Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy–Associated Adverse Events

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Abstract

Context: Although intravesical therapy is an integral part of the management of non-muscle invasive bladder cancer (NMIBC), both intravesical chemotherapy and bacillus Calmette-Guérin (BCG) have potential side effects that may lead to treatment cessation and incomplete treatment courses.

Objective: To provide evidence-based strategies for the prevention and management of intravesical therapy–associated adverse events.

Evidence acquisition: A committee of international leaders in bladder cancer management, known as the International Bladder Cancer Group (IBCG), was convened in October 2006 to review current literature surrounding adverse events associated with intravesical therapy. Following the inaugural meeting in October 2006, the IBCG met on three subsequent occasions to exchange ideas and to develop practical recommendations for the prevention and management of these adverse events.

Evidence synthesis: The IBCG provided an overview of adverse events associated with BCG and intravesical chemotherapy as well as practical recommendations for the prevention and management of these side effects based on current evidence.

Conclusions: Cystitis and hematuria are side effects common to both chemotherapy and BCG. Other rare complications common to both intravesical therapies include contracted bladder and ureteral obstructions. BCG-specific adverse events include granulomatous prostatitis, epididymo-orchitis, systemic BCG reactions, and allergic reactions, while side effects specific to intravesical chemotherapy include contact dermatitis, bladder calcifications, and myelosuppression. The keys to management of these adverse events are education, prevention, and awareness. Preventive strategies include instructing health care professionals about proper catheterisation techniques and instilling BCG at least 2 wk following a TURBT; if catheterisation is traumatic or the patient has a urinary tract infection, BCG instillations should be deferred for 1 wk. Furthermore, the use of prophylactic ofloxacin 200 mg given twice after BCG instillations appears to be a simple and practical method of improving BCG tolerability while maintaining its efficacy. BCG dose reduction may also be a reasonable option, particularly for those patients known to be intolerant to standard-dose BCG.

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1. Introduction

Intravesical therapy is an integral part of the management of non-muscle invasive bladder cancer (NMIBC). Both intravesical chemotherapy and bacillus Calmette-Gue\'rin (BCG) have potential side effects which can be described as local or systemic. Local side effects are common for both therapies and can lead to treatment cessation and incomplete treatment, resulting in suboptimal outcomes. BCG-related adverse events can be treated successfully in most patients, even those patients with serious side effects [1]. The keys to management of these adverse events are education, prevention, and awareness. Furthermore, it should be noted that BCG-associated side effects are generally seen during induction and during the first 6 mo of maintenance BCG [1,2]. During further maintenance, BCG-related adverse events do not significantly increase, and instillations are generally well tolerated [1].

This article summarizes the local and systemic side effects associated with intravesical therapy and presents the International Bladder Cancer Group’s (IBCG) recommendations for the effective management of these adverse events based on currently available evidence. Strategies for the prevention of BCG-related adverse events, such as education, dose reductions, and the use of ofloxacin are also reviewed.

2. Local side effects common to both intravesical chemotherapy and bacillus Calmette-Gue\’rin

Cystitis and hematuria are the most common local side effects of intravesical therapy, but they usually resolve 48 h after instillation. More severe, but less common, are local adverse events that include contracted bladder and ureteral obstruction.

2.1. Cystitis

Cystitis is the most common side effect of BCG, occurring in approximately 80% of patients [3], and it is the most frequently cited reason for postponement of BCG instillations. Chemical cystitis is also a common side effect of intravesical chemotherapy, occurring in as many as 56% of doxorubicin-treated patients, 41% of mitomycin C-treated patients [4], and approximately one-third of epirubicin-treated subjects [5].

Therapeutic options for cystitis include oxybutynin, phenazopyridine, or propantheline bromide. Prophylactic tuberculostatics, such as isoniazid, have not been shown to be beneficial for the management of BCG-related cystitis [6]. If cystitis persists beyond 48 h, postponement of therapy, subsequent dose reductions, or the use of a quinolone antibiotic (for BCG-related cystitis only) should be considered [7].

2.2. Hematuria

Hematuria is reported in up to 90% of BCG-treated patients [8] and in up to 40% of patients treated with intravesical chemotherapy [4]. It frequently occurs with cystitis and appears to be related to the extent of the previous transurethral resection of the bladder tumour (TURBT). In patients experiencing hematuria, it is important to perform a urine culture to exclude bacterial cystitis and to postpone instillations until the urine is clear. If the hematuria persists, it is important to consider cystoscopy in order to rule out any tumour persistence. In rare instances, catheterisation and bladder irrigation of clots may be required.

