Prevention and Treatment of Hemorrhagic Cystitis

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Hemorrhagic cystitis is a syndrome associated with certain disease states as well as exposure to drugs, viruses, and toxins. It manifests as diffuse bleeding of the endothelial lining of the bladder. Treatment includes intravesical, systemic, and nonpharmacologic therapies, all of which have advantages and disadvantages.
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Summary

Hemorrhagic cystitis is a syndrome of diffuse bleeding of the endothelial lining of the bladder. The majority of cases are associated with drug therapy, but other causes must be ruled out to ensure the best response to treatment. Although the incidence is low when appropriate prophylaxis and monitoring are employed, the syndrome is associated with high morbidity. Therefore, clinicians should be familiar with available treatments and implement them immediately on diagnosis. Therapy options range from simple, nontoxic procedures to more invasive methods that are associated with severe adverse effects.

Background

Hemorrhagic cystitis results from an assault on the bladder wall by toxins, viruses, irradiation, drugs, or disease (Table 1). Cyclophosphamide is the drug most frequently implicated in the syndrome. Damage to the bladder wall is due to contact with the acrolein metabolite of cyclophosphamide, which causes sloughing, thinning, and inflammation of the epithelium.[1–4]

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Table 1. Causes of Hemorrhagic Cystitis

General Cause	Specific Cause
Drugs	Anabolic steroids
	Busulfan
	Cyclophosphamide
	Ifosphamide
	Immune agents
	Methenamine maleate
	Thiotepa
Diseases	Carcinoma
	Amyloidosis
	Rheumatoid arthritis
Viruses	Adenovirus
	BK virus
	Cytomegalovirus
	Herpes simplex virus
	Influenza A
	JC virus
	Papovavirus
Toxins	Dyes
	Insecticides
	Turpentine
Radiation therapy	

Adapted from references 1–10.

Symptoms may arise during therapy or several days or months afterward. Bleeding most commonly occurs soon after administration of high-dose intravenous cyclophosphamide or after long-term therapy (several months) of smaller oral dosages. Factors that affect the risk of developing hemorrhagic cystitis are rate of infusion, route of administration, dose, and rate of metabolism of cyclophosphamide, as well as the hydration status, urine output, frequency of emptying the bladder, and concurrent exposure to other urotoxic drugs or irradiation.[1,3]

If no means of prevention are taken, the incidence of cyclophosphamide-induced hemorrhagic cystitis is 40–60%. When 2-mercaptoethane sulfonate

(mesna) is given as prophylaxis, the incidence is decreased to approximately 5%.[5] The incidence associated with high-dose cyclophosphamide after bone marrow transplantation is 8–27%.[1] The rate of mortality from uncontrolled hemorrhagic cystitis has been reported as 4%.[2]

Radiation therapy for treating genitourinary malignancies can inflict damage to the bladder that is cumulative with repeat treatments. Patients who receive concurrent cyclophosphamide therapy or who have an infection are at added risk. As with postchemotherapy toxicity, the bladder may become edematous, erythematous, and necrotic.[3]

Patients with autoimmune diseases (e.g., rheumatoid arthritis) occasionally develop hemorrhagic cystitis, most commonly after long-term oral administration of cyclophosphamide. Cases secondary to amyloidosis have been reported as well.[6] Other chronic diseases such as carcinoma of the bladder and necrotizing vasculitis may also manifest as cystitis.[3, 6, 7]

Viruses, including adenovirus, BK virus, and cytomegalovirus, can infect the bladder wall and induce the disorder.[3, 8–10] This usually occurs in immunocompromised populations such as patients who have undergone bone marrow transplantation. The patient may first develop viremia, which spreads to the urine where it comes in contact with the bladder wall. Another pathway of infection is retrograde colonization through the urethra. In the case of adenovirus, the original source may be stool, and the virus may spread from the gastrointestinal tract through the pelvic lymph system.[8]

The clinical diagnosis of hemorrhagic cystitis is based on nonspecific symptoms, such as hematuria, dysuria, urgency, and increased frequency of urination. Urinalysis reveals large cells with hyperchromatic, oversized nuclei with oddly shaped cytoplasm, and microscopic hematuria.[2, 3] The diagnosis can be confirmed by cystoscopy. Damage ranges from minor telangiectatic bleeding to diffuse necrotic ulceration. When severe, the syndrome may lead to constriction of the bladder, anemia, recurrent urinary tract infections, hydronephrosis, bladder perforation, renal failure, and death.[11]

