopheresis	Ultraviolet A treatment of mononucleated blood cells via leukapheresis	≥ Second line	Best responses in skin, mouth, liver and bronchiolitis obliterans[41,42] 67% (complete response = 23%; partial response = 44%) in 48 patients with steroid-refractory cGvHD[42] Overall survival: 53–78% at one year[42–45]	Vascular access complications[40]	Phase 2 randomized trial
Mycophenolate mofetil	Antimetabolite immunosuppressant	≥ Third line	26–64%[45,46] Overall survival: 67–96% at one year[45]	Viral reactivation, hypertension, pneumonia, and post-transplant lymphoproliferative disease[40]	Retrospective cohorts
Rituximab	CD20 (B cell surface antigen) monoclonal antibody	≥ Third line	17–70% in patients with steroid-refractory cGvHD (complete response = 10%)[46–48] Overall survival: 72% at one year; 76% at two years[45]	Infections, infusion-related symptoms and late neutropenia[47,49]	Phase 2b randomized trial
Sirolimus	mTOR inhibitor	≥ Third line	81% (complete response = 38%; partial response = 43%) in 47 patients with steroid-refractory cGvHD[50]; 94% of 16 patients with steroid-refractory GvHD[51] Overall survival: -	Thrombotic microangiopathy, renal insufficiency, and proteinuria[50–52]	Phase 2a trials
Imatinib	Multi-kinase inhibitor	≥ Third line	79% (complete response = 37%; partial response = 42%) in 19 patients with steroid-refractory cGvHD[53]; 26% in 35 patients in sclerotic cGvHD[50] Overall survival: 84% at 1.5 year[53]	Fluid retention, myelosuppression, and anemia[53]	Phase 2b trial
Cyclophosphamide (either pulse or low dose)	Alkylating agent	≥ Third line	100% of four patients with cGvHD showed response in skin and oral cavity and 70% of 10 patients[54]; 60% of 15 patients showed improvement after 8–12 monthly cycles[55] Overall survival: -	Short term myelosuppression, neutropenia, fatigue, and nauseas[54–56]	Retrospective cohorts

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Belumosudil	ROCK 2 inhibitor	≥ Third line	74% (complete response = 3%, partial response = 71%) of 132 patients with cGvHD[57] Failure-free survival 77% at six months[57]	Pneumonia, hypertension, hyperglycemia, and increased gamma-glutamyltransferase[57]	Phase 2 open label, randomized clinical trial
Low-dose total lymphoid irradiation	Radiation therapy	> Second line	54% of 13 patients with cGvHD achieved partial response[58]; 75% of 12 patients achieved clinical response at six months[59] Overall survival: median 13 months (3–113 months) in responders *versus* 10 months (0–41 months) in non-responders[58]	Thrombocytopenia, neutropenia[58,59]	Retrospective cohorts
Mesenchymal stem cells	Stem cells	≥ Third line	74% (complete response = 21%; partial response = 53%) in 19 patients with steroid-refractory cGvHD[60]; 66% overall response in patients cGvHD (complete response = 23%)[61] Overall survival: 78% at two years[60]	None reported[60]	Phase 2 trial
Thalidomide	Glutamic acid derivative, tumor necrosis factor-α	≥ Third line	38% (complete response = 3%, partial response = 35%) of 37 patients with steroid-refractory cGvHD[62] Overall survival: 41% at two years in steroid-refractory cGvHD[62]	Birth defects, constipation, rash, fatigue, somnolence, and neuropathy[62]	Phase 2 trial
Abatacept	T-cell activation inhibitor	≥ Third line	Overall response rate = 58% of 36 patients steroid-refractory cGvHD with 58% partial response and no complete response[63] Overall survival: -	Neutropenia, fatigue, headache, and upper respiratory infection[63]	Phase 2 clinical trial
Ixazomib	Proteasome inhibitor	> Second line	40% of 50 patients had partial/complete response[64] Overall survival: 90% at 12 months[64]	Thrombocytopenia, fatigue, diarrhea, infection[64]	Phase 2 trial
Baricitinib	Janus kinase 1/2 inhibitor	≥ Third line	90% of 20 patients with steroid-refractory cGvHD at any time during the study[65] Overall survival: failure-free survival 74% at one year, 37% at two years[65]	Viral reactivation, neutropenia, hypophosphatemia, hypertriglyceridemia, upper respiratory tract infections[65]	Phase 1/2 single arm clinical trial
Axatilimab	IgG4 antibody targeting the CSF-1 receptor	Available in clinical trial only	58% of 12 patients with cGvHD across doses[66]; 50–74% overall response according to dose[67] Overall survival: -	Increased gamma-glutamyltransferase and creatine phosphokinase, periorbital edema[66]	Phase 1/2 dose escalation and dose expansion study

