Current Bladder Dysfunction Reports (2019) 14:58–66
https://doi.org/10.1007/s11884-019-00506-x

INFLAMMATORY/INFECTIOUS BLADDER DISORDERS (MS MOURAD, SECTION EDITOR)

Effects and Complications of Intravesical Instillation of Bacillus Calmette-Guerin Therapy

J. Spencer Keith[1] · Mahmoud I. Khalil[1] · Mohamed H. Kamel[1] · Rodney Davis[1] · Ehab Eltahawy[1]

Published online: 8 April 2019

Abstract

Purpose of Review This review will address the current literature available regarding complications after intravesical Bacillus Calmette-Guerin (BCG) therapy for bladder cancer. Topics include intravesical BCG therapy–related complications, role of BCG therapy in immunosuppression, and future directions in the context of BCG-related complications.

Recent Findings There are several new reviews and case reports discussing unique complications following intravesical BCG therapy that should raise awareness of possible short-term and long-term effects after using this common treatment modality in bladder cancer patients.

Summary Since intravesical BCG is a common treatment option for non-muscle invasive bladder cancer and can cause a variety of complications, it is important to recognize this aspect of the patient's history when evaluating patients who present with symptoms similar to the ones discussed in this review. This will allow for prompt delivery of treatment as well as preventing unnecessary morbidity and mortality.

Keywords Intravesical Bacillus Calmette-Guerin therapy · BCG · Non-muscle invasive bladder cancer · Immunosuppression · BCG complications

Abbreviations

AFB	Acid-fast bacilli
AKI	Acute kidney injury
Anti-TB	Anti-tuberculosis
BCG	Bacillus Calmette-Guerin
CIS	Carcinoma in situ
CKD	Chronic kidney disease
INH	Isoniazid
LFTs	Liver function tests
LUTs	Lower urinary tract symptoms
MSK	Musculoskeletal
NMIBC	Non-muscle invasive bladder cancer
NSAIDs	Non-steroidal anti-inflammatory drugs
RIF	Rifampin
TUR	Transurethral resection

This article is part of the Topical Collection on *Inflammatory/Infectious Bladder Disorders*

✉ Ehab Eltahawy
eeltahawy@uams.edu

[1] Department of Urology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Little Rock, AR 72205, USA

Introduction

Intravesical instillation of Bacillus Calmette-Guerin (BCG) has been a mainstay of adjunctive therapy for non-muscle invasive bladder cancer (NMIBC): stages Ta, T1, or carcinoma in situ (CIS) since the 1970s [1]. Intravesical BCG is recommended for intermediate and high-risk urothelial cancer but not for low-risk disease (low-grade Ta) [2, 3]. Meta-analyses have shown that intravesical BCG following transurethral resection (TUR) of a bladder tumor reduces the recurrence and progression of the disease when compared with TUR alone [4–6]. Although intravesical instillation exhibits a favorable safety profile, both local and systemic BCG-related complication may occur since it contains viable attenuated mycobacteria. Hence, it might necessitate anti-tuberculosis (anti-TB) medications should systemic effects occur. Complications of therapy have been reported on a wide spectrum of severity and timing, ranging from irritative lower urinary tract symptoms (LUTs) and generalized infection soon after instillation to localized organ involvement outside the bladder months to years after therapy. Since the majority of patients requiring BCG therapy for bladder cancer are generally older with multiple comorbidities, clinicians must

understand the potential risks, complications, and their possible management.

The BCG vaccine was first administered successfully in humans in 1921 after Albert Calmette and Camille Guerin began their quest of developing a vaccine against tuberculosis. The first trial of intravesical BCG instillation for bladder cancer was orchestrated by Morales in 1976 [7]. He based a plan of six weekly instillations to allow enough time to establish a delayed hypersensitivity reaction. Morales's trial demonstrated a decrease in the recurrence rate of bladder tumors along with inhibition of progression and tumor spread [1]. Several studies continued to demonstrate similar findings, leading to the approval by the Federal Drug Administration of the use of intravesical BCG in patients with non-invasive urothelial carcinoma in 1990 [8, 9].

