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Review

Bacille Calmette-Guérin preparation and intravesical administration to patients with bladder cancer: Risks to healthcare personnel and patients, and mitigation strategies

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Abstract

Intravesical Bacillus Calmette-Guérin (BCG) is a standard therapy for non–muscle-invasive bladder cancer used in urology clinics and inpatient settings. We present a review of infection risks to patients receiving intravesical BCG, healthcare personnel who prepare and administer BCG, and other patients treated in facilities where BCG is prepared and administered. Knowledge of these risks and relevant regulations informs appropriate infection prevention measures.

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Bacillus Calmette-Guérin (BCG) is a live, attenuated form of *Mycobacterium bovis* used for immunotherapy of non–muscle-invasive bladder cancer (NMIBC). The introduction of vector-mediated therapies and lytic viruses in commercial and investigational settings prompted our center to re-evaluate BCG and our handling of biologics within the pharmacy. We evaluated available data concerning risks of intravesical BCG to patients receiving it, healthcare personnel (HCP) preparing and administering BCG, and patients treated at the same facility where BCG is prepared or administered. Knowledge of risks will help inform effective infection prevention interventions to reduce risk of possible healthcare-facility transmission of *M. bovis*.

Methods

Published papers written in English were searched in PubMed, Embase, Scopus, and Google Scholar from date of inception to April 1, 2023, using keywords and subject headings. An experienced health-science librarian guided our literature searches (see Supplementary Material online for search strategy). Citations relevant to risk among HCP or patients who did not receive BCG for NMBIC were reviewed by 2 authors to confirm inclusion.

BCG for patients with non–muscle-invasive bladder cancer (NMIBC)

Approximately 82,000 new cases of bladder cancer are reported annually in the United States, and among them, 80% are NMIBC.[1] Intravesical instillation of BCG is the preferred approach for high-risk NMIBC, and an option for intermediate-risk NMIBC per the American Urological Association (AUA) guidelines.[2] Although risk categories differ somewhat between AUA, the European Association of Urology (EUA), and the US National Comprehensive Cancer Network (NCCN) guidelines, all recommend BCG as the preferred therapy for intermediate- and high-risk NMIBC. Following transurethral bladder tumor resection and staging, patients who qualify for BCG undergo a 6-week induction cycle. At each weekly visit, a vial of BCG is diluted and instilled into the bladder for contact time of 90–120 minutes. If the patient tolerates therapy and response is demonstrated on repeat cystoscopy after the 6 weeks of therapy, a maintenance phase may be continued for up to 1 year for intermediate-risk patients or up to 3 years for high-risk patients.[2–5] Although the optimal timing and schedule for maintenance remains unknown, a typical schedule is weekly for 3 weeks during months 3 and 6, then every 6 months thereafter.[2] BCG therapy is associated with complete resolution in ~80% of patients at the end of induction and 55% at the end of 3 years.[5] Due to worldwide BCG shortages since 2019, the AUA recommends prioritizing BCG for high-risk NMIBC patients undergoing induction therapy and considering reduced doses (splitting vials among qualifying patients) if necessary.[6–8] Few alternatives exist for high-risk patients who cannot receive BCG due to the shortage or those who fail to respond to BCG.[5]

Infectious risks to patients receiving intravesical BCG

Infectious risks to patients receiving BCG have been well documented in the literature and are reported with low incidence (<1%), theorized to be associated with traumatic catheterization during procedure or to systemic spread within

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Table 1. Case Reports of Infections in HCP Related to Preparing or Administering Bacillus Calmette-Guérin (BCG) Therapy

Author	HCP Role/ Exposure	Description of Infection	Management of Adverse Effect and Outcome
Atiyeh et al[17]	Surgical resident; needlestick while administering intravesical BCG	Cutaneous *M. bovis* infection, limited to subcutaneous tissues of left ring finger	Surgical debridement and oral isonicatine hydrazine and rifampicin for 8 weeks. Regained full function at 4 months.
Vigler et al[18]	Nurse practitioner; needlestick while preparing intravesical BCG	Chronic infection of dorsal hand web with sinus tract	Underwent >6 months of antituberculosis therapy plus several hand surgeries with full recovery.
Mundinger et al[19]	Medical technologist; needlestick reconstituting BCG vial for intravesical administration (undiluted product)	Acute flexor tenosynovitis	Immediate flexor tendon exploration and washout; 6 months of antituberculosis therapy.[a] Returned to work without limitation but did not regain full range of motion.

