

*Full Length Research Paper*

# Symptomatic BCG balanitis occurring after induction of intravesical BCG immunotherapy. What is the optimal treatment duration and regimen?

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**Intravesical Bacillus Calmette Guerin (BCG) immunotherapy is the standard initial therapy for patients with high-grade urothelial bladder cancer without muscle invasion. While minor complications due to intravesical BCG immunotherapy are common, cutaneous infections of the glans penis are quite rare. Granulomatous balanitis can be devastating if not identified and treated early. A well-established treatment regimen and duration of therapy is lacking. We review the English literature to define an optimal treatment strategy. To date there have been 12 reports of BCG balanitis occurrences after intravesical instillation of BCG for non-muscle invasive bladder cancer. In general, there appears to exist both under-diagnosis and failure of early diagnosis of the disease. Additionally, there are still many unanswered questions such as: What is the optimal regimen and duration of the treatment? Is repeated intravesical BCG administration safe, in patients with prior balanitis, for managing tumor recurrence or maintenance of BCG protocols? What are the clinical signs and symptoms of BCG balanitis? Isoniazid therapy of at least three months with adjuvant Rifampicin therapy for a minimum of two weeks is an optimal regimen. Repeated and maintained administration of intravesical BCG after prior balanitis is affordable. Early diagnosis and treatment of BCG balanitis usually leads to complete resolution and minimal morbidity.**

**Key words:** Balanitis, Intravesical BCG, Bladder cancer, Balanoposthitis, Granulomatous balanitis, Granulomatous balanoposthitis.

## INTRODUCTION

BCG balanitis is a rare and potentially morbid condition if not recognized and treated early. This is currently no consensus amongst Urologist or infectious disease specialist for the optimal treatment regimen or duration of BCG balanitis. We aim to define an optimal treatment regimen and duration, clarify common questions regarding repeated intravesical BCG therapy in the presence of prior balanitis and to draw attention to the symptoms and signs for early disease. Herr et al. (2008) recalled an insightful study that paved the way for current bladder cancer therapy. This was an autopsy

study came out in 1929, which included patients infected with tuberculosis at John's Hopkins that showed an overall lower frequency of various malignancies when compared to non-infected patients. Over the next 50 years it was found that intravesical Bacillus Calmette-Guerin (BCG) immunotherapy could theoretically be used in cancer therapy as it elicits an indirect immune response after binding to fibronectin sites, activates T cells and subsequently kills the cancer cells. Morales et al. (1976) proposed a treatment protocol for superficial bladder cancer with intravesical BCG. This demonstrated satisfactory treatment with no recurrence in seven patients. The published success of intravesical BCG and the subsequent confirmation of its clinical utility by the National Cancer Institute, led in 1990 to the Federal Drug Administration's (FDA) approval of intravesical BCG for the

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the treatment of superficial bladder cancers (Herr et al., 2008). Since the first successful report of intravesical BCG therapy for superficial bladder cancer (non-muscle invasive high-grade urothelial carcinoma) in 1976, it has been widely used as first line treatment after Transurethral Resection of Bladder Tumor (TURBT). Intravesical BCG immunotherapy induces a delayed hypersensitivity response in the bladder through the introduction of a viable attenuated mycobacterium bovis bacillus to the organ. This ultimately leads to macrophage activation, amongst other immune mediated responses, which actually results in the destruction of the urothelial carcinoma. Additionally, the documented benefits of decreased bladder cancer recurrence and progression have made it a standard of care for urologists (Morales et al., 1976).

Lamm et al. (1992) demonstrated the ever so important local and systemic side effects of intravesical BCG immunotherapy. They reported that the most common systemic side effects were due to an immediate hypersensitivity reaction to BCG and consisted of fever (< 101.3 °F), myalgia and shivering. More serious systemic complications occurred in 10-15% of cases and included organ/blood borne infection by dissemination of the BCG that necessitated prompt treatment with antitubercular agents. The most common local complication was cystitis (30-60%) associated with dysuria (80%) and hematuria (40%), with other local infections (epididymitis, prostatitis, ureter obstruction) being far less frequent (Lamm et al., 1992; Erol et al., 1995; Ribera et al., 1995).

