REVIEW

Hemorrhagic cystitis: a review of the literature and treatment options

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Introduction: Hemorrhagic cystitis (HC) is a morbid condition for patients and can be challenging for urologists to manage. There are many potential contributing etiologies and the severity of bleeding can be variable. It is important to consider each clinical scenario when formulating management strategies in order to provide the highest quality of care to patients. We provide a review of the literature including diagnosis and treatment options.
Materials and methods: We performed a literature search on PubMed using the following keywords: hemorrhagic cystitis, cystitis, gross hematuria, intractable hematuria. We considered all available published articles with no specific inclusion or exclusion criteria for the purposes of this review.

Results: We reviewed a total of 41 articles and identified a broad differential diagnosis for intractable hemorrhagic cystitis including infection, chemical exposure, malignancy, nephropathy, trauma, radiation therapy, and idiopathic etiology. Depending on the severity of bleeding, many treatments have been described. These range from conservative strategies (bladder fulguration and continuous irrigation) to more extreme and morbid therapies (intravesical instillations, embolization, and urinary diversion).
Conclusion: Hemorrhagic cystitis is a relatively common and can be a difficult condition to manage for urologists. It is important to understand the etiology and available treatments options in order to best treat our patients. We provide a comprehensive and thorough review of the literature and propose a stepwise treatment approach.

Key Words: hemorrhagic cystitis, hematuria

Introduction

Intractable hemorrhagic cystitis (HC) is a challenging clinical condition characterized by diffuse inflammation and bleeding of the bladder urothelium that can be both difficult to manage for the urologist and quite morbid for patients. The differential diagnosis of

HC is broad, including infection, chemical exposure, malignancy, nephropathy, and radiation therapy. The degree of hematuria associated with HC ranges from mild bleeding that resolves on its own to life threatening persistent hemorrhage requiring blood transfusion and surgical intervention. There are two published classifications for HC. The DeVries Classification categorizes HC as mild if there has been no change in hematocrit level, moderate if there is gross hematuria leading to blood transfusion (less than 6 units), or severe if the patient with gross hematuria has required transfusion of more than 6 units of blood, Table 1.[1] The Vela-Ojeda Classification uses grade one

TABLE 1. The DeVries classification

Mild	No change in hematocrit
Moderate	Gross hematuria requiring transfusion (< 6 units)
Severe	Gross hematuria requiring transfusion (> 6 units)

TABLE 2. The Vela-Ojeda classification

Grade 1	Microscopic hematuria
Grade 2	Macroscopic hematuria
Grade 3	Hematuria with clots
Grade 4	Hematuria with clots and obstruction, azotemia

for microscopic hematuria, grade two for macroscopic hematuria, grade three for hematuria with clots, and grade four for gross hematuria with clots as well as

obstruction and azotemia, Table 2.[2] These systems can be helpful to stratify patients when considering management.

Many treatment paradigms have been described, usually starting with conservative management, and escalating to more aggressive therapies as needed. If manual irrigation through a three-way foley catheter and subsequent continuous bladder irrigation fails, patients may go to the operating room for manual clot evacuation and fulguration of bleeding lesions. If hematuria persists despite conservative operative intervention, there are intravesical and extravesical treatment options to address bleeding, though these treatments are often morbid with significant side effects and varying efficacy. Intravesical treatments include bladder irrigation with alum, silver nitrate, Amicar, prostaglandins, and formalin, Table 3. Extravesical treatments include hyperbaric oxygen, bladder embolization, and cystectomy with urinary diversion.

Although HC is common, literature on etiology and management is relatively sparse. We aim to review hemorrhagic cystitis including diagnosis, management, treatment regimens and side effects. Additionally, we propose a stepwise approach to treating intractable HC.