2.3. Contracted bladder

A contracted bladder due to extravasation of intravesical therapy, although rare, is a serious complication and appears to be associated with multiple TURBTs and maintenance instillations. Management includes withholding intravesical therapy, hydrodistention and, on occasion, cystectomy. Cystoprostatectomy with orthotopic neobladder reconstruction may be the optimal solution to alleviate severe lower urinary tract symptoms and to remove the risk of subsequent urothelial malignancy [9].

2.4. Ureteral obstruction

A ureteral obstruction is a rare complication that may be due to resection and subsequent fibrosis around the ureteral orifice. It is generally temporary and self-limited after cessation of intravesical instillations; however, the presence of carcinoma in situ (CIS) or muscle-invasive (T2) bladder cancer should be excluded. Occasionally, percutaneous drainage or stenting of the kidney may be required [10].

3. Local side effects specifically associated with bacillus Calmette-Gue\’rin

More severe local side effects associated with BCG therapy include granulomatous prostatitis and epididymo-orchitis.

3.1. Granulomatous prostatitis

Granulomatous prostatitis is a common occurrence in BCG-treated patients that is caused by BCG-
contaminated urine; however, it is usually asymptomatic, with local and systemic reactions occurring in only 1–3% of patients [10,11].

On digital rectal examination, the prostate is occasionally indurated. The prostate-specific antigen (PSA) level may be elevated, and ultrasound may show hypoechoic zones [7]. The granulomas generally appear as distinct, intensely hypoechoic anterior lesions within the transition zone of the prostate [12].

Up to 5% of patients with BCG-associated granulomatous prostatitis will require symptomatic treatment which involves a combination of isoniazid and rifampicin for 3 mo, plus high-dose fluoroquinolones and steroids for persistent symptoms. Suspension of instillations is also required.

The local disease course should be monitored clinically and by laboratory parameters and ultrasound, and a diagnosis of prostate cancer should be considered if the appearance of the granuloma does not return to normal [7].

3.2. Epididymo-orchitis

Epididymo-orchitis is also caused by BCG-contaminated urine. Epididymo-orchitis that occurs during instillations is primarily due to Gram-negative bacilli resulting from catheterisation, while later appearance of the condition is related to mycobacteria [13].

Krege et al reported that epididymo-orchitis occurs in approximately 10% of BCG-treated patients [14]; however, other studies have reported incidence rates as low as 0.2% [7]. In the event of epididymo-orchitis, the presence of a nosocomial infection should be excluded; treatment should include isoniazid and rifampicin [7]. Because Gram-negative bacteria are usually the cause of epididymo-orchitis, treatment with high-dose fluoroquinolone therapy is also recommended. Durek et al have shown that BCG is susceptible to both ciprofloxacin and ofloxacin [15,16]. The use of steroids following high-dose fluoroquinolones is recommended for persistent symptoms. Severe and persistent epididymo-orchitis or the development of an abscess secondary to epididymo-orchitis may require orchidectomy.

4. Local side effects specifically associated with intravesical chemotherapy

4.1. Contact dermatitis

Contact dermatitis has been reported in up to 19% of patients treated with intravesical mitomycin C [4] and often leads to eczema-like desquamation of the skin on the palms, soles, perineum, chest, and face [17]. A case of penile gangrene resulting from contact dermatitis following intravesical administration of mitomycin C has recently been reported. The gangrene required penectomy 3 mo after the instillation [18].

Careful cleansing of the hands after drug-handling and cleansing of the genitals and perineum after voiding may help prevent contact dermatitis associated with intravesical mitomycin C [17]. Management of this adverse event requires cessation of therapy; the use of topical steroid creams usually relieves symptoms.

4.2. Bladder calcifications

Case reports of bladder wall calcifications have also been reported with intravesical mitomycin C [19,20].

5. Systemic side effects associated with bacillus Calmette-Guérin

Systemic side effects are less frequent than local side effects but are more likely to be severe. The most common systemic side effects associated with BCG therapy are general malaise, fever, myalgia, and nausea. Low-grade fever has been shown to develop in about 30.5% of BCG-treated patients, while fever greater than 39 °C has been reported in 5–20%. These side effects generally resolve within 48 h with or without the use of antipyretics as symptomatic treatment; however, persistent high-grade fever (ie, >38.5 °C for >48 h) requires permanent discontinuation of BCG instillations, immediate evaluation and treatment with two or more antimicrobial agents (while diagnostic evaluation, including cultures, is conducted), and consultation with an infectious diseases specialist.