Cutaneous manifestations of the glans penis are extremely rare and to date there have been 12 reports of BCG balanitis (balanoposthitis) occurrences after intravesical instillation of BCG for non-muscle invasive bladder cancer (Erol et al., 1995; Ribera et al., 1995; Baniel et al., 1996; Latini et al., 2000; French et al., 2001; Kureshi et al., 2006; Yusuke et al., 2006; Michelet et al., 2008; Hillyer et al., 2009; Yoshida et al., 2009; Lestre et al., 2011, Sharma et al., 2011). We will utilize a recent case in our clinic (department) of a 49 year-old male with BCG balanitis, occurring after the six weeks induction course of intravesical BCG, in order to illustrate our points. The adverse effects of BCG therapy are largely due to the nature of the vaccine and the fact that the bacillus used is in fact viable. There is a risk of hematogenous dissemination as reported previously (Lamm et al., 1992; Rischmann et al., 2000). The risk of a serious adverse effect is 10-15% and is usually a local reaction. Widespread dissemination is quite rare. However, numerous precautions have been recommended to prevent serious complications and these are: i.) Delaying use of intravesical BCG immunotherapy on patients for at least 1-2 weeks after TURBT or bladder biopsy, ii) avoiding this kind of therapy if gross hematuria or a traumatic catheterization is present and iii) seeking an alternative treatment if the patient is immune-compromised or have an active urinary

tract infection (UTI) or Tuberculosis infection (Lestre et al., 2011; Rischmann et al., 2000).

## METHOD

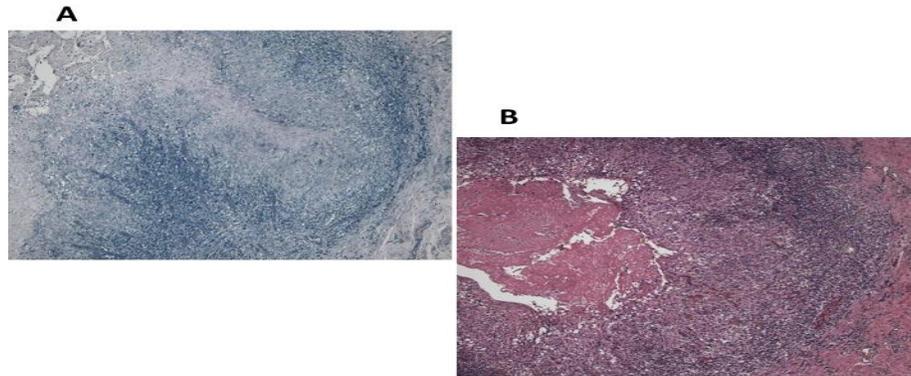
We conducted a systematic review of the English literature utilizing the key words: BCG balanitis or balanoposthitis, granulomatous balanitis or balanoposthitis, bladder cancer and intravesical BCG. We found 14 relevant publications over a period of eighteen years as determined by the two authors who abstracted the data. We utilized these 14 publications and a recent case in our department to illustrate the lack of consensus in the treatment of BCG balanitis and attempted to determine the following: How can we prevent BCG balanitis? What are the clinical signs and symptoms of BCG balanitis? What is the optimal treatment regimen? What is the optimal duration of the treatment? Should a patient with BCG balanitis be offered maintenance of intravesical BCG therapy or even repeated intravesical BCG treatment in case of a tumor recurrence?

## Topics

### Case Presentation

A 49 year-old, otherwise healthy, male presented with a one-week history of irritative voiding symptoms and pink urine. Workup revealed stage pT1 bladder cancer. Two weeks following resection, the patient commenced a weekly cycle of intravesical TICE® BCG over six weeks without spillage of BCG, traumatic catheterization or hematuria prior to instillation. Two weeks following completion of therapy, the patient developed dysuria, low-grade fevers, chills, tenderness and swelling of the glans penis, not significantly improved with oral Bactrim BID. There was no growth of bacteria in the performed urine culture. One week later he presented at the emergency unit with new onset of glans penis redness, discharge, ulceration and worsening tenderness. He denied fever, chills, gross hematuria and inability to void. The highest temperature documented by us was 99.2°F, with otherwise normal vital signs. His circumcised genitalia showed hyperemia, edema, tenderness and palpable nodularity along the entire glans surface with shallow ulcerations of the meatus. The hematological investigation found only a mild leukocytosis.

