

# Bacillus Calmette-Guérin (BCG) Infection Following Intravesical BCG Administration as Adjunctive Therapy For Bladder Cancer

## *Incidence, Risk Factors, and Outcome in a Single-Institution Series and Review of the Literature*

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**Abstract:** Bacillus Calmette-Guérin (BCG) is the most effective intravesical immunotherapy for superficial bladder cancer. Although generally well tolerated, BCG-related infectious complications may occur following instillation. Much of the current knowledge about this complication comes from single case reports, with heterogeneous diagnostic and therapeutic approaches and no investigation on risk factors for its occurrence. We retrospectively analyzed 256 patients treated with intravesical BCG in our institution during a 6-year period, with a minimum follow-up of 6 months after the last instillation. We also conducted a comprehensive review and pooled analysis of additional cases reported in the literature since 1975. Eleven patients (4.3%) developed systemic BCG infection in our institution, with miliary tuberculosis as the most common form (6 cases). A 3-drug antituberculosis regimen was initiated in all but 1 patient, with a favorable outcome in 9/10 cases. There were no significant differences in the mean number of transurethral resections prior to the first instillation, the time interval between both procedures, the overall mean number of instillations, or the presence of underlying immunosuppression between patients with or without BCG infection. We included 282 patients in the pooled analysis (271 from the literature and 11 from our institution). Disseminated (34.4%), genitourinary (23.4%), and osteomuscular (19.9%) infections were the most common presentations of disease. Specimens for microbiologic diagnosis were obtained in 87.2% of

cases, and the diagnostic performances for acid-fast staining, conventional culture, and polymerase chain reaction (PCR)-based assays were 25.3%, 40.9%, and 41.8%, respectively. Most patients (82.5%) received antituberculosis therapy for a median of 6.0 (interquartile range: 4.0–9.0) months. Patients with disseminated infection more commonly received antituberculosis therapy and adjuvant corticosteroids, whereas those with reactive arthritis were frequently treated only with nonsteroidal antiinflammatory drugs ( $p < 0.001$  for all comparisons). Attributable mortality was higher for patients aged  $\geq 65$  years (7.4% vs 2.1%;  $p = 0.091$ ) and those with disseminated infection (9.9% vs 3.0%;  $p = 0.040$ ) and vascular involvement (16.7% vs 4.6%;  $p = 0.064$ ). The scheduled BCG regimen was resumed in only 2 of 36 patients with available data (5.6%), with an uneventful outcome. In the absence of an apparent predictor of the development of disseminated BCG infection after intravesical therapy, and considering the protean variety of clinical manifestations, it is essential to keep a high index of suspicion to initiate adequate therapy promptly and to evaluate carefully the risk-benefit balance of resuming intravesical BCG immunotherapy.

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**Abbreviations:** ALP = alkaline phosphatase, BCG = bacillus Calmette-Guérin, COPD = chronic obstructive pulmonary disease, CT = computerized tomography, EMB = ethambutol, ESRD = end-stage renal disease, GGT = gamma-glutamyl transpeptidase, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, INH = isoniazid, IS = immunosuppression, LEV = levofloxacin, NR = not reported, NSAID = nonsteroidal antiinflammatory drug, PCR = polymerase chain reaction, PPD = purified protein derivative, PZA = pyrazinamide, RCT = randomized clinical trial, RIF = rifampicin, SD = standard deviation, TB = tuberculosis, TST = tuberculin skin test, TUR = transurethral resection.

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## INTRODUCTION

The intravesical administration of bacillus Calmette-Guérin (BCG), an attenuated live strain of *Mycobacterium bovis*, has become a mainstay of adjunctive therapy for superficial bladder cancer.<sup>139,191,194</sup> Although usually well tolerated, both local and systemic BCG-related complications may occur following instillation.<sup>103</sup> While these events are uncommon, with a cumulative incidence lower than 5%,<sup>106,199</sup> its wide

range of presentations and potential severity poses a challenge for the clinician. However, much of our knowledge on the infectious complications related to intravesical BCG therapy comes from individual case reports, thus hampering a comprehensive understanding of this entity.

The pathogenic mechanisms underlying the development of complications following BCG instillation remain not fully understood, and considerable debate exists about whether it represents a form of hypersensitivity reaction—on the basis of the histologic finding of granulomas in the absence of recoverable microorganisms—or an active mycobacterial infection—since some authors have demonstrated viable bacilli in a variety of tissues.<sup>51</sup> In addition, the predisposing factors for developing an intravesical BCG-related complication are not well known. It has been suggested that some conditions may result in the hematogenous dissemination of the bacilli (that is, disruption of the urothelial barrier due to traumatic urinary catheterization, early instillation after transurethral resection [TUR] of bladder cancer, or concurrent urinary tract infection), but there are still limited data on other potential risk factors, namely the presence of underlying immunosuppression.<sup>93,230</sup>

In the present study we aimed at analyzing a large cohort of patients who underwent intravesical BCG instillation in our institution during a 6-year period in order to determine the incidence, risk factors, and outcome of systemic BCG infection. An exhaustive review and pooled analysis of the cases of BCG infection following intravesical immunotherapy reported in the literature since 1975 is also presented, with particular focus on the nature of complication (local or systemic), therapeutic approach, and outcome.

## PATIENTS AND METHODS

### Study Setting and Data Collection

This study was performed at the University Hospital “12 de Octubre” (Madrid, Spain), a 1300-bed tertiary care center with a reference population that ranged from 536,450 to 405,577 inhabitants during the study inclusion period (December 31, 2003, to October 31, 2009). By means of a retrospective search of the institutional database we identified a total of 315 patients who received  $\geq 1$  instillations of intravesical BCG (Connaught strain, 81 mg in 50 mL of sterile saline) as adjunctive treatment of superficial bladder cancer throughout this period. We excluded 59 patients (18.7%) due to the lack of clinical data, so 256 patients were finally included. All the patients were followed for at least 6 months after the last intravesical instillation. The need for specific informed consent was waived by the institutional review board due to the strictly retrospective and non-interventional nature of the investigation.

The following variables were retrospectively assessed by medical record review using a standardized data collection form: demographics; number of TURs prior to the first BCG instillation; overall number of BCG instillations; time interval between the last TUR and the first instillation; prior history of tuberculin skin test (TST) or active tuberculosis disease; alcohol and smoking habits; comorbid conditions; and immunosuppression. We recorded the total leukocyte and lymphocyte counts just before the first instillation as a proxy for the patient's immune status.<sup>230</sup> A number of additional variables were also recorded for those patients who developed systemic BCG infection (as defined below):

time interval between the first BCG instillation and the diagnosis of the complication; type of infection; presence of miliary pattern on chest imaging studies (simple radiography or computerized tomography [CT] scan); histologic and microbiologic findings; treatment; and outcome. One of these cases has been previously published.<sup>120</sup>

### Definitions Used in the Institutional Cohort Study

*Systemic BCG infection* was defined by the presence of miliary tuberculosis (clinical presentation consistent with active tuberculosis associated to a typical miliary pattern on chest imaging), hepatitis, nephritis, lymphocytic meningitis, arthritis, or osteomyelitis, following  $\geq 1$  instillations of intravesical BCG, responding to antituberculosis treatment, and with no alternative diagnosis. Microbiologic (positivity for *Mycobacterium tuberculosis* complex by culture or by polymerase chain reaction [PCR] assay) and/or histopathologic evidence of mycobacterial infection (that is, caseating granulomas in biopsy specimens) were not deemed necessary for diagnosis. We also included in such definition the occurrence, within the first 4 hours after BCG instillation, of persistent fever ( $\geq 38^\circ\text{C}$  for more than 72 h) and night sweating, with rapid defervescence after initiation of antituberculosis treatment, and no alternative clinical cause or microbiologic documentation (other than the isolation of *M. bovis* in urine samples).<sup>106,172</sup> *Immunosuppression* was defined by the presence of  $\geq 1$  of the following conditions: long-term corticosteroid therapy ( $\geq 5$  mg daily of prednisone or equivalent for  $>2$  wk), use of other immunosuppressive or cytostatic agents within the previous 6 months, advanced human immunodeficiency virus (HIV) infection (CD4+ T-cell count  $\leq 0.200 \times 10^3$  cells/ $\mu\text{L}$ ), neutropenia (absolute neutrophil count  $\leq 0.500 \times 10^3$  cells/ $\mu\text{L}$ ), other primary or secondary immunodeficiencies, and asplenia.

