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Review

Haemorrhagic cystitis: a review of management strategies and emerging treatments

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Haemorrhagic cystitis (HC) is characterised by persistent haematuria and lower urinary tract symptoms following radiotherapy or chemotherapy. Its pathogenesis is poorly understood but thought to be related to acrolein toxicity following chemotherapy or fibrosis/vascular remodelling after radiotherapy. There is no standard of care for patients with HC, although existing strategies including fulguration, hyperbaric oxygen therapy, botulinum toxin A, and other intravesical therapies have demonstrated short-term efficacy in cohort studies. Novel agents including liposomal tacrolimus are promising targets for further research. This review summarises the incidence and pathogenesis of HC as well as current evidence supporting its different management strategies.

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Haemorrhagic Cystitis Incidence and Severity

Haemorrhagic cystitis (HC) is a complication of radiotherapy (RT) or chemotherapy characterised by haematuria, LUTS, and/or clotting and life-threatening bleeding [1]. Thought to be due to bladder urothelium disruption, HC varies in incidence by aetiology. Studies have shown HC incidence rates of ~11.1% after RT for pelvic malignancies (prostate 11.1%, cervix 3%–6.7%, bladder 2%–10%) and 5%–18% after systemic cyclophosphamide or ifosfamide [2–4]. The estimated combined incidence of RT- and chemotherapy-induced HC combined ranges from 50 000 to 125 000 cases annually [5]. HC may manifest early or late after treatment. Onset times range from weeks to months for chemotherapy and as late as 20 years for RT [6]. Risk factors associated with RT-induced HC include higher total RT dose and higher surface-area of bladder irradiated. Chemotherapy-induced HC is associated with higher individual and cumulative chemotherapy doses, use of androgen-deprivation therapy, and history of TURP [7–9].

Haemorrhagic cystitis is challenging to manage given its relative rarity, high morbidity, and lack of definitive standard treatment. Severe cases of HC may result in prolonged hospitalisation or death and even mild cases of HC are associated with disabling symptoms including frequency, urgency, and pelvic pain in the bladder or urethra [10]. The underlying aetiological causes, such as viral infections, RT, or other factors, may contribute to both the development of HC and the manifestation of symptoms. The variable presentation of HC has led to multiple grading schemes to categorise severity. The Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG/EORTC) proposed a grading scheme that takes into account the late effects of RT on tissue (Table 1) [4]. Other scales include the Common Terminology Criteria for Adverse Events (CTCAE) and the Late Effects of Normal Tissues/Subjective-Objective Management Analytic (LENT-SOMA). The CTCAE criteria, which categorise severity by level of required intervention, is commonly used in oncology outcomes reporting. The LENT/SOMA scale was designed to

Table 1 RTOG/EORTC grading criteria for HC.

Grade	Presentation
Grade 0	Normal
Grade 1	Slight epithelial atrophy Minor telangiectasia Microscopic haematuria
Grade 2	Moderate frequency Generalised telangiectasia Intermittent macroscopic haematuria
Grade 3	Severe frequency and dysuria Severe generalised telangiectasia with petechiae Frequent haematuria Reduction in bladder capacity (<150 mL)
Grade 4	Necrosis Contracted bladder (<100 mL) Severe HC

Adapted from Anacak et al. (2001) [4].

replace RTOG/EORTC criteria and is more comprehensive (five to six modules covering rectum, bladder, skin, uterus, vagina, urethra), but burdensome to administer [4].