A diagnosis of BCG balanitis was made. He was started on Isoniazid (INH) 300 mg daily. After he was referred to a infectious-disease specialist, Rifampicin in a dose of 600 mg daily was added to the initial therapeutic schema. A biopsy of glans penis lesion revealed a granulomatous inflammation (Figure 1). The therapy with INH and Rifampicin was completed in 12 weeks and two



**Figure 1.** Penile lesion Biopsy - Caseating granuloma. **(A)** Acid-fast bacillus stain appears negative for Mycobacteria and other organisms. **(B)** Caseating granuloma - composed of epithelioid histiocytes and central necrosis, with surrounding chronic inflammation.



**Figure 2.** **(A)** 6 weeks after initiating treatment - Phallus with slowly resolving glans erythema and nodularity of coronal sulcus. **(B)** 12 weeks after initiating treatment - complete resolution of glans penis erythema with mild residual peri-meatal ulceration and small residual coronal sulcus nodules.

weeks, respectively. His initial surveillance cystoscopy and biopsy of the bladder tumor resection sites showed granulomatous inflammatory reaction with no residual tumor. The patient showed no evidence of disease after one year and he had complete resolution of his balanitis (Figure 2).

### How can we prevent BCG Balanitis?

There is currently a very poor understanding of the pathophysiology of systemic complications related to the usage of BCG intravesical therapy, thus it is impossible to predict with any accuracy which specific complication a patient might experience. Therefore, this question is less about prevention of BCG balanitis and more about

prevention of systemic complications of intravesical BCG immunotherapy. The current American Urological Association (AUA) guidelines for intravesical BCG immunotherapy recommends a delay of 2-3 weeks following TURBT in order to allow healing of urothelium and thus decrease the risk of systemic side effects (Hall et al., 2007). Meta-analysis of available literature on intravesical BCG immunotherapy for non-muscle invasive bladder cancer showed associated rates of systemic complications ranging between 17-19% (Koya et al., 2006; Shelley et al., 2004). There are two studies that evaluated systemic complication rates in patients who were given intravesical BCG immunotherapy with a delay under 2 weeks after TURBT. Both studies had patients who initiated intravesical BCG therapy within one week after TURBT with van der Meijden's reporting an unacceptably