Note. HCP, healthcare personnel.
[a]Underwent 4 months of ethambutol, pyrazinamide, isoniazid, rifampin plus 2 months of treatment with isoniazid and rifampin.

immunocompromised hosts.[9–16] Infections secondary to BCG may result in localized or disseminated BCG with various organ involvement. Patients may present with infection symptoms early (within 3 months) or late (>1 year) after BCG administration.[16] Although there are no treatment recommendations for post-intravesical BCG infections, treatment has generally been provided for symptomatic patients.

Risks to healthcare personnel related to preparation or administration of BCG

Few publications have documented direct risks to HCP related to intravesical administration, despite use spanning almost 50 years. Three case reports detail hand infections after needlesticks in HCP who were preparing or administering BCG for intravesical administration (Table 1).[17–19] Use of needleless systems for all biologic transfers is a best practice that may reduce needlestick exposures.[20] The other documented HCP BCG infections were skin-test conversions due to secondary transmission from a pediatric patient who developed disseminated BCG and respiratory infection after being treated in the same healthcare facility where BCG was prepared, but who did not receive BCG.[21] Contact tracing of 46 HCP revealed 2 new skin-test conversions. Details are insufficient to determine a specific risk that led to these secondary transmission events.

HCP infections may be underrepresented in the literature for several reasons. First, BCG-related infection may be culture-negative or not identified to the species-level within the *M. tuberculosis* (MTB) complex. For BCG cases that are culture positive, clinical laboratories may not routinely provide genotyping.[22] Genotypic reporting from the National Tuberculosis Genotyping Service may be delayed, and phenotypic susceptibilities (eg, intrinsic resistance to pyrazinamide) may be the first clue that differentiates *M. bovis* from other members of the MTB complex. Second, the lack of required reporting of *M. bovis* infections (when identified to species level) decreases recognition of this and nontuberculous mycobacterial infections.[23] A review of 118 BCG cases reported to the US National Tuberculosis Surveillance System between 2004 and 2015 postulated that confusion between case definitions of the US Council of State and Territorial Epidemiologists (CSTE) and Centers for Disease Control and Prevention (which specifically discourages reporting of *M. bovis*) contributed to reporting of only some cases of BCG infection.[24] Potential lack of recall or recognition of BCG preparation or administration activities as a potential risk exposure in HCP may also contribute to underreporting. Temporal delays from exposure to disease development due to latency decrease the likelihood that BCG would be linked to infection, should it occur. Finally, for HCP from countries where BCG is employed as a vaccination strategy, infections may be classified as endogenous reactivation of the vaccine strain rather new exposure. For these reasons, we expect there have been additional HCP cases that were not captured and/or could not be linked to BCG exposure.

Risks to patients treated at the facility where BCG is prepared or administered

Several case reports detail suspected or confirmed BCG infections related cross contamination within the healthcare facility where BCG was prepared or administered (Table 2).[21,25–31] Serious BCG infections, including meningitis and disseminated disease, have been reported among immunocompromised patients who received chemotherapy or other products mixed in the same biological safety cabinets (BSC) as BCG.[20,24,25,27] Some investigations never identified gaps in preparation or administration procedures, despite extensive review.[21,25,26] Aerosol contamination in the pharmacy was considered the most likely cause in these instances, but the same administrator or shared equipment could not be excluded.

Vos et al[28] assessed Dutch hospital pharmacy procedures and identified gaps in biosafety procedures. Preparers did not routinely change gloves, the same BSC was used for BCG and other hazardous preparations in succession, and the BSC was not routinely cleaned after each preparation. Spills were managed with tap water rather than a proven disinfectant and decontaminant. Dust collected from the spill trough of the BSC and the pharmacy technician's gloves were PCR-positive for MTB complex DNA. At the time, OncoTICE was supplied in an ampule rather than a vial, which increased spill and aerosolization risk.