5.1. Systemic bacillus Calmette-Guérin reactions

Although rare, a systemic BCG reaction is a systemic granulomatous illness that may occur subsequent to BCG exposure. Because it is usually difficult to isolate BCG organisms from affected organs, the extent to which such a reaction is caused by an infectious process versus an inflammatory hypersensitivity reaction is often unclear, hence the term “systemic BCG reaction.”

BCG infection is rare and usually occurs immediately after instillation. It is generally associated with high-grade fever and may progress to multiple organ failure. Clinical examination is often non-specific but may reveal hepatomegaly and bilateral lower lung crepitations. Blood tests often
reveal impaired hemodynamic status, leukopenia, and abnormal liver function tests [7].

BCG infection generally occurs in patients receiving BCG soon after TURBT and may be associated with intravenous absorption resulting from traumatic catheterisation. Therefore, to prevent infection, it is recommended that BCG therapy be initiated at least 2 wk post TURBT if there are no signs of hematuria.

The management of severe systemic BCG reactions requires cessation of BCG therapy and treatment with isoniazid, rifampicin, and ethambutol for 6 mo [7], plus early, high-dose fluoroquinolones and high-dose corticosteroids as long as symptoms persist. Investigations in animal models have shown that the addition of steroid treatment to antimicrobial therapy following secondary BCG infection prolongs survival compared to antimicrobials alone [21]. An empirical non-specific antibiotic to treat Gram-negative bacteria and/or Enterococcus is also recommended [7].

5.2. Allergic reactions

Allergic reactions to intravesical BCG are rare but may involve skin rashes and arthralgia. Treatment of these reactions generally involves antihistamines and anti-inflammatory agents. For severe or persistent reactions, BCG should be discontinued, and the addition of isoniazid and rifampicin plus corticosteroids should be considered [7].

6. Systemic side effects associated with intravesical chemotherapy

6.1. Myelosuppression

Although rare, myelosuppression has been noted in patients treated with mitomycin C [22,23] and may result from the use of high-concentration instillations into a bladder that has recently been traumatized [4].

The management of myelosuppression involves cessation of intravesical chemotherapy and monitoring of white blood cell (WBC) count.

7. The International Bladder Cancer Group’s recommendations for the management of intravesical therapy-associated adverse events

The IBCG’s recommendations for the management of intravesical therapy-associated adverse events are summarized in Table 1. This table also includes the following World Health Organization grading of toxic drug effects, which can be used as a guide for determining when intravesical therapy may be contraindicated [7]:

- Grade 1: Moderate and <48 h (usually require no modification of intravesical therapy)
- Grade 2: Severe and/or >48 h (usually require suspension of instillations until resolution of symptoms)
- Grade 3: Local, regional, systemic, and immune-allergic (usually require suspension of instillations until resolution of symptoms)
- Grade 4: Systemic BCG reactions (cessation of BCG therapy is required).

8. Strategies for the prevention of bacillus Calmette-Guérin–associated adverse events

Strategies that may help prevent BCG-associated adverse events include education, dose reductions, and the use of ofloxacin. Other strategies that have been proposed but not reviewed in this section include concomitant use of isoniazid, decreasing the dwell time of BCG, and the addition of other immune-modulators.

8.1. Education

The success of BCG immunotherapy relies on the intravesical administration of live BCG and the generation of a localized immune response in the bladder. Since BCG is a live bacteria, it has the potential to produce systemic adverse events as described in the previous section. Historically, poor technique and non-recognition of BCG-related, systemic adverse events have led to serious morbidity and, in rare instances, to mortality. The keys to management of these adverse events are education, prevention, and awareness.