### Literature Review and Pooled Analysis of Cases

We conducted a computer-based MEDLINE (National Library of Medicine, Bethesda, MD) search with the terms “intravesical instillation” and “bacillus Calmette-Guérin” and “BCG infection” or “tuberculosis, miliary” or “complications” to identify literature pertaining to the subject published between January 1975 and April 2013. Overall, we retrieved 390 articles (including case reports, case series, review articles, and randomized clinical trials [RCTs]). First, we excluded papers in languages other than English, French, Spanish, Italian, or Portuguese (28 articles). After a detailed evaluation, we also excluded those papers that clearly referred to other subjects, which overall added up to 137 (antitumor mechanism of BCG [26 articles], efficacy of intravesical BCG as treatment for bladder cancer [38 articles], comparative analyses of different doses and strains of BCG [4 articles], alternative treatments for superficial bladder cancer [12 articles], comparative analyses between BCG and other intravesical agents [10 articles], alternative routes for the administration of BCG [9 articles], detection of *M. bovis* in asymptomatic patients after receiving intravesical BCG [10 articles], and potential efficacy of isoniazid [INH] or quinolones for prevention of BCG complications [3 articles], among others). We excluded the case previously reported from our institution, which had been included into our cohort study.<sup>120</sup> We also excluded 9 literature reviews with no original data, 7 studies based on animal models, 4 guidelines, 1 article based

**TABLE 1. Underlying Conditions, Clinical Characteristics, Therapeutic Approaches and Outcome in 11 Patients With Systemic BCG Infection, Present Report**

Patient	Age/ Sex	Underlying Condition	IS	No. of TUR/ Time Inter- val	No. of Intravesi- cal BCG Instilla- tions	Traumatic Instillation	Time Interval Between BCG Instillation and Diagnosis	Type of BCG Infection	Miliary Pattern	Isolation of <i>M. Bovis</i> on Culture	Therapy	Outcome
1	73 y/M	Hypertension, diabetes, ESRD, kidney carcinoma	No	1/34 d	7	NR	6 d	Lymphocytic meningitis	No	Yes (urine)	INH + RIF + LEV (6 mo)	Resolution
2	56 y/M	Hypertension, active smoking and alcohol use	No	1/16 d	6	Yes	13 d	Miliary tuberculous	Yes	No	INH + RIF + EMB (6 mo)	Resolution
3	74 y/M	Previous tuberculous	No	1/37 d	7	NR	13 d	Arthritis, conjunctivitis	No	No	INH + RIF + EMB (6 mo)	Resolution
4	70 y/M	None	No	3/35 d	2	NR	1 d	Persistent fever	No	Yes (urine)	INH + RIF + EMB (6 mo)	Resolution
5	56 y/M	Hypertension	No	1/40 d	10	NR	16 d	Miliary tuberculous, hepatitis	Yes	No	INH + RIF + EMB (6 mo)	Resolution
6	71 y/M	Hypertension, diabetes, ESRD	No	6/49 d	14	NR	2 d	Persistent fever	No	No	INH + RIF + EMB (6 mo)	Resolution
7	72 y/M	Hypertension, active smoking, COPD	No	3/24 d	11	NR	1 d	Miliary tuberculous	Yes	Yes (urine)	INH + RIF + EMB (6 mo)	Resolution
8	58 y/M	Active smoking	No	1/33 d	14	NR	1 d	Miliary tuberculous	Yes	Yes (urine)	INH + RIF + EMB (6 mo)	Resolution
9	73 y/M	Active smoking, COPD	No	2/22 d	9	NR	10 d	Miliary tuberculous	Yes	No	INH + EMB + LEV (6 mo)	Resolution
10	76 y/M	Hypertension	No	2/29 d	9	NR	19 d	Tubulointerstitial nephritis <sup>20</sup>	No	No <sup>†</sup>	Corticosteroids (3 mo)	ESRD (stage 4)
11	76 y/M	Active smoking and alcohol use, colorectal carcinoma	Yes*	2/42 d	12	NR	9 d	Miliary tuberculous	Yes	No <sup>‡</sup>	INH + RIF + EMB	Multiorgan failure and death

\* Splenectomy.

† Kidney biopsy showed a diffuse and dense interstitial cellular infiltrate composed of lymphocytes, plasmatic cells, and eosinophils, with no interstitial or perivascular granulomas.

‡ Necropsy revealed miliary granulomatosis in the lungs.

on a pooled analysis of cases (thus making impossible to characterize each patient separately), and 1 comment to a previous article. In addition, we reviewed the bibliographies of the selected articles for additional relevant references, adding 34 further articles. Thirty-three references (13.9%) were not included due to the impossibility to obtain the complete article. Therefore, we included a total of 201 articles comprising 271 cases of BCG infection after intravesical instillation published since 1975.<sup>1–14,17–19,21–31,33–39,41–49,51–71,73–80,82–84,87–97,99,101,102,104,105,107–119,121–138,140–151,153–168,170,171,173–180,182–189,192,193,195–202,205–208,210–214,218,219,221–223,225–232</sup> Of these, 170 were individually detailed cases, and 31 were summarized in reports containing 2–13 cases. All data shown here were extracted from these case reports and case series, but occasionally articles lacked relevant clinical or microbiologic data. Thus, denominators for various analyses differed, as the data were included only if the results for a particular variable were explicitly stated in the report.

**Definitions Used in the Literature Review**

For the purpose of the pooled analysis we considered as *systemic complications* any of the following scenarios: *disseminated BCG infection* (further defined as 1) sepsis with fever, hypotension, multiorgan failure and coagulopathy; 2) miliary tuberculosis; or 3) fever associated with bone marrow and/or liver involvement and/or dyspnea and hypoxemia, but with no demonstration of miliary pattern on chest imaging); *persistent fever* (as previously defined); and *any organ involvement* excluding the genitourinary tract. We considered as *local complications* those exclusively involving the genitourinary tract. In all cases, the authors should specify that alternative diagnoses had been reasonably

excluded. *Immunosuppression* was defined by the aforementioned criteria.

**Statistical Analysis**

Quantitative data were shown as the mean ± standard deviation (SD), or the median with absolute or interquartile (Q<sub>1</sub>–Q<sub>3</sub>) ranges, as appropriate. Qualitative variables were summarized with absolute and relative frequencies and 95% confidence intervals (CIs). Comparisons between groups were made by the Student unpaired *t* test (or Mann–Whitney U test when the assumption of normality did not hold) for continuous variables, and with the chi-square test (or the Fisher exact test) for proportions. Given the long time frame of this study, an era effect was included in the mortality analysis by dividing the literature review period in 2 (cases reported in 1975–1999 [n = 128] and those reported in 2000–2013 [n = 154]). All significance tests were 2-tailed, and differences were considered significant at p < 0.05. The statistical analysis was carried out using SPSS v. 15.0 (SPSS Inc, Chicago, IL).

**RESULTS**

**Institutional Cohort Study**

Overall, we analyzed 256 patients (227 males; mean age: 67.9 ± 8.7 yr) treated with intravesical BCG at our institution. Eleven of them developed a systemic BCG infection throughout the follow-up, yielding a cumulative incidence of 4.3% (95% CI: 2.4–7.5%). The time interval between the last instillation and the onset of the complication was 8.3 ± 6.5 days. As detailed in Table 1, the forms of BCG infection included miliary tuberculosis (6 cases, 1 of them associated with hepatitis), persistent fever (2 cases), lymphocytic meningitis, arthritis, and tubulointerstitial nephritis

**TABLE 2.** Demographics, Underlying Conditions, and Bladder Cancer Treatment-Related Variables in Patients With and Without Systemic BCG Infection After Intravesical BCG Instillation

Variable	BCG Infection (n = 11)	No BCG Infection (n = 245)	P
Age, yr (mean ± SD)	68.6 ± 8.1	67.9 ± 8.8	0.753
Sex, male (%)	11 (100.0)	216 (88.2)	0.619
Active smoking (%)	5 (45.5)	133 (54.3)	0.565
Active alcohol use (%)	2 (18.2)	11 (4.5)	0.100
Chronic comorbidities (%)			
Hypertension	6 (54.6)	105 (42.9)	0.539
Diabetes mellitus	2 (18.2)	45 (18.4)	1.000
Renal insufficiency	2 (18.2)	19 (7.8)	0.225
Liver cirrhosis	0 (0.0)	2 (0.8)	1.000
COPD	2 (0.0)	33 (13.5)	0.650
Other non-bladder malignancy (%)	2 (18.2)	31 (12.7)	0.638
Immunosuppression (%) <sup>*</sup>	1 (9.1)	10 (4.1)	0.389
Previous active tuberculosis (%)	1 (9.1)	4 (1.6)	0.199
Previous positive TST (%)	0 (0.0)	5 (2.1)	1.000
No. of previous TURs (mean ± SD)	2.1 ± 1.5	2.3 ± 1.6	0.772
Time interval between the last TUR and the first BCG instillation, d (mean ± SD)	32.8 ± 9.6	40.6 ± 24.4	0.169
No. of intravesical BCG instillations (mean ± SD)	9.2 ± 3.6	9.9 ± 5.6	0.863
Total leukocyte count, x 10 <sup>3</sup> cells/μL (mean ± SD) <sup>*</sup>	8.2 ± 2.3	7.7 ± 1.9	0.468
Total lymphocyte count, x 10 <sup>3</sup> cells/μL (mean ± SD) <sup>*</sup>	2.5 ± 0.6	2.3 ± 1.0	0.123

<sup>\*</sup>At the time of the first intravesical BCG instillation.



