ARTICLE

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An expert consensus on prevention, diagnosis, and management of hemorrhagic cystitis in pediatric hematopoietic cell transplantation, on behalf of the Infectious Disease and Hematopoietic Cell Transplant Working groups of Italian Pediatric Hematology Oncology Association (AIEOP)

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The optimal management of hemorrhagic cystitis (HC) in hematopoietic stem cell transplantation (HCT) is debated, both for early onset HC (EOHC) secondary to chemotherapy toxicity and BK Polyomavirus (BKPyV)-related HC, due to the lack of controlled trials, particularly referred to pediatric setting. Actually, clinical practice is mainly based on guidelines of the European Conference on Infections in Leukemia, 6th edition, which considers both adult and pediatric populations but concludes that, despite much progress in understanding the pathogenesis, epidemiology, and risk factors, this complication still represents a disabling unmet clinical need with limited prophylactic and therapeutic options. Additionally, the Guidelines of the American Society of Clinical Oncology define the management of chemotherapeutic toxicity independently from the patients' population. A panel of experts belonging to the Hematopoietic Cell Transplant and Infectious Disease Working Group (WG) of Associazione Italiana di Emato-Oncologia Pediatrica (AIEOP) developed a consensus to define the best practices in prevention, diagnosis, and management of HC in pediatric HCT setting.

Bone Marrow Transplantation; https://doi.org/10.1038/s41409-024-02320-4

INTRODUCTION

Hemorrhagic cystitis (HC) occurs after hematopoietic stem cell transplantation (HCT) with an incidence up to 25% in pediatric settings [1–3]. HC is characterized by urinary symptoms, abdominal pain and bleeding, graded according to microscopic or macroscopic hematuria (1–2), macro-hematuria with clots [3], and postrenal failure secondary to urinary tract obstruction [4].

Early onset HC (EOHC) occurs within 48 hours from radiotherapy or alkylating agents such as cyclophosphamide (Cy) [2], an oxazaphosphorine agent administered in conditioning regimens or at higher doses on days +3 and +5 as an immunosuppressant agent in haploidentical HCT [5] based on Post-Transplant Cyclophosphamide (PTCy).

Late-onset HC (LOHC) develops in periengraftment period up to 6 months after HCT, associated with BK Polyomavirus (BKPyV) reactivation. Other potential infectious causes of HC (Cytomegalovirus, Adenovirus, JC polyomavirus, bacteria, parasites) must be ruled out. Risk factors for BKPyV reactivation are donor/recipient HLA disparity, acute/chronic GvHD, myeloablative conditioning, PTCy, or antithymocyte globulin [1, 6–9].

HC increases in-hospital stay and overall mortality [10], but its management remains challenging due to low-quality evidence

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Received: 9 March 2024 Revised: 15 May 2024 Accepted: 23 May 2024
Published online: 22 June 2024

available in the literature. ECIL guidelines summarized recommendations for BkPyV-HC in HCT recipients of all ages, but only grade II or III evidences were reported [1]. Specific features related to pediatric age and non-homogenous strategies among different centers described in the literature led to the need of defining shared consensus recommendations to support patients' management and also provide the ground for future trials.

The Infectious Disease Working Group (ID-WG) and Hematopoietic Cell Transplant Working Group (HCT-WG) of Associazione Italiana di Emato-Oncologia Pediatrica (AIEOP) organized a consensus meeting to define best practices for HC in the pediatric setting.

METHODS

The chairmen of ID-WG (SC) of HCT-WG (DP) and the team leader (MF) appointed an expert panel (EO) among members of both WGs and two external pediatric urologists (MC and MC). MF developed a survey questionnaire and GDO performed a literature review about HC. The EO convened in October 2023 to share the results of the survey and literature evidence.