Education begins with teaching proper catheterisation techniques to the administering health care professional. BCG should be instilled a minimum of 2 wk following a TURBT in order to allow the bladder mucosa to re-epithelialize. If gross hematuria is present, BCG should be delayed until this has resolved. If the patient has a urinary tract infection (UTI), then BCG treatment should be deferred until resolution of the UTI with antibiotics. If the catheterisation is traumatic, then BCG instillations should be deferred for 1 wk. Furthermore, BCG should be instilled passively by gravity. If a BCG systemic reaction is suspected, then early initiation of antitubercular and quinolone antibiotics is recommended. Recognition and early treatment of
<table>
<thead>
<tr>
<th>Side effect</th>
<th>Grade</th>
<th>Management options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local side effects common to intravesical chemotherapy and BCG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-bacterial or chemical cystitis</td>
<td>1</td>
<td>Oxybutynin, phenazopyridine, propantheline bromide, or anti-inflammatory agents (NSAIDs)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Consider postponement of intravesical therapy and subsequent dose reductions if cystitis persists beyond 48 h</td>
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<tr>
<td></td>
<td></td>
<td>For prolonged BCG cystitis, consider use of a quinolone antibiotic</td>
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<tr>
<td>Gross hematuria</td>
<td>1–2</td>
<td>Perform urine culture to exclude hemorrhagic cystitis</td>
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<td></td>
<td></td>
<td>Suspend instillations until urine clears</td>
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<td></td>
<td></td>
<td>Catheterisation and bladder irrigation for clots may be required</td>
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<tr>
<td>Contracted bladder</td>
<td>≥2</td>
<td>Suspend instillations until resolution of symptoms</td>
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<td></td>
<td></td>
<td>Hydrodistention</td>
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<td></td>
<td></td>
<td>Cystectomy may be required in some instances</td>
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<tr>
<td>Ureteral obstruction</td>
<td>≥2</td>
<td>Usually temporary and self-limited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclude presence of CIS or muscle-invasive (T2) bladder cancer</td>
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<tr>
<td></td>
<td></td>
<td>Percutaneous drainage or stenting of the kidney may be required</td>
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<tr>
<td><strong>Local side effects associated with BCG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic granulomatous prostatitis</td>
<td>&gt;2</td>
<td>High-dose fluoroquinolones</td>
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<tr>
<td></td>
<td></td>
<td>Isoniazid and rifampicin for 3 mo, plus quinolones and steroids</td>
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<td></td>
<td></td>
<td>Suspension of intravesical therapy</td>
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<tr>
<td>Epididymo-orchitis</td>
<td>&gt;2</td>
<td>High-dose fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isoniazid and rifampicin for 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension of intravesical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orchidectomy if severe and persistent</td>
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<tr>
<td><strong>Local side effects associated with intravesical chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>≥2</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Careful cleansing of hands after drug handling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cleansing of genitals and perineum after voiding</td>
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<tr>
<td></td>
<td></td>
<td>Cessation of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical steroids for relief of symptoms</td>
</tr>
<tr>
<td><strong>Systemic side effects associated with BCG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General malaise, fever</td>
<td>1</td>
<td>Generally resolve within 48 h with or without antipyretics</td>
</tr>
<tr>
<td>Persistent high-grade fever (&gt;38.5 °C for &gt;48 h)</td>
<td>≥2</td>
<td>Permanent discontinuation of BCG instillations</td>
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<td></td>
<td></td>
<td>Immediate evaluation</td>
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<tr>
<td></td>
<td></td>
<td>Prompt treatment with two or more antimicrobial agents (eg, fluoroquinolones, isoniazid, rifampicin) while diagnostic evaluation, including cultures, is conducted</td>
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<tr>
<td></td>
<td></td>
<td>Consultation with an infectious diseases specialist</td>
</tr>
<tr>
<td><strong>Systemic BCG reactions</strong></td>
<td>4</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Initiate BCG at least 2 wk post TURBT (if no signs and symptoms of hematuria)</td>
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<td></td>
<td></td>
<td>Cessation of BCG</td>
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<tr>
<td></td>
<td></td>
<td>For severe infection</td>
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<tr>
<td></td>
<td></td>
<td>• High-dose fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Isoniazid, rifampicin, and ethambutol daily for 6 mo</td>
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<td></td>
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<td>• Early, high-dose corticosteroids as long as symptoms persist</td>
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<tr>
<td></td>
<td></td>
<td>• Consider an empirical non-specific antibiotic to treat Gram-negative bacteria and/or Enterococcus</td>
</tr>
<tr>
<td><strong>Allergic reactions</strong></td>
<td>1–2</td>
<td>Antihistamines and NSAIDs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider suspension of BCG instillations</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>Discontinue BCG instillations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider isoniazid and rifampicin plus corticosteroids for persistent symptoms</td>
</tr>
<tr>
<td><strong>Systemic side effects associated with intravesical chemotherapy</strong></td>
<td>3–4</td>
<td>Cessation of intravesical therapy</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td></td>
<td>Monitor white blood cell (WBC) count</td>
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</table>

Abbreviations: BCG, bacillus Calmette-Guérin; NSAIDs, non-steroidal anti-inflammatory drugs; TURBT, transurethral resection of the bladder tumour.
suspected BCG systemic reactions will help eliminate virtually all serious adverse events.