Prevention

Several methods are available to reduce the risk of cyclophosphamide-induced hemorrhagic cystitis, including intravenous hydration with diuresis, concurrent intravenous administration of mesna, and frequent voiding or bladder catheterization with irrigation.[12, 13] The goal is to reduce the time the toxins are in contact with the bladder wall. Intravenous hydration should begin begin 12–24 hours before administration of intravenous cyclophosphamide at a rate of approximately twice that of maintenance, and should be continued for 24–48 hours after completion of cyclophosphamide therapy. Diuretics such as furosemide are administered if urine production declines (< 100 ml/m^2/hr). Mesna is administered at 100–160% of the daily cyclophosphamide dose by continuous infusion, or divided into four doses given intermittently beginning 15–30 minutes before the start of cyclophosphamide infusion. Some clinicians give continuous bladder irrigation of normal saline 250–1000 ml/hour to facilitate removal of toxins from the bladder. However, the presence of the catheter carries a risk of infection and local trauma. When bladder catheterization is not employed, the patient should be required to urinate every 2–4 hours.

The success of mesna as a uroprotectant after high-dose cyclophosphamide was compared with that of hyperhydration with forced diuresis or bladder irrigation in several trials, mostly involving patients undergoing bone marrow transplantation.[14–22] In prospective comparisons of mesna with forced diuresis, patients in the mesna group had less macrohematuria, 13% versus 35%[19] and 11% versus 44%, respectively.[22]

In a similar comparison, mesna administered at 160% of the cyclophosphamide dose was compared with 3 L/m^2 of fluid daily with intravenous furosemide for low urine output.[17] Severe hemorrhagic cystitis (passage of clots, persistent macrohematuria, need for medical intervention) was more common in the mesna group (10% vs 6%), and the frequency of either severe or consistent hematuria was 33% in the mesna arm versus 20% in the hydration arm. The authors concluded that there is no significant difference in efficacy between the two methods.

A randomized trial in 200 patients compared continuous bladder irrigation with continuous intravenous mesna at 100% of the cyclophosphamide dose.[16] All patients also received hyperhydration. Overall, the frequency of hematuria in the bladder irrigation group was 76% and 53% in the patients who received mesna. However, the frequency of severe hematuria was the same (18%), and the investigators resolved that the methods were

Table 2. Treatment of Hemorrhagic Cystitis

Therapy	Administration	Duration	Advantages	Disadvantages
Normal saline	Continuous bladder irrigation	Until urine is clear.	No adverse effects.	Not effective as monotherapy in severe hemorrhagic cystitis.
Alum	1% solution continuous bladder irrigation	Until urine is clear.	Mild adverse effects, no anesthesia required.	Recurrence common, aluminum toxicity rare.
Prostaglandins	PGE_1 375–750 µg Carboprost tromethamine 0.1–0.8 mg% instilled into bladder daily, dwell time 1–4 hrs	4–7 days.	Very few adverse effects, no anesthesia required.	Expensive, close monitoring required, uncertain efficacy.
Silver nitrate	0.5–1.0% solution instilled into bladder, dwell time 10–20 min	Single application, repeat if no response.	Patients may respond after failing other therapies.	Short duration of response, anesthesia required, limited data in literature.
Estrogens	5 mg p.o./day, with or without 1 mg/kg i.v. b.i.d. for first 2 days of therapy	Until bleeding ceases: 7–10 days.	Easily administered.	Increased risk of cardiovascular complications, limited data in literature.
Formalin	1–10% solution instilled into bladder, dwell time 5–30 min	Single application, repeat if no response.	Successful response common.	Anesthesia required, painful, risk of vesicoureteral reflux.
Phenol	Bladder instillation of 100% solution Dwell time 1 min	Single application.	Used in refractory hemorrhagic cystitis.	Limited data in literature.
Vasopressin	Continuous i.v. infusion at 0.4 U/min	Until bleeding ceases.	Used in refractory hemorrhagic cystitis.	Limited data in literature, systemic adverse effects, limited duration of response.
Aminocaproic acid	5 g i.v. q6h, then 300 mg/kg/day p.o. or continuous bladder irrigation (12 g/L) at 50 ml/hr	Until bleeding ceases.	Used in refractory hemorrhagic cystitis.	Limited data in literature, systemic adverse effects, limited duration of response.

equally effective in this patient population. Thus the method of uroprotection—mesna administration, bladder irrigation, or hyperhydration with forced diuresis—depends on the preference of the clinician.