TABLE 3. Treatment regimens for hemorrhagic cystitis beyond irrigation and fulguration

Treatment	Dosage/Regimen*	Notes
Alum (aluminum potassium sulfate)	50g/5L sterile water 1% solution instillation @ 250-300mL/hr	Irrigation for 2-3 days; check serum aluminum with prolonged irrigation or renal insufficiency; can be given without anesthesia.
Silver nitrate	0.5%-1% solution	Instilled for 20-30 minutes
Aminocaproic acid (Amicar)	200mg aminocaproic acid/L NS acid/L NSS	
Prostaglandins (PGE-2, others)	8-10 mg/L at 100 mL/h Or 0.4 to 1% solution with CBI for 2 hours QID with NS CBI between	Up to 10 hours at a time with NS CBI between
Formalin	1-2% solution, up to 10% 10-300mL	Instill under gravity <15cm above pubic bone for 10-15 minutes max; r/o ureteral reflux before; requires anesthesia
Hyperbaric oxygen	100% oxygen at 1.5-3 atm for 60-120 minutes	Up to 20-40 sessions

*solutions by indwelling bladder catheter; NS = normal saline; CBI = continuous bladder irrigation

Design

We performed a literature search on PubMed using the following keywords: hemorrhagic cystitis, cystitis, gross hematuria, intractable hematuria. We considered all available published articles with no specific inclusion or exclusion criteria for the purposes of this review. We reviewed a total of 41 publications.

Differential diagnosis

There is a broad differential diagnosis for hemorrhagic cystitis. Therefore, these patients should be thoroughly evaluated with a history and physical exam and may also require upper tract imaging with either a CT urogram (preferred) or retrograde pyelograms, cystoscopy, and urine cytology. Upper tract imaging and cystoscopy should be used to rule out malignancy or bleeding from the upper urinary tract if the cause for gross hematuria is unknown.

Causes of HC are numerous and commonly include infection, malignancy, chemical exposure, and radiation therapy. In patients with severe HC, one contemporary series reported pelvic radiation as the most common cause.[3,4] Presentation after radiation is often delayed, and the median time to presentation has been reported as 35 months after treatment.[4-7] Infections can be bacterial, fungal, or viral. The most commonly diagnosed viruses include BK virus, JC virus, adenovirus, cytomegalovirus, or Epstein Barr virus. Chemical causes include cyclophosphamide, ifosfamide, thiotepa, or analine dye. Other less common causes include systemic diseases such as nephropathy syndromes, Crohn's disease, amyloidosis, medication induced nephropathy, vascular malformation, and trauma.[1]

Overall, infectious causes are more common in immunocompromised patients. BK virus almost exclusively occurs in patients who are immunocompromised. The virus replicates in urothelial cells and causes tissue injury, which increases the local inflammatory response. This virus is detected in 25%-100% of stem cell transplant recipients, of which 40% may develop hemorrhagic cystitis.[8] BK virus has been associated with HC in patients receiving oxazophosphorine chemotherapy, and these patients tend to present early with more prolonged HC.[9] Adenovirus is more common in children and renal transplant recipients, and can cause nephropathy syndromes.[10] In these cases the management of hematuria is largely supportive with hydration, bladder irrigation, and blood transfusion as needed, and should resolve with treatment of the underlying infection.

Chemical exposure may also cause HC. Cyclophosphamide and ifosfamide are within a class of chemotherapeutic drugs called oxazaphosphorines. Up to 50% of patients may develop microscopic hematuria, and up to 15% develop gross hematuria. Development of HC is dose dependent and typically develops within 48 hours. The toxicity results from renal excretion of the metabolite acrolein, which directly stimulates bladder mucosal sloughing with resulting tissue edema and fibrosis.[11] Mesna can be given along with treatment, which binds acrolein and decreases the risk of developing HC. However, 10%-40% of patients will still develop HC after mesna and there is conflicting evidence in the literature regarding its benefit.[12] As is the case with infectious etiology, the treatment is largely supportive.