8.2. Dose reductions

Variations in the reported frequency of BCG-associated adverse events appear to be caused by variations in the dose of BCG instillations. Therefore, dose reductions may be a reasonable option for the prevention of BCG-associated adverse events, particularly for those patients known to be intolerant to standard-dose BCG.

Martinez-Pineiro et al found that a one-third dose of BCG gave similar results for recurrence and progression as did the standard-dose of BCG [24,25]. However, patients with multifocal tumours fared better with the standard dose, and there was a trend toward lower recurrence rates in patients with high-risk tumours who received the full-dose of BCG [24]. Fewer class 1 and class 2 adverse events were noted in patients receiving the one-third dose of BCG; however, there was no significant difference between the one-third dose and standard dose in terms of severe adverse events [24]. Ojea et al found that one-sixth of the standard BCG dose was significantly less effective than one-third of the standard dose for the treatment of intermediate-risk NMIBC, suggesting that a one-third dose is the minimum effective dose of BCG in these patients [26].

Final results from the randomised European Organization for Research and Treatment of Cancer (EORTC) trial comparing a standard dose with a one-third dose of BCG and comparing 1 yr of maintenance therapy with 3 yr of maintenance therapy in intermediate- and high-risk patients (protocol 30962) may provide further insight into the optimal BCG administration schedule for the prevention of BCG-associated adverse events.

8.3. Ofloxacin

Recent clinical trial evidence suggests that prophylaxis with ofloxacin could help reduce BCG-associated adverse events and improve tolerance to therapy. In a recent randomised, double-blind, multicenter study, 115 patients with primary or recurrent superficial bladder cancer (Ta/T1, CIS, G1–G3) and no prior BCG treatment were randomised to treatment with six plus three weekly instillations of BCG (81 mg, Connaught strain) plus ofloxacin (200 mg; group A) or BCG plus placebo (group B). Two capsules of ofloxacin or placebo were given 6 h and 18 h after the first urination post instillation. Severity of BCG adverse events was assessed using a four-class scale [27,28].

Results of the study showed that ofloxacin significantly decreased the incidence of class 2 adverse events by 22.2% between instillations 4 and 6 (p = 0.017), and the incidence of class 3 adverse events by 21.5% between instillations 1 and 9 (p = 0.019; see Fig. 1). Compliance with full BCG treatment was also improved: 80.7% of patients in group A received nine instillations compared with 65.5% in group B (p = 0.092) [27].

BCG treatment was stopped for toxicity reasons in seven patients in Group A versus 14 patients in Group B. Moreover, a significant impact of ofloxacin on the need for antituberculosis treatment was observed, with three patients in Group A requiring such treatment versus eight in Group B. [27]. At 24 mo, there were no significant differences between the two groups in terms of disease recurrence or progression. The recurrence rate was 18.2% in the
BCG plus ofloxacin group and 20.6% in the BCG plus placebo group. The percentage of patients that were tumour-free at 24 mo was 78.8% in the ofloxacin group and 79.4% in the placebo group [28].

The use of prophylactic ofloxacin 200 mg given twice after BCG instillations appears to be a simple and practical method of improving BCG tolerability while maintaining efficacy. Large-scale randomised, controlled trials are required to confirm these initial promising findings.

9. The International Bladder Cancer Group’s recommendations for the prevention of bacillus Calmette-Guérin–associated adverse events

Based on the review of potential strategies for the prevention of BCG-associated adverse events, the IBCG has proposed the following recommendations:

- Instill BCG after a minimum of 2 wk following a TURBT.
- Teach proper catheterisation techniques to administering health care professionals.
- Defer BCG instillations for 1 wk if catheterisation is traumatic.
- If gross hematuria is present, delay BCG until this has resolved.
- If the patient has a UTI, then defer BCG for 1 wk until resolution of the UTI with antibiotics.
- Consider the use of ofloxacin 200 mg given twice after each BCG instillation.
- If a BCG systemic reaction is suspected, then initiate multiple antimicrobial therapies early and consult with an infectious diseases specialist (if available).
- Consider dose reductions in patients known to be intolerant to standard-dose BCG.

BCG is an integral part of the management of NMIBC; therefore, the prevention and management of BCG-related adverse events is essential for optimizing treatment outcomes. Through education, prevention, and awareness, these adverse events can be effectively managed in most BCG-treated patients.

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