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Journal of Clinical Urology published online 25 November 2013
DOI: 10.1177/2051415813512647

The online version of this article can be found at:
http://uro.sagepub.com/content/early/2013/11/25/2051415813512647

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What is This?
Guidelines for the diagnosis, prevention and management of chemical- and radiation-induced cystitis

A Thompson¹, A Adamson², A Bahl³, J Borwell⁴, D Dodds⁵, C Heath⁶, R Huddart⁷, R McMenemin⁸, P Patel⁹, J Peters¹⁰ and H Payne¹¹

Abstract
Objective: Haemorrhagic cystitis (HC) is a relatively common complication of chemotherapy and radiotherapy to the pelvic area, but can be a challenging condition to treat, particularly since there is currently a lack of UK-led guidelines available on how it should optimally be defined and managed.

Materials and methods: A comprehensive literature search was undertaken to evaluate the evidence for the diagnosis, prevention and management of cancer treatment-induced HC.

Results: Recommendations and a proposed management algorithm for the diagnosis, prevention and treatment of HC, as well as the management of intractable haematuria, have been developed based on the expert opinion of the multidisciplinary consensus panel following a comprehensive review of the available clinical data.

Conclusion: These guidelines are relevant and applicable to current clinical practice and will help clinicians optimally define and manage this potentially serious condition.

Keywords
Guidelines, radiation cystitis, chemical cystitis, haemorrhagic cystitis, intractable haematuria, sodium hyaluronate, hyperbaric oxygen, diagnosis, prevention, treatment

Date received: 27 August 2013; revised: 2 October 2013; accepted: 16 October 2013

Background
Haemorrhagic cystitis (HC) is most commonly caused by intravenous chemotherapy drugs, notably cyclophosphamide,¹ ² administration of treatments directly into the bladder (e.g. bacillus Calmette-Guérin),³ ⁴ or radiation therapy to the pelvic area.⁵ Cases of HC have also been reported with the use of other therapeutic agents,² ⁶–⁹ recreational drugs¹⁰ and environmental toxins.¹¹ HC has a spectrum of manifestations that range from non-visible (or microscopic) haematuria to gross (visible) haematuria with clots,¹² and has a reported incidence from less than 10% up to 35%.⁴ ⁵ ¹³–¹⁵ Severe HC can be a challenging condition to treat and may give rise to serious complications,¹⁶ leading to prolonged hospitalisation and occasional mortality.¹²

Several reviews of the available preventive and therapeutic options for chemical- and radiation-induced cystitis...
have been published. A recently published review of the evidence found a lack of robust data and variability in treatment strategies used and highlighted the need for further research, as well as best practice guidance and consensus on how this potentially serious complication should optimally be defined and managed. Recent surveys undertaken by the British Association of Urological Surgeons (BAUS), the British Uro-oncology Group (BUG), and the British Association of Urological Nurses (BAUN) reported that 360 of the 367 surveyed (98%) would be supportive of the development of best practice guidelines on optimal treatment. This guideline has therefore been designed to provide direction to clinicians on how to diagnose, prevent and treat chemical- and radiation-induced HC, and improve patient outcomes.

Methodology

A multidisciplinary consensus panel, comprising urologists, oncologists and specialist nurses in the United Kingdom (UK) was convened in August 2012 to develop recommendations and review associated evidence for the diagnosis, prevention and management of chemical- and radiation-induced HC. A comprehensive literature search was undertaken in PubMed to retrieve studies and case reports, published in English, relating to its treatment from 1980 to March 2013. The search was conducted using a comprehensive search strategy, including the terms ‘haemorrhagic cystitis’, ‘chemical cystitis’, ‘radiation cystitis’ in combination with ‘risk factors’, ‘chemotherapeutic drugs’, ‘hyaluronic acid’, ‘sodium hyaluronate’, ‘hyperbaric oxygen’, ‘mesna’, ‘hyperhydration’, ‘bladder irrigation’, ‘pentosanpolysulphate’, ‘oestrogen’, ‘recombinant factor VII’, ‘formalin’, and ‘prostaglandin’. The search results were supplemented by review of the bibliographies of key articles for additional studies and inclusion of relevant abstracts presented at key meetings.