Source: adapted from Kim et al.[2] and Wolff et al.[33].

Best responses: skin, mouth, eyes, liver, and lungs. Sclerotic or widespread disease is often refractory to first-line therapy and may require the use of ECP, systemic corticosteroids, immunosuppressants, or biological treatments[69].

Posology: treatment schedules of ECP for pediatric cGvHD most often involve two procedures applied every other week—initially order 26 kits[1]. The EBMT consensus in 2024 proposed using ECP as combination partner therapy as a future perspective of research for first or salvage treatment in acute and cGvHD[70].

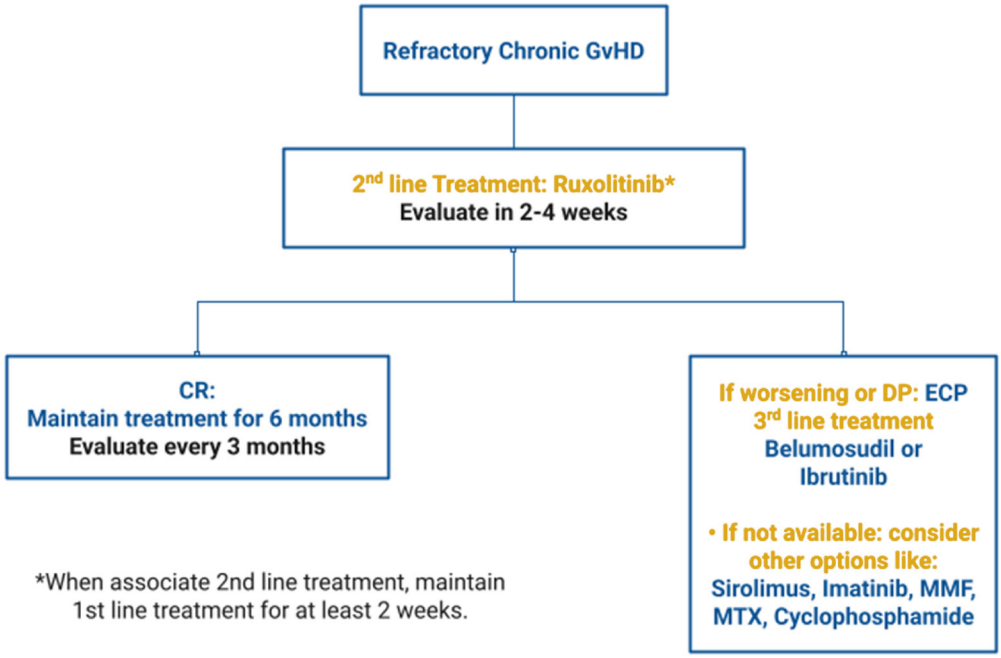
Disadvantages: high cost and the requirement of a rigid central catheter for the apheresis machine.

Mesenchymal stromal cells (2b-C)

Advantages: mesenchymal stromal cells (MSC) induce a shift from a pro to an anti-inflammatory environment[61].

Best responses: skin and lungs (overall response rate = 66%; complete response = 23%; after 1–10 infusions of 0.6–2.28 × 106 MSCs/kg).

Disadvantages: limited accessibility; response and safety are mainly determined by the conditions of MSC cultivation, as well as the way of administration and the dosage of MSCs. Two meta-analyses recommend administering MSC at day 0 in patients undergoing hematopoietic stem cell transplantation, in order to prevent cGvHD, and to carry out a clinical trial using MSCs as an adjuvant therapy from disease onset[71] (Fig. 3–6; Table 6).