**Table 1.** Presenting clinical signs of BCG balanitis.

| Author                        | Clinical Signs on Glans Penis                                     | Other Clinical Symptoms                      | Complication in instillation?                           | 2 week delay between TURBT and BCG Tx? |
|-------------------------------|---|--|---|--|
| Erol (1995) <sup>4</sup>      | painless necrotic crusts  | bilateral tender inguinal lymphadenopathy    | No  | Yes                                    |
| Ribera (1995) <sup>5</sup>    | painful red plaque with yellow papules                            | right tender inguinal lymphadenopathy        | Yes, spillage of vaccine onto glans                     | Yes                                    |
| Baniel (1996) <sup>6</sup>    | painful edema and ulceration                                      | bilateral nontender inguinal lymphadenopathy | No  | N/A                                    |
|                               | painful edema and ulceration                                      | bilateral nontender inguinal lymphadenopathy | No  | No                                     |
| Latini (2000) <sup>7</sup>    | painless diffuse erythema and abscess                             | bilateral nontender inguinal lymphadenopathy | Yes, hematuria and dysuria                              | N/A                                    |
| French (2001) <sup>8</sup>    | painful induration on ventral glans with diffuse painless papules |  | No  | Yes                                    |
| Kureshi (2006) <sup>9</sup>   | painless ulceration, papules                                      | bilateral nontender inguinal lymphadenopathy | Yes, spillage or traumatic catheterization              | Unknown                                |
| Yasuke (2006) <sup>10</sup>   | painless firm papules   | foreskin edema                               | Ant. Urethra narrowed causing difficult catheterization | Yes                                    |
| Michelet (2008) <sup>11</sup> | painful ulceration with papules                                   |  | No  | N/A                                    |
|                               | papular nodules with sclerosing lesions                           |  | Yes, traumatic catheterization                          | N/A                                    |
| Yoshida (2008) <sup>13</sup>  | painless red plaque with yellow papules                           | bilateral nontender inguinal lymphadenopathy | No  | Unknown                                |
| Hillyer (2009) <sup>12</sup>  | painless erythema with central ulceration                         | cough and flu like symptoms                  | Yes, hematuria and urgency                              | Yes                                    |
| Lestre (2011) <sup>14</sup>   | painless erythematous nodules                                     | flu like symptoms                            | Yes, spillage of vaccine onto glans                     | Yes                                    |
| Sharma (2011) <sup>15</sup>   | diffuse edema with painless firm papules                          | bilateral nontender inguinal lymphadenopathy | Yes, traumatic catheterization                          | N/A                                    |
| Our Case (2012)               | painful edema and ulceration                                      | flu like symptoms                            | No  | Yes                                    |

high 39.4% risk of systemic side effects (Van der Meijden et al., 2003; Lamm et al. 2000).

It should be noted that the comparison of these two delay regimens is flawed because of the greater power associated with the studies of 2-3 weeks delays. Bearing that in mind, it is still noteworthy that there is such a stark difference in systemic complications between the two delay protocols (< 2 weeks delay vs. 2-3 weeks delay). Therefore, it can be inferred that following the established guidelines with delay of 2-3 weeks following TURBT will lead to a lower rate of systemic complications and thus a lower rate of BCG balanitis.

### What are the clinical signs and symptoms of BCG balanitis?

We found 14 cases of BCG balanitis in the current literature (Table 1). In addition to these main presenting symptoms, 8/14 (57%) cases had secondary symptoms of inguinal lymphadenopathy with 7/8 (88%) being bilateral. While fever and flu like symptoms are the highest reported systemic complications in intravesical BCG immunotherapy, only 2/14 (14%) cases of BCG balanitis showed these symptoms (Koya et al., 2006; Shelley et al., 2004; Van der Meijden et al., 2003; Lamm et al., 2000; Han et al., 2005; Mugiya et al., 2005; Martinez-Pineiro et al., 2005).

Excluding BCG induced balanitis from the differential diagnosis of the possible causes resulting in balanitis can lead to delay in therapy with increased rate of adverse

outcomes. In numerous published reports, initial therapy was aimed towards the more common causes of balanitis that included Candida and bacterial organisms despite the recent patient's history of intravesical BCG immunotherapy (Erol et al., 1995; Ribera et al., 1995; Baniel et al., 1996; Latini et al., 2000; French et al., 2001; Kureshi et al., 2006; Yasuke et al., 2006; Michelet et al., 2007; Hillyer et al., 2009; Yoshida et al., 2009). This led to failed trials of antibiotic/antifungal therapy and a subsequent delay in the diagnosis and treatment of BCG induced balanitis. A high degree of suspicion for BCG balanitis, as opposed to other common causes of balanitis, should be reserved for patients with a known history of intravesical BCG immunotherapy. We recommend that patients who present with Balanitis and have a recent history (< 1 year) of intravesical BCG immunotherapy should be evaluated for BCG Balanitis. The diagnosis can be confirmed by penile lesion biopsy. Furthermore, two reports demonstrated that cutaneous manifestations can occur even after one year from the initial BCG immunotherapy. Consequently, we should be aware of a possible BCG induced balanitis, also in cases that there is a long time interval between intravesical BCG immunotherapy and symptom occurrence (Hillyer et al. 2009; Lestre et al., 2011).