The clinical recommendations were based on the expert opinion of the panel following a comprehensive review of the predominantly low-level evidence. Other than sodium hyaluronate (Cystistat®; Teva UK Limited), which is approved as a class II medical device for the temporary replacement of the glycosaminoglycan (GAG) layer in the bladder, none of the interventions mentioned are specifically licensed for the management of chemical- and radiation-induced cystitis.

Definition and grading

**Definition.** HC has been defined as ‘the presence of sustained haematuria and lower urinary tract symptoms (e.g. dysuria, frequency, urgency) in the absence of active tumour and other conditions, such as vaginal bleeding, general bleeding diathesis, and bacterial or fungal urinary tract infections’. This guideline relates to patients with HC who have received chemotherapy or radiation therapy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Non-visible haematuria</td>
</tr>
<tr>
<td>II</td>
<td>Macroscopic haematuria</td>
</tr>
<tr>
<td>III</td>
<td>Macroscopic haematuria with small clots</td>
</tr>
<tr>
<td>IV</td>
<td>Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation</td>
</tr>
</tbody>
</table>

**Grading.** Over the years, several grading systems for the severity of HC have been proposed, including those by Droller et al. (Table 1).

**Classification**

Based on the time of appearance, HC can be classified as early- or late-onset. Early-onset disease in the first few days after cyclophosphamide administration appears to be caused by acrolein, a urotoxic metabolite of cyclophosphamide. HC can also develop weeks to months after treatment in 20%–25% of patients who receive high dose cyclophosphamide. The effects of radiation-induced cystitis may be acute or delayed, occurring long after radiation treatment has ended, from two months to 15 years later. In contrast to acute changes, late radiation injuries are usually irreversible and progressive.

**Signs and symptoms**

The symptoms of acute- and late-onset HC are shown in Table 2.

**Diagnostic approach**

A key goal of the evaluation of chemical- and radiation-induced HC is to identify and exclude other disorders that may be causing symptoms. Components of a basic assessment should include the following:

- History
- Physical examination
- Urinalysis
- Urine culture
- Cystoscopy under general anaesthetic (consider hydrodistention if symptoms are due to reduced bladder capacity)
- Cytology (when indicated)

The diagnosis may be supported by a computed tomography (CT) urogram or magnetic resonance imaging (MRI)
scan of the pelvis and abdomen, as well as relevant tumour markers.

Clinical history. Patients with HC can present with variable degrees of haematuria, ranging from non-visible (or microscopic) haematuria to gross (visible) haematuria with clots. A detailed history should be taken of voiding symptoms, pelvic pain or discomfort, urinary frequency and urgency, and nocturia.

Physical examination. A thorough physical examination should be carried out in all patients with HC, including a pelvic examination, to determine the cause.

Laboratory tests. The basic laboratory examination includes a urinalysis and urine culture to exclude infection. Any infection should be treated appropriately. If the patient has received chemotherapy, clotting disorders should be considered. Other laboratory evaluations should include haemoglobin, complete blood count, blood urea, serum creatinine and coagulation profile.

Cystoscopy. If haematuria is present, cystoscopy with possible biopsy under general anaesthesia is required to rule out other pathology, e.g. renal stones or cancer. Additionally, if a pathologically small bladder is found, hydrodistention of the bladder may give some symptomatic relief of frequency and urgency postoperatively but it can increase haematuria. Some temporary improvement in bladder pain can also follow hydrodistention.

Cytology. Urine cytology may be considered for patients at high risk of bladder cancer, but is often difficult to interpret, especially after radiotherapy.