(1 case each). *M. bovis* was isolated in urine specimens from 3/11 patients (27.3%). A 3-drug antituberculosis regimen was initiated in all but 1 patient, with a favorable outcome in 9/10 cases (90%) after completion of a 6-month course. One patient with miliary tuberculosis died due to a multiorgan failure despite treatment with INH, rifampicin (RIF) and ethambutol (EMB) (Case 11). The patient diagnosed with tubulointerstitial nephritis was treated only with systemic corticosteroids (intravenous boluses of methylprednisolone for 3 consecutive d, followed by oral prednisone [1 mg/kg per d] with progressive tapering over 4 mo), as the pathogenic mechanism was deemed to be immune-mediated (Case 10); only a partial recovery of renal function was obtained, as detailed elsewhere.<sup>120</sup>

We found no significant differences in terms of demographics, comorbidities, or previous diagnosis of active or latent tuberculosis infection between patients with and without systemic BCG infection. There were either no significant differences in the mean number of TURs prior to the first BCG instillation, the overall mean number of instillations, or the time interval between the last TUR procedure and the first instillation (Table 2).

A total of 12 patients (4.7% of the entire cohort) had some form of immunosuppression at the time of the first instillation, with no significant differences between groups ( $p=0.389$ ). In the group with systemic BCG infection, 1 of 11 patients (9.1%) had undergone a splenectomy. In the group without BCG infection, 10 of 245 patients (4.1%) had a condition conferring some degree of immunosuppression: long-term corticosteroid therapy (5 cases), other immunosuppressive therapies (2 cases), hypogammaglobulinemia (3 cases) and splenectomy (1 case). Finally, there were no differences between both groups in total leukocyte and lymphocyte counts at the time of the first BCG instillation either (see Table 2).

### Pooled Analysis of the Literature

We jointly analyzed a total of 282 patients (11 new cases from our institution and 271 from the literature). Basic demographics (age and sex) were available for 276 and 279 patients, respectively: 96.1% were men, with a mean age at diagnosis of  $66.6 \pm 11.0$  years. Major comorbidities are detailed in Table 3.

### Clinical Presentation

The different forms of BCG infection are shown in Table 4. Disseminated infection was the most common manifestation, reported in 97 cases (34.4%). In detail, this complication consisted of miliary tuberculosis in 71 cases (25.2%), fever associated to bone marrow and/or liver infiltration in 19 (6.7%), and sepsis with multiorgan failure in 7 (2.5%). Four patients (1.4%) had persistent fever responding to antituberculosis treatment as the unique clinical manifestation.

Osteoarticular involvement was seen in 56 patients (19.9%), mostly in form of mono-, oligo- or polyarthritis affecting the extremities and, in some cases, the temporomandibular articulation. Reactive arthritis (arthritis associated with genitourinary symptoms and ocular involvement such as conjunctivitis or uveitis) was diagnosed in 16 patients (5.7%), usually positive for human leukocyte antigen (HLA)-B27 (9 of 14 cases with available data). Prosthetic material infection was described in 5 patients (1.8%), with the hip

being the affected joint. Thoracolumbar spondylodiscitis constituted another rare complication of BCG instillation (10 cases [3.5%]), occasionally associated with paraspinal or psoas abscesses (4 and 3 patients, respectively). Muscle abscess constituted the only clinical manifestation in 5 cases (1.8%), with involvement of psoas, iliac, adductor, and perineal groups.

Mycotic aneurysms and pseudoaneurysms were seen in 16 patients (5.7%), affecting abdominal (12 cases) and thoracic aorta (1 case) and carotid and femoral arteries (2 cases each); 1 patient presented simultaneously with mycotic aneurysms in the abdominal aorta and the superficial femoral artery. Some aneurysms complicated with aorto-enteric (4 cases) and carotid-cutaneous fistulas (1 case) and secondary psoas abscess (2 cases). There were 2 cases of infection of vascular bypass grafts (axilo-femoral and femoro-femoral).

Isolated ocular involvement, outside the setting of reactive arthritis, was rare (9 cases [3.2%]) and included panuveitis (4 cases), granulomatous anterior uveitis (3 cases), endophthalmitis and autoimmune retinopathy (1 case each). Visual loss was present in all cases, and the fundoscopic examination revealed choroidal tubercles in 3 of 4 patients with panuveitis.

Hepatitis (reported as isolated manifestation in 16 cases [5.7%]) presented with fever, anorexia, jaundice and alteration of liver function tests, typically with a cholestatic pattern of serum liver tests (gamma-glutamyl transpeptidase [GGT] range: 110–885 IU/L; alkaline phosphatase [ALP] range: 116–1460 IU/L); liver biopsy revealed granulomas in all cases.

Local (genitourinary) complications were reported in 66 patients (23.4%), and encompassed different manifestations. Bladder involvement was present in 17 patients (5.9%): 13 of them had a solitary bladder ulcer on cystoscopy (with caseating granulomas found in all 7 cases with histologic analysis), whereas the remaining 4 presented with cystitis and sterile pyuria. Penile lesions (17 cases

**TABLE 3.** Demographics, Chronic Comorbidities and Underlying Factors in 282 Patients Diagnosed With BCG Infection Following Intravesical BCG Instillation (Pooled Analysis of Institutional Series and Case Reports From the Literature)

Variable*	No. of Patients (%)
Age, yr (mean $\pm$ SD) [276]	66.6 $\pm$ 11.0
Sex, male [279]	268 (96.1)
Active smoking [112]	19 (16.9)
Active alcohol use [112]	4 (3.6)
Chronic comorbidities [112]	
Hypertension	26 (23.2)
Diabetes mellitus	16 (14.3)
Renal insufficiency	8 (7.1)
Liver cirrhosis	0 (0.0)
COPD	14 (12.5)
Other non-bladder malignancy [282]	21 (7.4)
Immunosuppression [282]	5 (1.8)
Previous active tuberculosis [282]	16 (5.7)
Previous positive TST [282]	3 (1.1)

\*Values in brackets represent number of patients for whom data were available.

[5.9%]) consisted of nodules, papules, plaques or ulcers, with or without inguinal lymph node enlargement. Prostate involvement was seen in 11 patients (3.5%), either as diffuse prostatic enlargement (5 cases) or focal nodule or abscess (6 cases). Kidney parenchymal involvement (10 patients [3.5%]) manifested in form of nephritis in 5 cases (with demonstration of granulomatous inflammation in all but 1 case) or renal masses on abdominal imaging in the remaining 5. Finally, epididymo-orchitis with painless testicular enlargement, abscesses or cutaneous fistula was reported in 10 cases (3.5%).

**Predisposing Factors**

Only 5 patients (1.8%) had an obvious cause of immunosuppression at the time of BCG instillation: active treatment with cytostatic drugs, HIV infection, long-term corticosteroid therapy, kidney transplantation, and splenectomy (1 case each). There was no difference in the prevalence of underlying immunosuppression between patients with or without disseminated BCG infection (3.1% vs 1.1%;  $p=0.343$ ). A previous diagnosis of *M. tuberculosis* infection, either latent infection or active disease, was present in 19 cases (6.7%).

Most patients had undergone previous TURs (161 of 166 evaluable cases), with a median of 1.0 (Q<sub>1</sub>–Q<sub>3</sub> range: 1.0–2.0) procedures prior to the first instillation. The median time interval between both therapeutic measures was 30.0 (Q<sub>1</sub>–Q<sub>3</sub> range: 21.0–41.0) days. The median number of instillations (reported in 279 cases) was 6.0 (Q<sub>1</sub>–Q<sub>3</sub> range: 4.0–9.0), and the median time interval between the last instillation and the onset of infection (reported in 182 cases) was 13.5 (Q<sub>1</sub>–Q<sub>3</sub> range: 2.0–195.0) days.