Between 2016 and 2021, the incidence of HC ≥ grade 2 ranged from 6% to 15% among the 13 responding centers. Controversial results of the survey were:

- Schedule of 2-mercaptoethane sodium sulphonate (Mesna) administration: 6/13 combined continuous infusion and intermittent administration, while 7/13 selected either one or the other strategy;
- Urine alkalinization in 6/13 centers as prophylaxis of EOHC;
- Heterogeneous urinary and/or plasma BKPyV load monitoring strategies;
- Different criteria to start antiviral treatment: 5 centers based on BKPyV viruria, 8 on BKPyV viruria and viremia;
- Different intravenous cidofovir dose/schedule;
- Supportive care.

The following topics were discussed: (1) prevention of EOHC related to chemotherapy; (2) screening of BKPyV and criteria to start antiviral treatment; (3) antiviral therapy and adoptive immunotherapy; (4) urological management; (5) supportive treatment. Overall, 16 statements were approved unanimously by participants.

Literature review and recommendations

Prevention of EOHC. Cy-derived metabolites such as acrolein induces local damage.

A prospective, randomized study [11] compared hyperhydration alone (given at 4 mL/kg/h beginning 12 hours before infusion of Cy and continued until 24 hours after administration of the last dose of Cy) versus standard hydration plus Mesna (2 mL/kg/h beginning 12 hours before Cy administration and continued until 24 hours after the last dose of Cy in association with Mesna 120% of Cy total daily dose (TDD) in five divided intravenous doses). Incidence of HC resulted similar in the two study arms (26.8% versus 23.7%, respectively), supporting the role of hyperhydration in reducing urothelium exposure to toxicity. Due to limited high-quality evidence, hyperhydration is supported by grade B II evidence in ECIL guidelines [1, 11]. Overall, different hyperhydration solutions were not directly compared in randomized studies.

1. ***Hyperhydration with 3 L/m^2 continuous infusion and electrolytes supplementation according to single center clinical practice is recommended, starting from 12 hours before Cy administration to be continued up to 24 hours after the end of Cy administration***.

   Mesna is recommended in the American Society of Clinical Oncology (ASCO) Guidelines since 1999 [12, 13]: it binds acrolein through a sulfhydryl group and the product of this reaction is harmless [14] and excreted through urine.

   A prospective phase II study described intermittent Mesna administration in 4 doses at 80% TDD of Cy in haploidentical PTCy HCT [15]: HC incidence was 20%, but at median onset of 24 days after HCT, 89% with BKPyV detection on urine. No level 1 evidence has shown results superior to Mesna for the prevention of EOHC [5].

   A retrospective study [16] compared Mesna in 3 intermittent doses with Mesna continuous infusion (both at 100% TDD of Cy), demonstrating a reduction of HC incidence in the continuous infusion group (5.6% versus 27.8%).

2. ***Mesna continuous infusion of 100% of total Cy dose, starting before chemotherapy administration, to be continued up to 30 hours after the end of chemotherapy administration, in association with intermittent Mesna administration of 30% of total Cy dose, is recommended, particularly with high-dose Cy doses administered for PTCy HCT. Intermittent administrations can be performed up to 3 times, before and after chemotherapy (+4 and + 8 hours)***.

   Bladder irrigation through Foley catheter was proposed to reduce urothelial exposure to toxic metabolites. However, only a reduction of mean duration of HC and hospitalization was found [17].

3. ***Bladder irrigation as prophylaxis for EOHC is not recommended, due to difficulties related to Foley catheter placement in a pediatric setting and the invasiveness of the procedure***.

   Forced diuresis is a common strategy to enhance the excretion of toxic drugs in urine [18]. However, in studies considering pediatric HCT patients, no details are reported, nor different diuretics were prospectively compared. Therefore, it is based on single-center protocols and according to urinary output and clinical evaluation of body weight during hyperhydration. Therefore, patient- or transplant-related features should be considered to individualize the diuretic schedule.

4. ***Forced diuresis with Furosemide should be performed as an adjunctive strategy with the administration of high-dose of Cy and hyperhydration, according to single-center protocols and patient- or HCT-specific features***.

