Acute graft-versus-host disease

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ABSTRACT

Despite current advances in graft-*versus*-host disease (GvHD) prophylaxis, it remains one of the leading causes of morbidity and mortality after hematopoietic cell transplantation (HCT). The first-line therapy for acute GvHD is systemic corticosteroids, but about half of affected patients needs a second-line treatment. Ruxolitinib has been recommended for steroid-refractory GvHD, but treatment costs and adverse events such as cytopenias and infections are limitations. The main second-line alternatives for children are: basilixmab, an anti-interleukin-2-receptor monoclonal antibody, which showed good responses in skin and gut manifestations; 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 before in severe acute GvHD. Novel therapeutical agents are emerging, but their efficacy and safety need further investigation in pediatric patients. We reviewed clinical studies and published recommendations on pediatric acute GvHD that were presented in debate rounds with GvHD experts of the Pediatric Group of the Brazilian Society for Cellular Therapy and Bone Marrow Transplantation. The goal of this consensus is to standardize the prophylaxis, diagnosis, grading, and treatment of acute GvHD among Brazilian pediatric HCT centers, to improve post-transplant outcomes.

Keywords: Hematopoietic Stem Cell Transplantation. Graft vs Host Disease. Risk Factors.

INTRODUCTION

Acute graft-*versus*-host disease (aGvHD) remains an important cause of morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT). However, compared to adults, aGvHD incidence is lower in children, ranging between 13 and 30%, due to key differences: a better organ function, resulting in greater tolerance to toxic drugs, and a better thymic function[1]. Recommendations on graft-*versus*-host disease (GvHD)

prophylaxis and treatment for children are challenging and must consider diagnosis, relapse and/or rejection risks and age-dependent GvHD risk, since age 2–12 is associated with a significant lower GvHD risk, compared with infants (< 2 years old) and teenagers (13–18 years old)[2].

In aGvHD setting, updates to the European Society for Blood and Marrow Transplantation's recommendations include: use of ruxolitinib in treatment of steroid-refractory aGvHD as the new standard of care, use of rabbit anti-thymocyte globulin (rATG) as standard prophylaxis in peripheral blood stem cell (PBSC) transplants from matched related donors, and use of rATG or post-transplantation cyclophosphamide (PTCy) for PBSC transplants from unrelated donors[3].

RISK FACTORS

The main risk factors for aGvHD are human leucocyte antigens (HLA) disparity between donor and recipient; myeloablative conditioning and/or total body irradiation; PBSC as cell source; unrelated donor; multiparous female donor; female donor to male recipient; advanced donor age; recipient age > 12; to receive donor lymphocyte infusion; minor ABO incompatibility; serious infections in the peri-transplant period; and occurrence of thrombotic microangiopathy[4].

IMMUNOPROPHYLAXIS

GvHD prevention begins with the selection of the most suitable donor and the choice of bone marrow as cell source, whenever possible[4]. Especially for children transplanted for acute leukemias, monotherapy with cyclosporine (CsA) for bone marrow matched related transplants is routinely used by many European centers[5]. This strategy is supported by well-designed pediatric studies, which show higher event-free survival and decreased relapse rate associated with grade II aGvHD occurrence in acute lymphoblastic leukemia patients[6–8]. Thus, while grade III–IV aGvHD needs to be avoided, achieving and allowing sufficient alloreactivity is necessary to target residual leukemic cells[1] (Tables 1 and 2).

Table 1. Standard graft-*versus*-host disease prophylaxis regimens used according to type of allo-HCT.

Type of HCT	Prophylaxis regimen	Level of evidence
MAC: MSD/MRD: MUD/MMURD:	CNI ± short MTX BM: CNI + MTX + rATG 6–7.5 mg/kg PB: Add rATG 6–7.5 mg/kg or PTCy	1a–A 1a–B 1a–B
Contraindication of MTX:	CNI + MMF	1a–B
RIC and NMA: MRD:	CNI + MMF PB: Add rATG 4.5 mg/kg	2b–B 1b–A
Haploidentical	PTCy + CNI + MMF	2b–B

HCT: hematopoietic cell transplantation; MAC: myeloablative conditioning; MSD/MRD: matched sibling donor/related donor; MUD/MMUD: matched/mismatched unrelated donor; MTX: methotrexate; RIC: reduced intensity conditioning; NMA: non-myeloablative; CNI: calcineurin inhibitor; BM: bone marrow; rATG: rabbit antithymocyte globulin; MMF: mycophenolate mofetil; PB: peripheral blood; PTCy: post-transplant cyclophosphamide. Source: Penack et al.[3].

