Canadian Urological Association Best Practice Report: Pediatric hemorrhagic cystitis

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Introduction

This best practice report aims to provide the general practicing urologist with basic background information regarding the pathophysiology and natural history of hemorrhagic cystitis (HC) in the pediatric population, as well as diagnostic and algorithmic therapeutic recommendations. Given that HC in the pediatric population is most frequently diagnosed in the setting of bone marrow (BMT) or stem cell transplantation (SCT), discussion and recommendations will focus largely on this population, but many of the diagnostic and treatment options can be expanded to broader pediatric populations affected by HC.

Methodology

A systematic literature search was performed in the PubMed, Medline, and Cochrane Library databases using the term "hemorrhagic cystitis." The search was limited to articles from 1998 to the present day, with some exceptions made for seminal articles referenced in the bibliographies of multiple manuscripts. Due to the paucity of high-quality systematic reviews, meta-analyses, and large comparative studies written on this topic, the majority of evidence and recommendations are based on lower-quality case series and case reports.

The websites for the American Urological Association, the European Association of Urology, the Societies for Pediatric Urology, the European Society for Pediatric Urology, the National Institute for Health Care and Excellence, the Children's Oncology Group, and the Société Internationale d'Oncologie Pédiatrique were examined for guidelines and policies regarding the management of pediatric HC, but none were available.

All manuscripts were reviewed using the modified Oxford Center for Evidence-Based Medicine grading system for guideline recommendations, as employed by the International Consultation on Urologic Disease (ICUD).

Definition

HC is defined by the presence of hematuria and lower urinary tract symptoms, such as dysuria, frequency, or urgency, in the absence of other potential contributing factors, such as vaginal bleeding or bacterial or fungal urinary tract infections.[1] Multiple grading criteria have been published to distinguish the varied presentations of HC. Frequently referenced grading schema are Droller and Arthur's, which are used to aid the clinician in discerning potential treatment options and inform the clinician about prognosis (Table 1).[2,3] The European Organization for Research and Treatment of Cancer has combined similar grading criteria, along with quality of life parameters to further relay the morbidity and mortality implications of each grade.[4]

Background and natural history

The reported incidence of HC ranges widely from 5–70% irrespective of grade.[5,6] Unlike in adults where radiation is the most common cause, the more frequent causes of HC in children are the immediate and late effects of stem cell and/or bone marrow transplantation for malignant and benign diseases. Rare reports of medications (risperidone) and other disease processes (ataxia telangiectasia) have also been linked to the development of HC.[7-9]

Early-onset HC characterizes the immediate phase following conditioning for transplantation, which carries no absolute definition but has been described as ranging anywhere from 48 hours to two weeks after conditioning.[6,10] The early-onset bleeding typically occurs as a result of either the conditioning regimen itself — chemotherapy and/or radiation — and/or the intended myelosuppression and resultant thrombocytopenia. The chemotherapeutic agents most frequently implicated in causing HC are the alkylating agents — cyclophosphamide, ifosfamide, and busulfan — that yield acrolein as a hepatic metabolite, which results in bladder mucosal inflammation, sloughing, and thinning.[6,11,12] To

Table 1. Grading definitions of hemorrhagic cystitis

	Droller 1982[2]	Arthur 1986[3]	CTCAE[4]
Grade 0		No hematuria	
Grade 1	Microscopic hematuria/ dysuria	More than 50 RBCs/HPF	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Macroscopic hematuria	Macroscopic hematuria	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL
Grade 3	Macroscopic hematuria with small clots passed with voiding	Macroscopic hematuria with clots	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiological or operative intervention indicated; limiting self-care ADL
Grade 4	Macroscopic hematuria with clots causing upper tract obstruction requiring instrumentation for clot evacuation	Macroscopic hematuria with clots and an elevated creatinine secondary to obstruction	Life-threatening consequences; urgent radiological or operative intervention indicated
Grade 5			Death

ADL: activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous; RBC/HPF: red blood cell per high-power field.

reduce some of these toxicities, attempts have been made to decrease the intensity of conditioning prior to transplantation with shorter durations of chemotherapy and the use of fludarabine with lower doses of total body irradiation.[5,13] Though Yamamoto et al found the frequency of developing HC was similar in both groups, there was a trend towards less severe grades of HC and shorter duration of HC (25 days vs, 45 days; p=0.016), and transfusion requirements were significantly less than conventional induction therapy.[13] Adopting a similar reduced intensity conditioning (RIC) regimen, Giraud et al found that HC was less common in patients receiving RIC (p<0.01).[5]

Late-onset HC is often immune-related and characterized by reactivation of normally latent, asymptomatic viruses, such as BKV, CMV, JC virus, adenovirus, and rarely simian virus SV40.[9,14,15]