The mechanism of tumor destruction by which BCG exerts its effects in bladder cancer is not fully understood. According to Fuge et al., the effect of BCG could be noted in this series of steps: internalization of BCG by urothelial cells, induction of an immune response, and subsequently elicitation of antineoplastic effect [10, 11]. The resultant immune response includes T helper-1 (Th-1) chemotaxis, leading to the production and release of IL-2, IL-12, IFN-γ, and TNF-β. Recently, these cytokines have been postulated for use as urinary inflammatory markers to predict individual patient response to maintenance BCG treatment [12]. Similarly, the mechanism of developing BCG-related complications is still debatable. Some authors believe there is a form of hypersensitivity reaction based on the absence of microorganisms in histologically examined granuloma, while others assume an active mycobacterial infection is responsible after demonstration of viable bacilli in a variety of tissues [13]. Factors associated with a greater risk of developing complications are BCG instillation following recent TUR or during active urinary tract infection, traumatic catheterization, hematuria, urethral stenosis, active tuberculosis, and prior BCG sepsis. We reviewed the literature on intravesical BCG therapy with particular emphasis on side effects, complications, and their management.

BCG-Related Complications

BCG-related complications have been reported with an estimated incidence of less than 5%. Since there is a lack of consensus for disease classification and diagnostic criteria for various side effects, there have been several different reports discussing ways to group the possible symptoms in a fashion that allows for improving diagnosis and prompt treatment [14]. We preferred to present the side effects according to the severity along with the time from the last instilled dose, which to some extent resembles the Cleveland Clinic grading [15].

Minor and Moderate Symptoms < 48 h (Grade 1)

Common side effects after BCG therapy typically develop after the third instillation [16•]. This includes irritative voiding symptoms, low-grade fever, and gross hematuria within the first 48 h after instillation. It is important to distinguish BCG cystitis from a concurrent urinary tract infection, as the latter would require antibiotics for treatment. A urine culture may be necessary to detect these two common diagnoses [15]. Most of these early mild symptoms are self-limiting and do not require additional treatment; however, patients should be observed. Some patients may need symptomatic management such as anti-cholinergics, analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs) [15, 17]. Gross hematuria generally arises following the second or third instillation in 1–34% of patients [18, 19]. It usually does not necessitate treatment unless persistent for 2–3 weeks of observation, at which time cystoscopy is warranted to exclude persistent tumor. Intravesical instillation should be withheld until improvement of hematuria. Patients may experience significant side effects soon after BCG instillation, occasionally prompting the need for systemic antibiotics and vasopressor support [20]. Therefore, it is important for clinicians to counsel patients about these common reactions, placing greater emphasis on the serious conditions.

Severe Symptoms > 48 h (Grade 2)

One review series consisting of 2600 patients with BCG-related side effects showed the most common being irritative LUTs, high-grade fever (≥ 39.5 °C), and macroscopic hematuria [21]. These adverse effects usually occur within the first 48 h of BCG instillation; however, they can occur anytime thereafter as well. These patients require a more in-depth workup as opposed to the patients mentioned previously because of the higher likelihood of possible sepsis development. Reaching a diagnosis with prompt treatment is important in such cases. Possible tests to order include urine culture, chest CT scan, and liver function tests (LFTs) [14, 15]. Chest CT scan is more sensitive than chest radiograph in detecting miliary tuberculosis related to BCG instillation, so this should be pursued in order to prevent delay of treatment. Pneumonitis secondary to BCG instillation usually differs in appearance compared with primary tuberculosis, taking on a bilateral diffuse reticulonodular appearance [20].

Since hepatitis is also a common complication in conjunction with pneumonitis, LFTs should be ordered as well. This pneumonitis/hepatitis presentation can be seen as early as 1 day after BCG instillation, reinforcing the importance of early use of this workup in patients presenting with fever, cough, dyspnea, and hepatomegaly [21]. In regard to more

severe BCG-related systemic symptoms, administration of isoniazid (INH) and rifampin (RIF) orally until symptom resolution is reasonable according to the Cleveland Clinic approach [15]. If patients experience systemic symptoms of fever and malaise after multiple cycles of BCG instillation, discontinuation of BCG therapy and pursuit of a different treatment option should be considered [22].

Serious Complications (Grade 3)

Grade 3 complications encompass a broad spectrum in regard to solid organ systems within the body. These can also involve hemodynamic instability due to sepsis and severe allergic reactions, which both require prompt treatment in order to prevent morbidity and mortality among this patient subset.

In general, the majority of patients with focal disease presented later after their last BCG instillation compared with patients experiencing systemic complications [14, 22, 23]. Gonzalez et al. distinguished early presentation from late presentation by making a cut-off time of 6 months after the most recent BCG instillation [23]. Ninety percent of patients who presented early had suspected BCG infection such as fever, malaise, and evidence of systemic infection outside the bladder, most commonly hepatitis and pneumonitis [23]. Sixty percent of patients in the late-presentation group had areas of localized infection compared with none of the early-presentation group [23].