Table 2. Standard graft-*versus*-host disease prophylaxis posology.

	Prophylaxis regimen
Cyclosporine	1.5 mg/kg BID over 2 h, starts on D-2 or -1, then adjusts according to blood levels. Reduce dose 75% with posaconazole and 50% with voriconazole
Tacrolimus	0.02–0.03 mg/kg/day IV, same as above
Short methotrexate	15 or 10 mg/m^2 on D+1 and 10 mg/m^2 on days +3, +6 and ± D+11 according to type of donor
Mycophenolate mofetil	15 mg/kg TID postoperatively, for RIC starts on D+1 to D+30-35. For HAPLO starts D+5 to D+35
Post-transplant cyclophosphamide	50 mg/kg/day on D+3 and D+4

BID: twice a day; TID: three times a day; RIC: reduced intensity conditioning; HAPLO: haploidentical hematopoietic cell transplant. Source: Elaborated by the authors.

CLASSIFICATION

- Classic: aGvHD between engraftment and 100 days after hematopoietic stem cell transplantation (HSCT);
- Recurrent: prior aGvHD with complete response;
- Persistent: prior active aGvHD with refractoriness;
- Late onset: aGvHD after 100 days after HSCT, usually while tapering immunosuppression[9,10] (Table 3).

Table 3. Diagnostic criteria MAGIC.

Stage	Skin (active erythema only)	Liver (bilirubin) mg/dL	Upper GI tract (nausea/vomiting)	Lower GI tract (stool output/day)
0	Not active rash	< 2	No nausea or vomiting	< 10 mL/kg/day or < 4 episodes/day
1	Maculopapular rash < 25% BSA	2–3	Persistent nausea, vomiting or anorexia	10–19.9 mL/kg/day or 4–6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1–6		20–30 mL/kg/day or 7–10 episodes/day
3	Maculopapular rash >5 0% BSA	6.1–15		> 30 mL/kg/day or > 10 episodes/day
4	Generalized erythroderma, bullous formation and desquamation > 5% BSA	> 15		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

GI: gastrointestinal tract; BSA: body surface area. Source: Elaborated by the authors.

Overall clinical grade (based upon most severe target organ involvement)[11]:

- Grade 0: no stage 1–4 of any organ;
- Grade I: stage 1–2 skin without liver, upper gastrointestinal tract (GI) or lower GI involvement;
- Grade II: stage 3 skin and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI;
- Grade III: stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI;
- Grade IV: stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI.

Although current classifications are limited to the classical organs affected by aGvHD, other targets of alloreactive T-cell responses have been identified, such as bone marrow, lymph nodes, thymus, lungs, ovary, central nervous system, and kidney[12].

HISTOPATHOLOGIC DIAGNOSIS

Skin biopsy in diagnosis is still controversial. As relevant differential diagnoses of skin aGvHD, histological confirmation should be considered to exclude infection and toxicity and to assess the extent of cutaneous damage histologically[13,14]. Remember that histological classification does not replace clinical grading.

- Grade I: vacuolar degeneration of basal keratinocytes;
- Grade II: vacuolar degeneration of keratinocytes with spongiosis and dyskeratosis or cytoid inclusion bodies, so-called Civatte bodies;
- Grade III: grade II plus additional epidermolysis with blistering;
- Grade IV: destruction of the epithelium, separation of dermis and epidermis (Table 4).

Table 4. Differential diagnosis.

Skin	Liver	Gastrointestinal tract tract
Engraftment syndrome Pharmacodermia Viral infection Staphylococcal scalded skin syndrome Conditioning toxicity Drug phototoxicity	Sinusoidal obstruction syndrome Viral infection Hepatotoxicity	Viral infection (Epstein Barr virus, cytomegalovirus, adenovirus, HHV6) Clostridium difficile Thrombotic microangiopathy Conditioning toxicity

Source: Elaborated by the authors.

FIRST-LINE TREATMENT

Topical treatment

Indication: first-line treatment acute GvHD grade I, but it can be used in any grade as an association[15]:

Intact skin: symptomatic treatment with emollient and antipruritic agents.