BKV, one of the polyomaviruses along with CMV, JCV, and SV40, is found in serum of up to 90% of healthy adults, despite being asymptomatic.[16] The virus lies dormant in the kidney following initial infection in childhood. Immunosuppressive states, such as post-chemotherapy[17] or bone marrow transplant, are thought to result in reactivation and replication of the latent virus. BKV can have various presentations, with HC being the manifestation of most urological interest. Arthur et al first reported the link between BK viruria and HC, noting that BK viruria frequently preceded the onset of hematuria.[3] HC was noted to be four times more likely in patients whose urine tested positive for BKV than those who did not. In 2004, Bogdanovic et al demonstrated that an arbitrarily determined urine viral load $>10^6$ copies/μl urine was predictive of the development of HC rather than the presence of BKV alone.[18] Additionally, the best correlation to the development of HC was seen in patients with $>10^6$ BKV copies/μl urine and acute graft-vs-host-disease (GVHD) combined (p=0.003). The authors proposed that possibly GVHD therapy with immunosuppressants allowed for BKV reactivation, large viral replication, and consequently the onset of HC. Cesaro et al demonstrated superior prognostic value of plasma rather than urine BKV viral loads. Plasma BKV viral load $>10^3$ copies/ml had a sensitivity of 100%, specificity of 86%, negative predictive value (NPV) of 100%, and positive predictive value (PPV) of 39% for developing HC, whereas urine BKV viral load had a sensitivity of 86%, specificity of 60%, NPV of 98%, and PPV of 14%.[19]

Though BKV is the most frequently identified viral etiology of HC among the post-allogeneic BMT population, accounting for 80.8% of viral culprits, Gorczynska et al noted adenovirus in 15.4% and JCV in 3.8% of patients with HC.[1] Furthermore, while not all patients positive for BKV developed HC, all patients positive for adenovirus progressed to HC. Fortunately, most hematuria is mild (69.2%) and of short symptomatic duration (mean 3.8 days, range 1–12), with a mean duration from day of BMT to hematuria onset of 41.2 days (range 9–144).[20]

Factors predicting a higher risk of developing HC have been widely studied. Among the most widely understood risk factors is undergoing allogeneic vs. autogeneic BMT/SCT with HC rates of 5.5% vs. 2.5%, respectively (p=0.003 and odds ratio [OR] 2.85 for allogeneic transplant on multivariate analysis).[3,21] Grafts from unrelated allogeneic donors were found to carry an OR 20 for HC.[5] Across various studies, the conditioning regimen (i.e., cyclophosphamide, busulfan, and/or radiation [XRT]), development of acute GVHD, and CMV reactivation were also considered risk factors for the development of HC.[6,21-23] Age less than five years was inversely correlated with HC occurrence (OR 0.21) on multivariate analysis.[21]

As might be expected, the presence of and higher grades of HC are associated with longer times to resolution and consequently longer hospital stays.[21,24] Higher HC grade (III–IV), pelvic XRT, BMT, hematological malignancy, ifosfamide exposure, and male gender also confer a higher risk of undergoing invasive urological intervention (p<0.05).[23,25] The development of HC in any patient undergoing BMT/SCT

is associated with a greater risk of mortality, particularly if HC presents before 200 days post-SCT (p=0.002).[20] Viral etiology did not affect post-SCT survival, rather hematological malignancy (OR 2.74) and ifosfamide exposure (OR 1.988) were associated with higher mortality.[20,23]

Initial management/prevention

Although the source of hematuria is quite clear in pediatric patients undergoing BMT/HSCT, all other potential etiologies (i.e., urinary tract infection, urolithiasis, and urothelial/renal malignancy) must be ruled out through a thorough history and physical examination and laboratory and microbiological investigations. Imaging with Doppler renal and bladder ultrasonography can aid with this evaluation.[26] Upper tract assessment may reveal hydronephrosis indicative of obstruction and subsequent need for operative management. Visualization of the bladder should incorporate measurement of the bladder wall thickness, which may be focally or diffusely increased in the setting of HC. Doppler investigation may also reveal focal or diffuse hypervascularity, as well as distinct bleeding, which may be amenable to targeted cautery during cystoscopic evaluation.

As there are no direct guidelines on treatment for this patient population, there is no definitive algorithm of options and recommendations throughout the progression of treatment. Fig. 1 provides suggestions for clinicians to guide them through treatment based on several systematic reviews and previously proposed algorithms.[6,21,25] The remainder of this report will follow a similar progression of severity and invasiveness of treatment options.