Treatment

Supportive Care

Treatment begins by discontinuing the offending agent. Fluid intake should be increased to hydrate the bladder and dilute the urinary concentration of the toxin. To decrease the amount of blood loss, the platelet count should be kept above 50,000/mm^3. Local symptoms may be relieved by administration of antispasmodics (oxybutinin or belladonna-opium) and narcotic analgesics. If hematuria does not improve or resolve, intravesical treatment should be initiated.

Intravesical Therapy

Several agents may be administered directly into the bladder to achieve local activity and avoid systemic toxicity (Table 2). Different rates of success have been reported in small patient populations or as case reports. No controlled studies have evaluated or compared the regimens. Adverse effects occur with each method, and in some cases, general anesthesia is required.

Bladder Irrigation

First-line therapy for hemorrhagic cystitis is placement of a large-bore urethral catheter and instituting saline lavage.[2,3] This will decompress the bladder and remove existing clots. If lavage does not free the clots, they must be visualized and freed manually with the aid of a resectoscope placed under anesthesia. Subsequent therapy is much more effective if the bladder wall is free of

Table 3. Preparation of Alum Irrigation Solution

Steps	Example
Weigh out desired amount of powdered alum USP (ammonium or potassium aluminum sulfate).	100 g
Dissolve in appropriate amount of sterile water for irrigation USP for a 10% solution.	900 ml, then add a quantity sufficient to yield 1000 ml.
Heat the mixture until boiling and completely dissolved.	Use hot plate or microwave.
Filter solution through a 0.22-μ filter.	Use hyperalimentation filter.
Add aliquot of filtered solution to sterile water for final concentration of 1% in a laminar air flow environment.	Remove 100 ml from 1-L bottle of sterile water and add 100 ml of filtered solution.

Adapted from reference 24.

debris. Once the lavage returns as a light pink or clear fluid, continuous bladder irrigation with normal saline should begin. If bleeding persists or worsens, treatment should be advanced to administration of another intravesical agent.

Alum

Alum (aluminum potassium sulfate or aluminum ammonium sulfate) has astringent activity on the bladder wall. It hardens the capillary endothelium, inhibiting the mobility of proteins. The urothelium contracts and becomes blanched, resulting in decreased local edema and inflammation.[23] Alum acts only on the surface of endothelial cells and in the interstitial spaces. It has very low permeability into cells and little chance of systemic absorption.[1]

Alum is available as a powder that must be dissolved and diluted in sterile water (Table 3).[2] A final concentration of 1% is most commonly used and may be increased to 2% or 4% to achieve better response.[25] The solution is administered as continuous irrigation through a three-way Foley catheter at a rate of 300–1000 ml/hour. When the appropriate rate is administered, the fluid that drains out through the catheter will be light pink to clear. The response is best when the bladder is evacuated of blood clots before alum therapy so that more of the bladder mucosa is exposed.

Many case reports describe treatment of hemorrhagic cystitis with alum.[23, 25–28] Fifteen patients, most of whom had bladder carcinoma, received alum 1% by continuous bladder irrigation.[26] They required an average of 6 L of irrigation over 21 hours (range 3–48 hrs). Complete response (no hematuria) was achieved in 10 patients (66%) and a partial response (reduced hematuria with no transfusion requirement) in 2 (13%).

Similar results were reported in a prospective evaluation of 12 patients who developed vesical hemorrhage from bladder carcinoma or radiation therapy.[29] All patients had persistent hematuria after clot evacuation and normal saline bladder irrigation. They were then treated with 1% alum solution 3–10 ml/minute for an average of 36.5 hours (range 10–52 hrs) . Six patients (50%) had a complete response, four (33%) partial, and 2 (17%) no response. Success rates in two reports involving 13 patients ranged from 50–100%.[27, 28] Most patients had not responded to normal saline irrigation or cauterization.