There were no significant differences between those patients with disseminated and nondisseminated BCG infection in the mean number of TURs before the instillation (1.0 in both groups;  $p=0.975$ ) or the median number of BCG instillations (6.0 in both groups;  $p=0.650$ ). However, we found a lower interval between the last instillation and the onset of the complication in the group with disseminated BCG infection as compared to the rest of the pooled patients (median interval: 2.0 vs 42.0 d;  $p < 0.001$ ).

Some degree of bladder mucosal disruption due to genitourinary tract manipulation prior to BCG instillation, other than TUR, was reported in 36 patients (12.8%), and included photodynamic therapy and fulguration (11 cases), intravesical chemotherapy administration (9 cases), local radiotherapy (6 cases), nephroureterectomy or cystectomy (8 cases), and nephrostomy, double J catheter insertion, and transurethral removal of urethral stone (1 case each). Patients with previous bladder mucosal disruption were more likely to develop nondisseminated forms of BCG infection, specifically spondylodiscitis (11.1% vs 2.4%;  $p = 0.027$ ).

**Diagnostic Approaches**

Specimens for microbiologic diagnosis were obtained in 246 patients (87.2%), whereas histologic examination was performed in 185 (65.6%). Only in 17 patients (6.0%) neither microbiologic nor histologic investigations were conducted, and the diagnosis was solely based on clinical manifestations and response to antituberculosis treatment. Such approach was more frequent in patients with isolated ocular involvement (29.4% vs 1.5%,  $p < 0.001$ ). The diagnostic performance rates for acid-fast bacilli staining, conventional

mycobacterial culture (Middlebrook and Löwenstein-Jensen media) and PCR-based assays were 25.3%, 40.9% and 41.8%, respectively (Table 5). Microbiologic-based diagnosis was more common in patients with nondisseminated forms of BCG infection (53.0% vs 37.8%;  $p = 0.024$ ). The histologic examination revealed granulomatous inflammation in 86.3% of biopsied cases.

**Treatment and Outcome**

Data on therapeutic management were available for 274 cases. Overall, 269 patients (98.2%) received some form of treatment: antituberculosis therapy alone (127 patients

**TABLE 4.** Type of BCG Infection in 282 Patients

Type of Complication	No. of Patients (%)
Systemic	
Disseminated BCG infection*	97 (34.4)
Persistent fever (as isolated manifestation)	4 (1.4)
Osteomuscular	56 (19.9)
Arthritis	20 (7.1)
Reactive arthritis	16 (5.7)
Spondylodiscitis	10 (3.5)
Prosthetic joint infection	5 (1.8)
Muscle abscess (as isolated manifestation)†	5 (1.8)
Vascular	19 (6.7)
Mycotic aneurysm or pseudoaneurysm‡	13 (4.6)
Mycotic aneurysm with fistulization	2 (0.7)
Aorto-enteric fistula	2 (0.7)
Infection of vascular bypass graft	2 (0.7)
Ocular (with no articular involvement)	9 (3.2)
Uveitis	7 (2.4)
Endophthalmitis	1 (0.4)
Autoimmune retinopathy	1 (0.4)
Hepatitis (as isolated manifestation)	16 (5.7)
Cutaneous§	4 (1.4)
Pulmonary (other than miliary tuberculosis)	2 (0.7)
Meningitis	1 (0.4)
Other¶	6 (2.1)
Mixed complications**	2 (0.7)
Local (genitourinary)	66 (23.4)
Bladder involvement	17 (5.9)
Penile lesions	17 (5.9)
Prostatitis	11 (3.5)
Kidney parenchymal involvement	10 (3.5)
Epididymo-orchitis	10 (3.5)
Pyeloureteral stenosis	1 (0.35)

\*See definition in text.

†Overall, 11 patients (3.9%) were diagnosed with muscle abscess: 3 additional cases were secondary to spondylodiscitis; 2 were secondary to mycotic aneurysm or pseudoaneurysm; and 1 was secondary to infection of hip prosthesis.

‡Overall, 16 patients (5.7%) were diagnosed with mycotic aneurysm: 1 additional case was secondary to spondylodiscitis.

§Includes subcutaneous nodules (2 cases), plaque and abscess (1 case each).

¶Includes peritoneal tuberculosis (2 cases), parotid gland tuberculosis, enteritis, rhabdomyolysis, and prevesical abscess (1 case each).

\*\*Includes 1 case of pleuropericardic effusion with arthritis and penile lesion, and 1 case of cold abscess of the chest wall with rash and penile lesion.

[46.4%]), antituberculosis therapy combined with systemic corticosteroids (55 [20.1%]), antituberculosis therapy and surgery (43 [15.7%]), nonsteroidal antiinflammatory drugs (NSAIDs) alone (22 [8.0%]), corticosteroid therapy alone (12 [4.4%]), surgical therapy alone (7 [2.6%]), and other regimens (3 [1.1%]).

The drug regimens used in the 226 patients that received antituberculosis therapy are detailed in Table 6. The most common regimen consisted of INH, RIF and ETB with

or without pyrazinamide (PZA), followed by the combination of INH and RIF (40.2% and 28.3% of patients, respectively). The median treatment duration in 171 evaluable patients was 6.0 (Q<sub>1</sub>–Q<sub>3</sub> range: 4.0–9.0) months.

A surgical approach, either alone or in combination with other therapy, was performed in 51 patients (18.6%): aneurysm or pseudoaneurysm resection and debridement with prosthetic graft interposition or extra-anatomic bypass (17 cases); orchietomy (10 cases); drainage of muscle or cutaneous abscess (6 cases); replacement or permanent resection arthroplasty, or debridement with prosthesis retention (6 cases); vertebral laminectomy, drainage of epidural abscess, and spinal stabilization (5 cases, all of them with spondylodiscitis); nephrectomy (3 cases); and subcutaneous nodulectomy and intestinal resection (1 case each).

Five patients (1.8%) received no specific treatment: 2 patients dying before treatment could be initiated (due to massive hematemesis secondary to an aortoesophageal fistula, and multiorgan failure in the setting of a miliary tuberculosis, respectively), 1 patient with a pulmonary infiltrate and granulomas in the lung biopsy specimens whose symptoms resolved spontaneously, 1 patient with a miliary pattern on the chest radiograph with complete radiologic resolution after 3 months of interruption of BCG instillations, and 1 patient with severe rhabdomyolysis and secondary renal failure—attributed to BCG therapy due to the close temporal association in the absence of an alternative cause—that resolved after interruption of intravesical instillations and initiation of renal replacement therapy.

The different therapeutic approaches used according to the type of BCG infection are shown in Table 7. The patients diagnosed with disseminated BCG infection more commonly received antituberculosis drugs (93.7% vs 76.5%; *p* < 0.001) and adjuvant systemic corticosteroids (43.0% vs 15.9%; *p* < 0.001), whereas those with reactive arthritis were frequently treated only with NSAIDs (50.0% vs 5.4%; *p* < 0.001).

**TABLE 5.** Diagnostic Procedures and Microbiologic and Histologic Findings

Variable*	No. of Patients (%)
Microbiologic diagnosis procedures, positive/total <sup>†</sup>	
Overall rate of microbiologic diagnosis	118/246 (48.0)
Positive stain for acid-fast bacilli	57/225 (25.3)
Positive culture for mycobacteria	99/242 (40.9)
Culture specimen [99] <sup>‡</sup>	
Biopsy tissue	42 (42.4)
Urine	24 (24.2)
Abscess material	21 (21.2)
Blood	5 (5.1)
Sputum or BAL fluid	5 (5.1)
Bone marrow	3 (3.0)
Other <sup>§</sup>	9 (9.1)
Positive PCR-based assay	23/55 (41.8)
Biopsy [281]	184 (65.5)
Biopsy tissue specimen [183] <sup>¶</sup>	
Lung or bronchial tissue	39 (21.3)
Bone marrow (aspirate and/or biopsy)	37 (20.2)
Liver	37 (20.2)
Penis	17 (9.3)
Kidney	14 (7.7)
Aneurysm wall and perianeurysmal tissue	13 (7.1)
Bladder	13 (7.1)
Prostate	12 (6.6)
Testicular	11 (6.0)
Synovial membrane or periarticular tissue	9 (4.9)
Lymph node	6 (3.3)
Skin	5 (2.7)
Other**	5 (2.7)
Granulomatous inflammation in tissue [175]	151 (86.3)

Abbreviations: BAL = bronchoalveolar lavage.

\*Values in brackets represent number of patients for whom data were available.

<sup>†</sup>Number of patients in whom the procedure led to microbiologic identification/total number of patients in whom the procedure was performed.

<sup>‡</sup>The number of culture specimens exceeds the number of patients because some patients had more than 1 positive culture in different specimens.

<sup>§</sup>Includes synovial fluid (3 cases), vitreous humor, gastric fluid, seminal fluid, pleural effusion, salivary gland, and lymph node aspirate (1 case each).