Imaging studies. A CT urogram should be performed to exclude bleeding from the upper urinary tract. A MRI scan may also be indicated if there is a past history of non-urological pelvic malignancy.

Recommendations

- The basic assessment should include a careful history, physical examination, and laboratory examination.
- Diagnosis of HC should be based on symptoms and exclusion of other conditions (e.g. bladder neoplasms), and bacterial or fungal urinary tract infections.
- A CT scan should be performed to exclude bleeding from the upper urinary tract.
- A MRI scan may be indicated if there is a past history of non-urological pelvic malignancy.

Prevention of haemorrhagic cystitis

The ideal strategy for iatrogenic chemical- and radiation-induced HC would be prevention. Accurately tailoring the irradiation field and limiting the radiation dose to the bladder should be employed to reduce the incidence of haematuria. Limiting the exposure of acrolein to the urothelium can also reduce the risk of HC.

Hyperhydration. Hyperhydration has been found to be effective in preventing HC associated with high-dose cyclophosphamide in bone marrow transplant (BMT) recipients, but data are limited. Ballen et al. studied 100 consecutive BMT recipients who received high-dose cyclophosphamide with hyperhydration using 5% dextrose normal saline and furosemide. Only two transplant patients developed clinically significant HC, of which one was a severe episode. There were no episodes of HC in the 71 patients who also received high-dose cyclophosphamide as mobilisation chemotherapy. Trotman et al. also

<table>
<thead>
<tr>
<th>Acute-onset</th>
<th>Late-onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria, which may be mild to severe</td>
<td>Dysuria, which may be mild to severe</td>
</tr>
<tr>
<td>Urinary frequency and urgency</td>
<td>Urinary frequency and urgency</td>
</tr>
<tr>
<td>Haematuria</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Usually self-limiting</td>
<td>Usually irreversible</td>
</tr>
<tr>
<td>Occasionally the reaction may be prolonged and continue into a late reaction</td>
<td>Possible sphincter dysfunction</td>
</tr>
<tr>
<td></td>
<td>Reduced bladder capacity</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Potential for perforation and fistulation</td>
</tr>
</tbody>
</table>

Table 2. Symptoms of acute- and late-onset haemorrhagic cystitis.
reported a low incidence of HC (18.2%) and grade III–IV disease (3.4%) in 681 haematopoietic stem cell transplantation (HSCT) patients, using a prophylactic regimen of hyperhydration and forced diuresis.

**Continuous bladder irrigation.** The few studies that have examined continuous bladder irrigation as a preventive measure have reported variable results. Turkeli et al. demonstrated that prophylactic continuous bladder irrigation significantly decreased the frequency of HC compared with no bladder irrigation (23% vs 53%, respectively; \( p < 0.004 \)) in BMT recipients receiving busulfan and cyclophosphamide. Similarly, Hadijibaba et al. reported that, compared with no bladder irrigation, continuous bladder irrigation with normal saline, in addition to mesna, hydration and alkalinisation, reduced the occurrence of HC (32.5% vs 50%, respectively; \( p = 0.11 \)) and late-onset HC, defined as occurring after transplant day 30 (7.7% vs 45%, respectively; \( p = 0.009 \)) following allogeneic haematopoietic cell transplantation. Conversely, Atkinson et al. found that bladder irrigation did not minimise the risk of HC in BMT recipients.

Although continuous bladder irrigation has been reported to be well tolerated, it is associated with complications, including infection, bleeding, patient discomfort and restricted mobility, and is no longer commonly used as a preventive measure in the UK.

**Mesna.** Mesna (sodium 2-mercaptoethane sulphonate), which was specifically developed to bind acrolein in the urine, has been extensively investigated as a prophylactic treatment during high-dose chemotherapy and transplantation with variable results. Although overall, it was well tolerated. Whilst mesna and continuous bladder irrigation or hyperhydration have been shown to be equally effective in preventing severe HC associated with high-dose cyclophosphamide and BMT, hows et al. reported that mesna is more effective than forced diuresis (\( p < 0.05 \)). Interestingly, Tsuboi et al. found that prophylactic administration of mesna (\( p = 0.0105 \)) and bladder irrigation (\( p = 0.0001 \)) were significant risk factors of early-onset HC in a multivariate analysis.