Genitourinary Involvement

The genitourinary tract is a harbinger for localized disease after BCG therapy (Fig. 1), with complications including cystitis, bladder contracture, granulomatous prostatitis, balanitis, granulomatous balanitis, epididymo-orchitis, seminal vesiculitis, and kidney manifestations [17, 20–22].

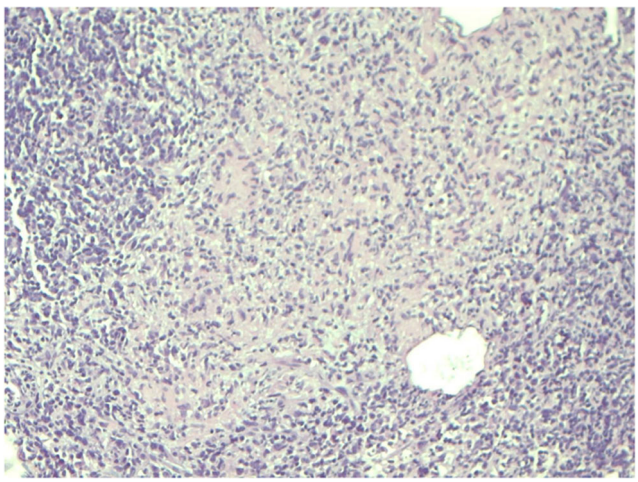

Fig. 1 This figure shows a large granuloma and giant cells seen in localized genitourinary disease after BCG therapy

Granulomatous Prostatitis

Symptomatic granulomatous prostatitis was seen in 1.3% of patients in one case series. Usually, the majority of patients are asymptomatic; however, acute prostatitis or acute urinary retention may occur. In one study, granulomatous prostatitis was found in 40% of patients undergoing prostate biopsy after BCG therapy [24]. Biopsy might be necessary when nodularity is present in order to rule out prostate cancer [20]. These patients require dual therapy with INH and RIF for 3 months, but asymptomatic patients do not need treatment.

Granulomatous Epididymo-orchitis

Granulomatous epididymo-orchitis is an uncommon complication and patients typically present with local pain and induration [18]. It can be misinterpreted as testicular cancer if appropriate history is not taken, oftentimes resulting in unnecessary orchiectomy with significant patient morbidity [21]. Treatment is with INH and RIF for 3–6 months according to case severity. Abscess formation requiring incision and drainage or even orchiectomy might occur [25].

Granulomatous Balanitis

Granulomatous balanitis is another rare complication that can cause painless penile nodules, plaques, ulcers, abscesses, or inguinal lymphadenopathy, requiring triple anti-TB treatment with INH, RIF, and ethambutol [20, 21]. It typically presents after multiple cycles of BCG.

Contracted Bladder

This condition has a low incidence of < 1% in a study by Lamm and colleagues [18]. Maintenance BCG may be a risk factor for developing such condition. In severe cases, cystectomy may be required; however, conservative measures of withholding BCG and offering hydrodistention should be considered first [26].

Ureteral Obstruction

Ureteral obstruction is a rare condition reported in 0.3% of patients [26]. Risk factors include CIS of the bladder and vesicoureteral reflux. It is thought to be a result of bladder mucosal inflammation; hence, it is deemed temporary and self-limiting. Treatment involves long-term antibiotics after withholding BCG therapy. Ureteral stenting can be done to drain the kidney, but more definitive endoscopic and surgical interventions should be deferred till after medical therapy is complete.

Renal Complications

BCG-related complications in the kidney can be difficult to detect because of the variable presentation and lack of constitutional symptoms. The most common renal complication after intravesical BCG therapy is acute kidney injury (AKI) due to interstitial nephritis with potential presence of granulomatous lesions. Case reports of other renal complications include AKI with glomerulonephritis, nephrotic syndrome, and AKI with concurrent hemolytic uremic syndrome, rhabdomyolysis, and multiorgan failure. Even though an acute presentation is more common, a single case report by Mohammed and Arastu demonstrated a chronic kidney disease (CKD) type of picture [27]. There was a direct correlation between the decline in the creatinine level and BCG therapy over a period of 1 year, with a plateau phase during the cessation of BCG therapy between cycles. This raises the concern that renal injury can be dose-related causing CKD as opposed to the AKI picture seen for many years before this report. The most common treatment regimen used in most reports involves INH plus RIF for 6–9 months, plus a course of corticosteroids initially [20].