### What is the optimal treatment regimen?

There are established treatment regimens for BCG induced conditions such as sepsis, fever without sepsis,

**Table 2.** Meta-analysis of Treatment Regimens for BCG Balanitis.

| Author                        | Treatment             | Treatment Duration               | Outcome  |
|-------------------------------|-----------------------|----------------------------------|--|
| Erol (1995) <sup>4</sup>      | I, R, E               | 3 Months                         | Full resolution, with scarring                     |
| Ribera (1995) <sup>5</sup>    | I, R, E               | 9 Months                         | Full resolution, without scarring                  |
| Baniel (1996) <sup>6</sup>    | I                     | 3 Months                         | Full resolution, with scarring                     |
|                               | I, R                  | 3 Months                         | Full resolution, without scarring                  |
| Latini (2000) <sup>7</sup>    | I, E                  | 6 Months                         | Full resolution, without scarring                  |
| French (2001) <sup>8</sup>    | I, R                  | 3 Months                         | Full resolution, with scarring                     |
| Kureshi (2006) <sup>9</sup>   | I, R, E               | 3 Months                         | Full resolution, without scarring                  |
| Yasuke (2006) <sup>10</sup>   | I                     | 12 Months                        | Full resolution, without scarring                  |
| Michelet (2008) <sup>11</sup> | I, R                  | 12 Months                        | Full resolution, with scarring                     |
|                               | I, R, E               | unknown (ongoing at publication) | unknown  |
| Yoshida (2008) <sup>13</sup>  | I, R                  | 6 Months                         | Full resolution, without scarring                  |
| Hillyer (2009) <sup>12</sup>  | I, R, E               | 6 Months                         | Full resolution, without scarring                  |
| Lestre (2011) <sup>14</sup>   | I, R, E               | I, R: 6 Months E:2 Months        | Full resolution, without scarring                  |
| Sharma (2011) <sup>15</sup>   | I, R, E, Pyrazinamide | Ongoing                          | Full resolution, with scarring (as of publication) |
| Our Case (2012)               | I, R                  | I: 3 Months, R: 2 Weeks          | Full resolution, with scarring                     |

*I = Isoniazid, R = Rifampin, E = Ethambutol*

symptomatic orchitis and/or epididymitis and symptomatic granulomatous prostatitis. BCG sepsis is traditionally treated with short-term steroids and anti-tuberculosis drugs (Isoniazid, Rifampicin and Ethambutol) for a total of six months. Fever without sepsis after intravesical BCG immunotherapy is usually treated with Isoniazid for three months and broad-spectrum antibiotics. Symptomatic orchitis, epididymitis or granulomatous prostatitis is usually treated with Isoniazid and Rifampicin for 3-6 months (Weder, 2007). BCG balanitis has no defined regimen. There are five reported treatment regimens for BCG Balanitis and 15 reported cases, including the current case (see Table 2). This is a reflection of its uncommon occurrence and under-diagnosis. These five treatment regimens differ in many aspects, but all include Isoniazid. The addition of other anti-tuberculosis drugs likely varies with the treating practitioners' instinct with respect to the seriousness of the Balanitis and may thus include one to two additional drugs. If the practitioner believes that Balanitis is close to BCG sepsis then the triple drug regimen will be offered and if the belief is that similar to a symptomatic orchitis, epididymitis or granulomatous prostatitis then dual therapy will be offered. Notably one case reported the use of quadruple therapy with the addition of Pyrazinamide, a medication known to have little to no utility in mycobacterium bovis infections (Sharma et al., 2011). Upon review of the 15

cases, 14 cases (93%) had complete resolution of their Balanitis and one had an unknown status due to ongoing treatment (Isoniazid, Rifampicin, Ethambutol) at the time of publication. While it is difficult to pinpoint the best treatment regimen, it should be noted once again that Isoniazid was the primary drug in all treatment protocols. One case was quadruple drug therapy, six cases were triple drug therapy, six were dual drug therapy and one case was monotherapy.

Of the 14 cases with complete resolution of Balanitis, eight had usable information regarding the presence or absence of organ scarring. There is no definite factor that appears to predict or promote organ scarring.

