Radiation-induced hemorrhagic cystitis

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Purpose of review
To better understand the mechanism of radiation-induced hemorrhagic cystitis and the advantages and disadvantages of available treatment options for bladder hemorrhage as well as preventive measures.

Recent findings
There have been several attempts recently to manage hemorrhagic cystitis with hyperbaric oxygen therapy, transurethral coagulation using Greenlight potassium-titanyl-phosphate laser and other different treatment modalities, but we still need more investigation on larger cohort studies.

Summary
Hemorrhagic cystitis is an uncommon urological problem. It is most often caused by radiation therapy and cyclophosphamide, but can be associated with other contributing factors. Technological advances in radiation therapy have resulted in greater treatment efficacy, with significant reduction in side-effects such as hemorrhagic cystitis. Higher dose radiation treatment, however, is more often associated with problematic hemorrhagic cystitis. Treatment of hemorrhagic cystitis is multifactorial and can range from simple bladder irrigation to cystectomy with urinary diversion.

Keywords
hematuria, hemorrhagic cystitis, radiation cystitis

INTRODUCTION

Treatment of hemorrhagic cystitis remains a challenge for urologists. It is defined as diffuse bladder mucosal bleeding and can result from several causes. Radiation and cyclophosphamide chemotherapy are the most common source. Other causes include bacterial, viral, fungal and parasitic infections, drugs as well as idiopathic disease [1–3].

Radiation-induced hemorrhagic cystitis can appear as late as 2 decades after treatment [4]. External-beam radiotherapy (EBRT) is a noninvasive local treatment modality used to target malignant cells but will also affect the surrounding normal tissue. Technological advances have resulted in greater treatment efficacy, with significant reduction in side-effects including toxicities to adjacent normal tissues. Nevertheless, late radiation tissue injuries, which include cystitis and proctitis, are the side-effects of radiation treatment to the pelvis that still occur. Tissues undergo a progressive deterioration influenced by a reduction of small blood vessels and increased fibrosis, replacing the normal tissue until localized hypoxia compromises normal function [5]. Hemorrhagic cystitis typically presents between 6 months and 10 years after radiotherapy, affecting approximately 6.5% of patients following pelvic radiation [6]. Patients typically present with hematuria, anemia, urinary frequency, dysuria and incontinence or retention secondary to blood clots obstructing the urethra. The risk of these complications increases with higher doses of radiation (>70 Gy) and larger treatment area [7].

Review of the current published literature has suggested several methods of treatment, including simple bladder irrigation, cystoscopic fulguration, intravesical treatment with alum or formalin, hyperbaric oxygenation (HBO), internal iliac embolization and, finally, cystectomy with urinary diversion. However, except for cystectomy, none of these treatments have any guarantee of long-term efficacy [8].

MECHANISM OF RADIATION-INDUCED HEMORRHAGIC CYSTITIS AND PREVENTIVE MODALITIES

Radiation induces mucosal edema and inflammation, although the hemorrhagic sequela usually

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KEY POINTS

- Hemorrhagic cystitis is a challenging problem for urologists.
- It is most often caused by radiation therapy and cyclophosphamide.
- Technological advances in radiation therapy have resulted in greater treatment efficacy, with significant reduction in side-effects such as hemorrhagic cystitis.
- The risk of hemorrhagic cystitis increases with higher doses of radiation (>70 Gy) and larger treatment area.
- Treatment of hemorrhagic cystitis can range from simple bladder irrigation to cystectomy with urinary diversion.

presents several months after treatment. Subsequently, diffuse mucosal edema leads to telangiectasia, submucosal hemorrhage and interstitial fibrosis [9]. Eventually, the fibrosis decreases bladder capacity and compliance, resulting in patients presenting with urinary frequency, urgency and dysuria. Finally, obliterative endarteritis leads to mucosal ischemia, ulceration and bleeding.