- Topical corticosteroids (1b-A): although low-potency topical steroids (Hydrocortisone 0.5–1%) are safe, medium (Betamethasone 0.02–0.05%, Triamcinolone 0.02%, Clobetasone 0.05%) and high potency (Betamethasone 0.1%, Triamcinolone 0.1%, Mometasone 0.1%) steroids can be needed and should be used in limited areas for a short time (< 3–4 weeks). The use of high potency steroids in children < 1 year old is not recommended. Topical steroids under occlusion are not recommended;
- Topical calcineurin inhibitors (2b-C): Pimecrolimus and tacrolimus are widely used as a corticosteroid-sparing agent. Tacrolimus has efficacy similar to moderate-to-strong topical corticosteroids, and pimecrolimus has efficacy akin to a mild corticosteroid. For children between 2–15 years old should be prescribed tacrolimus ointment 0.03%. Apply the cream cold or mixed with a moisturizing cream to reduce the burning.

Non-intact skin: In the naked area, topical antimicrobials (mupirocin and fusidic acid), products containing 1% silver sulfadiazine with/without cerium, and alginate hydrogel, protective films based on petrolatum can be used to improve healing.

Oral antihistamines: Pruritus in GvHD can have several origins such as dry skin, skin lesions, or the only symptom of disease activity. The second-generation oral antihistamines (less hepatic metabolism, such as fexofenadine, epinastine, and bilastine), and the first generation for more intense cases (hydroxyzine) are indicated to reduce itching. For refractory symptoms, the use of gabapentin (300 mg) or low-dose thalidomide (100 mg) may be associated.

Corticosteroid

Indication: First-line treatment aGvHD grade ≥ II[4,10,16].

Posology: methylprednisolone (MP) or prednisolone (PDN) 2 mg/kg/day twice daily for grade ≥ II (1a-A). When tapering < 1 mg/kg/day, adjust the dose to once a day.

Children aged 2 to 11 years old undergoing HCT with sibling donor for acute leukemia with absent low gastrointestinal symptoms is acceptable PDN 0.5 mg/kg/day + calcineurin inhibitor (CNI) + adjuvant treatment due to the lower risk of severe GvHD and higher risk of relapse.

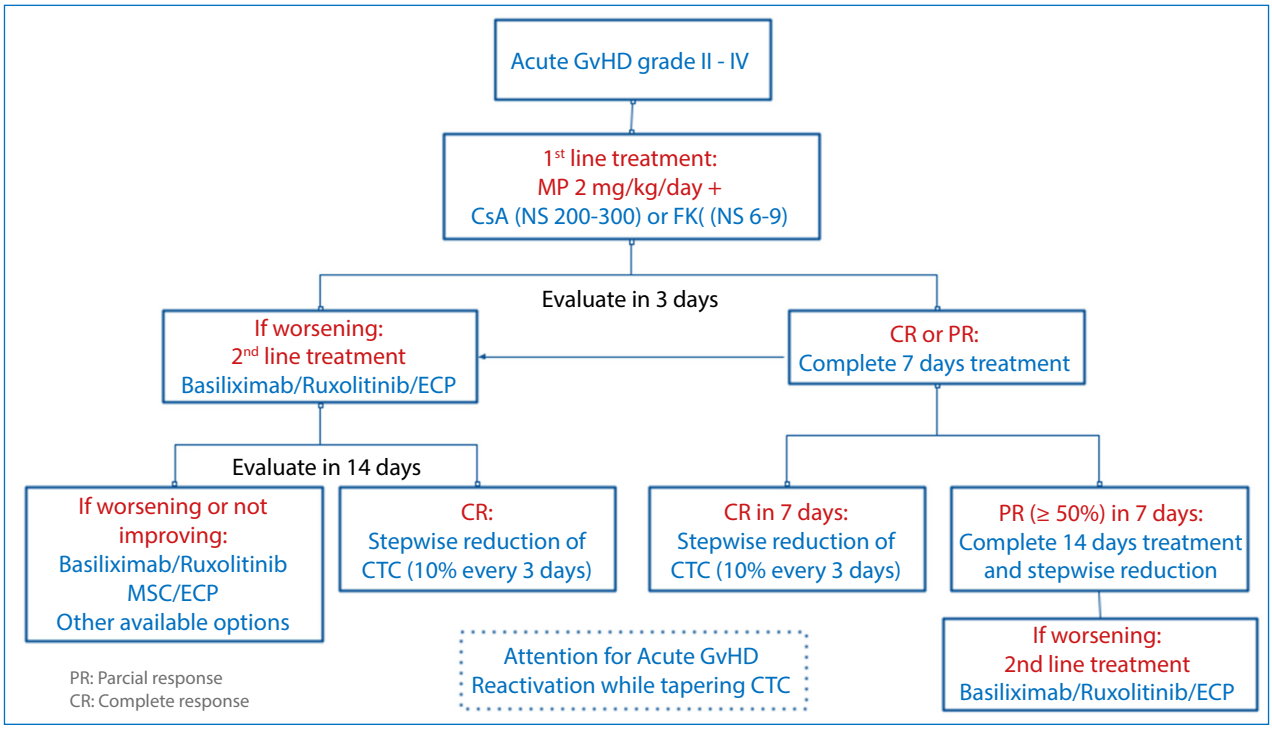
Expected response: Initial clinical improvement is typically observed within 3–7 days. Only 60% of patients respond to standard corticosteroid therapy. Additional agents such as mycophenolate mofetil, rATG, infliximab, anti-IL2 antibody or higher MP doses did not improve outcomes and decreased survival. The addition of ruxolitinib (5 mg/day) to MP (1 mg/kg/day) resulted in higher GvHD response as initial therapy for aGvHD in one randomized phase III study[17].