#### **What is the optimal duration of the treatment regimen?**

As shown in Table 2, 13 of the 15 available cases reported treatment durations. These ranged from a minimum of three months (as in our case) to a maximum of 12 months. All cases had complete resolution with differences in resultant organ (penile) scarring, medication adverse effects and medication tolerance. There is no single treatment duration that offers superior results over the others (see Table 2). While this small sample group lacks the power to definitively identify the

optimal treatment duration, some recommendations can be made:

- ❖ Minimum duration of Isoniazid therapy should be at least three months, with an increased duration strongly suggested for a better cosmetic outcome.
- ❖ If dual therapy with Isoniazid is considered:
  - Rifampicin can be added for optimal results in organ cosmetic and symptom resolution. The duration of total treatment should be at least three months.
  - Ethambutol can be added for optimal results in organ cosmetic and symptom resolution. The duration of total treatment should be at least six months.
- ❖ Triple therapy with Isoniazid, Rifampicin, and Ethambutol appears equally effective to dual therapy with Isoniazid and Rifampicin only. The addition of Ethambutol does not appear to offer a shorter treatment duration or better organ cosmetic.

While it is difficult to identify the optimal treatment regimen for any future patients, it is safe to say that dual therapy with Isoniazid (with an appropriate replacement of Vitamin B6) and Rifampicin should be offered for at least three months duration. Furthermore, it appears that a longer duration of therapy may lead to a better cosmetic outcome (less scarring) but this has to be weighed against the risk of adverse medication side effects and likely cost to the patient.

#### **Should maintenance intravesical BCG therapy be recommended to a patient with prior BCG balanitis?**

Current American Urological Association guidelines recommends intravesical BCG immunotherapy using the SWOG regimen with an induction course of six weeks followed by a three-week maintenance dose at 3, 6, 12, 18, 24, 30 and 36 months if tolerated by the patient (Hall et al., 2007). A patient that develops BCG balanitis has by definition not tolerated the therapy well and thus is most likely not to be suitable for maintenance therapy. This can theoretically place the patient at increased risk for recurrence of bladder tumor, but a report by (Herr et al., 2011) suggests that this may not be the case. They argue that the data shows lower rates of recurrence in patients with maintenance therapy in comparison to those without maintenance therapy due to large number of high-risk patients in the second cohort. Furthermore, the compliance with maintenance intravesical BCG is terrible and may further skew the true efficacy of maintenance therapy. The study further suggests that carrying out repeated TURBT followed by second induction course of intravesical BCG therapy, in cases of tumor recurrence, could offer better or comparable oncologic outcomes than maintenance therapy.

However, because BCG balanitis has been treated with complete resolution in all known cases and since there is currently an overwhelming amount of literature that argues for maintenance intravesical therapy, the option to use this kind of treatment should be offered to the patient rather than recommended. Furthermore, if the patient chooses against maintenance therapy, proper follow up would ensure early identification and prompt treatment of any tumor recurrence.

#### **Should repeat intravesical BCG for a tumor recurrence be offered to a patient with prior BCG balanitis?**

None of the cases reviewed here, including ours, have had any documented tumor recurrence thus it is impossible to show the safety of repeated intravesical BCG therapy. Contraindications to intravesical BCG are traumatic catheterization, urinary tract infection, sepsis, high fever, immune compromise, TURBT performed less than two weeks prior, gross hematuria and prior severe BCG reaction. A severe BCG reaction refers only to BCG sepsis, not to balanitis and as such is the treatment, whenever the second condition exists, not contraindicated. The demonstrated efficacy of repeated intravesical BCG exceeds the risks of a non-severe reaction and should be offered to patients who have previously experienced BCG Balanitis (Herr et al., 2007; Han et al., 2006; Herr et al., 2011). However, the patient might refuse repeat BCG therapy as the phallus is considered a "vital" organ and any therapy that disfigures it will likely be avoided. When the treating practitioner is confronted with such a situation, he should explain to the patient that in all known cases of BCG balanitis, early identification and treatment have lead to complete resolution and minimal morbidity.