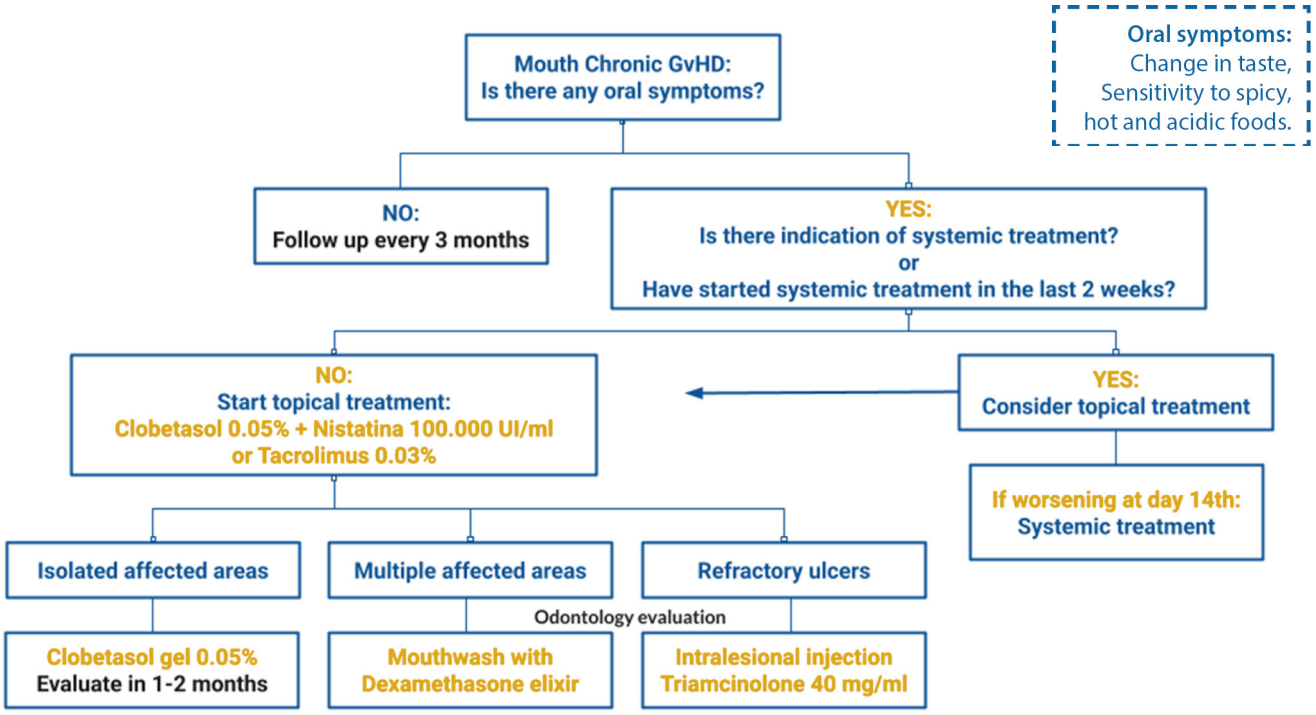


GvHD: graft-*versus*-host-disease; CR: complete response; DP: disease progression; ECP: extracorporeal photopheresis; MMF: mycophenolate mofetil; MTX: methotrexate.
Source: Elaborated by the authors.

Figure 3. Algorithm second- and third-line treatment.