<sup>¶</sup>The number of biopsy sites exceeds the number of patients because some patients had more than 1 tissue specimen.

\*\*Includes salivary gland, spleen, peritoneum, mediastinal tissue, and vitreous humor (1 case each).

**TABLE 6.** Drug Regimens Used in 226 Patients Who Received Antituberculosis Therapy

Regimen	No. of Patients (%)	Duration, Mo [mean (Q <sub>1</sub> –Q <sub>3</sub> Range)]
INH	13 (5.8)	3 (2–4)
INH + RIF	64 (28.3)	6 (3–6)
INH + EMB	5 (2.2)	8 (5–12)
RIF + EMB	3 (1.3)	6 (6–12)
INH + RIF + EMB	74 (32.7)	6.5 (6–9) <sup>†</sup>
INH + RIF + PZA	16 (7.1)	6 (5–6) <sup>†</sup>
INH + EMB + PZA	1 (0.4)	3
INH + RIF* + EMB + PZA	17 (7.5)	6.5 (3.75–12) <sup>†</sup>
INH + RIF + aminoglycoside	5 (2.2)	9 (6–12)
INH + RIF + quinolone	2 (0.9)	6
INH + RIF + EMB + aminoglycoside	1 (0.4)	12 <sup>†</sup>
INH + RIF + EMB + quinolone	3 (1.3)	12 (9–15) <sup>†</sup>
Other combinations	13 (5.8)	
Not specified	9 (4.0)	

\*Includes 1 case treated with rifabutin.

<sup>†</sup>In most cases comprises a 3- or 4-drug regimen during the first 2 months, followed by INH + RIF until completion of therapy.

**TABLE 7.** Therapeutic Approaches According to the Type of BCG Infection in 274 Patients With Available Information

Type of Infection*	Type of Therapeutic Approach							
	Antituberculosis Therapy Alone	Corticosteroids Alone	Surgery Alone	Antituberculosis Therapy and Corticosteroids	Antituberculosis Therapy and Surgery	NSAID	Other†	None
Systemic								
Disseminated infection [95]	50 (52.6)	2 (2.1)		38 (40.0)	1 (1.1)	—	2 (2.1)	2 (2.1)
Persistent fever [4]	3 (75.0)	—	—	1 (25.0)	—	—	—	—
Arthritis [20]	2 (10.0)	1 (5.0)	—	1 (5.0)	2 (10.0)	14 (70.0)	—	—
Reactive arthritis [16]	2 (12.5)	2 (12.5)	—	4 (25.0)	—	8 (50.0)	—	—
Spondylodiscitis [10]	5 (50.0)	—	—	—	5 (50.0)	—	—	—
Prosthetic joint infection [5]	1 (20.0)	—	—	—	4 (80.0)	—	—	—
Muscle abscess [5]	1 (20.0)	—	—	—	4 (80.0)	—	—	—
Vascular involvement [19]	2 (10.5)	—	1 (5.3)	—	15 (78.9)	—	—	1 (5.3)
Ocular involvement [9]	2 (22.2)	5 (55.6)	—	2 (22.2)	—	—	—	—
Hepatitis [16]	8 (50.0)	1 (6.3)	—	7 (43.8)	—	—	—	—
Cutaneous involvement [4]	2 (50.0)	—	—	—	2 (50.0)	—	—	—
Pulmonary involvement [2]	1 (50.0)	—	—	—	—	—	—	1 (50.0)
Other [9]	5 (55.6)	—	1 (11.1)	—	1 (11.1)	—	1 (11.1)	1 (11.1)
Local (genitourinary)								
Penile lesion [17]	17 (100.0)	—	—	—	—	—	—	—
Bladder involvement [15]	14 (93.3)	—	—	1 (6.6)	—	—	—	—
Epididymo-orchitis [10]	—	—	3 (30.0)	—	7 (70.0)	—	—	—
Kidney parenchyma [10]	5 (50.0)	1 (10.0)	2 (20.0)	1 (10.0)	1 (10.0)	—	—	—
Prostatitis [7]	6 (85.7)	—	—	—	1 (14.3)	—	—	—
Pyeloureteral stenosis [1]	1 (100.0)	—	—	—	—	—	—	—

\*Values in brackets represent the number of patients in each type of infection for whom data on therapy were available.

†Includes 1 patient treated with empiric antibiotic therapy with no specific activity against *Mycobacteria*, and other treated with antituberculosis therapy, corticosteroids, and surgery.



Status at hospital discharge was reported in 258 patients (91.5%), with a median follow-up of 12.0 (Q<sub>1</sub>–Q<sub>3</sub> range: 6.0–23.0) months in 44 evaluable cases. All-cause and BCG infection-attributable mortality rates were 6.9% (18/258) and 5.4% (14/258), respectively. Attributable mortality was higher for patients aged  $\geq 65$  years at diagnosis (7.4% vs 2.1%;  $p=0.091$ ), those with disseminated BCG infection (9.9% vs 3.0%;  $p=0.040$ ), and those with vascular involvement (16.7% vs 4.6%;  $p=0.064$ ). We found no differences in mortality according to the study period (5.0% in cases reported in 1975–1999 vs 5.8% in those reported in 2000–2013;  $p=0.801$ ) or the use of a PZA-containing antituberculosis regimen (5.9% vs 7.4%;  $p=0.546$ ). The causes of attributable death were multiorgan failure (10 patients), rupture of mycotic aneurysm, liver failure, massive hematemesis secondary to an aortoesophageal fistula, and perforation of anastomotic leak after surgical repair of a mycotic aneurysm (1 case each). Nineteen patients (7.4%) developed some form of long-term complication following treatment, including permanent loss of visual acuity (5 cases), chronic arthralgia (5 cases), end-stage renal disease (4 cases), chronic respiratory insufficiency and retractile bladder (1 case each). The outcome was deemed satisfactory in the remaining 221 patients (85.7%).

Among the 36 patients for whom such information was specifically reported, only in 2 (5.6%) the scheduled regimen of intravesical instillations was restarted once the treatment for the BCG infection had been completed. The first case was a 47-year-old male with a firm subcutaneous nodule that was treated with surgical excision and RIF plus INH for a nonspecified period of time, with continuation of intravesical BCG therapy and no new complications after 1 year. The second case was a 35-year-old female diagnosed with peritoneal tuberculosis and treated with INH, RIF, and EMB for 2 months, followed by dual treatment with INH and RIF for 7 further months; 10 months after the end of antituberculosis therapy, intravesical BCG administration was completed to 6 doses, with an uneventful 2-year follow-up period.

## DISCUSSION

Throughout the decades, BCG immunotherapy remains as the standard of care in patients with high-risk superficial bladder cancer, being the most commonly used and the most effective intravesical agent for this malignancy.<sup>40,190</sup> BCG effectively eradicates existing carcinoma in situ, decreases the likelihood of tumor recurrence, and reduces the odds of disease progression after TUR.<sup>204</sup> Although its intravesical instillation usually exhibits a favorable safety profile, since it contains viable attenuated mycobacteria the potential for serious adverse events exists.<sup>103</sup> To date, most of the data on BCG infection come from single case reports, with only a few observational cohort studies aimed at establishing its incidence.<sup>106,167,199,230</sup> An additional drawback lies on the lack of consensus diagnostic criteria accurate enough to differentiate true infection from self-limited post-instillation symptoms, and there is not a common disease classification consistently used through the literature. In an attempt to shed some light on this uncommon complication, we have performed the present institutional cohort study and pooled analysis of previous case reports.

The immune response triggered by the adhesion of BCG to the bladder urothelium activates the production of

cytokines and promotes local migration of polymorphonuclear leukocytes and macrophages, ultimately leading to the death of tumor cells.<sup>181,220</sup> As an inherent event following this inflammatory challenge, most of patients experience irritative voiding (urgency, dysuria, frequency and, occasionally, hematuria) and flu-like symptoms, including low-grade fever and malaise for less than 24–48 hours after instillation.<sup>103,220</sup> Such a phenomenon, far from being considered as adverse events, has been regarded as a marker for adequate antitumor effect exerted by the BCG.<sup>16</sup>

Apart from these self-limiting symptoms, BCG immunotherapy is long known to be associated to a protean constellation of localized and systemic complications. A variety of terms have been traditionally used to describe the occurrence of adverse events—other than merely mechanical complications during the catheterization procedure—in patients undergoing intravesical BCG instillations, such as “tuberculosis,” “BCGitis,” “hypersensitivity reaction,” “granulomatous complication,” or simply, “*M. bovis* infection.” Such terminology heterogeneity is likely mirroring the incomplete understanding of the pathogenic mechanisms underlying these complications. In an attempt to systematize the present review we categorized as “local complications” those confined to the structures of the genitourinary tract and, therefore, in direct contact with the bacilli. On the opposite, the term “systemic complication” implies some degree of distant hematogenous dissemination (that is, miliary tuberculosis) or cross-reactivity between tissue self-antigens and mycobacterial antigens (that is, reactive arthritis, also called Reiter syndrome).