Because of the well-reported incidence of gross hematuria and HC in patients undergoing conditioning for allogeneic BMT/SCT, these patients are routinely prophylactically treated with continuous bladder irrigation (CBI), 2-mercaptoethanesulfonic acid (mesna), and hyperhydration during their myelosuppressive conditioning. Whereas previously, CBI use was based on anecdotal practice, Hadjibabaie et

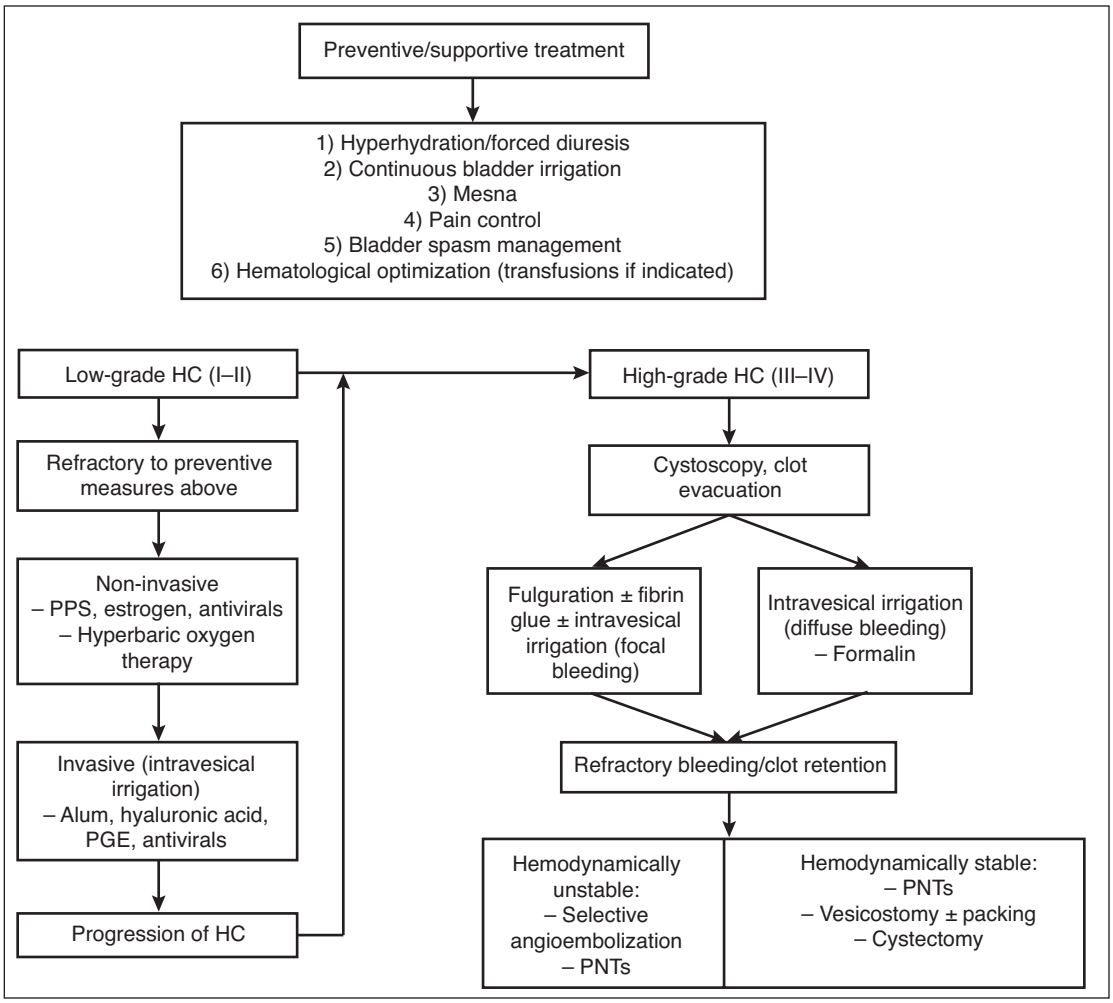

Fig. 1. Proposed algorithm for treatment of pediatric hemorrhagic cystitis. HC: hemorrhagic cystitis; PGE: prostaglandin E; PNT: percutaneous nephrostomy tubes; PPS: pentosan polysulfate.