There have been no preventive modalities to decrease the incidence of radiation-induced hemorrhagic cystitis except dose modification [7]. Prevention of radiation-induced hemorrhagic cystitis has been investigated using various oral agents (steroids, vitamin E, trypsin and orgotein), but efficacy has not been clearly demonstrated. Current approaches focus on sculpting the irradiation field and limiting the radiation dose to the bladder.

TREATMENT

The clinician must conduct investigations to assess for other treatable causes of hematuria such as urinary calculi, tumors and infections. Bleeding anomalies (medications and coagulopathies) and other nonbladder sources of bleeding (renal, ureter and prostate urethra) need to be evaluated by the urine and serum studies, cystoscopy and imaging. Computerized tomography with intravenous contrast if feasible would be the imaging study of choice for the gross hematuria. Other urological studies would include retrograde pyelography, upper tract ureteroscopy if there is any suspicion of upper urinary tract abnormality.

Intravenous, endoscopic and instillation therapy

As for all treatment pathways, beginning treatment with minimally invasive therapies is always recommended. As long as the patient is hemodynamically stable, clot removal and urinary drainage are the basis for initial treatment.

Mild hematuria responds to hydration and diuresis. However, it is important for the patient to be free of bladder clots. To achieve this goal, treatment can range from vigorous flushing of the bladder to cystoscopy with clot evacuation and fulguration. Once all clots are removed, continuous bladder irrigation is started to prevent further clot formation. Bladder perforation can occur if the catheter obstructs, so care must be taken to monitor irrigation. Serial hemoglobin level should also be assessed and, if necessary, transfusion of packed red blood cells should be provided in addition to platelets and fresh frozen plasma (FFP) if indicated.

Aminocaproic acid can be administered orally, parenterally or intravesically via continuous bladder irrigation. It is an inhibitor of plasminogen activator, which counteracts the effects of urokinase. A total of 4–5 g aminocaproic acid is given intravenously during the first hour, followed by a continuous infusion of 1 g per hour (Xanodyne Pharmaceuticals Inc. Company insert for Amicar 2005).

The major disadvantage of aminocaproic acid is the formation of hard clots that are not easily flushed from the bladder. Deysine *et al.* recommend that a total dose of 12 g daily should not be exceeded because of the increased risk of thromboembolic events [10]. Singh and Laungani [11] described the use of aminocaproic acid 200 mg/l of 0.9% isotonic sodium chloride saline solution for continuous bladder irrigation. Once the hematuria resolved, the irrigations were continued for an additional 24 h, which resulted in resolution of hematuria in 91.6% (34 of 37) of patients.

Alum (aluminum ammonium sulfate or aluminum potassium sulfate) irrigation acts as an astringent at the sites of bleeding, causing a protein precipitation at the urothelial surface [12]. Care must be taken as alum irrigation can result in a precipitant that can lead to blockage of the Foley catheter. It is desired to use 1% alum solution that consists of 50 g alum dissolved into a 5-l bag of sterile water, with irrigating the bladder at a rate of 200–300 ml/h [13].

Silver nitrate solution is used with a concentration ranging from 0.5 to 1% and is instilled for 10–20 min in duration, as bladder instillation causes a chemical coagulation and eschar formation at the bleeding sites. Ragavaiah and Soloway [14] reported a case of renal failure secondary to silver nitrate salts, precipitating and causing occlusion of the upper tracts, which mandate ruling out reflux before intravascular instillation of silver nitrate, phenol and formalin.

Phenol instillation requires the use of suprapubic and urethral catheters to allow large volume flushing of the bladder. Phenol solution consists of 100% of phenol with 30 ml glycine, and is administered intravesically via a Foley catheter and drained after 1 min. The next step is instillation and drainage of a 95% ethanol solution. Finally, the bladder is flushed with copious amounts of isotonic sodium chloride saline. If phenol remains in the bladder, methemoglobinemia may result [15].