Previous studies have reported an incidence of systemic BCG infection ranging from 3%<sup>199</sup> to 7%.<sup>167</sup> Lamm et al included over 2600 patients having BCG therapy and found an incidence of 1% for local and 4.8% for systemic complications,<sup>106</sup> a figure comparable to that we have found in our series. A recent RCT showed a cumulative incidence at 3 years of 30.6%, although the definition used for “systemic side effect” included the occurrence of influenza-like symptoms and general malaise; in fact, the incidence rates for sepsis and pulmonary BCG infection were notably lower (0.3% and 0.4%, respectively).<sup>20</sup> The variability of clinical features and the fact that the onset of the complication can be delayed months to years after the last instillation (median of 13.5 d in our review) may hinder prompt diagnosis and treatment. The longest interval between BCG administration and occurrence of the complication (epididymo-orchitis) ever reported was 17 years.<sup>178</sup> Mavrogenis et al diagnosed a case of spondylodiscitis 11 years after the end of therapy.<sup>127</sup> In this regard, it has been documented the recovery of bacilli from the urinary tract various months after the completion of intravesical therapy.<sup>217</sup> As in the review by Gonzalez et al,<sup>70</sup> we have found that the interval between the instillation and the onset of the complication was lower in patients with disseminated infection (mainly miliary tuberculosis), whereas late-presentation disease usually involved the genitourinary tract and other localized sites.

Disseminated BCG infection, in the form of miliary tuberculosis, sepsis, or fever associated with organ involvement, constituted the most commonly reported form of BCG infection in the literature, accounting for one-third of cases. However, it is noteworthy the wide range of clinical manifestations that emerged from our review, including anecdotal reports of prosthetic joint infection,<sup>23,69,75,164,184</sup> parotid gland tuberculosis,<sup>49</sup> endogenous endophthalmitis

with infiltrative retinitis,<sup>111</sup> or lymphocytic meningitis (present Case 1). Of note, BCG infection had been missed from the initial differential diagnosis in most of these cases until microbiologic documentation of *M. bovis* was obtained by culture or PCR assay, thus emphasizing the need of maintaining a high index of clinical suspicion based on a previous history of BCG exposure.

To date, the predisposing factors for developing BCG infection after intravesical instillation remains to be well characterized. Historically, poor technique during BCG administration, with traumatic instillation or concurrent urinary tract infection, has been regarded as a major risk factor.<sup>106,155,199,221</sup> Unfortunately, accurate information on the urinary catheterization procedure was provided for only 56 of 282 patients included in the pooled analysis, preventing us from separately analyzing this variable. Interestingly, we have found that the existence of breaches in the bladder mucosal barrier at the initiation of instillations acts as a specific predisposing factor for the occurrence of spondylodiscitis, with cases following prostatectomy,<sup>28</sup> transurethral removal of urethral stone,<sup>101</sup> and nephroureterectomy.<sup>145</sup> In addition, the history of progressive bladder cancer often present in these patients may lead to the misdiagnosis of spinal bone metastasis.<sup>157</sup> The spread of the mycobacteria from the lower urinary tract to the spine via the Batson venous plexus may be the pathogenic mechanism underlying this association.<sup>147</sup> The precocity in the onset of intravesical instillations after the immediately preceding TUR would in theory favor that the bacilli gain access to lymphatics and bloodstream through the disruption of the urothelial integrity.<sup>106</sup> Nevertheless, in our institutional cohort there were no differences in the time interval between those procedures according to the subsequent development of complications. The mean time between the last TUR and the first BCG instillation both in our experience and in the pooled literature review was around 30 days, similar to that recommended in current guidelines, which indicate a delay of 2 to 3 weeks between TUR and instillation to assure the healing of the mucosa at resection sites.<sup>32</sup> A recent RCT aimed at comparing different maintenance regimens of BCG (one-third vs full dose for 1 or 3 yr) failed to demonstrate significant differences either in the frequency of toxicity or in the rate of treatment discontinuation due to side effects between the study arms.<sup>20</sup> Although such data were not available in our institutional cohort study, we find no differences in the number of BCG instillations between those with or without infection. Overall, these findings suggest that the odds for developing BCG-related complications likely depend mostly on the host's characteristics (that is, presence of major bladder mucosal damage or certain underlying conditions) or on the accuracy of the instillation technique, rather than on the BCG dose, the number of treatment courses or the interval elapsed since the last preceding TUR.

Since cigarette smoking is a well-recognized risk factor for urinary tract cancer, many patients undergoing BCG immunotherapy are or have been heavy smokers and face a significant risk for diffuse atherosclerotic disease. We have identified 19 cases of vascular complication following intravesical BCG instillations, most of them in form of mycotic aneurysm or pseudoaneurysm<sup>17,34,35,83,87,173–175,183,227</sup> or infection of vascular prosthetic grafts.<sup>183,187</sup> This form of disease may occur either by hematogenous seeding of the vasa vasorum of the arterial wall or as a result of direct extension from a contiguous infected site, typically spondy-

lodiscitis<sup>36</sup> or perivascular lymph nodes.<sup>67,183</sup> The vascular infection often follows a protracted course with low-grade fever, malaise and weight loss<sup>83,126</sup>; the median time interval between the previous instillation and the diagnosis was 16.7 months in our review. The prognosis is dismal, with an attributable mortality rate of 15.8%.<sup>126,173,196</sup> Although it is usually unclear whether this complication develops on a pre-existing atherothrombotic aneurysm or emerges from the primary infection of a normal vessel with subsequent aneurysm formation, clinicians should be particularly aware of this complication in patients undergoing BCG instillations and previous evidence of atherosclerotic disease in various vascular territories or multiple cardiovascular risk factors. In this sense, some authors have proposed the use of prophylaxis and close imaging follow-up in patients with recent vascular graft insertion.<sup>83,183</sup>

It has been theoretically argued that intravesical BCG should not be administered in the setting of immunosuppression since its antitumor therapeutic efficacy could be decreased due to the impaired immunomodulating effect.<sup>230</sup> In addition, safety concerns regarding the potential for systemic BCG infection have usually led to avoid the use of this therapy in immunosuppressed hosts. Nevertheless, the data on this specific population are scarce. Sun et al<sup>203</sup> reviewed the experience with intravesical BCG after kidney transplantation and identified 7 cases through the literature,<sup>98,152,209,224</sup> concluding that the tolerance was overall good, with no BCG-related complications after a median follow-up period of 17 months; on the other hand, the recurrence rate of the bladder cancer was higher than that expected in the general population. No graft rejection following instillation was observed, a relevant finding since Th1 responses, which play a crucial role in alloreactivity, have been involved in the antitumor activity of BCG. In our institutional cohort study we found that nearly 5% of the patients exerted various degrees of immunosuppression at BCG instillation, mainly long-term steroid therapy and hypogammaglobulinemia. There was a numerically higher prevalence of immunosuppressive conditions in those patients who subsequently developed a disseminated BCG infection (9.1% vs 4.1%), although not reaching statistical significance. Moreover, the underlying comorbidity in the only patient included in the former group was splenectomy, a condition not directly affecting the cell-mediated immune response and, therefore, with a presumably little impact on the odds of mycobacterial infection. To our knowledge, only 1 further study has been specifically focused on the potential impact of other forms of immunosuppression on the occurrence of BCG infection. Yossepowitch et al reviewed 697 patients treated with BCG instillations at their institution and found that 24 of them had an underlying condition affecting immune function (mainly oral and inhaled steroid use and lymphoproliferative disorders). Only 1 patient on steroids experienced self-limited febrile disease, and both the response rate and safety profile were comparable to those reported in the general immunocompetent population.<sup>230</sup> In the pooled literature analysis we identified an even lower prevalence of immunosuppression (1.8%), including administration of corticosteroids<sup>35</sup> and cytostatic drugs,<sup>223</sup> HIV infection,<sup>104</sup> and previous kidney transplantation with non-functioning graft.<sup>51</sup> This group did not suffer from more severe forms of BCG infection as compared to the remaining patients. Although limited by the low number of subjects and the heterogeneity in the nature of the underlying conditions, this

evidence supports that intravesical BCG should be deemed a viable therapeutic option in immunosuppressed hosts.