Pelvic radiation is a common treatment modality
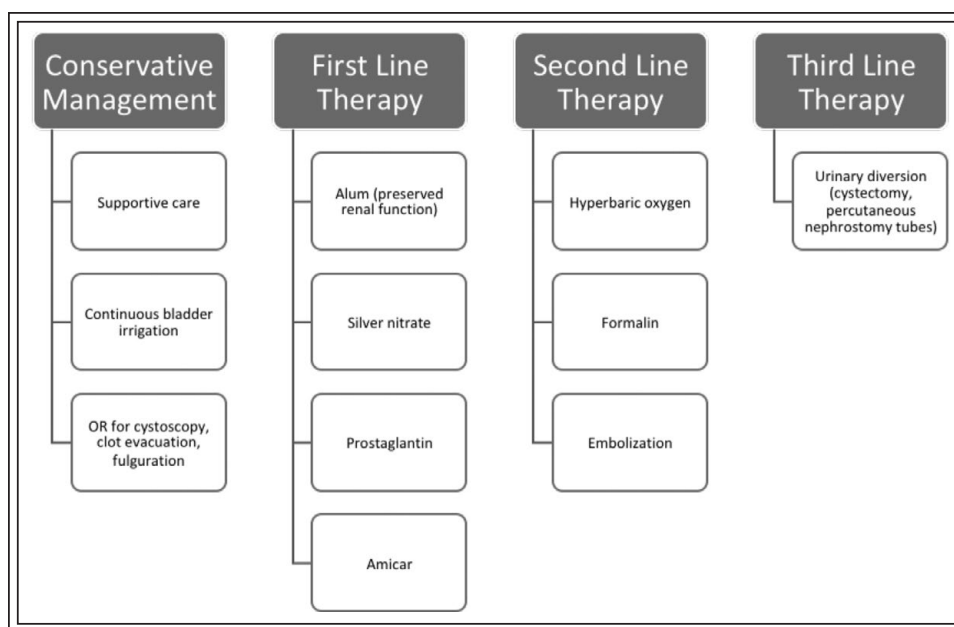
Figure 1. Algorithm for managing hemorrhagic cystitis.

for many cancers of the genitourinary, gastrointestinal, and reproductive tracts. After pelvic radiation, up to 5% of patients may develop moderate to severe gross hematuria due to radiation-induced cystitis.[6] There is a broad range for time of onset, with studies reporting onset within 6 months to 10 years after the completion of radiation therapy. Risk has been reported to start at 45Gy and may increase with escalating dosages. Radiation damages the vascular endothelium and induces progressive endarteritis. This leads to tissue ischemia and necrosis with subsequent mucosal sloughing and neovascularity. Ultimately, this culminates in fibrosis and secondary inflammation with poor tissue healing.[13]

Treatment

Initial management includes hydration, continuous bladder irrigation (CBI), supportive care with transfusion as needed, and addressing correctable factors such as infection, coagulopathy, and tumor burden. Attempts should be made to evacuate the bladder of all clots, ideally with manual irrigation through a large bore three-way catheter. If hematuria continues despite conservative measures, the patient may need to be taken to the operating room for cystoscopy with clot evacuation and fulguration. In a series of 33 patients with HC from radiation or cyclophosphamide, 42% had resolution of hematuria after cystoscopy and clot evacuation with or without fulguration, requiring no further treatment.[14] If gross hematuria persists beyond more conservative operative interventions, there are a number of treatment options including alternate intravesical and extravesical therapies to consider, as outlined in Figure 1.[3]

Alum

Alum is an intravesical option for patients with HC with normal renal function. This treatment includes aluminum ammonium sulfate or aluminum potassium sulfate and was first described by Ostroff and Chenault in 1982.[15] Alum works by causing protein precipitation on urothelial lining to stimulate vasoconstriction and sclerosis of capillary endothelium.[16] Typically 50g of alum in 5L of sterile water is given, creating a 1% solution instilled at 250-300 mL/hour via CBI. Prior to initiating intravesical alum therapy, the bladder must be completely evacuated of all clot burden as the solution can cause significant clot aggregation that is difficult to dissolve. Patients do not require anesthesia for this treatment, which makes it a favorable option. Overall alum is well tolerated, and cell penetration is low, thus its effect is limited to the cell surface. Alum

is renally excreted and therefore should be reserved for patients without renal impairment, as it can be rarely systemically absorbed. Signs of systemic absorption manifest primarily as mental status changes, and patients with chronic kidney disease are at particular risk. Overall, success rates of 60%-100% have been reported in the literature.[15,17-20]

Westerman et al analyzed 80 patients from 1997-2014 with severe intractable HC who underwent 1% alum instillation. In this cohort, 95% of patients had prior radiation therapy, and gross hematuria occurred at a median of 93 months after treatment. The majority of the cohort (78%) had previously undergone cystoscopy with clot evacuation, and 12% failed an alternate intravesical agent. The median duration of alum instillation was 2 days. By 17 months after alum instillation, 54% required no further intervention. Adverse effects were reported as spasms (35%) and transient delirium (5%).[21]