Another case report detailed cross contamination in the operating room.[31] A case patient with multiple *S. aureus* breast abscesses grew BCG from one sample, though the patient had never received BCG. Through tracing, the case was linked with a source patient with large BCG intra-abdominal abscess due to complication of intravesical BCG administration drained in the same operating room 48 hours earlier. Retraining of staff on proper disinfection was required after 2 gaps were identified in operating-room turnover cleaning; investigators could not determine whether any equipment was shared. Improper disinfection and use of protective equipment contributed to 9 cases of BCG infection that occurred at outpatient clinics providing central venous catheter care and BCG instillation.[29]These cases highlight

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Table 2. Case Reports of Infections in Patients Who Did Not Receive Bacillus Calmette-Guérin (BCG) Therapy Due to Suspected Cross Contamination During BCG Preparation

Author Location	Likely Exposure	Summary of Adverse Effect	Management of Adverse Effect and Outcome
Coppes et al[25] Canada	Patient receiving chemotherapy. No source confirmed.	Female aged 6 years with BCG brain abscess.	Antituberculosis treatment for 12 months. Resolved.
Waecker et al[21] Shope et al[26] United States	Suspected chemotherapy cross contamination within pharmacy as BCG prepared on same day in same biological safety cabinet.	Male aged 2.5 years with trisomy 21 an acute megalokaryocytic leukemia in remission. Presented with epithelioid granulomas and +AFB on open lung biopsy. *M. bovis* identical strain TICE BCG.	Antituberculosis treatment for 20 months. Resolved.
		Female aged 13 years with ALL in remission with miliary TB. BAL and skin lesion AFB+ *M. bovis* identical strain TICE BCG.	Antituberculosis treatment for 22 months. Death related to severe milary disease.
		Male aged 6 years with ALL with posterior spinal epidural abscess with *M. bovis.*	Emergent total laminectomy and recovery.
	Probable respiratory transmission from nosocomial infected patient to HCP.	2 HCP had new skin test conversions upon contact tracing; 1 worked in the clinic where induced sputum was performed and 1 worked on the unit where the patient was admitted.	Not reported.
Stone et al[27] United States	Suspected cross chemotherapy contamination within pharmacy, but community exposure could not be ruled out. No surface contamination or gaps in pharmacy procedure identified.	Female aged 3 years with ALL and BCG meningitis. BCG identified.	Antituberculosis treatment for 12 months. Resolved.
		Male aged 5 years with ALL and BCG meningitis. BCG identified.	
Vos et al[28] Netherlands[a]	Suspected cross chemotherapy contamination within pharmacy. BCG prepared before chemotherapy on same days at hospital pharmacy on multiple occasions. Ruled out Dutch vaccine strain.	Female aged 11 years with ALL and disseminated *M. bovis*–BCG infection with identical BCG OncoTICE strain.	Antituberculosis treatment and death at 9 months. Autopsy revealed recurrent ALL and CSF positive for *M. tuberculosis* complex.
		Female aged 13 years with Hodgkin disease and granulomatous lesions of lung with positive *M. bovis*–BCG biopsy culture.	Resolved.
		Male aged 39 years with pulmonary nodules with positive transbronchial biopsy, bone marrow, and gastric aspirates with *M. bovis*–BCG.	Not reported.
	Originally suspected reactivation 12 years after vaccination but cannot rule out pharmacy as received chemotherapy.	Male aged 30 years with advanced HIV and Burkitt-like non-Hodgkin lymphoma. *M. bovis*–BCG + in CSF.	Antituberculosis treatment and death 11 days later.
	Suspected cross chemotherapy contamination within pharmacy. No other patients or personnel encountered BCG.	Female aged 4 years with pre-B cell ALL with no prior BCG vaccination and granulomatous reaction and osteomyelitis. 8 months after chemotherapy BAL + BCG. Bone-marrow biopsy AFB+.	Antituberculosis treatment.
	Suspected pharmacy cross contamination; unclear source. Hospital pharmacy prepares BCG OncoTICE on site.	2 patients identified from national database of 77 *M. bovis*–BCG strain samples. Positive for identical BCG OncoTICE strain. Did not receive BCG OncoTICE therapy nor did interacting HCP handle BCG.	Not reported.
Meije Y et al[29] Spain	Suspected outpatient clinic rooms used for instillations and oncology catheter care. Nursing prepared BCG at clinic without any biosafety or cleaning procedures.	9 patients with history of solid-tumor cancer not on chemotherapy and cancer free at the time of pulmonary TB infection. BAL + for OncoTICE strain.	Antituberculosis treatment for 9 to 30 months. One patient required catheter removal. Resolved.
Gupte et al[30] United States	Suspected contamination of equipment (cystoscope) and/or mitomycin at the time of bladder instillation.	Male aged 72 years male with bladder cancer and mitomycin instillation presented with BCG spinal osteomyelitis *M. bovis.*	Antituberculosis treatment.
Aqua JK et al[31] United States	Suspected surface contamination in OR from improper cleaning 48 h after another patient case of intra-abdominal BCG infection (which was a secondary complication of BCG instillation).	Female aged 48 years; OR case with HIV and multiple breast abscess and pulmonary calcified granuloma. *M. bovis.*	*M. bovis* culture managed as false positive due to OR contamination.