Steroid refractory criteria (SR-aGvHD)

Worsening of aGvHD in the first three days of corticosteroid treatment or treatment failure in seven days: MP or PDN 2 mg/kg/day + CsA (NS 200–300).

Response criteria

- Complete response: resolution of all manifestations in each organ or site;
- Partial response: improvement in at least one organ or site without progression in any other organ or site;
- Disease progression: increasing stage/grade of aGvHD or new organ involvement (Fig. 1).



GvHD: graft-versus-host disease; MP: metilprednisolone; CsA: cyclosporine; ECP: extracorporeal photopheresis; CTC: corticosteroid. Source: Elaborated by the authors.

Figure 1. Algorithm first-line treatment.

SECOND-LINE TREATMENT

There is no standard second-line treatment for SR-aGvHD. Current practice is to prescribe one of the following drugs. For second-line treatment, centers should follow their institutional guidelines, and patients should be treated in clinical trials when possible.

Ruxolitinib (1a-A)

Indication: second-line treatment for SR-aGvHD[17–19].

Posology: weight > 35 kg: 10 mg twice daily; 35–25 kg: 5 mg twice daily; 25–9 kg: 2.5 mg twice daily (or 4 mg/m^2/day).

Dose adjustment according to toxicity: a one-step dose reduction is recommended (10 mg twice daily → 5 mg twice daily or 5 mg twice daily → 5 mg once daily) if:

- Platelets < 20,000/mm^3, absolute neutrophil count (ANC) ≥ 500/mm^3 to < 750/mm^3 or bilirubin three to five times the upper limit of normal (ULN).

Discontinue ruxolitinib if:

- Platelets < 15,000/mm^3, ANC < 500/mm^3 or bilirubin > 5 times ULN.

Stepwise tapering corticosteroid dose: one week after starting Ruxolitinib, every five days: 1.5 mg/kg/day → 1 mg/kg/day → 0.8 mg/kg/day → 0.6 mg/kg/day → 0.4 mg/kg/day → 0.3 mg/kg/day → 0.2 mg/kg/day → 0.1 mg/kg/day

Expected response: initial clinical improvement is typically observed within 14–28 days, with the best response expected between days 28 and 56. REACH2 for SR-aGvHD, randomized phase 3, age ≥ 12, overall response rate (ORR) 62% (*versus* 39% control) at day 28. REACH4 for pediatric SR-aGvHD, phase 1/2, age < 12, ORR 84.4% at day 28 (all patients)[18].

Refractoriness criteria[20]:

- Progression after five to ten days of treatment;
- No improvement after 14 days of treatment;
- Loss of response at any time after initial improvement;
- No complete response or very good partial response after 28 days.

Basiliximab (anti-interleukin 2 receptor antibody therapy) (2b-B)

Indication: second-line treatment for SR-aGvHD[21–23].

Posology: weight > 35 kg: 20 mg, and < 35 kg: 10 mg, intravenously, on days 1, 3, and 8, and then repeated weekly until aGvHD is less than grade II.

Expected response: ORR of 63.5% at any time and 54% on day 28 after basiliximab treatment[23]. The best responses by organs are in the skin (84%) and gut (48%)[22].