Pathophysiology of HC

Chemotherapy

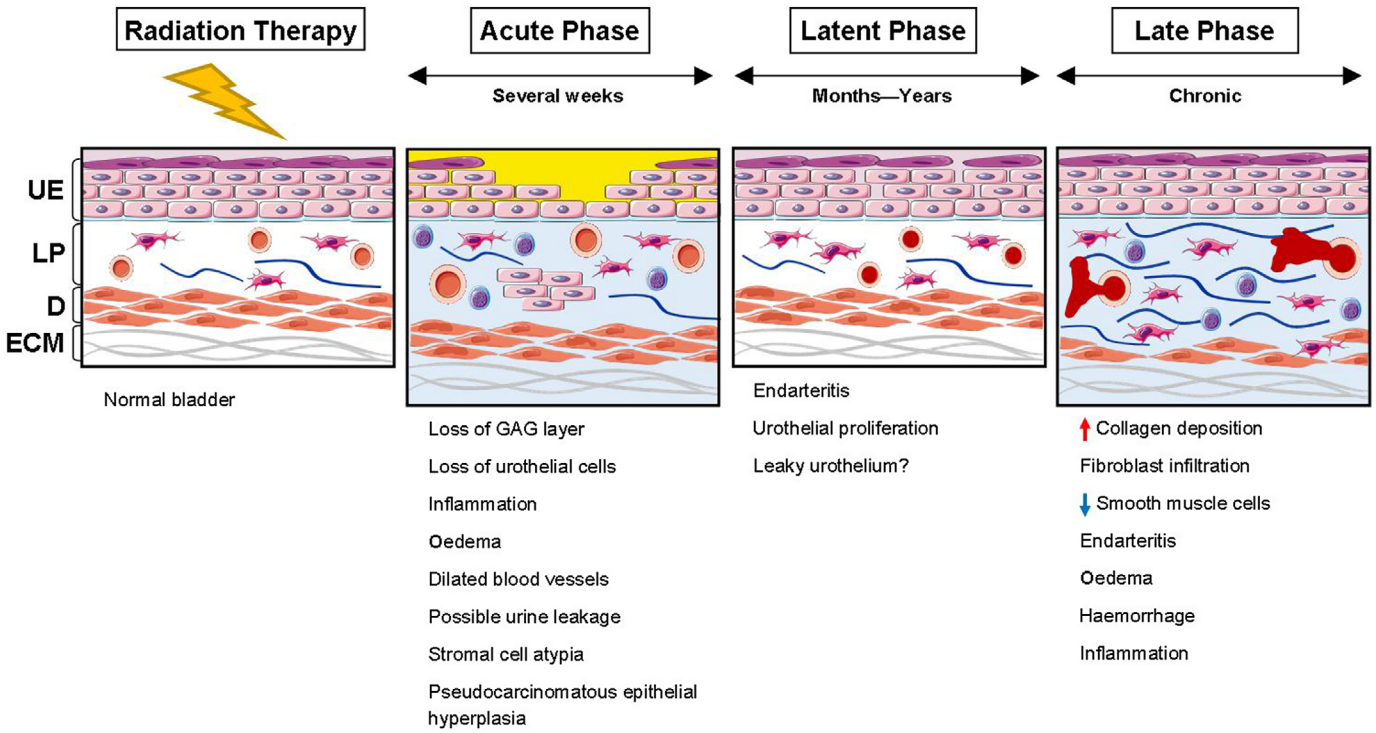
The pathogenesis of HC is thought to be related to bladder inflammation and subsequent endarteritis and fibrosis [10].

Cyclophosphamide and ifosfamide-induced HC is primarily mediated through acrolein and its cascades. Acrolein is a product of cyclophosphamide and ifosfamide hepatic metabolism that is filtered by the kidneys and subsequently concentrated in the bladder. Acrolein leads to inflammatory cell death in the bladder urothelium through upregulation of reactive oxygen species (ROS) and increased production of nitric oxide through induction of nitric oxide synthase. ROS and nitric oxide produce lipid- and protein-toxic peroxynitrites, induce breakage of DNA strands, and activate transcription factors (nuclear factor κ-light-chain-enhancer of activated B cells [NF-kB], activator protein), which result in pro-inflammatory cytokine and interleukin (IL)-1B gene expression and bladder ulceration [11].