#### **Key Points**

- Patient with penile glans erythema, swelling, tenderness, nodularity and inguinal lymphadenopathy, in the setting of recent intravesical BCG therapy, should be evaluated for BCG balanitis.
- A delay of at least two weeks following TURBT will lead to a lower rate of systemic complications and of BCG balanitis.
- Isoniazid therapy for a duration of at least three months with concomitant Rifampicin for a minimum of two weeks results in complete resolution and is equally effective as therapies with additional drugs and longer duration.
- Urologists shall consider the use of intravesical BCG therapy at the time of tumor recurrence or the maintenance of treatment in patients with a history of prior BCG balanitis, as this is not considered a severe reaction or contraindication.

## CONCLUSION AND OUTLOOK

The index of suspicion of BCG infection should be very high in any patient with a history of intravesical BCG therapy presenting with a lesion on the glans penis. Failure to consider this diagnosis will lead to delay in appropriate treatment and increased morbidity.

The rarity of this complication has also led to a multitude of regimens being used. However, every single case report so far has used at least Isoniazid in the treatment protocol with complete resolution achieved in every case. While there are no current guidelines for the treatment of BCG balanitis, it appears that Isoniazid therapy for at least three months with concomitant Rifampicin for a minimum of two weeks is as effective as regimens with additional drugs and of longer duration.

BCG balanitis can be easily treated with minimal associated morbidity and as such we recommend that every Urologist should have in mind the use of intravesical BCG therapy at the time of tumor recurrence or for maintenance purposes in patients with a history of prior BCG balanitis.

Our manuscript and recommendations are based on the best available level of evidence (case series and case reports) and has inherent limitations due to such study type. These include the low number of published cases, lack of treatment randomization, lack of control groups with which to compare outcomes and an inability to provide statistically significant data.

In order to better assess the optimal drug therapy and to provide statistically driven data a appropriately powered multi-centered prospective randomized controlled double blinded study can be performed. Unfortunately, the limitations in accruing an adequate number of patients to power the study would very likely be an hindrance.