Musculoskeletal Involvement

Arthritis/Arthralgia

It is not uncommon for patients to present with arthritis and arthralgias following BCG instillation. Complications involving the musculoskeletal (MSK) system include arthritis ± uveitis and dysuria, polyarthritis commonly affecting the knees and ankles, osteomyelitis, septic arthritis, and psoas and epidural abscesses [20, 21]. Presentation with arthritis generally occurs early after a course of BCG therapy, while the rest of these complications present months to years after the last instillation. Given the broad differential, it is important to take a meticulous history with a high index of suspicion to diagnose BCG-related osteoarthritis, especially since arthrocentesis with acid-fast bacilli (AFB) culture takes several weeks to get results.

Reactive Arthritis

Reactive arthritis is less common than other MSK complications, with an estimated incidence of 0.5–1% [28]. It is treated with NSAIDs, occasionally requiring addition of corticosteroids and anti-TB drugs; however, tocilizumab was used successfully in a single case report [20, 21, 28]. Of those diagnosed with reactive arthritis secondary to BCG therapy, the human leukocyte antigen (HLA) B27 has been shown to be positive between 42 and 64% of the time [14, 20, 21].

Other Rare Conditions

BCG osteomyelitis can occur late after BCG therapy. Risk factors include recent placement of joint prosthesis, recent fracture, and impaired wound healing [21]. Other complications include thoracolumbar spondylodiscitis and paraspinal or psoas abscesses [14]. One extremely rare rheumatologic finding in regard to BCG complications is a polyarthritis with accompanying edema of the hands and feet, lack of bony erosions, and lack of rheumatoid factor, known as remitting seronegative symmetrical synovitis pitting edema (RS3PE) [21]. It is typically treated with high-dose NSAIDs along with cessation of BCG.

MSK problems are very common among elderly patients in general, so it is important to be able to pinpoint BCG therapy in a patient's history so that they may be treated appropriately.

Vascular Involvement

Although vascular involvement in BCG complications is quite rare, it is considered one of the factors associated with higher mortality, in addition to age ≥ 65 years and disseminated infection [14]. Patients affected by BCG vasculitis generally present late because of non-specific findings. The one unique finding with BCG vasculitis is that the tissue specimens are often positive for AFB, unlike most other complications seen in relation to intravesical BCG therapy [21]. Mycotic aneurysms have been known to occur in the aorta, carotid arteries, and femoral arteries, with the most common location being the infrarenal aorta [14, 20]. Fistulas and adjacent abscesses can complicate aneurysms as well, creating a challenging treatment course that involves surgery and an anti-TB regimen, usually lasting at least 1 year.

Disseminated BCG Infection

Disseminated BCG infection causing constitutional symptoms occurred in 34.4% of patients in one large case series. However, development of sepsis and multiorgan failure is rare (0.4–2.5%) [14, 20]. Patients with sepsis secondary to BCG therapy present with hemodynamic compromise, fever, malaise, and occasional hematuria. Diagnosis of disseminated BCG infection immediately following instillation is more straightforward than most other complications because of the acute presentation after treatment. One unique finding in these patients with concurrent tuberculous peritonitis is elevated serum cancer antigen (CA-125) levels, occasionally reaching levels as high as those in ovarian cancer [29]. This lab finding could be of value for physicians to use when suspected BCG complication arises.

Treatment of disseminated BCG infection can be complex, with most patients receiving anti-TB drugs and adjuvant systemic corticosteroids at a higher rate than other

complications [14]. However, immunocompetent patients have been seen to clear the infection on their own, as reported by Vasudeva and colleagues [20]. In general, physicians should initiate early high-dose corticosteroids in addition to four tuberculostatic agents for rapid response in patients suspected to have septicemia and multiorgan failure [17, 21]. Tuberculostatic drugs that are effective against BCG include INH, RIF, ethambutol, fluoroquinolones, clarithromycin, aminoglycosides, and doxycycline [17]. Pyrazinamide is globally avoided in suspected BCG-related complications because of the well-known resistance that *Mycobacterium bovis* has towards it.

Prophylaxis for BCG-Related Complications

In an effort to decrease the rates of treatment cessation and limit the number of side effects seen with BCG therapy, several studies have looked at a number of different prophylactic agents that might be reasonable options. One randomized trial performed in the late 1990s showed no significant difference in the percent of local and systemic BCG-related complications among the group using INH prophylaxis vs. the group without prophylaxis. Additionally, patients in the INH group experienced liver toxicity based on elevated LFTs [30].

In a study done by Colombel and colleagues discussing the effects of ofloxacin, a fluoroquinolone with tuberculostatic properties, authors found that the use of ofloxacin significantly reduced the percent of patients experiencing moderate or severe adverse effects after instillation while retaining the recurrence-free survival rate [30]. The issues related to this study include inadequate power based on a limited number of study subjects and possibility of patients experiencing tendinopathy associated with ofloxacin use.

