# *Severe sepsis and Stevens Johnson syndrome after intravesical bacillus Calmette-Guerin (BCG) instillation. A case report and short review of the literature*

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## ABSTRACT

**Severe sepsis and Stevens Johnson syndrome after intravesical bacillus Calmette-Guerin (BCG) instillation. A case report and short review of the literature**

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Intravesical bacillus Calmette-Guerin (BCG) therapy, recommended for superficial bladder tumors, triggers side effects in fewer than 5% of patients. Yet, when encountered, high level of suspition and early detection is essential for their succesfull management. In the present article, we present a case of severe sepsis and Steven Johnson syndrome in a male patient after intravesical BCG instillation.

## INTRODUCTION

Intravesical instillation of Bacillus Calmette-Guérin (BCG) is frequently used as the treatment of choice for carcinoma in situ and non-invasive high-grade superficial tumor of the urinary bladder[1]. BCG is a live attenuated strain of *Mycobacterium bovis* and is the most widely used intravesical agent[2]. Adverse events occur in fewer than 5 % of cases, ranging from mild local symptoms to severe sepsis and death[1-3]. In the present article, we report a case of successful management of septic shock with concomitant Steven Johnson syndrome after intravesical BCG instillation and perform a short review of the relevant literature.

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## CASE REPORT

An 83-yearold man with a history of bladder cancer ($ICD_{10}$-C67), treated initially with transurethral resection and subsequent intravesical BCG instillations, presented to our hospital for fever (38°C),general fatigue and hematuria, soon after the second BCG instillation.No prophylactic isoniazid had been given during their BCG instillation treatment. His medical

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history also included arterial hypertension. ($ICD_{10}$-I10) and chronic kidney disease stage IIIa ($ICD_{10}$ –N18.2) with bad compliance to therapy.

Upon hospital admission, he further developed dyspnea with tachypnea (respiratory rate of 25 /min) with measured oxygen saturation SpO2 82%. Arterial blood gases exam revealed severe acidosis (pH 7.185, $PaCO_2$ 41mmHg and $PaO_2$ 52.6mmHg), with worsening hemodynamics (blood pressure of 60/35 mmHg and heart rate of 105 bpm) and gradually worsening of his mental status (Glasgow Coma Scale E3/V1/M4). Epidermolysis with blisters in his body and ulcers in his mouth were also noted.

An emergency dermatology consultation set the diagnosis of Steven Johnson syndrome. Management with oxygen therapy, fluids infusion and intravenous vancomycin and clindamycin was not effective; thus the patient was intubated and transported to ICU for further management 6 hours later.

**Table 1**.Laboratory values course

| Day | Hct | WBC | PLT | Ur | Cr | Bilt | Bild | LDH | SGOT | SGPT | γ-GT | CPK | ALP | CRP | PCT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 32.1 | 10.1 | 74 | 122 | 3.0 | 2.3 | 1.5 | 700 | 419 | 155 | 263 | 18530 | 75 | 12.9 | 155 |
| **2** | 35.5 | 12.9 | 82 | 142 | 3.2 | 2.8 | 2.1 | 703 | 281 | 152 | 229 | 6126 | 74 | 20.1 | 104.7 |
| **3** | 35.1 | 11.1 | 51 | 169 | 3.7 | 3.1 | 2.4 | 583 | 152 | 130 | 190 | 1902 | 69 | 14.6 | 106.2 |
| **4** | 35 | 9.7 | 30 | 196 | 3.9 | 3.2 | 2.3 | 483 | 91 | 104 | 273 | 705 | 96 | 8.3 | 73.5 |
| **5** | 33.7 | 9.2 | 33 | 220 | 3.6 | 3.6 | 2.6 | 503 | 76 | 85 | 487 | 364 | 137 | 4.4 | 41.3 |
| **6** | 33.5 | 7.3 | 33 | 245 | 3.4 | 3.6 | 2.6 | 513 | 71 | 66 | 598 | 272 | 179 | 3.9 | 19.5 |
| **7** | 33.7 | 10.9 | 50 | 262 | 3.4 | 4.6 | 3.4 | 505 | 64 | 51 | 528 | 258 | 169 | 11 | 10.9 |
| **8** | 27.9 | 10.7 | 66 | 236 | 2.9 | 5.4 | 4.3 | 435 | 77 | 45 | 414 | 439 | 159 | 17 | 5.4 |
| **9** | 29.7 | 17.2 | 87 | 182 | 2.3 | 6.5 | 4.7 | 464 | 77 | 54 | 509 | 143 | 261 | 17.7 | 2.3 |
| **10** | 27.1 | 9.9 | 79 | 149 | 2.1 | 5.9 | 4.4 | 468 | 78 | 55 | 509 | 145 | 260 | 20 | 1.4 |
| **11** | 26.5 | 7.4 | 86 | 129 | 2.0 | 4.8 | 3.5 | 475 | 64 | 40 | 416 | 76 | 268 | 22.6 | 0.9 |
| **12** | 26 | 4.8 | 88 | 106 | 1.7 | 3.8 | 3 | 315 | 55 | 37 | 376 | 41 | 249 | 21.1 | 0.6 |
| **13** | 26.8 | 4.1 | 104 | 94 | 1.6 | 2.7 | 2.1 | 282 | 77 | 56 | 410 | 43 | 287 | 11.9 | 0.4 |
| **17** | 23.4 | 3.9 | 106 | 72 | 1.4 | 2.2 | 1.7 | 287 | 107 | 94 | 521 | 47 | 400 | 4.9 | 0.3 |
| **19** | 22.1 | 3.3 | 98 | 60 | 1.2 | 2 | 1.5 | 280 | 100 | 95 | 500 | 45 | 350 | 4.8 | 0.3 |
| **21** | 28.1 | 3.4 | 126 | 41 | 1.1 | 1.8 | 1.2 | 231 | 34 | 71 | 396 | 25 | 274 | 4.8 | 0.2 |
| **23** | 26.4 | 6 | 129 | 30 | 1.2 | 1.4 | 1.1 | 269 | 30 | 50 | 324 | 70 | 218 | 5 | 0.2 |
| **25** | 23.6 | 4.2 | 122 | 31 | 1.0 | 1.1 | 0.9 | 210 | 24 | 36 | 246 | 37 | 159 | 4 | 0.2 |
| **27** | 25.9 | 5.4 | 149 | 37 | 1.0 | 1 | 0.7 | 199 | 23 | 35 | 249 | 23 | 143 | 1.9 | 0.1 |