Note. ALL, acute lymphocytic leukemia; AFB, acid-fast baccilli; BAL, bronchoalveolar lavage; BCG, Bacillus Calmette-Guérin; CSF, cerebrospinal fluid; HCP, healthcare personnel; HIV, human immunodeficiency virus; IAI, intrabdominal infection; OR, operating room.

[a]28 suspected patients were identified. Only 10 patient samples were assessed; all were negative. Also, 8 living patients had symptoms that resolved spontaneously. Although 1 patient died 13 months after receiving chemotherapy, BCG OncoTICE–related infection was not confirmed.

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Table 3. AUA and SUNA Universal Protocol to Reduce Healthcare Personnel Exposure to Hazardous Drugs[35]

• Universal hand washing practices. This includes proper hand washing before and after any contact with the drug or agent, patient's waste, plastic back absorptive drapes/liners and equipment. Repeat thorough hand washing after the clean-up. Hand washing should occur before and after any glove use.
• Aseptic technique is required for urethral catheterization.
• Biohazardous or chemotherapy waste container
• Spill kit
• Eyewash station
• Personal protective equipment (PPE): chemotherapy gloves (nonpowdered, polyvinylchloride or nitrile gloves) or double gloves; disposable, nonpermeable gown; surgical mask or face shield; protective eye gear. An N-95 respirator may be used if preferred by local institution policy.
• Safe work practices include adherence to recommended work practices and use of engineering controls (ie, use of biological safety cabinets or closed systems) and PPE.
• All equipment, supplies, and receptacles in contact with BCG are handled and disposed of as biohazards. Utilize a separate biohazard bag for all disposable equipment and drug disposal in procedure room for immediate disposal.
• To avoid cross contamination, parental drugs are not prepared in areas where BCG has been prepared.

Note. AUA, American Urological Association; BCG, Bacillus Calmette-Guérin; SUNA, Society of Urologic Nurses and Associates.

the need for reinforcement, accountability, and periodic re-education to ensure that appropriate cleaning and disinfection are performed.

Guidance concerning BCG preparation and administration

Several groups have statements on BCG safe handling. The TICE BCG package insert recommends: (1) a dedicated area and BSC when available and (2) other operations should be ceased or fully segregated while BCG is prepared.[32] The latter recommendation is impractical for the contemporary pharmacy clean room. Currently, the US National Institute for Occupational Safety and Health (NIOSH) lists BCG as a "hazardous" drug.[33] As a NIOSH hazardous drug, the *US Pharmacopeia* (USP) chapters 797 and 800 have additional specific requirements for the appropriate transport, storage, handling, and preparation of BCG. These regulations resulted in removal of BCG preparation from many urology clinics into pharmacy cleanrooms.[34] The AUA and the Society of Urologic Nurses and Associates (SUNA) provides guidance on administration and waste disposal for HCP within the urology clinic and patient education to decrease risk of transmission (Table 3).[35] Issues that remain concerning handling of BCG in clinics and health systems are presented in Figure 1.