Radiation

Haemorrhagic cystitis from RT is termed 'radiation cystitis'. The pathogenesis of radiation cystitis proceeds through three phases (Fig. 1 [40]). The acute phase results from direct RT damage to the bladder mucosa, resulting in inflammation and tissue oedema. This desquamates the urothelium and compromises urothelial regeneration [12]. Radiation cystitis can occur months to many years after treatment (i.e., latent-chronic radiation cystitis). The pathophysiology of latent-chronic radiation cystitis is poorly understood, but research has shown that fibrosis and vascular remodelling are its core

Fig. 1 Pathophysiology of radiation cystitis. D, detrusor; ECM, extracellular matrix; GAG, glycosaminoglycan; LP, lamina propria; UE, uroepithelium. Adapted with permission from Zwaans et al. (2015) [40].



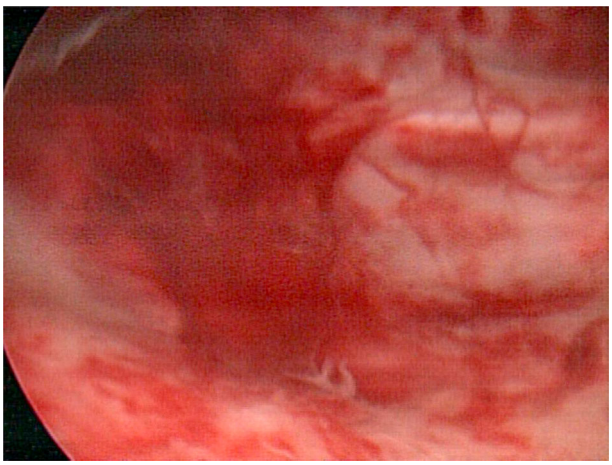
features [12]. Fibrosis of the vascular intima results in vessel damage and endarteritis, which ultimately causes urothelial atrophy due to poor perfusion and subsequent ischaemia. This then triggers neovascularisation and telangiectatic vessels that are friable and prone to bleed. Furthermore, bladder smooth muscle cells are replaced with fibroblasts, leading to collagen deposition and additional fibrosis. At end stages, complete bladder fibrosis, fistulation, and ulcers result in a contracted bladder with severely reduced capacity and compliance [12].

In rare cases HC may be idiopathic, and this is not frequently described in the literature. In a case report of idiopathic severe HC in a renal transplant patient, treatment with intravenous conjugated oestrogen followed by oral doses resulted in rapid and complete resolution of haematuria within 48 h, without any observed complications or side-effects [13].

Evaluation of HC

Symptoms of HC overlap with those of infection or malignancy; hence, HC is a diagnosis of exclusion. The initial evaluation for HC includes a thorough history (haematuria, LUTS, exclusion of UTI/tumour/urolithiasis, past/present medications) and physical examination. Standard laboratory evaluation for haematuria (full blood count, urine culture, cytology) should be performed. Postvoid residuals and urodynamics may be considered if the patient has significant LUTS with unclear aetiology. Most importantly, cystoscopy (Fig. 2 [46]) and upper tract imaging are important to rule out malignancy or calculi. In a retrospective review of men with prostate cancer treated by RT presenting with haematuria and/or LUTS, 9.7% and 3.2% had bladder tumours or calculi on cystoscopy, respectively (7% with radiation cystitis) [14]. In more severe presentations, a rapid assessment of haemodynamic stability and bladder drainage should be prioritised. Patients with no signs of infection, malignancy, or urolithiasis who have haematuria and a history of chemotherapy or RT exposure are likely to have HC.