**Sodium hyaluronate.** Sodium hyaluronate, a derivative of hyaluronic acid, has been developed to temporarily replenish the deficient GAG layer. Intravesical sodium hyaluronate has been used successfully in the treatment of refractory interstitial cystitis and has been proposed as preventive treatment of radiation-induced HC. Its protective effect on the urinary bladder mucosa has been demonstrated in a small study of patients with advanced cervical cancer treated with pelvic radiotherapy, weekly chemotherapy and high-dose-rate brachytherapy. Samper Ots et al. also found that, compared with no sodium hyaluronate, intravesical installations with 40 mg/50 ml sodium hyaluronate solution prior to each brachytherapy session significantly reduced the incidence of radiation-induced cystitis in patients with cervical and endometrial cancer after the second (20.8% vs 40.4%, respectively; \( p < 0.05 \)) and fourth session (10.9% vs 31.9%, respectively; \( p < 0.05 \)). In addition, a trend towards a reduction in late toxicity was observed, though it did not reach statistical significance. Further data come from an earlier retrospective study in which weekly instillations of sodium hyaluronate solution were shown to exert a protective effect on the bladder, reducing the incidence and grade of radio-induced cystitis and the risk of infection. The completion of treatment in the scheduled time was also achieved with this therapeutic approach. In both studies, the treatment was well tolerated and no related adverse events were reported.

**Cranberry juice.** Cranberry juice is widely cited as a prophylactic measure and in some centres is considered a standard of preventive treatment. However, the mechanism of its effect has been widely debated and is still largely unknown. Although earlier studies showed statistically insignificant or negative results, data from a study by Bonetta and Di Pierro suggest that enteric-coated cranberry extract has a generally protective effect on the bladder mucosa.

In this study, 370 consecutive patients with prostatic adenocarcinoma were treated with radical, adjuvant, or salvage radiotherapy to the prostatic area; 184 of these patients received cranberry extract as preventive therapy and 186 served as controls. In the cranberry cohort, 16 lower urinary tract infections (LUTIs) (8.7%) were observed, while in the control group 45 LUTIs (24.2%) were recorded. Additional research is required to further explore the role of cranberry juice as preventive therapy in patients who require radiation therapy to the pelvic area.

**Other preventive measures.** Data from a small pilot study of 20 patients undergoing radiotherapy for gynaecological malignancies indicate that prophylactic intravesical installations with 40 ml chondroitin sulphate 0.2% solution reduce the symptoms of acute radiation cystitis. The effectiveness of this preventive measure needs to be assessed in more robust trials.

**Recommendations**

- Unless medically contraindicated, provision of sufficient hydration to maintain adequate high urine flow should be a component of all prophylactic regimens.

- Sodium hyaluronate 40 mg/50 ml is proposed as an option for patients considered at increased risk of HC (e.g. patients receiving external beam radiation therapy and brachytherapy for cervical or endometrial cancer).
• Treatment should be initiated with weekly instillations for six weeks, potentially followed by two fortnightly instillations, then maintained using monthly instillations whilst the patient is responding.
• Drinking one large daily glass of cranberry juice may help to reduce the risk of HC.
• Cranberry juice tablets can also be used.