Adverse effects attributed to alum therapy include suprapubic pain, fever, bladder spasm, and urinary retention or frequency.[23, 25–29] They may be relieved by analgesics and antispasmodics. The solution's low pH of 4.5 may be a reason for the local effects. Any attempts to neutralize to a physiologic pH will result in precipitation of the salt. Precipitation of alum can occur in the bladder for this and other reasons, clogging the catheter and causing interruptions in therapy. In most cases the obstruction can be cleared by increasing the flow rate through the catheter.[27] Allergic reactions were reported[2] that required discontinuation of therapy.

A remote but serious risk for which patients should be monitored is aluminum toxicity, which manifests as encephalopathy, dementia, speech disorders, and seizure. It is assumed to arise due to increased systemic absorption. It is very unlikely for blood concentrations to reach a dangerous level in the average patient. However, serum aluminum levels should be measured in patients with marked renal dysfunction[30, 31] or those who have received prolonged alum therapy (several days or longer) and experience central nervous system symptoms.

Advantages of alum therapy include no need for anesthesia and low incidence of toxicity. However, the cessation of bleeding is rarely permanent, lasting only while the therapy is being administered. In addition, the precipitate that develops in the bladder can clog the catheter, causing mechanical difficulties.[1]

Prostaglandins

Prostaglandins (PG)E_1, E_2, and F_2 are natural

products of the kidneys and bladder. Release of these substances from the mucosa is regulated by glutathione, which is a membrane protectant. The production of prostaglandins is reduced when the bladder is distended, in conditions such as diabetes mellitus, with disruption of normal urine pH and osmolality, and after contact with carcinogens.[2]

Prostaglandins heal a damaged bladder by repairing the microvasculature and epithelium by several mechanisms.[32-40] In general, cell membranes are strengthened in the presence of prostaglandins, and edema resolves. These substances may also stimulate platelet aggregation and cause local vasoconstriction, leading to decreased hematuria. Specifically, PGF_2 mediates contractility of smooth muscle, which may control bleeding, and PGE_2 has cytoprotective action, which may prevent further damage to the bladder wall.

Carboprost tromethamine, a synthetic derivative of PGF_2, is administered as a solution of 0.1–0.8 mg/dl. It is instilled into the bladder and allowed to dwell for 1–4 hours. This procedure is repeated 3–4 times/day until bleeding subsides, generally in 5–7 days.

In the largest series reported, 24 patients developed hemorrhagic cystitis within 180 days after bone marrow transplantation.[39] The syndrome did not respond to hydrocortisone bladder irrigation and platelet transfusions. After evacuation of clots from the bladder, carboprost tromethamine in 50 ml saline was instilled for 60 minutes every 6 hours. Between doses, continuous irrigation with 0.02% hydrocortisone was administered. Eleven patients participated in the first phase. The initial carboprost dose was 0.2 mg/dl and was increased by 0.2 mg/dl once/day (maximum 1 mg/dl) until a complete response was achieved. Treatment was discontinued after 48 hours of the effective dose, or a maximum of 14 days. Thirteen patients participated in the second phase, which called for an initial dose of 0.8 mg/dl with gradual increases to 1.0 mg/dl after four doses. Therapy was continued for 48 hours after hematuria resolved or for 7 days One patient dropped out due to an unrelated illness. Fifteen patients (65%) responded, one each at doses of 0.4 and 0.6 mg/dl, seven (30%) at 0.8 mg/dl, and six (26%) at 1.0 mg/dl. Within 17 days (median 7 days) nine patients had a recurrence of hematuria, one responded to another course of carboprost, four responded to other treatments, and four had no response.