If the hazardous drug designation were lifted for BCG, as suggested in a prior draft document,[36] care would be needed to support facility-level risk assessment of BCG. Facility-level risk assessment is the current standard for gene and cellular biologics and is a systematic process by which individual facilities designate the safe and proper handling of an agent.[37] A consistent, clear framework is needed to evaluate risks of these therapies to patients, HCP, and other patients who might be exposed. For an assessment of BCG, multidisciplinary teams including pharmacy, nursing, urology, infection prevention, and waste management should work together to develop a plan for patient, HCP, and environmental safety. Many health systems are developing and implementing biosafety categories and associated risk-mitigation policies to

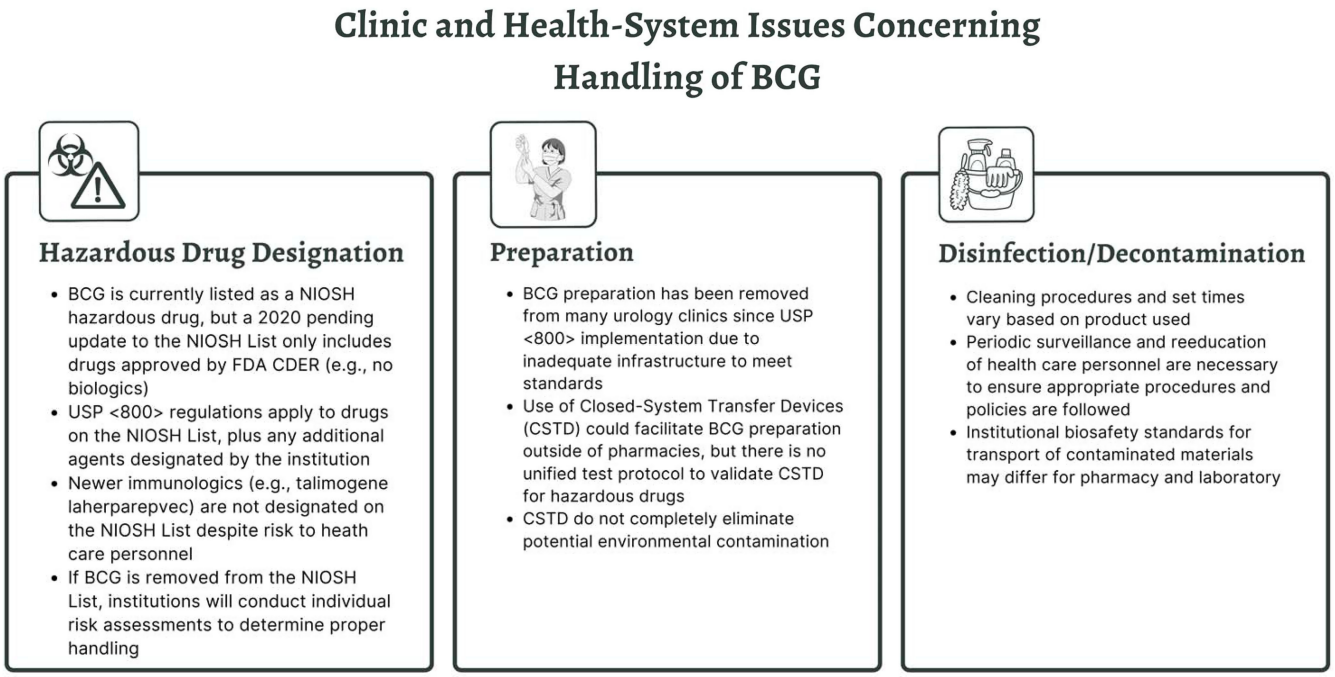

Figure 1. Clinic and health-system issues concerning handling of BCG.

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standardize operational procedures for biologics.[38] Our medical center has chosen to prepare BCG and novel biologics in a segregated room or dedicated BSC away from oncolytic preparations as infrastructure allows. A deactivation, decontamination, and cleaning procedure is conducted between preparations to prevent cross contamination using solution dwell times that have efficacy against BCG.

In conclusion, BCG has been the standard immunotherapy for intermediate- and high-risk NMIBC for decades. Infection risk of intravesical BCG to patients receiving the therapy is low and well characterized. The risks to HCP and other patients treated at facilities where BCG is prepared and administered are rare and potentially limited by recognition and reporting in the medical literature. BCG poses biohazard and infection risks that warrant handling and preparation aligned with elements of USP 800, even if no longer deemed 'hazardous' by NIOSH standards. Consistent use and regular re-education on best practices for infection prevention are important to maintain safety and mitigate risks of this highly effective therapy.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2023.259

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