al conducted a study of patients receiving cyclophosphamide conditioning prior to allogeneic BMT who were treated with CBI and compared to historical controls who did not receive CBI.[27] The treatment group received CBI with normal saline at 300 ml/hour via a three-way Foley catheter 12 hours before their first dose of cyclophosphamide through until 48 hours after their last dose of cyclophosphamide, at which point the catheter was removed. The incidence of HC in the treatment group was 32.5% compared to 50% in the control group (p=0.11), and there was no significant difference of the grades of HC. There was, however, a shorter duration of HC and shorter hospitalization in the treatment group, was well as a lower incidence of late-onset HC (7.7% in CBI group, 45% in control group; p=0.009). Though no comparative studies have evaluated its effectiveness alone, using similar rationale to that of CBI, many conditioning protocols incorporate the use of IV hyperhydration (4–5 L D5 with 0.45% normal saline [NS] with 20 mEq KCl/day, starting 24 hours prior to infusion of cyclophosphamide) and forced diuresis (as needed to maintain urine output of 150–200 ml/hour) in attempts to dilute potential damaging therapy byproducts.[2,28]

The addition of mesna to therapy during conditioning targets the acrolein metabolite of cyclophosphamide through binding with mesna's sulfhydryl group and consequent deactivation of acrolein. In a prospective, controlled study, Jiang et al compared intermittent to continuous intravenous (IV) mesna during cyclophosphamide conditioning.[11] Patients in the continuous treatment group had significantly less HC occurrences at both 30 and 60 days (continuous: 30 days – 0%, 60 days – 5.88%; intermittent: 30 days – 34.4%, 60 days – 40.6; p<0.002 for both).

Control of the dysuria or bladder spasms that may be associated with HC and/or Foley catheterization for its prevention and/or treatment is routine. Options for pain management include treatment through the use of various short- and long-acting narcotics, (i.e., morphine and derivatives), anticholinergics (i.e., solifenacin, oxybutynin, and tolterodine), penazopyridine, and intravesical lidocaine/bupivacaine.[21,28,29] Many of these patients will also experience marked myelosuppression, therefore, close monitoring and replacement of red blood cells, platelets, and plasma is required to ensure the safe and successful resolution of HC.[28]

Recommendation: Routine history and physical with imaging should be performed to confirm the etiology of HC at onset. All patients undergoing chemotherapeutic conditioning prior to allogeneic BMT/SCT should receive preventative hyperhydration, CBI, and mesna, as well as, supportive analgesia with systemic and targeted medications at the onset of HC with symptoms *(Level 3 evidence, Grade C recommendation)*.

Non-invasive treatment

Antivirals

Given the aforementioned prevalence of viral sources of HC, some have recommended following BK virus titers in urine and blood using DNA PCR assays during the course of conditioning for BMT/SCT.[19] Alternatively, at the onset of HC, viral cultures and viral loads can be measured to target therapeutic intervention. The antiviral cidofovir has become the mainstay of treatment for polyomaviruses, such as BKV and JCV, and adenovirus, though its route of administration, and dosage are quite varied in the literature. Given its potential nephrotoxicity and potential pre-existing renal compromise in this patient population, lower doses (0.25–1 mg/kg/week vs. traditional 3–5 mg/kg/week), administration through an intravesical route via urethral catheter (invasive), or combination with probenecid have all been proposed to reduce potential renal injury.[30-32] Other antivirals, leflunomide to treat BKV and ribavirin to treat adenovirus, have also been studied in pediatric patients with virus-induced HC, but rigorous trials assessing their efficacy in this patient population are lacking.[33,34]

Recommendation: In patients with HC proven to be due to a virus on urine culture or urine PCR, targeted treatment with IV or intravesical antivirals is recommended as a relatively low-risk treatment *(Level 3 evidence, Grade C recommendation)*.

Pentosan polysulfate (PPS)

The use of PPS has been primarily studied in interstitial cystitis. As a semisynthetic glycosaminoglycan, its proposed mechanism of action is through adherence to the bladder wall glycosaminoglycan layer and replacement of already damaged areas in order to protect the bladder from irritants such as urine, bacteria, and other toxic substances.[6] Duthie et al tested the application of PPS to the pediatric post-BMT HC population through the introduction of a protocol for HC management and retrospectively compared this to historical controls.[35] Once HC was diagnosed, protocol patients were hydrated and treated with analgesia and oral PPS 100 mg three times daily. Bladder catheterization was avoided, escalating from in/out to CBI if patients had repeat clot retention and cystoscopy with clot evacuation in refractory bleeding. The authors noted that the diagnosis of HC was made significantly quicker with the introduction of the protocol (39 vs. 76 days; p<0.01) and transfusions of blood and platelets were significantly reduced in the protocol group. No side effects of the drug were noted. Both groups had similar duration of HC (protocol 32 days vs. control 36 days; p=0.84), although 4/5 controls died with active

HC and 0/5 protocol patients died, so this may not reflect the full duration of HC.

Recommendation: There is limited evidence on the positive benefits of using PPS in pediatric patients with HC, therefore, further studies are needed prior to broad implementation *(Level 4 evidence, Grade D recommendation)*.