Treatment of HC

Controlling and treatment of HC symptoms in the early stage promotes prevention of the development of HC of lesser grades to severe grades (grades III and IV). Since HC occurs on a spectrum of severity, a multimodality stepwise approach to treatment should be taken. Therapies for established HC are varied; the choice depends on the degree of haematuria present. Once HC is established, the treatment principles are generally the same, irrespective of the cause.\textsuperscript{12}

Conservative therapy

Initially, in the absence of obstructing clots and if the patient is voiding well, intravenous hydration with careful observation may be the only treatment required. Other conservative measures for grades I–II/III HC include analgesia and spasmolytic drugs.\textsuperscript{12} Oral tranexamic acid 1 g three times daily may be considered for haemorrhage or risk of haemorrhage to increase blood clotting.

Recommendations

- A multimodality stepwise approach to treatment should be taken.
- The choice of therapy depends on the degree of haematuria present.
- Grades I–II/III HC can be controlled by conservative methods, including bladder irrigation, rehydration and promotion of diuresis.
- Oral tranexamic acid 1 g three times daily may be considered for haemorrhage or risk of haemorrhage.

Management of intractable haematuria

The management of intractable haematuria (grades III/IV) begins with evacuation of all clots from the bladder before the initiation of any treatment.\textsuperscript{55} Evacuation can be by bladder irrigation through a large-bore three-way catheter on the ward, or by cystoscopic bladder irrigation in the theatre.\textsuperscript{55} Patients not responding to clot evacuation and those with diffuse bleeding will require supplemental therapeutic techniques with intravesical or systemic agents.\textsuperscript{2}

Normal saline bladder irrigation

If conservative therapy proves unsuccessful, the next course of treatment should be normal saline continuous bladder irrigation.\textsuperscript{12} It is vital that clots are evacuated prior to therapy as the success of subsequent irrigation often depends upon the thoroughness of this procedure. The use of appropriate analgesia during irrigation is also important.\textsuperscript{12}

Intravesical therapy

Intravesical therapy is often necessary with continued HC. In recent years, GAG replenishment therapy has widened the therapeutic options.

Sodium hyaluronate. Sommariva et al.\textsuperscript{56} demonstrated that sodium hyaluronate solution relieved the symptoms of chemical- and radiation-induced cystitis, with 67 of 69 (97\%) patients reporting complete relief of dysuria and pain. Patients with chemical-induced cystitis were found to respond slightly better than those who had radiation-induced cystitis. Bladder instillation of sodium hyaluronate has also been shown to be as effective as hyperbaric oxygen therapy (HBOT) in the treatment of patients with pelvic malignancies and radiation-induced cystitis, resulting in a sustained decrease of bladder bleeding, pelvic pain and frequency of voiding for at least 12 months.\textsuperscript{29}

Sodium hyaluronate 40 mg/50 ml solution is slowly installed into the bladder via a urethral catheter each week for up to six weeks. It is well tolerated and causes few, if any, adverse effects, although the insertion of the catheter may cause some urethral irritation. It may be given with or without cytostimulation. Prior to receiving treatment, the clinician should check that the patient is able to empty the bladder well and has no evidence of a urinary tract infection or tumour recurrence.

Chondroitin sulphate. Few data are available on the use of chondroitin sulphate. A large, prospective, observational study indicated that intravesical replenishment of chondroitin sulphate leads to improved clinical symptoms of chronic forms of cystitis, including radiation cystitis, especially urinary frequency and urgency and pelvic pain.\textsuperscript{57} The authors note, however, that these results need to be confirmed in a controlled study.\textsuperscript{57}

Prostaglandin. Although the exact mechanism of action is unclear, data from several published case series\textsuperscript{58,59} and case reports\textsuperscript{60–63} suggest that intravesical prostaglandins (PGE\textsubscript{1}, PGE\textsubscript{2} and PGF\textsubscript{2} alpha (\(\alpha\))) may be useful to prevent or treat HC secondary to radiation therapy or cyclophosphamide therapy. The advantages of intravesical prostaglandins for treating HC include good tolerance with no significant toxicity, and no anaesthetic requirement or bedside administration.\textsuperscript{55} However, flushing and severe bladder spasms have been reported.\textsuperscript{33,58,59}