Refractoriness criteria: no response after four doses of basiliximab[24].

Narrow band ultraviolet B phototherapy (2b-B): adjuvant therapy

Indication: skin steroid-dependent aGvHD with no gut/liver involvement[25,26].

Posology: the dose increases throughout the treatment, according to skin tolerance. Patients can have skin sensibility like erythema, as an adverse effect, and it does not mean disease progression. It should be done three times a week until complete tolerance.

Refractoriness criteria: no response after reaching maximum phototherapy dose.

Extracorporeal photopheresis (1b-A)

Indication: considered early during SR-aGvHD before significant irreversible end organ damage has been established. Steroid-sparing is another important benefit of extracorporeal photopheresis (ECP) therapy[27–29].

Posology: to initiate treatment, a rigid central catheter is required for leukapheresis, the blood is incubated with the photoactive and photosensitizing drug 8-methoxypsoralen (8-MOP), exposed to ultraviolet A (UV-A) light and then reinfused into the patient. ECP therapy is recommended two or three times weekly, until a response can be established. Subsequently, ECP can be reduced to every two weeks and phase out. Weekly monitoring of aGvHD activity.

Expected response: ORR 58% in SR-aGvHD at three months of ECP therapy *versus* 47% in the ruxolitinib arm. Better responses with early start. Cutaneous aGvHD is more responsive to ECP than liver or gut aGvHD, but ECP combined with ruxolitinib has shown encouraging results[29].

Refractoriness criteria: no response after 26 doses of ECP.

Mesenchymal stem cells (2b-B)

Indication: alternative for SR-aGVHD. Advantage for their immunomodulatory properties as inhibitory effects on the proliferation and cytotoxic activity of immune system cells[30–32].

Posology: infusion of third-party, HLA-unrelated, or related bone marrow donor mesenchymal stem cells, once weekly for two or three weeks (2×10^6 MSCs/ kg). Time of infusion is 15 minutes in the central catheter, and can be administered on an outpatient basis, but the patient should stay in observation for 1 hour after at least.

Expected response: initial clinical improvement is typically observed within 14–28 days, with the best response expected in 28. ORR 83% in SR-aGvHD at day 28. Best response with preeminent skin GvHD but not liver involvement[4,32].

Refractoriness criteria: fail to achieve PR/CR at day 28, GvHD progression despite therapy or require additional systemic immunosuppression.

Alpha 1-antitrypsin (2b-C)

Indication: alternative for SR-aGVHD, especially in GI involvement, when oral therapies (*e.g.*, ruxolitinib) are ineffective due to malabsorption or standard immunosuppression is unsuitable or unavailable[33,34].

Posology: eight doses of 60 mg/kg intravenously, administered over four weeks on Days 1, 4, 8, 12, 16, 20, 24, and 28.

Expected response: initial clinical improvement is typically observed within 14–28 days, with the best response expected between days 28 and 60. Reported response rates range from 68–70.6% for skin involvement, 57% for liver involvement, and 61–67% for GI involvement, with CR rates reaching up to 50% in GI GvHD[34].

Refractoriness criteria: fail to achieve PR/CR by day 28, GvHD progression despite therapy or requiring additional systemic immunosuppression.

Entocort (1b-A)

Indication: GI aGvHD when used in combination with systemic corticosteroids reduces the risk of GvHD treatment failure by > 60% and reduces mortality one year after randomization by 45%, with fewer deaths due to infection and recurrent malignancy.

Posology: non-absorbable oral steroids, like budesonide (9 mg per day) or oral beclomethasone (3 mg four times a day), can be given in addition to systemic corticosteroids as treatment of GI aGvHD for 28 days[35,36].

Sirolimus (2b-B)

Indication: alternative for SR-aGvHD[37–39].

Posology: a loading dose (15 mg/m^2) may be given on the first day, followed by 5 mg/m^2/day to target therapeutic through levels between 4 and 12 ng/mL. However, as its half-life is around 70 h, it should only be dosed once a week during the initial adjustment.

Toxicity: significant toxicity is associated with sirolimus as very high plasma levels were targeted, like thrombocytopenia, neutropenia, increased blood triglycerides and cholesterol, and hemolytic uremic syndrome or thrombotic microangiopathy concurrently with CNI. Avoid co-administration of sirolimus and voriconazole and posaconazole, if highly necessary, reduce sirolimus dose by 50% and by 60–80%, respectively. Isavuconazole also increases the area under the curve (AUC) of sirolimus, but by much less about 1.5 times, so monitor plasma levels for adjustments.