Selected Case Reports

In addition to the many different BCG-related complications that can affect nearly all the organs of the body, these case reports present important signs and symptoms that physicians may encounter in the context of BCG-related complications that can guide them away from less likely differential diagnoses (Table 1).

AAA, abdominal aortic aneurysm; *BCG*, Bacillus Calmette-Guerin; *DIC*, disseminated intravascular coagulation; *EMB*, ethambutol; *HD*, hemodialysis; *HSP*, Henoch-Schonlein purpura; *INH*, isoniazid; *M. bovis*, *Mycobacterium bovis*; *NMIBC*, non-muscle invasive bladder cancer; *RIF*, rifampin; *TB*, tuberculosis

BCG Role in the Immunosuppression State

BCG expresses its anti-tumor effect by stimulating a marked inflammatory response, eventually ridding the bladder of tumor cells. The problem with this enhanced inflammatory response is the potential for graft rejection in renal transplant patients. In addition, administering intravesical BCG to patients with suppressed immune systems for NMIBC allows for an increased risk of potential toxicity compared with the immunocompetent population. Intravesical BCG therapy for NMIBC hence has been deemed in some reports to be contraindicated in those who are immunosuppressed [39, 40].

Herr et al. looked at a group of 45 immunosuppressed patients with high-grade NMIBC who received BCG therapy to determine its efficacy and evaluate the rate of complications compared with the immunocompetent population. The studied population included patients receiving anti-rejection drugs to support a solid organ transplant, high-dose steroids for autoimmune inflammatory disease, or concomitant systemic chemotherapy for unrelated malignant neoplasms. They all received 6-week induction intravesical BCG and were allowed to receive a second course of therapy if necessary. However, maintenance therapy was avoided because of potential cumulative toxicity and failure to show great benefit at their institution. In terms of effectiveness, 91% of patients had a complete response to BCG, defined as negative biopsy and urine cytology by 6 months. This compares well with the reported complete response rate of 79% in immunocompetent patients in a previous study consisting of 1021 patients [41]. These results clearly differ from what is expected based on the proposed mechanism of BCG and necessity of an intact immune system. The smaller patient population may have skewed these numbers a bit, but the study still demonstrates the high probability that intravesical BCG therapy can be effective in the immunosuppressed population. Authors found that none of the patients developed bacterial or BCG sepsis, concluding that administration of intravesical BCG therapy in this cohort of patients is safe [39].

Roumeguere et al. looked at a unique subset of patients who had undergone renal transplantation for end-stage aristolochic acid nephropathy and developed NMIBC or CIS. Mitomycin C was given in the early 2000s because of the contraindication to BCG in immunosuppressed patients at that time. After many failures and recurrences with mitomycin C, they looked into the use of BCG in transplant patients to see if there was any evidence to back up the contraindication. There were eight patients in the trial who had undergone bilateral nephroureterectomy for prior aristolochic acid exposure. Precautionary measures with the immunosuppressant regimens and anti-tuberculous prophylaxis were taken to optimize the BCG treatment and minimize BCG-induced toxicity. After a mean follow-up period of 50 months, only one patient had a recurrence of CIS requiring cystectomy.

Table 1 A list of uncommon complications following BCG therapy for NMIBC

Author/reference	Age/gender	Complication	No. of BCG instillations before complication	Time from BCG to symptoms	Symptoms	Treatment/outcome
Macleod et al. [[21]]	74 years old, male	Periurethral diverticulum formation w/ *M. bovis* infection	3	1 week	Perineal mass posterior to scrotum	Observation
Tsukada et al. [[31]]	80 years old, male	HSP nephritis	–	4 months	Systemic edema, diarrhea, purpura on lower legs	3 sessions of plasmapheresis and HD + pulsed methyl prednisolone; oral prednisolone
Samadian et al. [[32]]	94 years old, male	Vertebral osteomyelitis and discitis, mycotic AAA	–	5 months	Lumbar back pain, malaise, functional impairment	Anti-TB therapy without pyrazinamide
Kusakabe et al. [33]	76 years old, male	Spondylitis with adjacent mycotic aortic aneurysm	6	14 months	Severe lower back pain at the L2/3 level	INH, RIF, EMB; drainage of abscess, AAA repair, L2/3 laminectomy/fusion
Parker et al. [34]	75 years old, male	Epididymo-orchitis	12 + 1 mitomycin	15 months	Right testicular pain	Orchiectomy; INH, RIF, EMB, pyrazinamide
Gao et al. [35]	61 years old, male	Hepatitis, pneumonitis, choroiditis, aortoduodenal fistula	6	15 months	Malaise, low-grade fever, night sweats, 50-lb weight loss	RIF 600 mg, INH 300 mg, EMB 1.2 g
Davis et al. [36]	64 years old, male	Mycotic multifocal thoracoabdominal aortic aneurysm	8	17 months	Abdominal pain with radiation to his back, 50-lb weight loss	Surgical repair; moxifloxacin and EMB due to INH resistance
Ziegler et al. [37]	75 years old, male	Disseminated BCG-induced sepsis in renal transplant patient	6	6 years	Fatigue, functional decline, generalized weakness, 6-kg weight loss	Levofloxacin, INH, rifabutin
Mavrogenis [38]	72 years old, male	Spondylitis, epidural abscess	12	12 years	Lower back and leg pain, anorexia, 5.2-kg weight loss, pitting LE edema	INH, RIF, EMB; drainage of abscess; L2-L5 fusion