Formalin. Intravesical formalin has been reported in the treatment of intractable chemotherapy- or radiation-induced
HC. A review by Choong et al. highlights that there is wide variation in the concentration and volume of formalin solution used, the contact time, technique and type of follow-up irrigation (saline, distilled water, alcohol and saline, alcohol only and no irrigation) after formalin instillation. Although formalin has been shown to be effective for controlling severe haematuria, serious complications may be encountered following treatment including anuria, vesicle fistula and death, as well as minor complications such as fever, transient tachycardia and recurrent haematuria. Because of the potential serious complications, intravesical formalin should be used with great caution and only after more conservative measures have failed.

Alum irrigation. There have been several reports on the use of alum irrigation in the management of cyclophosphamide- and radiation-induced HC with varying degrees of success. Alum is an astringent that causes protein precipitation over bleeding surfaces and is commonly delivered as a 1% solution via a three-way catheter at a maximal rate of 300 cc/h. Although systemic toxicity is low as the urothelial permeability to aluminium is minimal, there have been several case reports of aluminium toxicity in children. The use of alum in those patients with renal insufficiency should generally be avoided and the risk for alum intoxication should be considered, especially in children.

Systemic treatment

Systemic treatments including HBOT, oestrogen, sodium pentosanpolysulphate, recombinant factor VII or VIII, and aminocaproic acid have been used with some success in the treatment of HC.

HBOT. Treatment with HBOT has been extensively evaluated in the management of adults with radiation-induced HC as well as those with cyclophosphamide-induced HC and has yielded good results. Although data in children are scarce, Zama et al. recently reported their single-centre experience with HBOT in late-onset HC. Between 2004 and 2011, 10 patients developed severe HC after a median of 26 days after HSCT. After a median of 10 sessions of HBOT, seven patients were in complete remission. Although HBOT appears to produce good short-term benefits, Del Pizzo et al. noted that it did not produce a definitive long-term cure of the disease process.

The protocol for HBOT proposed by Choong et al. suggests 20 sessions of 100% oxygen inhalation at 0.3 MPa in a hyperbaric chamber (90 min/session). Treatment consists of daily sessions five or six times a week, and the number of sessions may be increased to 40. Although effective, there are several issues which may prevent more widespread application of HBOT for chemotherapy- and radiation therapy-induced HC. Potential side effects caused by barometric pressure changes or toxicity may be associated with HBOT. Furthermore, there are currently very few centres in the UK offering HBOT.

Sodium pentosanpolysulphate. There are few published studies on the use of sodium pentosanpolysulphate in patients with HC and only one small retrospective case note review in the paediatric population with HC post-stem cell transplant/chemotherapy. The authors found that sodium pentosanpolysulphate significantly reduced blood transfusion requirements and mortality from HC. The initial dosage is 100 mg three times a day, which is gradually reduced to a maintenance dose of 100 mg daily. Sodium pentosanpolysulphate is generally well tolerated and requires one to eight weeks to reduce the degree of haematuria.

Oestrogen. Several small reports have reported a role for oestrogen in the control of HC in adult and paediatric populations. Although generally well tolerated, concerns regarding its use include liver dysfunction, hypercoagulability, hypertension, flushing, feminisation in males, and malignant transformation.

Recombinant factor VIII/factor XIII. The use of recombinant factor VII or XIII in the treatment of cyclophosphamide- and radiation-induced HC has been described by a number of authors after BMT and to treat radiation-induced HC. The recommended dose is 90 µg/kg and a second dose may be administered after 20 minutes if the desired effect is not achieved. However, concerns remain regarding the potential thrombogenicity of this agent.

Aminocaproic acid. The use of aminocaproic acid for the management of HC has been described in the literature. The maximum recommended dose in 24 hours is 30 g. However, this treatment modality should be viewed with caution as the safety and efficacy have yet to be established in randomised studies. The main disadvantage of aminocaproic acid is the formation of hard clots that are not easily flushed from the bladder and therefore the patient should be clot free prior to starting treatment.