In another report, eighteen patients, the majority of whom had undergone bone marrow transplantation, developed hemorrhagic cystitis due to cyclophosphamide therapy.[33] Before receiving PGF_2, each subject failed treatment with normal saline bladder irrigation or diuresis and required at least 1 U packed red blood cells/day, or had undergone several clot evacuation procedures. Urine viral cultures were negative in all patients, and therefore cyclophosphamide was presumed to be the only cause of hemorrhagic cystitis. After evacuating existing blood clots, the patients were given a 50-ml instillation of carboprost tromethamine 0.2–0.8 mg/dl for 2 hours 4 times/day. They received a total dose of 3.6–15.8 g over 2–7 days (median 6 days). Nine patients (50%) achieved a complete response after 7 days of therapy. A partial response, with treatment for longer than 7 days, was seen in eight patients, and there was one nonresponder. Bladder spasm occurred in 14 patients but was well controlled by administration of oxybutinin. There were no systemic side effects.

The authors concluded that carboprost tromethamine is an effective treatment with low morbidity compared with alternative therapies. They noted that patients who responded poorly were more thrombocytopenic and required more packed red blood cell transfusions than the other subjects. Of those who had a bone marrow transplant, patients treated on an allogeneic protocol fared worse than those who received an autologous graft.

Several trials reported successful treatment with PGE_1 and PGE_2.[35, 36, 40] Six children who developed hemorrhagic cystitis from cyclophosphamide with or without radiation therapy received intravesical PGE_1 750 µg in 100 ml with a dwell time of 1 hour/day for at least 7 days.[35] Five patients responded with complete elimination of gross hematuria within 7 days. Results were more favorable in 10 patients who had viral-induced hemorrhagic cystitis after bone marrow transplantation.[40] Prostaglandin E_2 0.75 mg in 200 ml normal saline was instilled and left to dwell for 4 hours. Hematuria resolved within 24 hours in 40% of patients, with a median time for all patients of 5 days.

Adverse effects from parenterally administered prostaglandins include pyrexia, vomiting, diarrhea, nausea, flushing, chills, and cough. Fortunately, local instillation of prostaglandins is associated only with bladder spasm and discomfort due to the distended bladder. Patients

can tolerate the treatment even if they are medically unstable,[32] and antispasmodics and analgesics relieve the side effects.

This intravesical therapy is costly, and although it is easily administered at the bedside without anesthesia, the patient must have intensive nursing care for instillation and drainage. Unlike alum, prostaglandins form no precipitate that may clog the catheter. However, the appropriate dosage for a reliable response has not been determined and further investigation is indicated.

Silver Nitrate

Silver nitrate coagulates proteins on the bladder mucosa, resulting in a cauterizing action.[2, 41] A 0.5–1.0% solution is instilled and remains in the bladder for 10–20 minutes; this may be followed by normal saline irrigation to flush out the bladder.[2] The procedure is painful, and the patient must be anesthetized.

In the largest report of this therapy, 10 children developed hemorrhagic cystitis 8 weeks–2.5 years after receiving cyclophosphamide, with or without radiation therapy.[42] Nine of them continued to require transfusions after failing such therapies as aminocaproic acid, saline irrigation, and intravesical steroids. The patients underwent cystoscopy, blood clot evacuation, and normal saline irrigation. Silver nitrate 0.5–1.0% was instilled for 10–15 minutes, after which saline bladder irrigation was given for 24–48 hours. Bleeding was completely controlled in 90% of patients within 24–48 hours. One patient failed to respond to the first course and was treated with phenol instead. Eight patients experienced 12 episodes of recurrence that appeared 1 day–2 years afterward and responded to repeat administration of silver nitrate. Bladder spasm occurred in three patients and subsided after treatment with meperidine and hydroxyzine.

A serious adverse effect that was reported in one patient after silver nitrate therapy is anuria. The patient developed significant obstruction of the ureters and collecting ducts due to crusty build-up that was thought to have arisen from the precipitation of silver nitrate to silver chloride.[41] The authors recommended performing cystoscopy before silver nitrate therapy to become familiar with the anatomy. If the bladder is too severely damaged, precipitation is likely due to an increased tendency of precipitate to form on ulcerated surfaces. The authors also advocated avoiding sodium chloride irrigation to lower the risk of precipitation. This severe reaction has not been reported subsequently, therefore the standard of practice for silver nitrate treatment does not preclude saline irrigation.