Estrogen

Conjugated estrogen has been used in the management of HC, either in oral or IV form. It is thought to treat HC by promoting stabilization of small blood vessels, suppressing the immune response, and facilitating the repair of injured tissues.[36,37] Potential side effects that have been proposed or observed, however, include liver dysfunction, hypercoagulability, hypertension, facial flushing, feminization in males, and malignant transformation, a grave risk in patients with pre-existing histories of malignancy. Heath et al evaluated 10 children with HC following high-dose chemotherapy and SCT who received estrogen.[38] The treatment was started via IV and transitioned to oral after 2–3 days; liver function tests (LFTs) were monitored every 48 hours. Duration of therapy ranged from 5–23 days, resulting in reductions in HC symptoms in 90%, although two patients required repeated IV and oral dosing after initially being partial or non-responders. One patient had existing liver GVHD and developed elevation in LFTs and, therefore, therapy was stopped. Mousavi et al's study of oral estrogen noted no benefit in the management of HC.[39] This randomized, case-control study of 56 adult and pediatric patients post-SCT demonstrated an insignificant downgrading of HC in treatment relative to control groups.

Recommendation: There is conflicting evidence regarding benefit vs. harm with estrogen therapy. Additional prospective, randomized, controlled studies are indicated to clarify its use in managing HC *(Level 4 evidence, Grade D recommendation)*.

Hyperbaric oxygen therapy (HOT)

HOT has wide-reaching uses within urology, particularly in the management of radiation-induced hematuria, but has also recently come to be recognized as a potential therapeutic option for pediatric patients with post-BMT HC. It is thought to assist in the resolution of HC by inducing neovascularity and permanent tissue healing in the damaged bladder tissue.[40] Following a positive case report by Furness et al, where the only notable side effect was bilateral otitis media, multiple institutions have reported case series on their similarly positive results.[41-43] Though the exact protocols of HOT therapy varied, it was typically initiated once HC reached grade II–III and patients had failed prior conservative therapies. Patients underwent multiple dives (total dive time 85–90 minutes) for 5–6 days a week at 2.1–2.5 atm with either 100% oxygen only or a mixture of 100% oxygen and chamber air dives. Complete resolution of HC in these studies has reportedly ranged from 70–94%. A median of 10–13 sessions were needed to yield complete resolution of HC. Savva-Bordalo et al also noted a strong correlation between the time from HC onset to the initiation of HOT and the time from HOT to HC resolution ($r=0.70$; $p<0.05$).[43] In this study, three patients did end therapy early due to ear barotrauma, pressure intolerance, and claustrophobia, indicating that patients with a history of claustrophobia and diving intolerance should avoid HOT. Patients with active cancer, active viral infection, or Fanconi's anemia are also advised to avoid HOT.[6,44]

Recommendation: HOT has been proven to be safe, effective, and relatively low-risk in treating pediatric patients with HC. Its widespread use, however, may be limited due to cost and access to facilities with HOT *(Grade 3 evidence, Level B recommendation)*.

Invasive treatment

Prostaglandin (E1/E2)

Several reports exist on the use of prostaglandin (PG) E for the management of HC, although the exact mechanism of action is not widely understood. In a review of practice, Cesaro et al noted that intravesical PGE2 use at the discretion of the physician for severe and/or refractory HC post-SCT in children resulted in 37% success, although success was not well-defined.[41] The therapy was diluted, instilled intravesically, and then allowed to dwell for 1–2 hours. Instillation was repeated daily until HC resolution or for at least one week until being considered unsuccessful. No patient experienced complications or intolerability necessitating therapy withdrawal despite concerns over its potential for inducing bladder spasms or flushing. Trigg et al noted more positive results in their pediatric post-BMT study with intravesical PGE1, as PGE2 was not commercially available in the U.S.[45] All children were sedated during therapy, which targeted a therapeutic dwell time of one hour. HC was eliminated in 5/6 patients over a seven-day course, and in some cleared in as little as 24 hours. No apparent side effects were noted.

Recommendation: PGs may be of modest benefit as an intravesical therapy in pediatric patients with HC with urethral catheters, although additional studies are needed to clarify its efficacy and if sedation or general anesthesia is needed to administer the therapy due to concerns for its potential to cause painful bladder spasms *(Level 3 evidence, Grade C recommendation)*.