*Hct - haematocrit (%), WBC – white cells (k/μl, PLT-platelets (k/μl), CRP - c reactive protein (mg/dl), PCT - procalcitonin (ng/ml), Bil - bilirubin (tot-total, dir-direct) (mg/dl), LDH - lactate dehydrogenase (iu/ml), γ - GT – gamma glutaryl transpherase(iu/ml), SGOT - Serum glutamicoxaloacetic transaminase (iu/ml), SGPT- Serum glutamicpyruvic transaminase(ui/ml), ALP - alcaline phosphatase (ui/ml), Cr – creatinine (mg/dl), Ur - urea (mg/dl), CPK - creatine phosphatase (mg/dl).*

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On ICU admission the patient had a severity APACHE IV score of 160/286; high fever ($39.3^0$ C).Modification of therapy upon admission included vasopressors (noradrenaline) infusion, broad spectrum intravenous antibiotics (levofloxacin, meropenem and teicoplanin), pulse steroid therapy, intravenous fungustatin and cream mometazone with septomide spray for the ulcers in his body.

Microbiological cultures from blood, bronchial secretions and urine turn out negative. Interferon-gamma (IFN-γ) release assay (QuantiFERON TB Gold test) for *Mycobacterium tuberculosis* was also negative. Yet, Tuberculosis- Polymerase Chain Reaction (PCR) test of urine was positive and mycobacterial therapy with rifampicin-isoniazid was also added. The course of its Laboratory exams values are in Table 1.

The patient's general condition improved very slowly, and he was finally discharged from ICU after 27 days.

**DISCUSSION**

BCG has been used for more than 40 year, with positive results in the majority of cases[2]. Several BCG strains have been developed since the original strain of 1921; yet there is no consensus about the appropriate use of each strain[2,4]. The mechanism of action of BCG therapy is complex and incompletely understood. The general concept, as reported by Fuge et al, can be divided in 3 stages:

1) infection of urothelial and/or bladder cancer cells, mediated by fibronectin and integrins

2) induction of immune response, mediated by various cell types (granulocytes, T helper (Th) cells, natural killers (NK) and macrophages), various immune molecules (major histocompatibility complex MHC class I, CD4+) and various cytokines (interleukin IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17, tumour necrosis factorTNF-α, interferon IFN- γ) ; and

3) induction of antitumor effects via acquired (Th1, CD4 and CD8 T cells) and innate (via Th2, NK, macrophages and neutrophil recruitment) immunity[2,5].

BCG administration may be associated with a broad spectrum of local and systemic side effects. Most cases include lower urinary tract irritation symptom (25-75%) while less frequent are fever over $39.5^o$C (2.9%) and haematuria (1%), granulomatous prostatitis, pneumonitis and/or hepatitis, arthralgia, epididymitis, renal abscess, contracted bladder or ureteral obstruction[6]. Severe BCG sepsis and rash are rare complication (0.4% and 0.3% of the cases respectively)[6]. Since BCG antitumor mechanism is unclear, the mechanism behind its infectious complications is also a matter of debate. One hypothesis considers these complications as hypersensitivity reaction (also called cytokine storm) based upon the presence of granulomas and the absence of recoverable

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organisms and a positive response to glucocorticoids. By contrast, other reports demonstrated viable organism in various tissues, supporting the idea of ongoing infection[6-7]. Despite the one that prevails, it seems that both mechanisms play a key role in the pathogenesis of BCG therapy complications. The latter is what we suggest that happened in our case, where Steven Johnson syndrome empowers cytokine storm hypothesis while PCR test confirms *M.bovis* presence. Literature displays large diversity in the management of such cases: antituberculosis therapy alone, antituberculosis therapy and surgery, nonsteroidal anti-inflammatory drugs alone, corticosteroid therapy alone, surgical therapy alone andother regimens[9]. However, the combination of antituberculosis therapy and systemic corticosteroids seems to prevail.The most common combination include isoniazid, rifampicin and ethambutol with or without pyrazinamide, followed by the combination of rifampicin – isoniazid[8-9].

## CONCLUSION

Disseminated infection is a very rare complication of intravesical BCG therapy. Nevertheless, clinician should always have it in mind, as early diagnosis is essential for successful management.

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**Key words:** BCG therapy, intravesical therapy, bladder tumor, sepsis.

**Author Disclosures:**

Authors have Karakosta P, Aslanidis Th, Thoma G, Agaliadou-Dioritou U have no conflicts of interest or financial ties to disclose.

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