One patient developed ileus, abdominal pain, and tenderness after silver nitrate instillation.[43] It was believed that silver nitrate extravasated and precipitated in the perinephric area. The patient underwent surgical diversion of the left ureter. Routine performance of an excretory urogram and a voiding cystogram is recommended to identify patients at risk for developing such severe reactions.

The success of silver nitrate application is variable and and the duration of response is often short. Also, the risks of the anesthesia must be taken into account when considering this treatment option.

Formalin

Formalin is the aqueous form of formaldehyde. It exerts its effect on the bladder wall by hydrolyzing protein, thereby coagulating tissue and controlling bleeding in the mucosa and submucosa. Cross-linking of proteins helps prevent further necrosis, sloughing, and blood loss.[2, 44] Formalin solution is diluted with sterile water to a concentration of 1–10%. It is instilled into the bladder at a volume of 50 ml or bladder capacity under general or local anesthesia and allowed to dwell for 5–30 minutes.[44–60] Anesthesia is required because contact of formalin with the bladder wall causes significant pain.

One group reviewed all the reports of patients who received treatment with formalin for hemorrhagic cystitis.[47] Of the 235 patients, 123 were treated with 10%, 91 with 5% (range 3–6%), and 21 with 1% (range 1–2%) solution. In most of them the bladder was filled to capacity under gravity. Complete response, defined as resolution of hematuria after one course of therapy, was 83%, 78%, and 71% in patients treated with solutions of 10%, 5%, and 1%, respectively. The average dwell time was 12, 23, and 14 minutes for the three solutions. The average duration of response was 3–4 months.

Complications were considered minor if no surgical intervention was required; these were fever, tachycardia, urinary frequency or urgency, elevated blood urea nitrogen or creatinine concentration, mild hydronephrosis, grade I–II vesicoureteral reflux, incontinence, suprapubic

pain, or decreased bladder capacity not requiring urinary diversion. If surgery was necessary, the complication was classified as major; these were anuria, acute tubular necrosis, papillary necrosis, ureteral or retroperitoneal fibrosis, ureterovesical or ureteropelvic junction obstruction, severe hydronephrosis, grades III–IV vesicoureteral reflux, any vesical fistula, and decreased bladder capacity requiring bladder diversion. Minor complications occurred in approximately 15% of patients receiving 1% solution, but increased to 35% for the 5% solution, and were significantly more frequent—80%—for the 10% solution. Major complications were also more frequent at higher concentrations, but the differences were not statistically significant. Patients with hemorrhagic cystitis from radiation treatment of bladder cancer responded best to the 10% solution. However, in those who developed hemorrhagic cystitis from cyclophosphamide or unresected bladder cancer, better results were produced with solutions in the 5% range.

Of 25 patients who were treated with formalin 10% or 4% solutions with dwell times of 5–15 minutes, 88% achieved a good response (hemodynamic stability).[59] After 4 months, there were four cases of recurrence. In 35 patients who received formalin 1%, 2%, or 4% over 20–30 minutes, complete response was observed in 86%, 90%, and 75%, respectively.[46] Recurrence was most frequent after treatment with 1% formalin (23%), as opposed to 0% and 2% with 4% and 2% solutions, respectively. Major complications (bilateral hydroureteronephrosis, vesicovaginal fistula, decreased bladder capacity requiring diversion, death) were more frequent with 4% (100%) than with 1% or 2% formalin (13.6% and 40%, respectively). The authors recommended the 1% solution since it is as efficacious as higher concentrations and associated with fewer severe adverse effects.

The greatest danger with formalin is vesicoureteral reflux, which may result in ureteral obstruction or hydronephrosis. Patients often undergo a cystogram before therapy to evaluate the risk of reflux. Then a balloon is placed and inflated to occlude passage of the drug into the ureter during treatment. Placing the patient in the reverse Trendelenburg position is also effective in preventing reflux. The risk of significant damage outside the bladder is decreased by lowering the concentration of the solution and by shortening the dwell time. Limiting the number of repeat instillations will also decrease the risk.