   Urine alkalinization is often reported in association with hyperhydration and diuretics. However, a biological study [19] described that the kinetics of enzymatic reaction leading to acrolein synthesis and the urotoxicity of acrolein are increased in an alkaline environment. Accordingly, ASCO Guidelines [13] do not recommend urinary alkalinization.

5. ***Urinary alkalinization as preventive strategy of EOHC or LOHC in pediatric HCT setting is not recommended***.

Screening of BKPyV and criteria to start antiviral treatment. Detection of BKPyV viruria is common in imunosuppressed patients. 80% of all HCT patients develop high-level BKPyV viruria, but only 5%–20% develop BKPyV-HC. Urinary BKPyV DNA load >10^7 showed a sensitivity 86%, specificity 60%, negative predictive value 98%, and positive predictive value 14% [20]. Leung et al. demonstrated that viruria was higher in patients developing HC [21].

A pathogenic model of LOHC [22–26] has been proposed: subclinical urothelial damage secondary to conditioning regimen leads to high-level BKPyV replication in the urothelial lining also due to an ineffective antiviral immune control from cytotoxic T cells in post-HCT phases. Bleeding represents a late consequence of inflammatory cells invasion following engraftment [22–26].

However, this model doesn't fully explain the pathogenesis of BKPyV-HC. In fact, an immunosuppressive approach (e.g. steroids) is neither effective nor recommended [1], and BKPyV-HC can develop also in association with post-HCT lymphopenia [24]. Additionally, specific anti-BKPyV T-cells are associated with viral clearance. Haploidentical HCT is associated to increased HC risk also due to delayed immune reconstitution and inefficient antigen-presentation and lymphocyte activation [9, 23, 24]. However, the reduction of immunosuppressive drugs to manage BKPyV reactivation should be carefully weighted according to the risk of potential onset/worsening of GvHD.

Urothelial damage can additionally promote systemic dissemination of BKPyV, and an increase in BKPyV-DNA viremia was demonstrated in HC [27]. A prospective study [20] demonstrated a sensitivity of 100%, specificity 86%, and negative predictive value 100% BKPyV-DNA load > 10^3, but a positive predictive value 39%. BKPyV-DNA viremia has been also associated to further outcomes: an increase > 3 logs compared to basal loads in 2 weeks predicts the onset of HC, a reduction of at least 1 log reflects the efficacy of antiviral treatment [7], and BKPyV viremia >10^4 in the first 3 months after-HCT predicts reduced glomerular filtration rate at 12 and 24 months after HCT and increased overall mortality [24].

Due to lack of effective pre-emptive treatment, BKPyV viruria/viraemia screening in asymptomatic HCT patients is not recommended outside clinical studies [1].

6. ***Screening in urine and blood by qPCR for BKPyV and other causes of HC (Adenovirus, JC polyomavirus, bacteria) is recommended in case of clinical suspicion (urinary symptoms, abdominal pain, with microscopic or macroscopic hematuria)***.

In case of BKPyV-HC, although the efficacy of antiviral therapy is not defined yet, it is conceivable that an early antiviral treatment may reduce duration and entity of viral infection. A threshold of BPyV load of $\geq 10^7$ copies/ml in urine and/or $>10^3$ copies/ml for plasma is suggested.

Antiviral therapy and adoptive immunotherapy for BKPyV-HC. Cidofovir (CDV), broad-spectrum nucleotide analogue of cystine, is characterized by in vitro activity against several viruses [28]. However, in vivo indication, dosing, efficacy, and supportive care are still debated [1, 29]. Renal tubular secretion and glomerular filtration lead to drug elimination and explaining nephrotoxicity; probenecid reduces drug clearance via inhibition of tubular secretion, resulting in nephroprotection [29–31].

A recent review [28] summarized CDV use in immunocompromised children. 167 BKPyV-HC patients were treated with two different schedules: high-dose (3-5 mg/kg/dose) with probenecid, or low-dose (1 mg/kg) without probenecid.