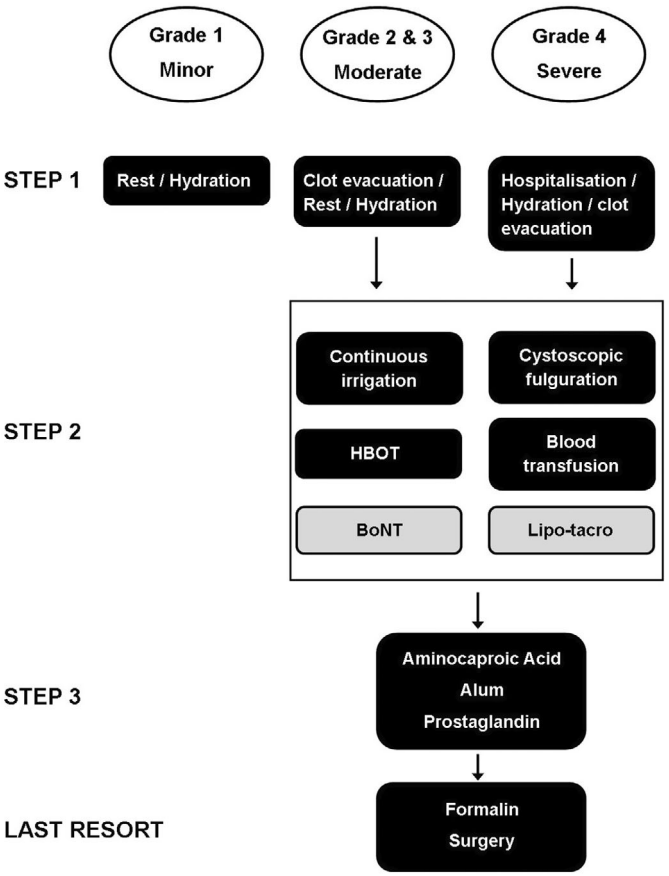
Fig. 2 Cystoscopy image of HC. Adapted from Tsai et al. (2014) [46] under a Creative Commons license.



Treatment of Acute HC

Currently no standard-of-care therapy exists for patients with HC and existing treatments may be ineffective, risky, or both. Guidelines about HC management are also limited. We recommend a tiered approach based on disease severity per RTOG/EORTC grading (Fig. 3 [40]). For Grade 1 HC, bladder rest and hydration is often sufficient to restore bladder function and promote healing [10]. Grades 2–4 require immediate haemodynamic stabilisation, resuscitation, hyper-hydration, and diuresis. Management strategies after these steps are similar for moderate-to-severe grade HC. First, cystoscopy and fulguration of bleeding vessels is performed to control haematuria. In a case series of 33 patients, 20 patients

Fig. 3 Treatment steps for HC. BoNT, botulinum toxin A; Lipo-tacro, liposomal tacrolimus (i.e. liposomal delivery of tacrolimus). Grey boxes represent experimental treatments. Adapted with permission from Zwaans et al. (2015) [40].



had complete resolution of HC (mean follow-up 76 months) after cystoscopy and clot evacuation ± fulguration [15]. Laser fulguration (potassium titanyl phosphate 530 nm wavelength or Xcelerated Performance System [XPS] 1064 nm wavelength) may also be considered if patients fail fulguration with electrocautery [16–18]. In a single-centre retrospective study, 21 patients with HC who had failed conservative treatment (including 52.4% electrocoagulation) underwent 980-nm diode laser coagulation and >75% had complete resolution of haematuria after one session [19]. Continuous bladder irrigation should be initiated to prevent clot reformation and blood transfusions should be given for excess blood loss. In cases where conservative treatments have been exhausted and persistent haematuria endures, surgical intervention, such as cystectomy with urinary diversion, may be considered as a rare last resort option as it can be associated with significant morbidity. In a cohort of 21 patients with refractory HC who underwent cystectomy, severe complications occurred in 42% of patients and 90-day mortality was 16% [20]. A related study of 100 men who underwent urinary diversion for urinary adverse events following RT reported Grade ≥IIIa Clavien–Dindo complications (i.e., requiring surgical, endoscopic, or radiological intervention) in 35% of men, and 38% required hospital re-admission within 6 weeks of surgery [21].