Phenol

Intravesical administration of phenol can successfully cause chemical cauterization in patients with hemorrhagic cystitis. A 12-year-old child with cyclophosphamide-induced hemorrhagic cystitis was treated with this agent.[61] Thirty milliliters of 100% phenol was combined with 30 ml glycerin, painted across the surface of the bladder, and suctioned out after 1 minute of contact. Then alcohol 60 ml was instilled and suctioned out after 1 minute. Finally, the bladder was irrigated with saline. The patient died of infection within 6 months of treatment but had no recurrence of hematuria.

As with other methods of cauterization, the effects of phenol can be short-lived and anesthesia is required. It is possible that the frequency of fibrosis in the bladder is less than that with formalin therapy.[2, 34, 61]

Systemic Agents

Systemic treatment is reserved for cases that are refractory to intravesical therapy. The literature contains few reports of these agents, and, as with intravesical therapy, no controlled trials have been conducted. General anesthesia is not a concern with this mode of treatment; however, since exposure is more than local, patients are at risk of developing systemic adverse effects associated with the drugs.

Conjugated Estrogens

Conjugated estrogens appear to control hematuria by strengthening the capillary walls of the microvasculature in the bladder mucosa.[62] Five patients who developed hemorrhagic cystitis due to radiation or cyclophosphamide therapy were treated with the agents.[63] Two received 1 mg/kg intravenously twice/day for 2 days, followed by 5 mg/day orally for several months. The remaining three received only the oral regimen. In four patients, the urine was clear within 1–7 days, and no recurrence was seen during follow-up of 12–22 months.

These positive results were replicated in seven patients with cyclophosphamide- and radiation-induced hemorrhagic cystitis who did not respond to formalin, phenol, or saline irrigation.[64] They received conjugated estrogens 2.5 mg orally twice/day. Six subjects had complete response with no gross hematuria within 10 days of therapy, and one did not respond. Other investigators, however, reported

failure of estrogens in managing the syndrome.[65]

Estrogen therapy increases a patient's risk of cardiovascular complications and should not be administered over the long term in patients who have a history of thromboembolic events, cardiovascular disease, or cerebrovascular disease until further studies have been performed.[64]

Vasopressin

Intravenous infusion of vasopressin lessens bleeding into the bladder through direct contraction of smooth muscle, resulting in vasoconstriction.[66] A 15-year-old patient who developed hemorrhagic cystitis after bone marrow transplantation with cyclophosphamide failed treatment with formalin, saline bladder irrigation, and silver nitrate, and still required blood transfusions.[66] Within 1 hour of initiation of vasopressin 0.4 U/minute the bleeding decreased. However, attempts to wean the patient from the infusion resulted in increased hematuria. The patient died of other complications.

Vasopressin may cause severe allergic reactions, such as tremor, sweating, vertigo, headache, abdominal cramping, urticaria, or bronchial constriction. If extravasation occurs, local tissue may necrose. The agent should not be administered unless intravesical therapy fails or if the patient's clinical status is so poor that immediate cessation of hematuria is necessary.

Aminocaproic Acid

Systemic aminocaproic acid can decrease blood loss by inhibiting plasminogen activator substances, thereby halting fibrinolysis. A 54-year-old man who developed hemorrhagic cystitis after cyclophosphamide and radiation therapy was treated with aminocaproic acid 5 g intravenously every 6 hours for 2 weeks, followed by 300 mg/kg/day orally.[67] Concurrently, he received bladder irrigation of aminocaproic acid 12 g/L at a rate of 50 ml/hour. The hematuria diminished within 6 hours, and after 24 hours he had only microscopic blood loss.

One danger associated with aminocaproic acid is that clots that form in the bladder could be too large to pass, resulting in urethral obstruction. Systemic administration may cause nausea, diarrhea, hypotension, malaise, myopathy, dizziness, headache, thrombosis, and rarely, grand mal seizure. However, like vasopressin, this is a useful alternative in the case of life-threatening bleeding that is unresponsive to intravesical therapy.

Hyperbaric Oxygen

In theory, hyperbaric oxygen heals the bladder by increasing tissue concentrations of oxygen, thereby promoting growth of healthy tissue.[68–72] The presence of hyperoxia in the bladder may also help decrease bleeding by causing vasoconstriction. Patients who failed traditional local therapy for hemorrhagic cystitis responded when exposed to hyperbaric oxygen.[68–72] Thirteen patients with radiation-induced hemorrhagic cystitis were placed in a hyperbaric oxygen chamber for 2 hours/day for 60 days.[69] The chamber provided 100% oxygen at 2 atm absolute pressure. Bleeding resolved permanently in 12 of these patients and no adverse effects were seen.