Other agents

A number of other oral agents, including the trycyclic antidepressant amitryptiline, prednisone and cimetidine, have been investigated in the treatment of symptomatic interstitial cystitis/painful bladder syndrome, with some success. However, no published studies were identified that specifically addressed the use of these drugs for the treatment of chemical- or radiation-induced HC.

Surgical procedures

Major surgical procedures, such as ligation of the hypogastric arteries and urinary diversion with or without cystectomy, are
Imaging studies:
CT urogram to exclude bleeding from the upper urinary tract
MRI scan may be indicated

Laboratory and other evaluations:
Urinalysis & urine culture - positive treat with antibiotics
Cystoscopy if haematuria present (consider hydrodistension)
Consider cytology for patients at high risk of bladder cancer
Blood tests (Hb, complete blood count, blood urea, serum creatinine, and coagulation profile)

Clinical diagnosis

Conservative measures (Grades I-II/III):
Intravenous hydration
One large glass of cranberry juice daily
Analgesia
Spasmolytic drugs
Consider oral tranexamic acid 1 g three times daily for patients with haemorrhage or at high risk of haemorrhage

Obstructive clots?

No

(Grades III/IV)
Evacuate clots
Continuous bladder irrigation

Assess response:
Not responding or diffuse bleeding

Assess response:
Symptomatic relief?

No

Intravesical therapy:
Cystistat (sodium hyaluronate) 40 mg/50 ml solution weekly for 6 weeks and monthly thereafter
Consider hyperbaric oxygen therapy (if available)

Assess response:
Refractory to irrigation and intravesical instillation

Consider selective embolisation/surgery

Figure 1. Management algorithm for radiation- and chemical-induced haemorrhagic cystitis.
CT: computed tomography; MRI: magnetic resonance imaging.
the last resort for the treatment of severe HC and are associated with high morbidity and mortality.\textsuperscript{105} The introduction of percutaneous arterial embolisation has provided a minimally invasive and less morbid option to patients suffering from severe HC. The technique of superselective embolisation of the vesical arteries potentially avoids extensive occlusion of peripheral vessels and may decrease the incidence of side effects, such as post-embolisation gluteal pain, claudication, genital injury, or tissue necrosis.\textsuperscript{105} Published case reports suggest that this procedure is a safe and effective procedure for achieving immediate control of refractory bladder haemorrhages.\textsuperscript{105,106}

Surgery is an option of last resort for patients whose symptoms are unresponsive to primary forms of treatment, and is rarely performed.

**Recommendations**

- Clots should be removed from the bladder before the initiation of any treatment.
- Grade IV HC will need more aggressive treatment, including cystoscopic clot evacuation and continuous irrigation.
- Sodium hyaluronate should be considered in all patients after conservative measures have failed.
- HBOT is an attractive treatment option, but there are currently very few centres in the UK offering HBOT.
- Severe HC, defined as haemorrhage refractory to irradiation and intravesical instillation, may necessitate further treatment, depending on whether the bladder disease is focal or diffuse.
- In extreme cases, when all other treatment options have failed, selective embolisation can be considered.
- Surgery is an option of last resort for patients whose symptoms are unresponsive to primary forms of treatment, and is rarely performed.

Based on the available data and the experience of the multidisciplinary consensus panel, a management algorithm for radiation- and chemical-induced haemorrhagic cystitis is provided in Figure 1.

**Acknowledgements**

Writing and editorial support was provided by Strategen Limited, Basingstoke, UK.

**Conflict of interest**

The authors received no financial support. All authors have previously served as advisors, speakers and/or investigators for Teva UK Limited and have received honoraria/research grants in this regard.

**Funding**

Teva UK Limited has provided arms’ length funding to support the production of this article. Teva UK Limited did not initiate this article, and has had no input into the editorial content or the final article.

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