Kidney function of all patients remained stable throughout the treatment process, with evidence from stable serum creatinine levels. Overall, the BCG therapy was well tolerated with few side effects, along with being very effective at treating the cancer [40].

In general, intravesical BCG use after TUR in patients with bladder cancer looks to be effective and safe among those with suppressed immune systems. As more data become available and BCG therapy increases in this population, it will be important to remain cognizant of possible new developments in the realm of related complications.

Personal Perspectives

Overall, the prognosis of most BCG-related complications is good, despite the non-negligible rates of morbidity and mortality in this review. This mandates proper diagnosis with timely management to hasten improvement and to achieve total cure. Assessment of factors predicting the development of complications in the overall population receiving intravesical BCG is not fully understood. Similarly, factors associated with poor outcomes if complications occurred are still difficult to expect. Studies discussing these issues are lacking and most of them showed only borderline significance.

In terms of the treatment modalities, more research efforts should be focused to find new anti-TB medications, to be used in most systemic BCG-related complications, because old medications possess a high profile of liver toxicity. Some studies demonstrated successful treatment of the Connaught BCG strain infection with fluoroquinolones like ciprofloxacin, moxifloxacin, and levofloxacin [23, 42–44]. Despite the potential safety profile of fluoroquinolones on liver functions, this has to be counterbalanced with established risk of tendinopathy associated with the long-term usage of these medications.

Conclusions

Intravesical BCG therapy will likely remain a primary treatment option of NMIBC and CIS for many years to come. Like many modalities used in the treatment of cancer, side effects and complications may arise. Proper knowledge of possible complications and their management is substantial for the urologist when using BCG. For this reason, it is important to recognize the patient's history of intravesical BCG therapy, onset, and duration of symptoms to quickly establish a diagnosis and initiate appropriate treatment. Delay in treatment could lead to dire consequences in those with more serious complications, especially in the elderly population who are more susceptible due to weakened immune systems.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116(2):180–3.
2. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C, et al. Guidelines on bladder cancer. Eur Urol. 2002;41(2):105–12.
3. Lamm DL, van der Meijden AP, Akaza H, Brendler C, Hedlund PO, Mizutani Y, et al. Intravesical chemotherapy and immunotherapy: how do we assess their effectiveness and what are their limitations and uses? Int J Urol. 1995;2(Suppl 2):23–5.
4. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004;93(4):485–90. https://doi.org/10.1111/j.1464-410X.2003.04655.x.
5. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, van der Meijden A, Parmar MK et al. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Party on Superficial Bladder Cancer. The J Urol 1996;156(6): 1934–40, discussion 40-1.
6. Witjes JA, van der Meijden AP, Collette L, Sylvester R, Debruyne FM, van Aubel A, et al. Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacilli Calmette-Guerin-RIVM and mitomycin C in superficial bladder cancer. EORTCGU Group and the Dutch South East Cooperative Urological Group. European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group. Urology. 1998;52(3):403–10. https://doi.org/10.1016/S0090-4295(98)00212-X.
7. Sakula A. BCG: who were Calmette and Guerin? Thorax. 1983;38(11):806–12.
8. Herr H, Morales A. History of bacillus Calmette-Guerin and bladder cancer. J Urol. 2008;179(1):53–6. https://doi.org/10.1016/j.juro.2007.08.122.
9. Kamat AM, Flaig TW, Grossman HB, Konety B, Lamm D, O'Donnell MA, et al. Consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer. Nat Rev Urol. 2015;12:225–35. https://doi.org/10.1038/nrurol.2015.58.
10. Jokisch J-F, Karl A, Stief C. Intravesical immunotherapy in nonmuscle invasive bladder cancer. Indian J Urol. 2015;31(4): 304–11. https://doi.org/10.4103/0970-1591.166452.