Expected response: organ-specific CR rates were as follows: skin 31%, GI 44% and liver 50%; with median time-to-best response of three or four weeks[1–8].

Refractoriness criteria: no response after 28 days of sirolimus.

Metotrexato (2c-C)

Indication: as there is no standard second-line therapy for SR-aGvHD, methotrexate (MTX) can be considered[40–44].

Posology: recommended doses vary from 5 to 10 mg/m^2 of body surface area at weekly intervals or every three or four days. Weekly administration of MTX at a median dose of 7.5 mg/m^2 seems to be safe with minimal toxicities and allowing for dose tapering of steroids.

Expected response: predictors of better responses were lower grade aGvHD, cutaneous involvement, and isolated organ involvement. Patients who demonstrated CR were able to have their steroid doses reduced to less than 50% of the initial dose within eight weeks of low-dose MTX initiation.

Refractoriness criteria: no response after 28 days of first dose of MTX.

Micofenolato mofetil (2b-C)

Indication: salvage of SR-aGvHD grades I-II[46].

Posology: initial dose of mycophenolate mofetil (MMF) is 15 mg/kg/dose twice a day and increased by 1.5–2 times if manifestations of GvHD did not improve. The maximum dose of MMF is 60 mg/kg/day[47]. Side-effects comprise both hematologic and GI toxicity, including myelosuppression and the development of ulcers of the intestinal mucosa[48,49].

Etanercept (2b-C)

Indication: salvage of SR-aGvHD grades I-II[50].

Posology: 25 mg subcutaneously twice a week for four weeks, followed by once a week for four weeks.

Expected response: the largest previous study (n = 58) of etanercept in SR-aGVHD reported a modest effect in these settings, with short-term responses around 50% on day +60. However, long-term survival remains poor. Grade IV aGvHD independently predicts poor outcomes and can be used to select a subpopulation in which etanercept alone is unlikely to provide significant benefits[50].

Faecal microbiota transplantation

Indication: while fecal microbiota transplantation is a well-established treatment for recurrent clostridium difficile colitis, only case reports and retrospective analyses are available regarding its use for treatment of GI-aGvHD.

Expected response: a multi-center, prospective, phase II study evaluating the pooled allogeneic fecal microbiota MaaT013, for steroid refractory GI-aGvHD was conducted. In a cohort of 24 steroid refractory GI-aGvHD, at day 28, the GI-overall response rate was 38% including five CR, two very good PR and two PR. Fifty-two additional patients with steroid refractory or steroid dependent GI-aGvHD were also treated within a compassionate use/expanded access program. In those patients, the day 28 GI-overall response rate was 58%[51].

Rabbit thymoglobulin and alemtuzumab

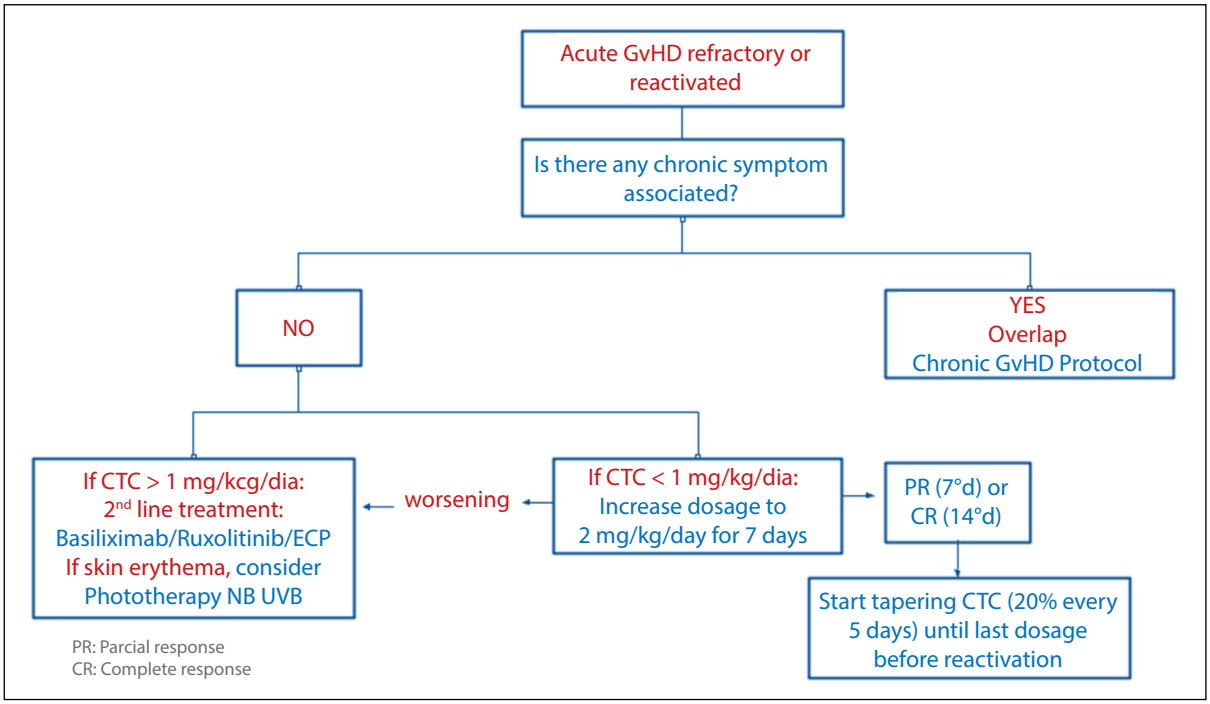
The use of rATG and alemtuzumab is not recommended for treatment due to higher incidence of any additional infection after treatment[45].