Overall, viremia complete viral response (CVR) was achieved in 76%; viruria CVR in 55%. High-dose and low-dose schedules were associated to HC symptomatic resolution in 78% and 80%, respectively, but low-dose CDV without probenecid was associated with lower nephrotoxicity (5% versus 23%) [28]. Most analysis are retrospective or characterized by concomitant medications; only a few patients are reported with low-dose schedules. Therefore, high-quality evidence is not available. ECIL guidelines consider that CDV may be an option, without providing specific recommendations on a specific dose schedule (grade C II) [1].

7. ***Low-dose cidofovir (1 mg/kg two or three times a week) is the preferred treatment for BKPyV-HC due to safety profile, efficacy and the possibility to avoid the co-administration of oral probenecid, available only as tablets for adults. Treatment is recommended until clinical and/or virological response is achieved (disappearance of macro-hematuria and at least 1 log decline BK viremia, respectively), in 4-6 weeks***.

   High-dose cidofovir (3–5 mg/kg once a week) with oral probenecid is recommended in case of HC due to Adenovirus systemic infection.

   Weekly clinical and virological assessment of response is recommended.

   Immunosuppression reduction is an option to consider versus risk of onset/worsening GVHD.

   Limited data are available about intravesical administration of CDV 5 mg/kg and evidence for direct efficacy is limited due to many other concomitant treatments [28]. In a retrospective analysis in pediatric patients, 4/10 children reported pain or discomfort during treatment instillation [32]. As reviewed in ECIL guidelines, response rates are not satisfactory despite the invasiveness of the procedure even in adults [1].
8. ***Intravesical CDV should not be routinely recommended in pediatric patients affected by BKPyV-HC***.

   Adoptive immunotherapy is under investigation in kidney transplantation and HCT [33].

   Phase-2 studies based on third-party or donor-derived T-lymphocytes demonstrated satisfactory response rates in the absence of infusion toxicity and with 1 reported onset of grade 2 skin GvHD [34, 35], but a 16-year old HCT patient due to DOCK8 deficiency complicated by HC and high BKPyV viremia suffered from significant cytokine release syndrome [36].
9. ***Adoptive cell therapy availability is limited, but it can represent an option in selected cases, particularly in phase 2 or phase 3 trial settings***.

Urological management. The urological management of HC is a key issue because of uncontrolled low-quality evidence in pediatric settings.

10. ***Early involvement of a urologist from the first clinical suspicion of HC is recommended***.

    Absent pain, normal urination, and normal urinary ultrasound allow to keep spontaneous urination.

    Dysuria, pain, and the need to evacuate existing clots and/or to start bladder irrigation or instillations to prevent progression of HC determine the indication to place a urinary catheter. Three-way urinary catheter is the most suitable choice. However, minimum calibers of 16 or 18 Fr may not suit for children urethral size [18, 37]. In addition, small calibers catheters are associated with a risk of recurrent obstruction [38].

    According to patient's clinical conditions and degree of compromise of the bladder mucosa, a potential alternative strategy is a placement of a percutaneous sovrapubic cystostomy catheter during cystoscopy [18, 37, 38], as small as possible, to be used for irrigation, along with transurethral two-way catheter as drainage route.

    Tip (Foley, Nelaton, Tieman, Dufour, Couvelaire, Mercier) and material (soft or semi-rigid) of the catheter should be based on clinical indications.

    100 mL/h is the recommended starting infusion rate for bladder irrigation; a higher rate can be applied over 10 years of age, in order to obtain clear, colorless urine, if tolerated.

    Regular ultrasonographic monitoring is recommended during bladder irrigation.
11. ***A three-way catheter to perform continuous bladder irrigation is recommended for patients with HC and severe bladder pain and/or risk/evidence of urinary obstruction; a two-way catheter-associated to a percutaneous sovrapubic cystostomy could be an alternative option***.