Hyaluronic acid (HA)

Much like PPS, the use of HA has predominantly been seen in the interstitial cystitis population for its role in enhancing connective tissue healing within the bladder.[10] Additionally, it has been proposed that the HA may alter a step of the polyomavirus' life cycle and that its breakdown products may trigger the secretion of various cytokines and chemokines by macrophages that inhibit viral replication.[46] In their case report of a 7.5-year-old boy with HC refractory to conservative therapy post-BMT, Cipe et al administered intravesical HA (40 mg in 50 ml solution) via catherization, clamped for one hour, drained, and then repeated dosing a week later after an initial partial response, and later complete resolution within four days of the second dose.[10] Miodosky et al used a similar protocol prospectively in a group of pediatric and adult post-SCT HC patients with no control group and repeat dosing after one week if no response in HC was noted.[47] Of the seven patients treated, four responded after an initial dose, and two responded after a second dose. Complete response was noted in five of the seven patients at a median of 12 days (range 7–23).

Recommendation: HA intravesical therapy may be of benefit in treating HC via bladder instillation, although repeated applications may be required and, thus, more robust evidence is required to demonstrate its efficacy *(Level 4 evidence, Grade D recommendation)*.

Alum

The use of intravesical alum in patients with gross hematuria is well-noted in the adult literature. Alum is thought to work by adhering to raw protein surfaces, resulting in decreased vascular permeability, vasoconstriction, and reduced inflammation.[48] As its mode of administration is relatively similar to CBI, it is commonly used when patients demonstrate HC refractory to CBI alone. Typically, a solution of 1% alum (10 g aluminum potassium sulfate mixed in 1 L distilled water) is instilled via a three-way Foley catheter at a rate of 300 ml/hour or less. Prior to initiation, patients must be cleared of all intravesical blood clots, either manually or surgically; otherwise, they may suffer from difficult to resolve "alum balls," which can precipitate urinary obstruction. Praveen at al evaluated the effectiveness of alum for treating hematuria in a prospective, randomized, controlled comparison with PGF2 instillation.[49] Of the nine patients treated with alum, six had complete resolution of hematuria and three had partial resolution; however, three had recurrent bleeding. Along with bladder spasms, as were seen in all of Praveen's alum patients, alum toxicity can lead to encephalopathy and seizures, particularly in patients with renal insufficiency.[6,28,50] Patients receiving alum therapy should be monitored with serial aluminum levels and evaluated regularly with a high index of suspicion for toxicity should any neuropsychiatric symptoms arise.

Recommendation: Alum bladder irrigation is effective in treating pediatric HC, although the patient's bladder must be fully cleared of blood clots prior to initiation of therapy. Patients must also be monitored closely for potential aluminum toxicity, particularly in the setting of renal failure *(Level 3 evidence, Grade C recommendation)*.

Cystoscopy, clot evacuation, and fulguration

Following failure of conservative therapies, cystoscopy offers both a diagnostic and therapeutic opportunity for the urologist to escalate management of the HC patient. Cystoscopic evaluation aids the clinician in ruling out any potential malignant causes of HC while also distinguishing bleeding as originating from a focal vessel or a diffuse source. The small diameter of the pediatric urethra, especially in prepubertal males, can be quite problematic, hence limiting the ability to pass a reasonably sized scope that will allow effective irrigation and evacuation of clots. When possible, with the larger diameter of the cystoscope relative to a Foley catheter, effective clot evacuation can proceed, possibly concomitant with the placement of a suprapubic catheter for more facile postoperative bladder irrigation.[6] Focal bleeding vessels can be cauterized either with a Bugbee electrode or laser fiber, though aggressive, diffuse fulguration risks potential late scar formation and bladder capacity compromise.[8,21]

Recommendation: Although evidence is lacking, cystoscopy, clot evacuation, and fulguration of bleeding are a mainstay of therapy in management of pediatric HC for their capacity to diagnose and treat HC, as well as provide symptom relief from patients in clot retention *(Level 4 evidence, Grade C recommendation)*.

Fibrin glue

Though a relatively new phenomenon, fibrin glue application at the time of cystoscopy has demonstrated substantial success in HC refractory to non-invasive conservative therapies. Tirindelli et al have published multiple accounts of their work with fibrin glue.[51,52] The fibrin glue is generated in 6 ml aliquots from 120 mls of the patient's own virus-inactivated blood or fresh-frozen plasma over 30 minutes. In their cases, cystoscopy is performed with a 24 Fr nephroscope and the bladder insufflated with carbon dioxide at 12 mmHg, and the glue then sprayed evenly over the bleeding, raw surfaces, where it polymerizes on contact and sets over several days. A catheter is left in place without CBI postoperatively. In their earlier study, 4/5 (80%) patients had a rapid, good response, one of whom was a 17-year-old female (the rest were adults).[51] In a later study with 35 patients, there was 83% complete response rate, which was achieved after one,

two, or ≥3 fibrin glue applications in 60%, 17%, and 6% of patents, respectively. The procedure was well-tolerated with no adverse events observed.[52] Given the protocol recommended by Tirindelli et al, however, the 24 Fr nephroscope will limit applicability in the pediatric population, as most children younger than adolescents will not be able to accommodate this caliber in their urethra.