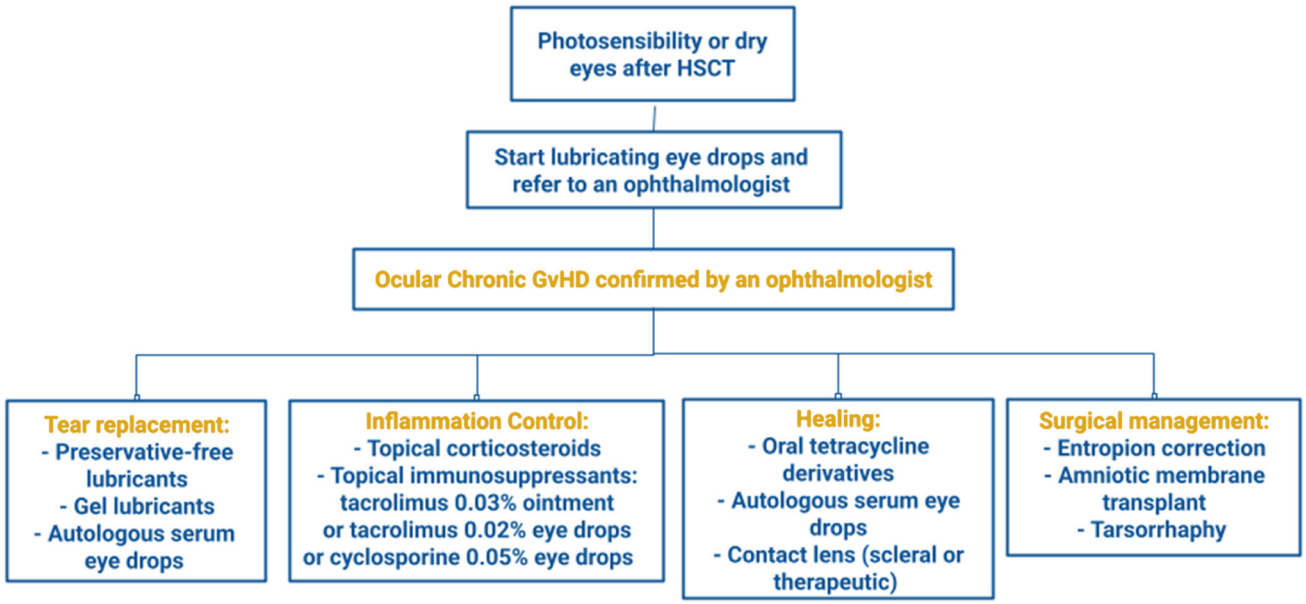
CONCLUSION

Chronic GvHD is a major cause of non-relapse morbidity and mortality after hematopoietic cell transplantation. Its incidence has increased due to more frequent use of unrelated and/or mismatched donors, reduced intensity conditioning regimens or intensified regimens and PBSC grafts. Since children are more susceptible to the long-term steroid side effects, development of steroid-free strategies for front-line therapy is crucial. For now, with current evidence, either CNI or sirolimus could be associated with the initial schema as steroid sparing agent. Sirolimus seems to be an interesting choice due to its capacity of inhibiting T-cells preserving the Tregs cells and antifibrotic, antineoplastic and antiviral activities. Fluticasone, azitromycin and montelucaste regimen is recommended in combination with systemic steroids for initial treatment of bronchiolitis obliterans. For steroid-refractory cGvHD, ruxolitinib is the standard of care, while ECP can be combined for better results. Other options approved for the third line and beyond are ibrutinib, belumosudil