    Several intravesical instillation have been proposed: silver nitrate, clotting factors, aminocaproic acid, prostaglandins, estrogen, glycosaminoglycans, and formalin. In 2019, endoscopic application of fibrin glue after cautery of bleeding lesions was described in 20 patients with grade >2 refractory HC, reporting an 80% success rate after a single treatment [39], and application of platelet-rich plasma (PRP) was described in 10 patients with BKPyV-induced grade 3-4 HC with 60% complete resolution at one-month follow-up [40]. Intravesical aluminium potassium sulfate (Alum) has been described in cases of radiation-induced HC but its efficacy in treating BKV-HC is still unproven and its use is limited due to potential nephrotoxicity [41]. Hyaluronic acid instillations have been shown to be effective in the treatment of interstitial cystitis and post-chemoradiotherapy-induced interstitial cystitis, as in 7 grade 3 HCs with complete response in 5 patients and partial response in 1 case [42].
12. ***Application of fibrin glue through the cystoscopic approach on a previously cauterized urothelial lesions or intravesical application via urinary catheter of hyaluronic acid (to be retained in the bladder for at least 30 minutes) twice a week are real-world available option to improve bleeding-related to HC***.

    Unresponsive HC despite conservative and endoscopic treatments can be treated by super-selective bladder artery embolization, as described in 26 patients suffering from HC after HCT, with 100% success rate 48 hours after treatment [43].

    More invasive surgical procedures such as urinary diversions or cystectomy should be limited to life-threatening events. Urinary diversion has been reported in several cases, by decreasing bladder distension, reducing mucosal microtrauma, and protecting bladder mucosa from urinary urokinase, which prevents clot formation and subsequent mucosal healing and bleeding cessation. The level of diversion depends on each patient: the percutaneous nephrostomy is the simplest one [44]. Cystectomy is a major procedure burdened with significant morbidity and mortality and should be reserved as a last resort procedure in refractory cases.
13. ***Super selective vesical artery embolization or urological surgery (e.g. cystectomy) are to be considered in very selected cases or life-threatening acute events***.

Supportive treatment. ECIL guidelines state that BKPyV-HC management is based on the best supportive therapy, such as hyperhydration and diuretics, pain management, and platelet transfusions (AIII) [1]. Other non-specific measures to improve the healing process of damaged urothelial mucosa can be recommended only with low-grade evidence (C III) [1]. EO re-analyzed some supportive care topics specifically for HCT in the pediatric setting.

Pain management: Studies on pain management specifically related to HC in pediatric settings are not available. Clinical practice is generally

Table 1. Statements.