Dietary steps for gastrointestinal GvHD

Bowel rest: Stool output > 1,000 mL/day, abdominal pain or intestinal bleeding. Parenteral nutrition. Step 1: Stool output < 500 mL/day, improvement of abdominal pain and reduction of nausea and vomiting. Dietary: Add sugar free liquids, except milk. Step 2: Absence of abdominal pain and more consistent stools. Dietary: Add simple carbohydrates, cooked vegetables and fruits. Step 3: Absence of abdominal pain and more consistent stools, step 2 was well tolerated. Dietary: Add proteins (chicken, fish, eggs and lactose-free milk). Step 4: Absence of abdominal pain and habitual stools, step 3 was well tolerated. Dietary: Add red meat and restore the patient's usual diet (Fig. 2).

CONCLUSION

Prevention and management of GvHD remains challenging in pediatrics, due to lack of prospective and randomized studies. The first-line treatment is still high-dose steroids in addition to CNIs, which can lead to higher infection and relapse rates. Early start of adjuvant therapy is important to potentialize response and allow steroid taper. Nevertheless, around one-third of the patients will be steroid-resistant/dependent. Ruxolitinib is the first choice for SR-GvHD, since it demonstrates remarkable efficacy, especially if started as soon as an unsatisfactory steroid response is detected. However, treatment costs and adverse events such as cytopenias and infections are limitations.



CTC: corticosteroid; ECP: extracorporeal photopheresis; NB: narrow band; UVB: ultraviolet B; PR: partial response; CR: complete response. Source: Elaborated by the authors.

Figure 2. Algorithm refractory/reactivated acute graft-*versus*-host disease (GvHD).

There are no prospective trials comparing second-line treatments. Anti-IL2R antibodies, a more available alternative in public centers, also provide good responses in skin and gut manifestations. ECP, with its GvL sparing and immunomodulatory effect and without serious side effects, seems beneficial since, in retrospective studies, its efficacy is comparable to ruxolitinib as a second-line option for both acute or chronic SR-GvHD. Combining anti-cytokine therapy with ECP or another non-pharmacologic treatment, such as MSCs, may be a better strategy for high-risk patients. Further evidence is awaited regarding the role of abatacept, vedolizumab, and fecal microbiota transplantation.

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, Breviglieri CNM, Silva MM, Gouveia RV, Fernandes Junior VCA and Bouzas LF. C**onception and design:** Rodrigues AM, Tavares RCBS, Breviglieri CNM, Silva MM, Gouveia RV, Fernandes Junior VCA and Bouzas LF. **Analysis and interpretation of data:** Rodrigues AM, Tavares RCBS, Breviglieri CNM, Silva MM, Gouveia RV, Fernandes Junior VCA and Bouzas LF. **Manuscript writing:** Rodrigues AM, Tavares RCBS, Breviglieri CNM, Silva MM, Gouveia RV, Fernandes Junior VCA and Bouzas LF. **Final approval:** Rodrigues AM, Tavares RCBS and Bouzas LF.

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