A second smaller cohort in the 1980s analyzed by Goel et al consisted of nine patients with intractable HC despite conservative measures, who also received 1% alum solution irrigation for 48-72 hours. Eight of these patients had HC secondary to urothelial tumors, and one had cystitis after radiation. There was a 100% response and all patients were able to discontinue bladder irrigation without further intervention. After alum treatment, five patients subsequently underwent transurethral resection of the bladder tumors and biopsy of normal appearing mucosa. Post alum biopsy specimens of normal mucosa showed no evidence of cellular damage. At 6 months, there was a 66% sustained response rate and there were no reported patients with new vesicoureteral reflux, voiding symptoms, urethritis, stricture, or burns of the genitalia.[19] There were several other small case series from the 1980s showing similar efficacy with low morbidity.[18,20] Overall, intravesical instillation of 1% alum solution is generally well tolerated and efficacious, and can be given easily without anesthetic requirement.

Silver nitrate

If patients have evidence of renal insufficiency, they may be treated instead with intravesical silver nitrate. Before using this treatment, patients must first undergo a cystogram to rule out vesicoureteral reflux, as this compound is converted to nitric acid, which causes chemical cauterization. Instillation with 0.5%-1% solution for 20 to 30 minutes may be completed on the hospital floor or in the operating room. Use has rarely been reported in the literature, which consists of

mostly case reports or small case series. Although it is well tolerated, it has been reported to have generally low success rates for bleeding control.

Montomgery et al reported nine patients who received silver nitrate for refractory HC from 2000 to 2015, eight of whom had radiation cystitis. None of the patients had resolution of hematuria after treatment, and all nine went on to further procedures. No patients suffered from any complications.[22] Overall there is a low amount of evidence to support the use of silver nitrate for HC.

Aminocaproic acid (Amicar)

Another option for patients with renal insufficiency includes aminocaproic acid (Amicar), which blocks activation of plasminogen, interrupts fibrinolysis, and counteracts urokinase. It is instilled via continuous bladder irrigation with 200mg aminocaprioic acid per liter normal saline. Symptom resolution has been reported in up to 92% of patients. Risks include clot retention, systemic absorption, and clotting risk. If the source of hematuria is from the upper tracts, caution must be used, as Amicar may form clots leading to obstruction.[23,24]

Singh et al looked at outcomes of 37 patients from 1974-1985 treated with Amicar. After treatment, 92% were able to stop continuous bladder irrigation within 48 hours. Among this cohort, the most common causes of HC were radiation (38%) and cyclophosphamide exposure (24%). Success rates were marginal if the etiology of bleeding was secondary to bladder tumor. The group presented without any immediate side effects but did not have long term follow up.[24]

Prostaglandins

Prostaglandins (PGE1, -E2 and -F2-alpha) may also be used to treat intractable HC and have mostly been studied in patients with viral and cyclophosphamide induced hematuria.[25-29] Prostaglandins act through an unclear mechanism which is hypothesized to include vasoconstriction, platelet aggregation, and cytoprotection via mucosal coating.[16] There have been multiple regimens described, including CBI at the bedside with 8-10 mg/L at 100 mL/h for up to 10 hours at a time. Success rates have been reported around 50%. Overall it appears well tolerated.[30] Drawbacks to this treatment include variable treatment duration, high costs, and difficulty with obtaining and storing the medication.

Levine et al treated 18 patients from 1988 to 1991 who had cyclophosphamide-induced HC with intravesical PGF2-alpha. Mesna was also given to 72% of the cohort. They received 0.4% to 1.0% solution with CBI for 2 hours, four times daily with saline CBI in between. Half of the cohort (50%) had complete resolution of gross hematuria within a median time of 6 days. The other half went on to receive a second therapy. They noted patients who received higher doses of cyclophosphamide were less likely to respond. In terms of immediate side effects, 78% of patients had bladder spasms. Longer term at 17 weeks of follow up, patients had no changes in renal function and no systemic complications.[29] Overall prostaglandins are a good option as treatment can be administered at the bedside and is well tolerated. However, generalizability is limited as prior use has mostly been reported after cyclophosphamide induced HC.