Recommendation: Intravesical fibrin glue application is a promising treatment option in patients undergoing cystoscopy with clot evacuation, as it can be applied focally or diffusely to hemorrhagic areas. Additional research is needed to expand its applicability, as current recommendations for large-caliber cystoscopes limits its use in children *(Level 3 evidence, Grade C recommendation)*.

Formalin

As in adults, in severe cases of refractory HC, sclerotherapy is a consideration in the pediatric population, but often a last resort prior to irreversible management options. The proposed mechanism of action of formalin, much like its derivative formaldehyde, is to precipitate proteins by reducing amino acids and fixing blood vessels, thus achieving hemostasis.[53] Due to pain associated with bladder instillation, general anesthesia is necessary whenever formalin is instilled intravesically. Furthermore, prior to any consideration of formalin instillation, patients must be evaluated for vesicoureteral reflux (VUR) with a voiding cystourethrogram due to potential for irreversible damage to the upper tracts with VUR. Should VUR be present, the ureteral orifices can be occluded during instillation with Fogarty catheters. Using traditional concentration of 4% formalin, Cheuk et al noted "satisfactory responses" in all five children with instillation of the solution, an indwelling period of 10–20 minutes, and then a washout.[24] Four of the five children had improvement after one treatment, whereas the fifth needed three treatments in two months to yield an adequate response. Other case reports have documented success with lower concentrations, such as 1% and 2%, though often with repeated courses of therapy needed.[21,54] Alternatively, cystotomy with application of 4% formalin soaked swabs or endoscopic placement of formalin soaked pledgets have also been reported in cases.[53] Silver nitrate irrigation has also been used to treat HC, but is notable for bladder fibrosis and contracture.[6] Formalin and silver nitrate are, therefore, typically avoided or considered last-resort options due to their potential for bladder scarring and long-term compromise of bladder function.[6] Especially in the pediatric population, significant consideration of long-term implications of therapy must be considered prior to pursuing these options.

Recommendation: Although effective, the need for anesthesia with formalin instillation and the potential long-term compromise of bladder function must be heavily considered when resorting to this therapeutic option for children with HC *(Level 3 evidence, Grade D recommendation)*.

Percutaneous nephrostomy tube (PNT)

Often considered a last resort stabilizing measure, urinary diversion with bilateral percutaneous PNTs has become more a commonly used option in patients with HC refractory to all conservative therapies whose next only option is cystectomy. The theory behind diverting upper tract urine with nephrostomy tubes is that downstream persistent urine bathes the bladder in urokinase, the proteolytic enzyme present in urine, which may contribute to persistent gross hematuria.[6] By removing this fibrinolytic activity, which degrades beneficial fibrinogen and fibrin clots, clot formation in the bladder can be promoted so that the bladder eventually becomes filled with clot and bleeding ceases. Eventually, clamping trials of PNTs can be attempted, the blood clot disintegrates, is passed per urethra, and the tubes are ultimately removed. Lukasewycz et al reported on PNTs placed in children undergoing HSCT with HC refractory to conservative measures.[55] Five of 11 had improvement within 30 days, and four of those five had complete response with the fifth passing of their disease. Two of the 11 were stabilized with the PNTs, one progressed and needed clot evacuation, and the remaining three passed of unrelated causes. The average time to stabilization was 12.4 days, and average duration of PNTs being in place was 8.8 weeks. No long-term sequelae were reported.

Recommendation: Bilateral PNT urinary diversion is a temporizing measure to allow the bladder to clot off, thus managing stable or unstable HC patients refractory to all other conservative and moderately invasive therapies short of performing irreversible surgical urinary diversion. Persistent bladder spasms from blood clots may limit its tolerability in pediatric patients *(Level 3 evidence, Grade C recommendation)*.

Treatment options for refractory, life-threatening HC

Supraselective bilateral vesical artery embolization (SVAE)

With progressive advances in interventional radiological techniques, targeted embolization of bladder vasculature has added an additional tool to the urologist's armamentarium for management of the acutely ill HC patient refractory to prior conservative and invasive therapies.[25,56,57] Embolization is employed using either gelatin sponge microparticles, gelfoam pledgets, or alcohol microspheres following angiography to identify the bilateral arterial vesical branch targets. Often SVAE is considered in patients with HC and hemorrhagic shock and massive blood product requirements, although it

may also be considered in patients for whom conservative and other less invasive therapies have proven ineffective and HC has persisted for months. García-Gámez et al noted complete resolution of HC within 1–2 weeks in their three patient case series of children with post-BMT/SCT HC.[56] Han et al reported on their aggressive case series of pediatric and adult patients with grade III–IV HC following post-allogeneic SCT who failed to improve with hyperhydration, platelet/blood transfusion, CBI, and pain management.[57] Patients had HC for a median of 20 days prior to undergoing SVAE. SVAE yielded a complete response in 60% and partial response in 20%, with a median time to complete response of 26 days. Morbidity was noted in 20% of patients who complained of gluteal claudication the day following embolization, however, this spontaneously resolved within one day of the intervention in all patients. Data are lacking on the long-term sequelae of bladder function following SVAE.