With aging, the immune system progressively declines in both its innate and adaptive arms. Elderly individuals would theoretically face an increased risk of complications after receiving intravesical BCG, and some authors have proposed that maintenance BCG therapy should be given with caution in patients aged 70 years or older.<sup>86</sup> However, a retrospective study did not find any difference in the occurrence of severe complications in patients over 80 years, with a relatively lower disease-free rate in this group as compared to younger patients.<sup>100</sup> We neither found an apparent association between age and the development of systemic infection in our institution. Furthermore, the mean age of patients diagnosed with BCG infection in the pooled literature analysis (66.6 yr) was close to that of patients undergoing an uneventful course of therapy both in our experience and in other series.<sup>230</sup> On the other hand, it has been suggested that a positive purified protein derivative (PPD) test before instillation could predict the subsequent occurrence of systemic side effects and, presumably, a better antitumor activity.<sup>15,216</sup> Unfortunately, data on previous PPD tests were reported in only 12 cases (4 of them with a positive result<sup>37,110,136</sup> [and present Case 3]), thus preventing us from drawing any conclusion on this point. However, previous reports do not contain clear recommendations regarding this issue.<sup>81</sup>

The exclusion of other entities and the prompt response to antituberculosis treatment should be considered the cornerstones of diagnosis of BCG infection since cultures often remain negative, as observed both in our institutional experience and in the literature review (culture positivity rate of 40.9% in the pooled analysis). It has been suggested that such low sensitivity could be explained by the rapid control of bacillary replication by the host's immune system, due to the attenuated virulence of BCG and the preexisting delayed-type hypersensitivity that leads to granuloma formation.<sup>31,70</sup> Our study underlies that the tissue biopsy specimen is the best sample for BCG detection by conventional culture (positive in 42.2% of cases with culture documentation), although the lack of comparative studies

prevents any firm conclusion on the potentially higher diagnostic yield of newer PCR-based assays in such or other samples. This fact, together with the high identification rate of granulomas in the histologic examination, makes the tissue sample particularly relevant in the diagnostic workup for BCG infection. Conversely, the positive predictive value of isolating *M. bovis* from urine samples is notably low, as each 50 mL of reconstituted suspension for intravesical instillation contains over  $2-8 \times 10^8$  colony forming units of BCG, most of which will be washed out with the first post-instillation void.<sup>20</sup> Nevertheless, a urine culture should be routinely performed in patients with suspected BCG infection in order to rule out the occurrence of urinary tract infection caused by conventional uropathogens, which represents a far more common cause of fever following genitourinary tract manipulation.<sup>172</sup> The advent of molecular-based techniques (that is, PCR assay) has progressively modified our understanding of the pathogenesis of BCG infection, as it has led to the increase in the overall rate of microbiologic diagnosis seen throughout the period encompassed by our review (42.1% in cases reported in 1975–1999 vs 52.5% in those reported in 2000–2013).<sup>85</sup> The detection of *M. tuberculosis* complex DNA in locations distant from the genitourinary tract, such as lung,<sup>29,31,104,211</sup> liver,<sup>63,108,222</sup> aortic wall,<sup>227</sup> or periprosthetic hip joint<sup>164</sup> samples, reinforces the hypothesis that the direct invasion and hematogenous spread of BCG underlie the development of the complication, rather than a mere hypersensitivity reaction. In keeping with this rationale, *M. bovis* has been recovered from the synovial fluid of patients with polyarthritis,<sup>13,219</sup> a manifestation generally deemed as immune-mediated. Chest imaging also play a crucial role in diagnosing disseminated BCG infection and the present review suggests that CT scan should always be preferred over conventional radiography, as the latter technique failed to reveal a miliary pattern in about one-quarter of the patients eventually found to have miliary tuberculosis.<sup>11,29,37,39,46,63,85,117,141,142,177,214,231</sup>

Our review underscores the great heterogeneity in the therapeutic approach to the intravesical BCG-related compli-

**TABLE 8.** Summary Box

#### When to suspect this complication?

The occurrence of mild voiding or flu-like symptoms within the first 24–48 hours following intravesical instillation is usually explained by the inflammatory reaction triggered by the BCG. Conversely, BCG infection should be suspected in any patient having previously received intravesical BCG who develops moderate-to-severe genitourinary or systemic symptoms (including high-grade fever for  $\geq 72$  hours) with no apparent cause.

#### How to approach the diagnosis?

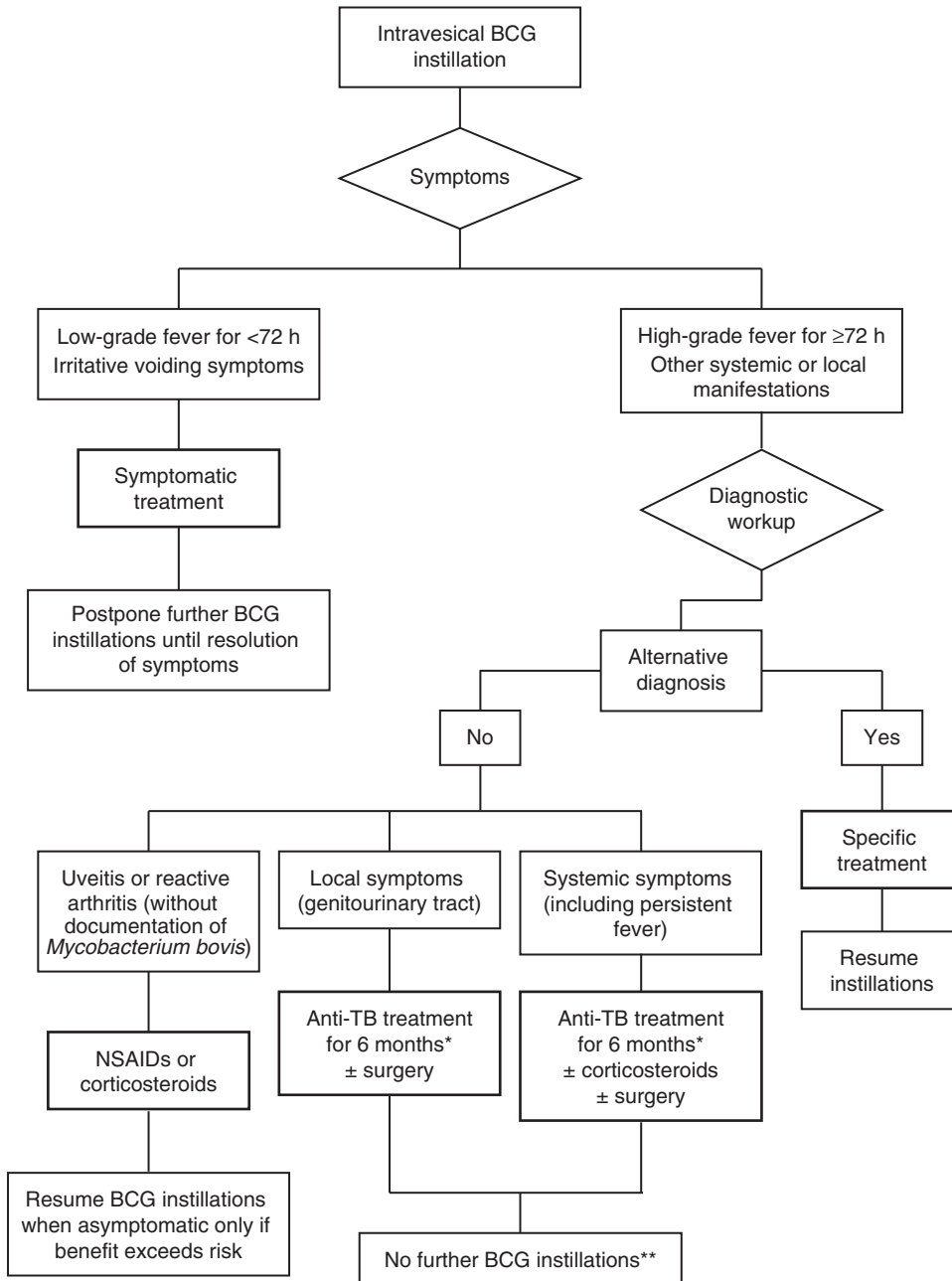
- Obtain samples for microbiologic diagnosis according to the clinical manifestations (i.e., blood, sputum, bronchoalveolar lavage, abscess drainage, synovial fluid).
- Note the low positive predictive value of isolating *M. bovis* in urine culture.
- If feasible, obtain a tissue biopsy specimen for conventional culture and histologic examination (in order to identify granulomatous inflammation).
- In presence of systemic symptoms, perform a chest imaging examination (preferably CT scan over conventional radiography) to rule out miliary involvement.
- Thoroughly exclude alternative diagnoses that could account for the clinical picture.