Formalin

Formalin (37% formaldehyde) is a highly caustic solution reserved for severe cases and is administered in the operating room. It induces cellular protein precipitation and capillary occlusion, causing inflammation and necrosis of superficial and deep bladder layers. Its use in the bladder was first described by Brown in 1969 for patients with advanced bladder cancer.[31] A cystogram must be obtained before usage to rule out vesicoureteral reflux. If reflux is seen on cystogram, formalin treatment should be carried out after insertion of ureteral catheters for occlusion.[17,32,33] The patient's skin must also be padded and protected.[13] The provider should start with 1%-2% solution, with the catheter on light traction to prevent urethral exposure, instilled under gravity less than 15 centimeters above the pubic bone for 10 to 15 minutes. There is wide variation in the literature in the concentration and volume of formalin instilled, however volumes range from 10-300 mL or up to bladder capacity, and Choong et al highlights that the concentration is most important, as complication rates rise with higher concentrations.[16] About 10%-30% of patients will require subsequent procedures with higher dosing if hematuria persists after using 1%-2% solution. This treatment has high reported success rates of 80%-90%, however significant risks include bladder fibrosis, decreased bladder capacity, ureteral and urethral strictures, and renal failure.[34]

A small series of eight patients, reported by Ziegelmann et al were treated with formalin for radiation cystitis refractory to alum, silver nitrite, or Amicar. The primary outcome assessed was resolution of HC without need for further intervention. Hematuria resolved in 75% of patients immediately,

with 50% maintaining a durable response at a median follow up of 8 months. There was one patient treated with 4% formalin solution who developed a severe bladder neck contracture and contracted bladder, ultimately requiring cystectomy with urinary diversion. In another series of patients from 1974, Fair et al treated 18 patients with refractory HC. The majority (90%) of patient's pathology was related to radiation cystitis, and the remainder had prior treatment with cyclophosphamide. Four of the patients received 10% formalin, while the other 14 received 1%. The group receiving 10% formalin had a 100% success rate in control of hematuria, however 75% of the group had severely reduced bladder capacity, and new hydronephrosis with vesicoureteral reflux. One of these patients ultimately required cystectomy, and pathology revealed marked fibrosis and scarring throughout superficial and deep layers of the bladder. After the first four patients were treated and observed to have significant adverse events, the remaining patients were treated with a reduced concentration. All of the patients receiving 1% formalin also responded initially, though 28% of patients had recurrence of hematuria. Recurrences were treated with repeat treatment of 1%-2% formalin, leading to 100% success rate at 6-36 months of follow up with no adverse reactions noted.[35] Godec and Gleish found similar results in a review of the literature, with overall lower complications reported from articles using 4% formalin compared to 10%.[33]

Formalin is a powerful agent in controlling HC, though best saved for severe or refractory cases in which patients have failed multiple other interventions. The risks associated with formalin instillation must be thoroughly discussed with the patient prior to proceeding with treatment.

Hyperbaric oxygen

Hyperbaric oxygen is a promising extravesical treatment option for patients with HC. Hyperbaric oxygen, which has been described since the 1980s, increases oxygen extraction by tissues. This results in diminished edema and promotes neovascularization with capillary ingrowth into previously hypoxic and scarred tissues. Among the treatments mentioned in this review, this is the only one which promotes tissue healing and angiogenesis. Patients inhale 100% oxygen at a pressure of 1.5-3 am for 60-120 minutes, and patients may require up to 20-40 sessions. Response rates over 90% have been reported in the literature. Notable side effects include otalgia (15%), vision disturbance (10%), vertigo, and paresthesias, though long term side effects are rare.[36]

Limitations to the use of hyperbaric oxygen include availability, long treatment duration, and high cost.[37]

Oscarsson et al performed a multicenter randomized control trial with hyperbaric oxygen therapy on 79 patients with HC from 2012-2017. They followed patients for 6 to 8 months using questionnaires to assess urinary symptoms (function, bother, incontinence, hematuria, pain) and cystoscopy to assess epithelial atrophy, telangiectasia, hematuria, and bladder capacity. Overall, 73% of the patients using hyperbaric oxygen showed improvement in patient perceived urinary symptoms compared to 34% of patients in the standard care group.[36]