Prevention of EOHC
Hyperhydration with 3 L/m^2 continuous infusion and electrolytes supplementation according to single-center clinical practice is recommended, starting from 12 hours before Cyclophosphamide administration to be continued up to 24 hours after the end of Cyclophosphamide administration.
Mesna continuous infusion of 100% of the total Cyclophosphamide dose, starting before chemotherapy administration, to be continued up to 30 hours after the end of chemotherapy administration, in association with intermittent Mesna administration of 30% of total Cyclophosphamide dose, is recommended, particularly with high-dose Cy doses administered for Post-Transplant Cyclophosphamide hematopoietic cell transplantation. Intermittent administrations can be performed up to 3 times, before and after chemotherapy (+4 and +8 hours).
Bladder irrigation as prophylaxis for early-onset hemorrhagic cystitis is not recommended, due to difficulties related to Foley catheter placement in a pediatric setting and the invasiveness of the procedure.
Forced diuresis with Furosemide should be performed as an adjunctive strategy with the administration of high-dose of Cyclophosphamide and hyperhydration, according to single-center protocols and patient- or transplant-specific features.
Urine alkalinization as a preventive strategy of early-onset or late-onset hemorrhagic cystitis in a pediatric hematopoietic cell transplantation setting is not recommended.
Screening of BKPyV and criteria to start antiviral treatment
Screening in urine and blood by qPCR for BKPyV and other causes of HC (Adenovirus, JC polyomavirus, bacteria) is recommended in case of clinical suspicion (urinary symptoms, abdominal pain, with microscopic or macroscopic hematuria). In the case of BKPyV-related hemorrhagic cystitis, although the efficacy of antiviral therapy is not defined yet, it is conceivable that early antiviral treatment may reduce the duration and entity of viral infection. A threshold of BPyV load of > 10^7 copies/ml in urine and/or > 10^3 copies/ml for plasma is suggested.
Antiviral therapy and adoptive immunotherapy for BKPyV-HC
Low-dose cidofovir (1 mg/kg two or three times a week) is the preferred treatment for BKPyV-related hemorrhagic cystitis due to its safety profile, efficacy, and the possibility to avoid the co-administration of oral probenecid, available only as tablets for adults. Treatment is recommended until clinical and/or virological response is achieved (disappearance of macro-hematuria and at least 1 log decline BK viremia, respectively), in 4-6 weeks. High-dose cidofovir (3-5 mg/kg once a week) with oral probenecid is recommended in case of hemorrhagic cystitis due to Adenovirus systemic infection. Weekly clinical and virological assessment of response is recommended. Immunosuppression reduction is an option to consider versus the risk of onset/worsening GVHD.
Intravesical CDV should not be routinely recommended in pediatric patients affected by BKPyV-related hemorrhagic cystitis.
Adoptive cell therapy availability is limited, but it can represent an option in selected cases, particularly in phase 2 or phase 3 trial settings.
Urological management
Early involvement of a urologist from the first clinical suspicion of hemorrhagic cystitis is recommended.
A three-way catheter to perform continuous bladder irrigation is recommended for patients with HC and severe bladder pain and/or risk/evidence of urinary obstruction; a two-way catheter-associated to a percutaneous sovrapubic cystostomy could be an alternative option.
Application of fibrin glue through cystoscopic approach on previously cauterized urothelial lesions or intravesical application via urinary catheter of hyaluronic acid (to be retained in the bladder for at least 30 minutes) twice a week are real-world available options to improve bleeding-related to HC.
Super selective vesical artery embolization or urological surgery (e.g. cystectomy) are to be considered in very selected cases or life-threatening acute events.
Supportive treatment
Treatment of pain with opiate derivatives that do not interfere with the coagulation process is recommended. Despite frequent use of antispasmodics, evidence of efficacy is limited in pediatric HCT patients and deserves further investigation.
Platelet transfusion trigger <50 × 10^9/L is recommended for patients with HC. In case of platelet refractoriness, a platelet threshold of 20 × 10^9/L is acceptable. The use of fresh frozen plasma or coagulation factor concentrates is limited to specific clinical problems (coagulopathy, reduced plasma levels of clotting factors, increased red blood cell transfusion requirement, uncontrolled bleeding).
Hyperbaric Oxygen Therapy is recommended for refractory or persistent hemorrhagic cystitis, while its benefit in the early phase of the clinical course is an area of clinical research.

based on experience and guidelines related to urinary symptoms in different contexts [45].

Non-Steroidal Anti-Inflammatory Drugs (NSAID) are not recommended due to the risk of bleeding. Opiate derivatives can represent a viscera-directed approach to bladder inflammatory pain.

Bladder inflammation causes bladder spasms, with primarily nociceptive but also neuropathic pain, further elicited by some treatment strategies themselves (bladder irrigation, catheter placement) [45].

Anticholinergic agents (oxybutynin, tolterodine) and β3 adrenergic agonists (mirabegron and vibegron) relax detrusor smooth muscle and increase bladder capacity; they are equally recommended in the adult population. Oxybutinine and tolterodine are approved beyond the age of 5 years [46], but no evidence study is available about efficacy in HC setting. β3 adrenergic agonists have been recently approved in pediatric age [47], however, only 1 report described its use in HCT setting [48]. Additionally, an interaction with sirolimus [49] has been reported.