#### How to treat BCG infection?

- NSAIDs or corticosteroids may be sufficient in cases of arthritis or uveitis with no microbiologic documentation of *M. bovis*.
- A 3-drug antituberculosis regimen should be used in the remaining cases with either local or systemic involvement (preferably INH, RIF, and EMB for 2 months followed by INH and RIF for  $\geq 4$  further months).
- Consider corticosteroid adjuvant therapy in presence of extensive miliary involvement and/or respiratory failure.
- Consider surgical treatment in presence of abscess, prosthetic or vascular infection, or genitourinary tract obstruction.

cations, and the absence of a clear consensus on the indication for antituberculosis therapy, the preferred regimen, or its duration. As previously commented, the early-onset of irritative voiding and flu-like symptoms should not prompt the administration of specific therapy other than symptomatic.<sup>106,172</sup> On the contrary, the use of antituberculosis drugs, either alone or in combination with corticosteroids or surgery, is common in both systemic and local forms of

BCG infection (82.2% of cases in the pooled analysis). Its role in cases of polyarthritis or reactive arthritis remains less clear, as most of them were successfully managed with NSAIDs.<sup>13,25,42,57,124,134,136,148,154,159,167,179,207,210</sup> Nevertheless, the aforementioned occasional documentation of *M. bovis* in articular samples in some cases<sup>13,219</sup> should be taken account in order to reevaluate the initiation of antituberculosis therapy, particularly if the evolution is not satisfactory.



**FIGURE 1.** Proposal of a diagnostic and therapeutic algorithm for patients with suspected BCG infection following BCG instillation. The terms “low-grade” and “high-grade fever” refer to body temperature <37.9°C and ≥38°C, respectively. \*Antituberculosis treatment should include INH, RIF, and EMB for 2 months, and INH and RIF for 4 more months. \*\*Continuation of BCG instillations could be considered in patients with persistent fever and no miliary pattern on chest imaging, once antituberculosis treatment has been completed, and only if the expected benefits of BCG therapy clearly exceed the risks (that is, high-grade carcinoma).



As an attenuated derivative of *M. bovis*, BCG is intrinsically resistant to PZA. In addition, the different BCG strains (Connaught, Tice and RIVM) have also been demonstrated to be resistant to cycloserine.<sup>50</sup> Despite this susceptibility profile, a PZA-containing regimen was used in as many as 15% of reported cases in the literature, with no apparent impact on the outcome. The most commonly prescribed drug combination in our institution consisted of INH and RIF for 6 months, with a 2-month intensive phase including ETB. Such regimen is based on the standard recommended therapy for *M. tuberculosis* infection, avoiding the use of PZA due to the lack of *in vitro* activity and its potential for additive liver toxicity. In the absence of specifically designed RCTs some authors have proposed an alternative regimen consisting of INH for 3 months for patients with high-degree fever as only clinical manifestation.<sup>20,72,106,169,217</sup> Nevertheless, the rationale underlying this recommendation seems obscure since if the direct invasion hypothesis is accepted, the therapeutic regimen should include various active antimycobacterial drugs. The Connaught BCG strain is highly susceptible to fluoroquinolones,<sup>50</sup> and some patients have been successfully treated with regimens containing ofloxacin,<sup>70,74</sup> ciprofloxacin,<sup>174</sup> moxifloxacin,<sup>64</sup> and levofloxacin,<sup>52,117</sup> [and present report Cases 1 and 9], occasionally instead of RIF or INH. This promising preliminary experience should be analyzed in future studies. On the other hand, the lower liver toxicity of these drug combinations has to be carefully counterbalanced against the well-known risk of tendinopathy associated with the long-term use of fluoroquinolones.<sup>233</sup> Not surprisingly, corticosteroids were frequently associated with the antituberculosis treatment in patients with disseminated BCG infection, mainly miliary tuberculosis, emphasizing again the probable dual role of both hypersensitivity reaction and active infection in the pathogenesis of systemic complications.<sup>1,52,169</sup>

Despite the exhaustive nature of the present review, no clear recommendations can be made regarding the potential risk posed by the reintroduction of intravesical instillations in subjects previously diagnosed with a BCG-related complication, although detailed data on follow-up were provided only for a minority of cases (12.8%). Most authors consider a preceding systemic BCG infection to be an absolute contraindication for restarting the course of therapy.<sup>106,169,172</sup> In a recent RCT the decision of whether instillations were to be only postponed or definitely interrupted was left to the treating physician according to the severity of symptoms.<sup>20</sup> In that line, it is generally assumed that therapy might be safely resumed after certain nonsevere manifestations such as isolated fever, reactive arthritis or uveitis. However, in our institution we administered no further instillations in patients with prolonged, otherwise unexplained fever, as we hypothesize that such scenario should be actually regarded as a systemic form of BCG infection (present Cases 4 and 6). Of note, 1 of the only 2 cases in which the scheduled regimen of instillations was restarted had been diagnosed with a systemic infection (peritoneal tuberculosis), with an uneventful outcome.<sup>197</sup>

Overall, the prognosis of BCG infection is good, although we have found nonnegligible rates of attributable mortality (5.4%) and long-term disability (7.4%). Interestingly, 3 factors linked with higher mortality (that is, age at diagnosis  $\geq 65$  yr, disseminated infection and vascular involvement) emerged from our pooled analysis, although some of these associations showed only borderline significance. No previous studies have specifically assessed factors predicting poor outcome in this complication. The attributable mortality rate in the study by Gonzalez

et al was slightly higher (11.6% [5/43]), with all the fatal cases having been diagnosed with disseminated BCG infection or mycotic aneurism.<sup>70</sup> By considerably increasing the sample size, our results are in line with those preliminary findings. Since we have not been able to identify risk factors predicting the development of complications in the overall population undergoing intravesical BCG therapy, maybe prevention strategies should be targeted to those subjects at the highest risk for poor evolution in the case of eventual BCG infection (older patients and those with pre-existing atherothrombotic aneurysms). A RCT reported a significant decrease in the rate of systemic complications requiring antituberculosis treatment with the prophylactic use of ofloxacin after each instillation.<sup>32</sup> Other RCT with INH given as prophylaxis failed to demonstrate a protective effect.<sup>215</sup> Furthermore, our review revealed cases of miliary tuberculosis,<sup>163</sup> hepatitis,<sup>208</sup> or aortoenteric fistula<sup>56</sup> despite the prophylactic administration of INH.

The present study has a number of limitations. As with all pooled analysis of previously reported cases, our data are heterogeneous in origin and to some extent incomplete (that is, reporting on traumatic instillation or eventual reintroduction of BCG therapy). We cannot exclude publication bias favoring cases with a more severe course. In the series by Lamm et al<sup>106</sup> isolated fever was the most frequent complication in patients treated with intravesical BCG (2.9%), although we have only identified 2 other single case reports in the literature,<sup>87,192</sup> thus suggesting some degree of underreporting of this presentation. The rate of long-term complications may be underestimated due to insufficient follow-up. In addition, the low incidence of systemic BCG infection in our institutional series (11 patients) made comparisons between groups prone to a type 2 error because of inadequate statistical power.

On the other hand, ours is one of the largest series of patients with BCG infection coming from a single institution and recruited throughout a relatively short period, therefore ensuring homogeneous diagnostic and therapeutic approaches. In addition, to our knowledge this is the most comprehensive review and pooled case report analysis to date, not limited to English literature. The review by Gonzalez et al was performed 1 decade ago and included only 43 cases from United States and Canada,<sup>70</sup> whereas more recent reviews have been focused on specific forms (that is, miliary tuberculosis,<sup>31</sup> reactive arthritis,<sup>210</sup> or vascular infection<sup>56,226</sup>). Due to the rarity of BCG infection and the difficulty to obtain a large multicenter series of cases in a prospective way, we think that this approach is a valid way to clarify some aspects regarding this occasionally life-threatening condition.

In conclusion, since apparently there are no obvious predictors that could help clinicians to identify patients at risk for developing BCG infection after intravesical instillations, and in view of the protean clinical manifestations of this complication, a high index of suspicion remains essential in order to promptly initiate antituberculosis therapy. Although this entity has an overall favorable prognosis, uncertainties about the safety of restarting intravesical BCG instillations frequently lead to noncompliance with the scheduled therapy regimen, thus jeopardizing the prognosis of the underlying malignancy. Prospective, multicenter studies should be performed to precisely address the risk factors for this complication as well as its optimal therapeutic approach. Meanwhile, we summarize our recommendations (Table 8) and propose a diagnostic and treatment algorithm for patients with suspected BCG infection based on our experience and the present literature review (Figure 1).

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