Recommendation: SVAE offers modest control of HC refractory to conservative therapy, however, outside of unstable patients, the appropriate time point for its use along the HC treatment pathway and the long-term safety of its application require further investigation *(Level 3 evidence, Grade C recommendation)*.

Cutaneous vesicostomy

Short of proceeding with cystectomy, an alternative to bilateral PNTs for urinary diversion is the cutaneous vesicostomy. Among the case reports describing its use, it is typically employed in the setting of hemodynamic instability with high transfusion requirements or in patients with terminal disease.[25,58] In Gander et al's case, a gel-port was used to secure the bladder mucosa against the abdominal wall, as severe bladder wall edema prevented adequate suture fixation.[25] A urinary ostomy bag can be applied overlying the vesicostomy to collect urine, more easily remove clots, and continue CBI through a urethral catheter if so desired.[58] In the author's experience, bladder-packing with lidocaine with epinephrine soaked sponges can also aid with local analgesia and vasoconstriction to reduce hematuria. This approach can allow for removal of urethral catheters, which, particularly in children, can be a source of much distress and discomfort.

Recommendation: Despite a lack of high-quality studies, cutaneous vesicostomy in the terminal or refractory pediatric patient offers potentially reversible direct bladder access for clot evacuation and application of topical therapies, while also allowing for possible removal of painful urethral catheters *(Level 4 evidence, Grade C recommendation)*.

Cystectomy

When all conventional and invasive options have been exhausted, and HC persists, the urologist can turn to extirpative surgery to remove the source of HC. As this is an irreversible option, it should only be considered in intractable, life-threatening HC. The surgical approach and urinary diversion selection are at the discretion of the patient and surgeon, however, most reports describe the construction of an ileal neobladder either with preservation of the bladder trigone and ureteral insertion or without trigonal preservation and ureteral reimplantation.[59] As with neobladder creation for other indications, the detubularized Studer type has largely become the surgical approach of choice due to its increased bladder capacity and decreased bladder spasms from gut peristalsis. Regarding management of the trigone, Sèbe et al favor subtotal cystectomy with bladder neck preservation if the ureters are unobstructed.[59] Should there be concern for irreversible ureteral obstruction, however, ureteral reimplantation is recommended.

Recommendation: Cystectomy is reserved as a treatment option when all other efforts to control HC have failed. Long-term implications of this option must be considered in the pediatric population, as well as the fitness and hemodynamic stability of the patient for whom it is chosen *(Level 4 evidence, Grade C recommendation)*.

Experimental therapies

Numerous experimental therapies are being studied for patients with HC that either focus on rebuilding injured bladder mucosa or augmenting the coagulation cascade. Recombinant human keratinocyte growth factor, epidermal growth factor, placenta-derived stromal cells, mesenchymal stem cells, and adoptive transfer of viral-specific T cells for virus-associated HC in patients with slow immune reconstitution have been studied in case reports in patients refractory to conservative therapies such as CBI and HOT. While preliminary reports with some of these therapies are promising, minimal evidence exists to support their effectiveness and safety.[60-63]

Recommendation: Due to the experimental nature of therapies such as recombinant human keratinocyte growth factor, epidermal growth factor, placenta-derived stromal cells, adoptive transfer of viral-specific T cells, factor VII, factor XIII, and mesenchymal stem cells, their therapeutic use to treat HC is not recommended until further robust trials demonstrate safety and benefit *(Level 4 evidence, Grade D recommendation)*.

Conclusions

Although the age-old saying, "children are not little adults," is true when dealing with most pediatric illnesses, many of the management strategies used to manage adult HC have been tested and successful in pediatric populations as well. HC in children more frequently rises from complications of oncological regimens and immunosuppression, while in

adults, radiation is often the culprit, similar management algorithms and therapies can yield effective illness resolution. Anatomical, psychosocial, and pain threshold considerations pose differences in these two populations, which may lead the clinician to one treatment over another. These pediatric-specific factors, along with each unique patient presentation must be factored into the experienced clinician's treatment plan for efficiently, effectively, and conscientiously treating this challenging disease entity.

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