Intravesical formaldehyde has been used in patients with persistent hemorrhagic cystitis. Several cases have reported that formalin completely resolved all hematuria in patients unresponsive to numerous therapies [16,17]; although it is probably the most effective treatment, formalin is also toxic [18]. It causes precipitation of cellular proteins of the bladder mucosa, and acts through its occluding and fixative action over telangiectasic tissue and small capillaries. Formaldehyde can cause edema, necrosis and inflammation throughout all layers of the bladder. It has potential side-effects, such as vesicoureteral reflux, ureteral stenosis and fibrosis of the bladder with reduced capacity and increased urinary frequency [19]. Spinal or general anesthesia is necessary. Evacuation of blood clots, petroleum jelly coating of the perineum, coagulation of major bleeding and cystoscopy or cystography to exclude reflux or bladder perforation are precautions that must be taken [18]. Using a 1–2% concentration of formalin without alcohol is recommended to start with, as well as limiting the time of contact with bladder epithelium by decreasing instillation volume (level of catheter in filled bladder not more than 15 cm above symphysis pubis) and time (should not exceed 15 min) while irrigating with saline or distilled water [20].

Epinephrine is a novel treatment, but it has been used only in animal studies to date. It is a potent alpha-adrenergic and beta-adrenergic receptor agonist and, therefore, is a clinically useful hemostatic agent [21].

Holstein *et al.* [22] recommended transurethral large balloon placement in the bladder. The balloon was left in place for 6 h after filled to a pressure level equal to the systolic blood pressure.

Hyperbaric oxygen therapy

Numerous studies have reported the use of hyperbaric oxygen in patients with radiation-induced hemorrhagic cystitis, with varying results, length of follow up and treatment protocols. Chong *et al.* [23] used an HBO protocol of 2.36 atmospheres of absolute pressure with 90 min of 100% oxygen breathing per treatment for a minimum total of 40 sessions. Early intervention (<6 months of hematuria) resulted in higher therapeutic response with complete (96%) or partial (66%) resolution of symptoms. Prior instillation therapy and type of radiotherapy (salvage, primary or adjuvant) did not affect the outcome in this patient population. Improvement rate was 76% in 50 patients with a history of prostate cancer treated with external-beam radiotherapy. Bevers *et al.* [24] reported one of the few prospective series of radiation-induced hemorrhagic cystitis. Patients underwent 20 sessions of 100% oxygen inhalation at 3 bars for 90 min. Cystoscopy with clot evacuation was required between sessions for some patients. At 3-month follow-up, hyperbaric oxygen therapy (HBOT) resulted in improvement or resolution of hematuria in 37 of 40 patients. Mean follow-up for the 40 patients was 23.1 months.

HBOT is considered effective in resolving or improving the symptoms of radiation-induced hemorrhagic cystitis irrespective of the patient's overall prognosis [23].

One of the first prospective studies to assess HBOT for hemorrhagic cystitis ($n = 40$) reported a complete response in 75% of patients, with only three patients experiencing recurrent hematuria after a mean follow-up of 29 months [24].

Oscarsson *et al.* [25▪] reported that HBOT can be an effective and well tolerated treatment modality for late radiation therapy-induced soft-tissue injuries in the pelvic region in their prospective cohort study. Shilo *et al.* [26] reported that bleeding was controlled in 84% of their 32 patients who were treated by HBO with 96% durable freedom of significant hematuria in those who achieved control of bleeding and concluded that HBO seems to be an effective and well tolerated modality in patients with hemorrhagic cystitis.

Vascular approaches

Embolization of the hypogastric arteries with autologous clot, Gelfoam, coils or ethanol can be used in such cases. Open ligation of the hypogastric artery can also be performed.

Hald and Mygind [27] were the first to report therapeutic nonselective embolization as a treatment for severe bladder hemorrhage, they used muscle fragments to occlude the internal iliac artery. Giulani *et al.* [28] have reported their success in selective embolization of the internal iliac arteries.

Recent advances in percutaneous catheters [29], embolization agents and fluoroscopic imaging have brought superselective embolization to the treatment of refractory bladder hematuria. McIvor *et al.* [30] reported successful control of severe hematuria in 92% (22 of 25) of patients.