The complete response rate (elimination of all symptoms) was 57% in 14 patients with radiation-induced hemorrhagic cystitis who received hyperbaric oxygen of 100% at 2.4 atmospheres absolute for 90 minutes 5–6 days/week for an average of 28 treatments.[70] Adverse effects in these patients were few and mild, including myopia, visual changes, and middle ear pressure.

Hyperbaric oxygen may cause harm to the body in the form of barotrauma to the ears, toxic effects to the brain (e.g., seizures), pneumothorax, cataracts, retinal vasoconstriction, stroke, and myocardial infarction. However, these effects are not likely to occur from the limited exposure necessary to control hematuria. This treatment modality is not available at all medical centers and should be saved for patients who do not respond to traditional therapy.

Cryosurgery

Another treatment that is not performed frequently is cryosurgery. Patients have benefited from direct administration of liquid nitrogen to the bladder lesions. This is done for four cycles of 2 minutes' duration. Bleeding was arrested for 3 months–5 years after this treatment.[73]

Nonpharmacologic Interventions

Invasive methods of controlling hematuria are reserved as a last resort.[74–78] They include urinary diversion, internal iliac artery embolization, unilateral hypogastric artery ligation, and, if all else fails, cystectomy.[2, 25, 78] Types of urinary diversions include nephrostomy, ureterostomy, ileal loop diversion, cutaneous ureterostomy, and ureterosigmoidostomy. Whenever possible, a reversible procedure is employed, however, some

patients benefit only from a permanent restructuring of the urinary system.

Percutaneous nephrostomy, the most common procedure, diverts urine from the bladder to prevent overdistention, which can cause vessels to rupture.[74] These procedures are reversible; the drains can be removed once the bladder is healed sufficiently. Potential complications, in addition to those generally associated with surgical procedures, are perirenal hematoma, occlusion of the nephrostomy tube, and pyelonephritis. Percutaneous nephrostomy is rarely associated with life-threatening complications. It requires only local anesthesia and can be repeated safely if hematuria recurs.

Nephrostomy tubes were placed in six patients who failed initial therapy and were left in place for 3–168 days (mean 68 days).[75] Fifty percent of subjects had complete resolution of hemorrhage. Others reported that 14 of 16 patients with intractable hemorrhagic cystitis who underwent urinary diversion responded very well and suffered no untoward effects.[76] Surgical methods such as these are not desirable for patients who are hemodynamically unstable.[2]

The goal of embolization of the internal iliac or hypogastric arteries is to prevent blood from reaching the bladder, thereby limiting its loss through the mucosal wall. The procedure is performed under local anesthesia and guided by fluoroscopy.[2, 77] Six of eight patients who underwent internal iliac embolization responded well.[77] Adverse effects include gluteal muscle pain and, in rare cases, paralysis and bladder necrosis.[2]

Additional treatment modalities to control bleeding provide symptomatic relief, but the duration of response is generally limited. For example, direct hydrostatic pressure to the bladder wall can be administered by inflating a balloon in the bladder to a pressure of 100 cm water for 4–6 hours. This technique achieved hemostasis in three of six patients.[79] It is technically difficult to perform and carries the risk of bladder perforation and damage to the function of the detrusor muscle.[2, 79] Direct irrigation with ice was helpful in radiation-induced hemorrhagic cystitis, acting as an astringent through local cooling.[2] Neither of these methods is a primary treatment.

Summary

Several methods for treating hemorrhagic cystitis provide various degrees of response. Ideally, patients at risk of the syndrome are identified early, and proper prophylactic measures are taken. Once hemorrhagic cystitis occurs, the patient should receive intravenous hydration and if clots are present, irrigation of the bladder is indicated. Patients who fail these therapies should be treated with bladder irrigations of prostaglandins or alum, followed by instillation of silver nitrate and formalin if no response is achieved. When these pharmacologic treatments provide no relief, surgical options such as nephrostomy should be considered.

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