In a prospective study, Bevers at al assessed 40 patients with varying degrees of HC who received 20 sessions of hyperbaric oxygen therapy at three atm for 90 minutes. The study included patients who had radiation for cervical, bladder, prostate, and colon cancer. Patients were followed for an average of 23 months, and 75% had no HC on follow up. Similar results were reported by Chong et al who followed 60 patients with radiation cystitis from 1988-2001 who received hyperbaric oxygen at 2.36 atm for 90 minutes for an average of 33 treatments. At 12 months, 80% of patients had total or partial resolution of their gross hematuria. Patients treated within 6 months of onset of gross hematuria tended to have better outcomes, as 96% of patients treated within 6 months had a complete or partial response to treatment compared to 80% of the group overall (p = 0.003). Outcomes did not appear affected by prior chemical instillation for HC treatment or time since radiation. This high response rate was also reported by Degener et al in patients receiving hyperbaric oxygen for refractory radiation or chemotherapy induced HC. With a mean follow up of 68 months, 80% of patients showed a sustained complete response to treatment. Overall, hyperbaric oxygen seems to be an effective, albeit inconvenient, treatment leading to tissue regeneration and healing to break the vicious cycle of chronic sloughing and scarring seen in hypoxic irradiated bladder tissue.[37]

Embolization

Vesical artery embolization for intractable hematuria due to HC is an option for patients who have failed other therapies and can be performed under local anesthesia. It was first described in 1974 by Hald and Mygiand for a patient with severe bleeding from radiation cystitis.[38] Mohan et al reported nine patients who received vesical artery embolization from 2003-2015. The majority (80%) of patients had previously treated urothelial cancer while other patients had exposure to cyclophosphamide (10%) or radiation

for cervical cancer (10%). All of the patients had previously failed intravesical therapy including alum, 1% formalin, or silver nitrate. Treatment consisted of polyvinyl alcohol particle embolization of the main vesicular branches off of the internal iliac artery bilaterally. Within 48 hours, there was a 100% success rate of complete resolution of hematuria, which was sustained in 78% of patients at a mean follow up of 14.5 months. None of the patients reported sexual or bladder dysfunction at follow up, however 33% had short term gluteal or thigh pain for several days.[39] In summary, vesical artery embolization is a safe and effective procedure that can be performed under local anesthesia to control hematuria in patients who have failed prior therapy and who may be otherwise unfit for general anesthesia in the operating room.

Other forms of extravesical therapy used to treat HC include nephrostomy tube drainage or cystectomy and diversion as a last line option.

Urinary diversion

If patients have failed or were unable to tolerate interventions mentioned thus far, urinary diversion may be considered for intractable hemorrhagic cystitis. Diversion with bilateral percutaneous nephrostomy tubes can be attempted, however it has been reported that up to 35% go on to subsequent cystectomy.[40,41] The decision to pursue cystectomy may be difficult as patients with intractable HC are often elderly with comorbidities. One retrospective cohort studied 21 patients who underwent cystectomy for HC. The median age was 77, and the majority of patients (95%) had HC after radiation therapy. There were severe complications in 42% of patients, and there was a 16% 90-day mortality rate in this group.[4] As demonstrated in this cohort, cystectomy for HC is associated with a high risk of perioperative complications and should be reserved as a last line therapy in treating HC.

Conclusion

Gross hematuria and intractable hemorrhagic cystitis are morbid conditions that can be challenging for urologists to treat. Many therapies have been described to be effective but have varying side effect profiles. Conservative measures with large bore three-way foley catheters, manual clot irrigation, and continuous bladder irrigation should be attempted for all patients prior to more invasive therapies. The decision for treatment if conservative measures fail depends on availability, need for anesthetic, patient

renal function, and risk of side effects. Alum, silver nitrate, and Amicar are intravesical options which may be trialed if cystoscopy with clot evacuation and fulguration fails. Prostaglandins are another intravesical option, however, they have only proved efficacious for cyclophosphamide-induced HC. Formalin is also an intravesical option, though should be used with great caution given severe side effects. If these measures fail, patients may pursue extravesical treatments including hyperbaric oxygen therapy, embolization, or in extreme cases, cystectomy with urinary diversion. □

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