11. Fuge O, Vasdev N, et al. Immunotherapy for bladder cancer. Res Rep Urol. 2015;7:65–79. https://doi.org/10.2147/RRU.S63447.
12. Zuiverloon TCM, Nieuweboer AJM, Vekony H, et al. Markers predicting response to bacillus calmette-guerin immunotherapy in high-risk bladder cancer patients: a systematic review. Eur Urol. 2012;61:128–45. https://doi.org/10.1016/j.eururo.2011.09.026.
13. Eichel L, Erturk E, Disant'Agnese A. Drug resistant Mycobacterium bovis cystitis following intravesical bacillus Calmette-Guerin treatment. J Urol. 1999;162(6):2096.
14. Perez-Jacoiste Asin MA, Fernandez-Ruiz M, Lopez-Medrano F, et al. Bacillus Calmette-Guerin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer. Medicine. 2014;93(17):236–54. https://doi.org/10.1097/MD.0000000000000119.
15. Jones JS, Larchian WA. Non-muscle-invasive bladder cancer (Ta, T1, CIS). In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. Tenth ed. Philadelphia, PA: Elsevier Saunders; 2012.
16.• Lamm DL. Complications of bacillus Calmette-Guerin immunotherapy. Urol Clin North Am. 1992;19(3):565–72 **Knowing when to give and when to withhold BCG will prevent most complications, but even when all precautions are taken, some complications will occur. This is a comprehensive and detailed landmark review of the literature of the diagnosis and management of different complications from BCG**.
17. Decaestecker K, Oosterlinck W. Managing the adverse events of intravesical bacillus calmette-guerin therapy. Res Rep Urol. 2015;7:157–63. https://doi.org/10.2147/RRU.S63448.
18. Lamm DL, van der Meijdan PM, Morales A, Brosman SA, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992;147(3):596–600.
19. Molina JM, Rabian C, D'Agay MF, Modai J. Hypersensitivity systemic reaction following intravesical bacillus Calmette-Guerin: successful treatment with steroids. J Urol. 1992;147(3):695–7.
20. Vasudeva S, Baffoe-Bonnie A. Intravesical BCG therapy and side effects-case reports and a review of literature. Mycobact Dis. 2018;8(4):1–6. https://doi.org/10.4172/2161-1068.1000270.
21. Macleod LC, Ngo TC, Gonzalgo ML. Complications of intravesical bacillus calmette-guerin. Can Urol Assoc J 2014:8(7–8):e540–4. Doi:https://doi.org/10.5489/cuaj.1411, 540, E544.
22. Bilsen MP, van Meijgaarden KE, de Jong HK, Joosten SA, Prins C, Kroft LJM, et al. A novel view on the pathogenesis of complications after intravesical BCG for bladder cancer. Int J Infect Dis. 2018;72:63–8. https://doi.org/10.1016/j.ijid.2018.05.006.
23. Gonzalez OY, Musher DM, Brar I, Furgeson S, Boktour MR, Septimus EJ, et al. Spectrum of Bacille Calmette-Guerin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis. 2003;36:140–8. https://doi.org/10.1086/344908.
24. Mukamel E, Konichezky M, Engelstein D, Cytron S, Abramovici A, Servadio C. Clinical and pathological findings in prostates following intravesical bacillus Calmette-Guerin instillations. J Urol. 1990;144(6):1399–400.
25. Hoag N, Pommerville PJ, Kibsey PC, Cavers DJ, Eddy RJ. Tuberculous epididymitis following intravesical Bacillus Calmette-Guerin immunotherapy. Can J Urol. 2009;16(2):4589–91.
26. Koya MP, Simon MA, Soloway MS. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol. 2006;175(6):2004–10. https://doi.org/10.1016/S0022-5347(06)00264-3.
27. Mohammed A, Arastu Z. Emerging concepts and spectrum of renal injury following intravesical BCG for non-muscle invasive bladder cancer. BMC Urol. 2017;17:114. https://doi.org/10.1186/s12894-017-0304-5.
28. Adelghani KB, Fazaa A, Souabni L, Zakraoui L. Reactive arthritis induced by intravesical BCG therapy for bladder cancer. BMJ Case Rep. 2014;2014:bcr2013202741. https://doi.org/10.1136/bcr-2013-202741.