14. ***Treatment of pain with opiate derivatives that do not interfere with the coagulation process is recommended. Despite the frequent use of antispasmodics, evidence of efficacy is limited in pediatric HCT patients and deserves further investigation***.

Transfusion and bleeding management: Guidelines for transfusion management for pediatric hematology and oncology patients [50] suggest a threshold of 20-50 × 10^9/L in patients with HC, according to previous studies [51], which however do not include pediatric patients.

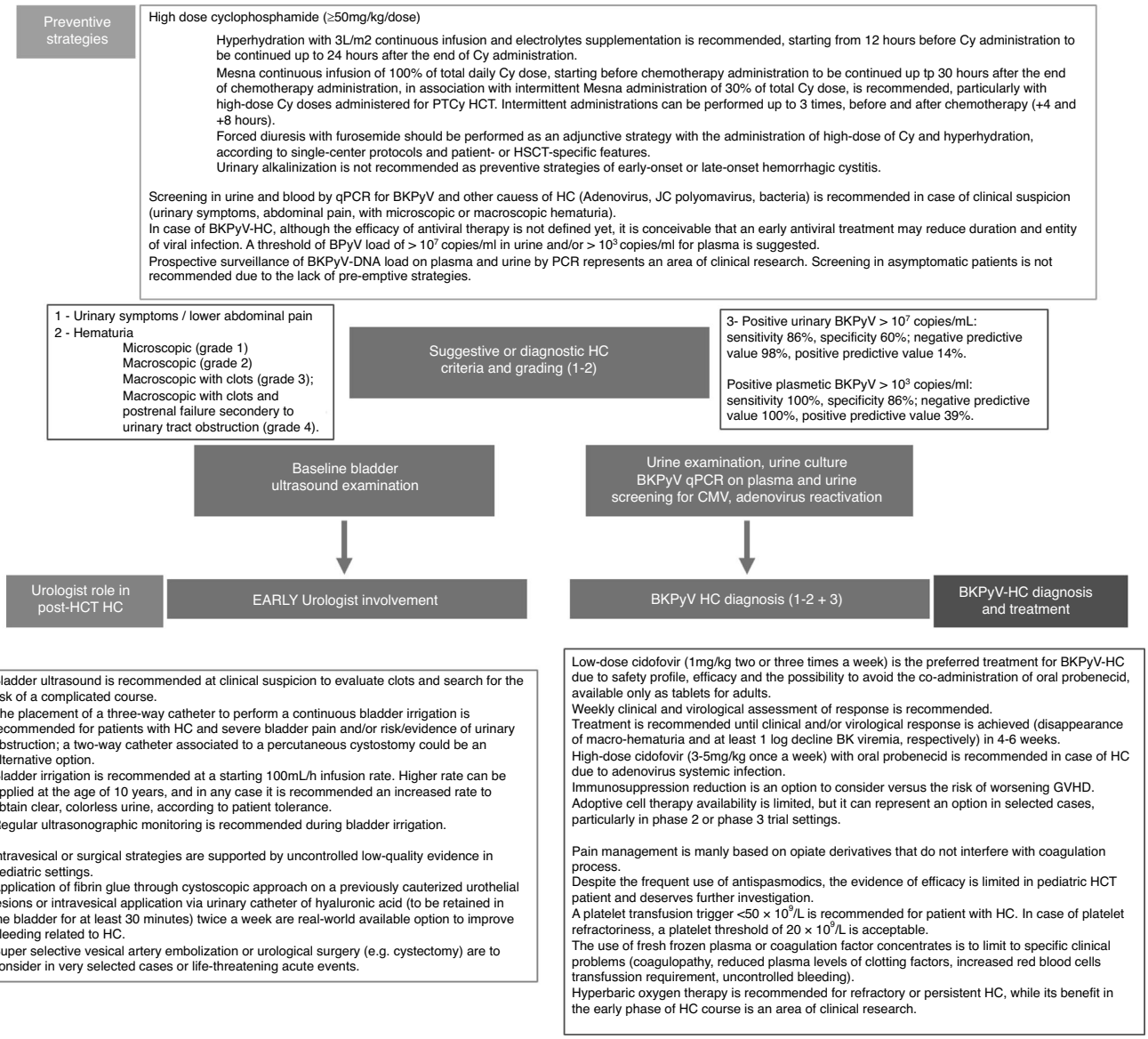

Fig. 1 Recommended practices in prevention, diagnosis, and management of HC in pediatric HCT setting. BKPyV BK Polyomavirus, Cy Cyclophosphamide, HC hemorrhagic cystitis, HCT hematopoietic cell transplantation, PTCy Post-Transplant Cyclophosphamide.

The use of tranexamic acid is not recommended for the risk of intra-bladder coagulation [52].

Anecdotical reports are available about the use of clotting factors, such as Factor XIII at a dose of 20 to 230 U/kg immediately after HC onset [53] or recombinant Factor VII at a dose of 90 ug/kg every 4–6 hours [54].

No specific trials on fresh frozen plasma in HC in pediatric settings in available.

15. ***Platelet transfusion trigger <50 × 10^9/L is recommended for patients with HC. In case of platelet refractoriness, a platelet threshold of 20 ×10^9/L is acceptable***.

The use of fresh frozen plasma or coagulation factor concentrates is limited to specific clinical problems (coagulopathy, reduced plasma levels of clotting factors, increased red blood cells transfusion requirement, uncontrolled bleeding).

Hyperbaric oxygen therapy: Hyperbaric oxygen therapy (HOT) increases the oxygen gradient between the urothelial bladder epithelial layer and surrounding tissue, promoting neoangiogenesis, fibroblasts, and stem cell recruitment [55, 56]. 4 reports in heterogeneous children cohorts showed an overall clinical response of about 80%. The procedure was limited by barotrauma or claustrophobia [57–60]. Other drawbacks of HOT [1] are its limited availability, dedicated hyperbaric room facilities, and the opportunity to perform the procedure in general anesthesia for children at younger ages.