Management Strategies for Persistent HC

Hyperbaric Oxygen Therapy (HBOT)

Hyperbaric oxygen therapy is the most well-studied HC treatment, which promotes neovascularisation and growth of healthy bladder tissue through hyperoxia. This is believed to increase local tissue oxygen tension, decrease oedema, increase new vessel formation, and improve wound healing [22]. A recent meta-analysis including one randomised control trial, two prospective trials, and 11 retrospective case series noted partial or complete response in 84% of patients [23]. There is evidence that HBOT treatment effects are durable long-term, lasting up to 10 years in 81% of patients [24,25]. Despite its potential benefits, HBOT's time-intensive regimen with frequent sessions (up to 30–60 over 2–3 months) proves less optimal for managing patients with HC with ongoing haematuria. HBOT is contraindicated in patients with claustrophobia, chronic obstructive pulmonary disease, seizures and may result in barotrauma and/or oxygen toxicity.

Intravesical Agents

Intravesical agents for treatment of HC include alum, aminocaproic acid, prostaglandin, and formalin. Alum is a non-specific agent that promotes protein precipitation to decrease capillary permeability, contract the intercellular space, vasoconstrict vessels, and harden the endothelium [26]. Its adverse effects include bladder spasms, urinary dysfunction, and nephrotoxicity. A case series of alum irrigation in 40 patients with HC demonstrated symptom improvement in 60% of patients with no further treatments required before discharge; however, only 32% patients required no further treatment at follow-up [27].

Similar case series have demonstrated limited success of aminocaproic acid in treating HC. The largest study of aminocaproic acid was performed in a cohort of 37 patients with intractable haematuria (23/37 due to HC or radiation cystitis), with 34/37 (92%) responding to treatment within 96 h [28]. Two other case studies have been published describing resolution of HC after treatment with aminocaproic acid in a 28-year-old female who received matched unrelated donor transplant and developed HC from adenovirus, as well as a 54-year-old patient with metastatic prostate cancer who developed radiation cystitis [29,30]. Further evidence including prospective trials and studies with greater sample sizes are limited [31].

There are relatively more case studies and series describing use of intravesical prostaglandins for treating HC [32,33–36]. Most describe resolution of HC symptoms (haematuria) in single patients who had not responded to conservative management with HC aetiologies including cyclophosphamide and RT with limited follow-up [32–35]. Studies done in larger populations (N = 10–20) demonstrate response rates ranging from 50% to 62% [33,36]. The most common side-effect was bladder spasm.

Formalin instillation is considered a treatment of last resort for HC as it is associated with reduced bladder function and extreme bladder pain, although efficacy is favourable if tolerated. The largest study included 25 patients with massive bladder haemorrhage (secondary to cyclophosphamide in one and pelvic RT in 15 cases) of whom 88% achieved haemostasis within 4 months. However, side-effects included vesico-rectal fistula, uretero-hydronephrosis, upper tract dilatation, and vesical extravasation, particularly at higher formalin concentrations (10% vs 4%) [37]. A more recent study done in 2017 demonstrated similar rates of efficacy and risks of bladder dysfunction following formalin [38].

Evidence on treatment efficacy of botulinum toxin A (BoNT-A) in HC is limited to small case series and animal model studies. BoNT-A primarily helps alleviate LUTS secondary to HC/radiation cystitis and does not improve bleeding. One series of eight patients with refractory radiation cystitis treated with 100 or 200 U BoNT-A injections demonstrated moderate improvement in five of six patients (increased bladder capacity from 105 to 250 mL, decreased urinary frequency from 14 to 11 episodes daily) corresponding to histological changes at 2 months after treatment [39]. Novel liposomal delivery methods of BoNT-A may further increase its efficacy in HC/radiation cystitis treatment.