29. Elzein F, Albogami N, Saad M, Tayeb NE, Alghamdi A, Elyamany G. Disseminated *Mycobacterium bovis* infection complicating intravesical BCG instillation for the treatment of superficial transitional cell carcinoma of the bladder. Clin Med Insights: Case Rep. 2016;9:71–3. https://doi.org/10.4137/CCRep.S39904.
30. Colombel M, Saint F, Chopin D, Malavaud B, Nicolas L, Rischmann P, et al. The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. J Urol. 2006;176:935–9. https://doi.org/10.1016/j.juro.2006.04.104.
31. Tsukada H, Miyakawa H. Henoch Schonlein Purpura nephritis associated with intravesical bacillus calmette-guerin (BCG) therapy. Intern Med. 2017;56:541–4. https://doi.org/10.2169/internalmedicine.56.7494.
32. Samadian S, Phillips FM, Deeab D. *Mycobacterium bovis* vertebral osteomyelitis and discitis with adjacent mycotic abdominal aortic aneurysm caused by intravesical BCG therapy: a case report in an elderly gentleman. Age Ageing. 2013;42:129–31. https://doi.org/10.1093/ageing/afs164.
33. Kusakabe T, Endo K, Nakamura I, Suzuki H, Nishimura H, Fukushima S, et al. Bacille calmette-guerin (BCG) spondylitis with adjacent mycotic aortic aneurysm after intravesical BCG therapy: a case report and literature review. BMC Infect Dis. 2018;18(1):290. https://doi.org/10.1186/s12879-018-3205-7.
34. Parker SG, Kommu SS. Post-intravesical BCG epididymo-orchitis: case report and a review of the literature. Int J Surg Case Rep. 2013;4:768–70. https://doi.org/10.1016/j.ijscr.2013.05.017.
35. Gao CQ, Mithani R, Leya J, Dawravoo L, Bhatia A, Antoine J, et al. Granulomatous hepatitis, choroiditis and aortoduodenal fistula complicating intravesical Bacillus Calmette-Guerin therapy: case report. BMC Infect Dis. 2011;11:260. https://doi.org/10.1186/1471-2334-11-260.
36. Davis FM, Miller DJ, Newton D, Arya S, Escobar GA. Successful treatment of a mycotic multifocal thoracoabdominal aortic aneurysm as a late sequelae of intravesical bacillus calmette-guerin therapy: case report and literature review. Ann Vasc Surg. 2015;29:840.e9–e13. https://doi.org/10.1016/j.avsg.2014.12.020.
37. Ziegler J, Ho J, Gibson IW, Nayak JG, Stein M, Walkty A, et al. Disseminated *Mycobacterium bovis* infection post-kidney transplant following remote intravesical BCG therapy for bladder cancer. Transpl Infect Dis. 2018;20:e12931. https://doi.org/10.1111/tid.12931.
38. Mavrogenis AF, Sakellariou VI, Tsiodras S, Papagelopoulos PJ. Late *Mycobacterium bovis* spondylitis after intravesical BCG therapy. Joint Bone Spine. 2009;76:296–300. https://doi.org/10.1016/j.jbspin.2008.10.011.
39. Herr HW, Dalbagni G. Intravesical Bacille Calmette-Guerin (BCG) in immunologically compromised patients with bladder cancer. BJU Int. 2013;111:984–7. https://doi.org/10.1111/j.1464-410X.2012.11778.x.
40. Roumeguere T, Broeders N, Jayaswal A, et al. Bacillus Calmette-Guerin therapy in non-muscle-invasive bladder carcinoma after renal transplantation for end-stage aristolochic acid nephropathy. Transpl Int. 2014;28:199–205. https://doi.org/10.1111/tri.12484.
41. Herr HW, Dalbagni G, Donat SM. Bacillus Calmette-Guerin without maintenance therapy for high-risk non-muscle-invasive bladder cancer. Eur Urol. 2011;60:32–6. https://doi.org/10.1016/j.eururo.2011.03.051.
42. Durek C, Rusch-Gerdes S, Jocham D, Bohle A. Sensitivity of BCG to modern antibiotics. Eur Urol. 2000;37(Suppl 1):21–5. https://doi.org/10.1159/000052378.
43. Manfredi R, Dentale N, Piergentili B, Pultrone C, Brunocilla E. Tubercular disease caused by Bacillus of Calmette-Guerin as a local

adjuvant treatment of relapsing bladder carcinoma. Cancer Biother Radiopharm. 2009;24(5):621–7. https://doi.org/10.1089/cbr.2009.0668.

44. Rozenblit A, Wasserman E, Marin ML, Veith FJ, Cynamon J, Rozenblit G. Infected aortic aneurysm and vertebral osteomyelitis after intravesical bacillus Calmette-Guerin therapy. AJR Am J Roentgenol. 1996;167(3):711–3. https://doi.org/10.2214/ajr.167.3.8751686.