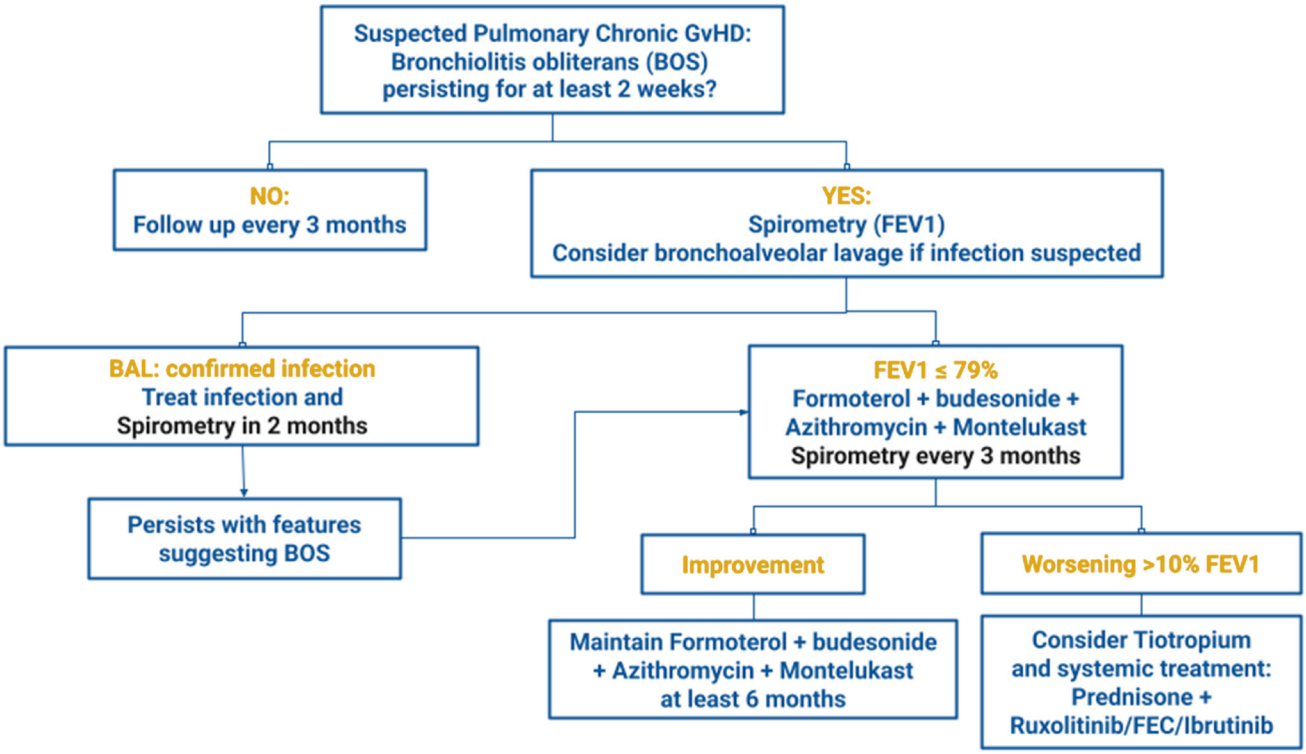
Source: Elaborated by the authors.

Figure 4. Algorithm oral graft-*versus*-host-disease (GvHD).



HSCT: hematopoietic stem cell transplantation. Source: Elaborated by the authors.

Figure 5. Algorithm ocular graft-*versus*-host-disease (GvHD).



FEV1: forced expiratory volume in first minute; BAL: bronchoalveolar lavage; FEC: extracorporeal photopheresis. Source: Elaborated by the authors.

Figure 6. Algorithm pulmonary graft-*versus*-host-disease (GvHD).

Table 6. Tapering prednisone in chronic graft-*versus*-host-disease*.

Even days (mg/kg/day)	Odd days	Maintain dose for
1	0.75 mg/kg/day	Seven days
1	0.5 mg/kg/day	Seven days
1	0.25 mg/kg/day	Seven days
1	ZERO	Three months
0.75	ZERO	Three months
0.5	ZERO	Three months
0.25	ZERO	Three months

*Interrupt the steroid taper in case of worsening or second-line treatment is required. After suspending prednisolone, stepwise tapering the others immunosuppressors every two to four weeks until complete removal. Source: Elaborated by the authors.

and axatilimab. Since access to novel drugs and ECP or MSCs is tough, conventional agents could be used such as imatinib, low dose-MTX, rituximab, however the expected response rates are lower. Further research on biomarkers is awaited to better understand the risks and to set up pre-emptive approaches to avoid highly morbid forms of cGvHD.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Rodrigues AM, Tavares RCBS, Macedo AV, Breviglieri CNB, Silva MM, Alves M, Ferreira RS, Gouveia RV, and Bouzas LF. **Analysis and interpretation of data:** Rodrigues AM, Tavares RCBS, Macedo AV, Breviglieri CNB, Silva MM, Alves M, Ferreira RS, Gouveia RV, and Bouzas LF. **Manuscript writing:** Rodrigues AM, Tavares RCBS, Macedo AV, Breviglieri CNB, Silva MM, Alves M, Ferreira RS, Gouveia RV, and Bouzas LF. **Final approval:** Rodrigues AM, Tavares RCBS, Bouzas LF.

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