Currently, there are several small series and case studies reporting comparable success rates [31–34]. The most common complication of pelvic embolization (iliac artery) is gluteal pain secondary to the occlusion of the superior gluteal artery. However, with the advent of superselective embolization by using microcatheters and more new and advanced embolization particles, there has been a decrease in the number of patients with gluteal pain and nontarget embolization.

Loffroy *et al.* [35▪] reported 90% success rate in patients when the vesical or prostatic arteries can be identified in their description of the current place of transcatheter arterial embolization in the management of severe bladder or prostate bleeding after failed conservative therapy.

Surgical options

Surgery is a final option for patients with refractory bladder hematuria. Options ranging from urinary diversion to cystectomy have been described. Urinary diversion can include nephrostomy tube placement with occlusion of the ureteral orifices

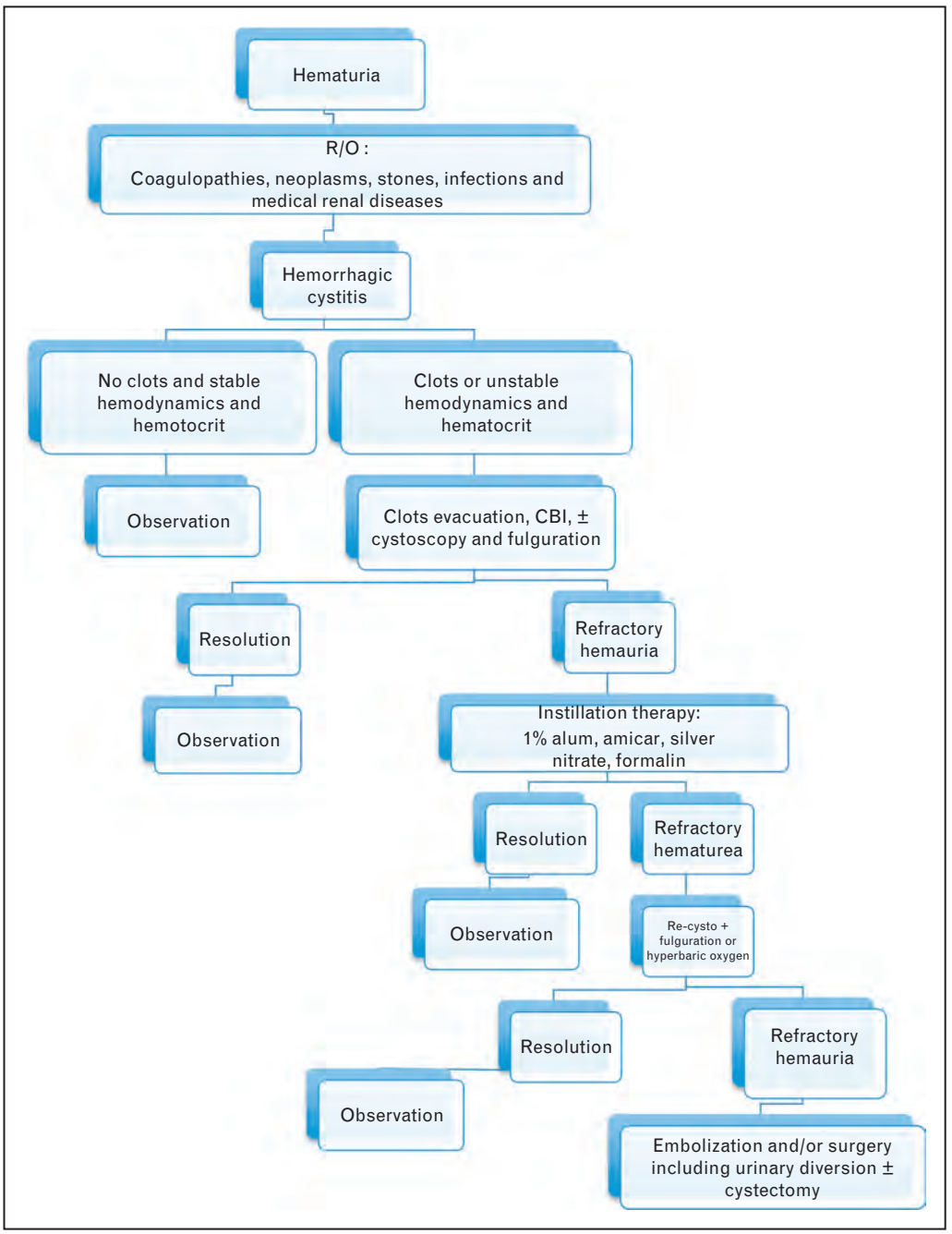

FIGURE 1. Algorithm for hematuria management.