16. ***HOT is recommended for refractory or persistent HC, while its benefit in the early phase of the clinical course is an area of clinical research***.

DISCUSSION

Table 1 summarizes the consensus statements about the discussed topics. An algorithm derived from the consensus statement is shown in Fig. 1.

Prevention of EOHC appears to rely on more standardized evidence in the literature about hyperhydration (3 L/m^2) in the association of Mesna in continuous infusion and/or in bolus.

Differently, approaches for LOHC are still under study. The consensus confirms that detecting BKPyV load in urine and in plasma is useful in case of clinical suspicion of HC; a threshold of

BKPyV viruria > 10^7 copies/mL and/or of BKPyV viremia > 10^3 copies/mL in a patient with HC > 2 can justify a therapeutic early intervention with CDV.

The involvement of urologists is essential not only late in the course of HC, to decide on surgical treatment, but also in the early phase of HC to decide the best modality of urinary catheterization, and to reduce the patient's discomfort and control pain.

In conclusion, this consensus aims to represent the starting point to make the treatment of HC more homogeneous among different pediatric transplant centers.

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AUTHOR CONTRIBUTIONS

GD performed the literature review, summarized the results of the survey and the consensus, conceived and designed the work and the algorithm, and drafted the manuscript. MC performed the urological review and drafted the urological section of the manuscript. MF performed the survey. SC, DP, and MF appointed the panel and supervised the methodology of the consensus. GDO, MC, SC, EO, FV, MC, FS, FC, NM, MCM, KP, ES, FPT, VT, DP, and MF attended the consensus meeting. MC reviewed the urological section of the consensus. SC, EO, AB, FV, MC, FS, FC, NM, MR, MCM, KP, ES, FPT, VT, DP, and MF reviewed the paper and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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