Emerging Treatments and Liposomal Tacrolimus

Liposomal tacrolimus is an experimental treatment for HC/radiation cystitis. It is an immunosuppressive agent which inhibits IL-2-dependent T-cell activation and cell-mediated reactions through binding of FK-binding protein 12 to decrease transcription of IL-2, tumour necrosis factor-alpha, IL-3, IL-4, CD40 ligand, and other pro-inflammatory signals [40]. It is administered intravesically, which may reduce adverse effects including nephrotoxicity and hypertension by promoting local absorption via liposomal fusion with target cell membranes [41,42]. Current evidence regarding effects of liposomal tacrolimus on HC are limited to one case report detailing compassionate use of intravesical lipo-tacrolimus in an 81-year-old man with a history of prostate cancer and RT with severe HC [43]. The two courses of liposomal tacrolimus were given by diluting a solution of tacrolimus injection (Prograf) in 40 mL sterile saline (0.125 mg/mL tacrolimus) and instilling it into the patient's urinary bladder via urethral catheter, with a 30-min retention time. The first course was administered on 4 June 2015, the second course on 5 June, 2015, and the patient was discharged on 8 June 2015 without further complications. Larger prospective investigations are ongoing, including a recent Phase II multicentre dose ranging study, 'The Safety, Tolerability and Efficacy of LP-10 in Subjects with Refractory Moderate to Severe Hemorrhagic Cystitis', which was recently completed with results to be reported in 2023 (ClinicalTrials.gov identifier: NCT03129126).

Prevention of HC

Prevention strategies for HC focus on use of sodium-2-mercaptoethanesulfonate (mesna) and forced saline diuresis in patients undergoing haematopoietic cell transplant. Mesna is a uroprotective agent that inactivates acrolein, reducing the risk of bladder toxicity. The American Society of Clinical Oncology guidelines recommend intravenous mesna as a protective agent during ifosfamide chemotherapy. Forced saline diuresis, involving intravenous normal saline at 250 mL/h and furosemide to maintain urinary output, can be used in conjunction with mesna for uroprotection. Although forced saline diuresis is considered more cost-effective, evidence comparing its effectiveness to mesna is mixed. A trial of 200 patients undergoing haematopoietic cell transplantation, the incidence of Grade 3 and 4 haematuria was comparable in mesna and continuous bladder irrigation (18%) [44].

There are no established guidelines for the use of mesna in non-cancer patients receiving cyclophosphamide or for prevention of late radiation cystitis in patients undergoing pelvic RT. Amifostine, an aminothiol with cytoprotective properties, has shown potential value in preventing acute bladder toxicity from RT. In a randomised trial of 205 patients, the rate of Grade >2 acute bladder toxicity was significantly less in the amifostine group (14% vs 5%) at 4–7 weeks, but data on longer-term efficacy is lacking [45].

Conclusions

Haemorrhagic cystitis may result from chemotherapy or RT and is highly morbid. Its pathophysiology is aetiology dependent. Acrolein mediates chemotherapy-related HC, while HC resulting from RT is driven by bladder urothelium fibrosis and telangiectatic vascular remodelling. HC is a diagnosis of exclusion and there is no standard management for patients. Current strategies include hydration along with clot evacuation and fulguration to stabilise patients acutely; while HBOT, intravesical agents, BoNT-A therapy, and surgery are utilised for persistent symptoms. Liposomal tacrolimus is a promising new immunosuppressive agent for HC, which inhibits IL-2-dependent T-cell activation implicated in HC. Clinical evidence is limited to one case report with further prospective trials ongoing. Prevention strategies include use of mesna/forced saline diuresis in transplant patients and amifostine in patients receiving pelvic RT.

Disclosure of Interests

Benjamin N. Breyer is a trial site Principal Investigator for a phase IIa clinical trial of liposomal tacrolimus for HC. Michael B. Chancellor is the Chief Medical Officer of Lipella, a clinical stage pharmaceutical company sponsoring the trial.

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Abbreviations: BoNT-A, botulinum toxin A; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; HBOT, hyperbaric oxygen therapy; HC, haemorrhagic cystitis; IL, interleukin; LENT-SOMA, Late Effects of Normal Tissues/Subjective-Objective Management Analytic scale; mesna,sodium 2-mercaptoethane sulphonate; ROS, reactive oxygen species; RT, radiotherapy; RTOG, Radiation Therapy Oncology Groups.