(balloons or glutaraldehyde cross-linked collagen) [36], cystostomy with ureteral catheters [37], ileal loop diversion, ureterosigmoidostomy, open packing of the bladder, cutaneous ureterostomy, ligation of hypogastric arteries and, finally, cystectomy with a formal diversion [4]. The goal of supravesical diversion is to decrease the exposure of the hemorrhagic areas to urokinase to allow for hemostasis. Eigner and Freiha [38] evaluated the outcome of supravesical diversion of the native bladder. The overall complication rate requiring re-hospitalization for treatment was 43%. They recommended serious consideration be given to cystectomy at the time of urinary diversion because of the high percentage of postoperative complications.

Other reported treatments

Conjugated estrogens have been reported as treatment for viral and radiation induced hemorrhagic cystitis. The proposed mechanism is estrogen stabilizing the microvasculature. Several small series describe oral and intravenous administration of conjugated estrogens with varying durations of therapy and continuous monitoring for side-effects. The success rates range from 60 to 86% [39–42]. Investigators have proposed the use of sodium pentosan polysulfate because of its uroprotective qualities to decrease the inflammatory response of the urothelium [43] Veerasarn *et al.* [44] performed a phase II evaluation of WF10 (Immunokine), a chlorite-based drug that counteracts the inflammatory process associated with radiation-induced submucosal endarteritis. After completion of WF10 therapy, hematuria improved to grade 0–1 in 14 of 16 patients (88%).

Periodic intravesical instillation of prostaglandins and prostaglandin analogs (carboprost) has also proved effective. They decrease the inflammatory response and reduce the hemorrhage. They can be used prophylactically or therapeutically [45].

Ouwenga *et al.* [46] reported using fibrin hemostatic agent (Floseal, Baxter, Hayward, CA, USA) in persistent hematuria after all other options had been exhausted in a single patient, including formalin instillations and HBO therapy. After cystoscopy and clot evacuation was performed, 5 ml aliquots of fibrin sealant were applied through a ^{7}Fr open-ended catheter via air distention to the entire surface of the bladder.

Suzuki *et al.* [47] reported their successful use of argon plasma coagulation using a gastrointestinal endoscope to treat hemorrhagic radiation cystitis in a 75-year-old male patient.

Zhu *et al.* [48▪] reported their experience in 10 patients and suggest that transurethral coagulation using Greenlight potassium-titanyl-phosphate (KTP) laser is a well tolerated and effective strategy for the treatment of hemorrhagic radiation cystitis with the power setting limited to 20–30 W.

In persistent cases, use of medical antishock trousers and cryotherapy has been reported [4].

Unfortunately, with failure of the conservative approaches, the ultimate modality for the treatment of refractory radiation-induced hemorrhagic cystitis is urinary diversion [49▪,50▪].

A practical algorithm for the management of hemorrhagic cystitis is outlined in Fig. 1.

CONCLUSION

Hemorrhagic cystitis is a challenging problem for the urological community because of its varying causes and refractive nature to conservative measures. The most common causes are cyclophosphamide chemotherapy and pelvic radiation. In patients presenting with hematuria, it is important to rule out other causes, such as stones, neoplasm, medical renal disease and an upper tract source of bleeding. A variety of intravesical agents is available. In the most persistent complicated cases, urinary diversion with or without cystectomy may be indicated.

Acknowledgements

None.

Conflicts of interest

Competing interests: The authors declare that they have no competing interests.

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- ▪ of special interest
- ▪▪ of outstanding interest

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