## ACKNOWLEDGEMENTS

None

## REFERENCE

- Herr HW, Morales A (2008). History of bacillus Calmette-Guerin and bladder cancer: an immunotherapy success story. *J. Urol.* 179: 53-56. doi:10.1016/j.juro.2007.08.122.
- Morales A, Eiding D, Bruce AW (1976). Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J. Urol.* 116: 180-183.
- Lamm DL, Van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, Soloway MS, Steg A, Debruyne FM (1992). Incidence and treatment of complications of Bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J. Urol.* 147: 596-600.
- Erol A, Ozgür S, Tahtali N, Akbay E, Dalva I, Cetin S (1995). Bacillus Calmette-Guerin (BCG) balanitis as a complication of intravesical BCG immunotherapy: a case report. *Int. Urol. Nephrol.* 27: 307-310.
- Ribera M, Bielsa J, Manterola JM, Fernandez MT, Ferrandiz C (1995). Mycobacterium bovis-BCG infection of the glans penis: a complication of intravesical administration of bacillus Calmette-Guerin. *Br. J. Dermatol.* 132: 309-310.
- Baniel J, Lev Z, Engelstein D, Servadio C (1996). Penile edema and meatal ulceration after intravesical instillation with bacillus Calmette-Guerin. *Urology*, 47: 932-934, doi:10.1016/S0090-4295(96)00054-4.
- Latini JM, Wang DS, Forgacs P, Bihrlé W (2000). Tuberculosis of the penis after intravesical bacillus Calmette-Guerin treatment. *J. Urol.* 163: 1870.
- French CG, Hickey L, Bell DG (2001). Caseating granulomas on the glans penis as a complication of bacille calmette-guerin intravesical therapy. *Rev. Urol.* 3: 36-38.
- Kureshi F, Kalaaji AN, Halvorson L, Pittelkow MR, Davis MD (2006). Cutaneous complications of intravesical treatments for bladder cancer: granulomatous inflammation of the penis following BCG therapy and penile gangrene following mitomycin therapy. *J. Am. Acad. Dermatol.* 55: 328-331, doi:10.1016/j.jaad.2005.07.041.
- Yusuke H, Yoshinori H, Kenichi M, Akio H (2006). Granulomatous balanoposthitis after intravesical Bacillus-Calmette-Guerin instillation therapy. *Int. J. Urol.* 13: 1361-1363, doi:10.1111/j.1442-2042.2006.01553.x.
- Michelet N, Spenatto N, Viraben R, Cuny JF, Mazet J, Trechot P, Barbaud A, Schmutz JL (2008). BCG infection of the glans penis after intravesical BCG therapy. *Ann. Dermatol. Venereol.* 135: 479-483, doi:10.1016/j.annder.2007.06.012.
- Hillyer S, Gulmi FA (2009). Cutaneous BCG of the penis after intravesical therapy for bladder cancer: a case report in a 66-year-old male. *Can. J. Urol.* 16: 4866-4869.
- Yoshida R, Kawasaki H, Miyajima A, Amagai M, Ohyama M (2009). Primary tuberculosis of the penis after intravesical bacillus Calmette-Guerin instillation therapy. *J. Eur. Acad. Dermatol. Venereol.* 23: 77-78, doi:10.1111/j.1468-3083.2008.02701.x.
- Lestre SI, Gameiro CD, Joao A, Lopes MJ (2011). Granulomas of the penis: a rare complication of intravesical therapy with Bacillus Calmette-Guerin. *Ann. Bras Dermatol.* 86: 759-762.
- Sharma VK, Sethy PK, Dogra PN, Singh U, Das P (2011). Primary tuberculosis of glans penis after intravesical Bacillus Calmette Guerin immunotherapy. *Indian J. Dermatol. Venereol. Leprol.* 77: 47-50.
- Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK (2000). BCG intravesical instillations: recommendations for side-effects management. *Eur. Urol.* 37 (Suppl 1): 33-36.

- Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, Wolf JS, Schellhammer PF (2007). Guideline for the Management of Nonmuscle Invasive Bladder Cancer: (Stages Ta, T1, and Tis): 2007 update. *J. Urol.* 178 (6): 2314-2330.
- Koya MP, Simon MA, Soloway MS (2006). Complications of intravesical therapy for urothelial cancer of the bladder. *J. Urol.* 175: 2004-2010, doi:10.1016/S0022-5347(06)00264-3.
- Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD (2004). 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.* 93: 485-490.
- Van der Meijden AP, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV, EORTC Genito-Urinary Tract Cancer Group (2003). Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur. Urol.* 44: 429-434.
- Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Lowe BA, Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED (2000). Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J. Urol.* 163: 1124-1129.
- Han RF, Pan JG (2006). Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology*, 67: 1216-1223, doi:10.1016/j.urology.2005.12.014.
- Mugiya S, Ozono S, Nagata M, Takayama T, Ito T, Maruyama S, Hadano S, Nagae H (2005). Long-term outcome of a low-dose intravesical bacillus Calmette-Guerin therapy for carcinoma in situ of the bladder: results after six successive instillations of 40 mg BCG. *Jpn. J. Clin. Oncol.* 35: 395-399, doi:10.1093/jjco/hyi111.
- Martinez-Pineiro JA, Martinez-Pineiro L, Solsana E, Rodriguez RH, Gomez JM, Martin MG, Molina JR, Collado AG, Flores N, Isorna S, Pertusa C, Rabadan M, Astobieta A, Camacho JE, Arribas S, Madero R, CUETO (2005). Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. *J. Urol.* 174: 1242-1247.
- Herr HW, Dalbagni G, Donat SM (2011). Bacillus Calmette-Guerin without maintenance therapy for high-risk non-muscle-invasive bladder cancer. *Eur. Urol.* 60: 32-36, doi:10.1016/j.eururo.2011.03.051.
- Weder JA (2007). Bladder cancer: Pocket Guide to Urology. 3<sup>rd</sup> ed. Caldwell, ID: Griffith publishing; 40-41.