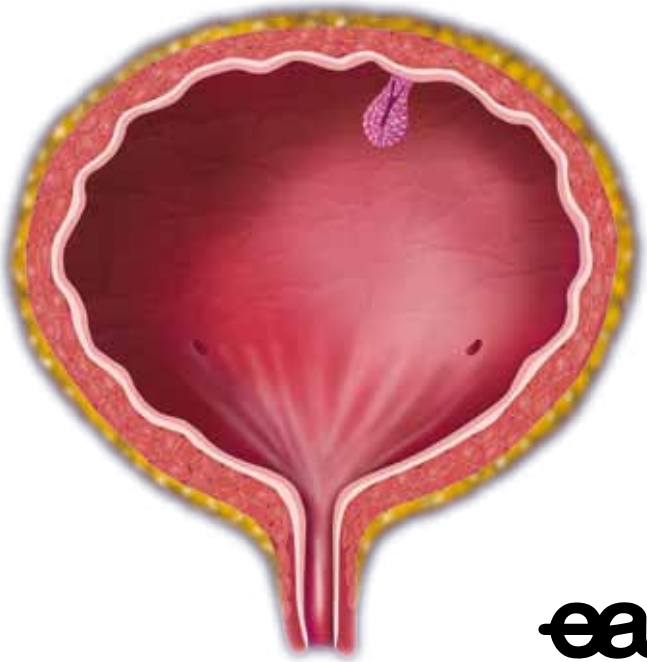
Evidence-based Guidelines for
Best Practice in Urological Health Care

Intravesical instillation

with mitomycin C or bacillus Calmette-Guérin
in non-muscle invasive bladder cancer

2015



European
Association
of Urology
Nurses

Evidence-based Guidelines for
Best Practice in Urological Health Care

Intravesical instillation
with mitomycin C or bacillus Calmette-Guérin in non-muscle invasive bladder cancer

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Introduction

The European Association of Urology Nurses (EAUN) was created in April 2000 to represent European urology nurses. The EAUN's underlying goal is to foster the highest standards of urological nursing care throughout Europe. With administrative, financial and advisory support from the European Association of Urology (EAU), the EAUN also encourages research and aspires to develop European standards for education and accreditation of urology nurses.

We believe that excellent health care goes beyond geographical boundaries. Improving current standards of urological nursing care has been top of our agenda, with the aim of directly helping our members develop or update their expertise. To fulfil this essential goal, we are publishing the latest addition to our Evidence-based Guidelines for Best Practice in Urological Health Care series; a comprehensive compilation of theoretical knowledge and practical guidelines on intravesical instillation. Although there is considerable literature on intravesical instillation, to the best of our knowledge, prior to this publication there was only limited evidence-based guidance for nurses available on this topic. The EAUN Guidelines Group believes there is a need to provide guidelines with recommendations that clearly state the level of evidence of each procedure, with the aim of improving current practices and delivering a standard and reliable protocol.

In this booklet, we include clear illustrations, extensive references, and annotated procedures to help nurses identify potential problem areas and safely carry out effective patient care. The working group decided to include topics such as indications and contraindications, safety precautions, nursing principles, and interventions in intravesical instillations, as well as education to patients. We would also like to highlight the psychological and social aspects unique to the experience of patients undergoing intravesical instillations as aspects that have influence on quality of life (QoL).

With our emphasis on delivering these guidelines based on a consensus process, we intend to support nurses and practitioners who are already assessed as competent in the procedure of intravesical instillations. Although these guidelines aim to be comprehensive, effective practice can only be achieved if the nurse or practitioner has a clear and thorough knowledge of the anatomy under discussion and the necessary understanding of basic nursing principles.

This publication focuses on intravesical instillations with mitomycin C and bacillus Calmette-Guérin. These guidelines are intended to complement, or provide support to, established clinical practice and should be used within the context of local policies and existing protocols and with recognition of the individual situation of the patient.

This text is made available to all individual EAUN members, both electronically and in print. The full text can be accessed on the EAUN website (http://nurses.uroweb.org/). Hard copies can be ordered through the EAU website via the webshop or by e-mail (eaun@uroweb.org).

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Introduction

Cancer of the urinary bladder

Bladder cancer is the most common malignant tumour of the urinary tract, with an EU incidence of 27 and 6 per 100,000 in men and women, respectively. Smoking is the single most important risk factor and is implicated in 50% of cases. Occupational exposure during paint processing, dye and petroleum industries represents another risk factor. [1]
At presentation, 75% of patients have non-muscle invasive bladder cancer (NMIBC), that is, tumours confined to the mucosa (tumours are called Ta in the TNM classification) or submucosa (tumours designated as T1), as opposed to muscle-invasive bladder cancer (MIBC). Primary treatment for NMIBC is transurethral resection of bladder tumour (TUR-BT). NMIBC has a high prevalence due to low progression rates and long-term survival in many cases. According to current European Association of Urology (EAU) guidelines, TUR-BT should be enhanced by intravesical medication. The use of intravesical agents to prevent/delay recurrence or delay progression of NMIBC has been available since the mid-1970s. [2] These guidelines deal with this particular aspect of treatment and care for NMIBC. Once the tumour has invaded the smooth muscle layer of the bladder, it cannot be controlled by TUR-BT. The biological characteristics, treatment and prognosis of MIBC are different. [1]

Scope

The scope of these guidelines was established at the start of the guidelines process. Fifteen PICO questions (see addendum 14.11 for description) were posed to guide the literature review process. The guidelines cover adults with NMIBC treated with intravesical instillation. The guidelines were developed to prevent unintended harm to patients or caregivers, and to enhance treatment compliance by addressing patient-related outcomes.
The guidelines provide guidance for the standard intravesical instillation of mitomycin C (MMC) and bacillus Calmette-Guérin (BCG), for health care professionals, patients and their families.
We describe evidence-based or best practice for safe administration and handling of the agents, based on articles found in a literature search, USA and EU regulations, and consensus in the Working Group.

1. Role of the nurse in different countries

The European Association of Urology Nurses (EAUN) is a professional organisation of European nurses who specialise in urological care. In Europe, there is great variation in the level of education and practical training of nurses in urology, with the roles and responsibilities of nurses differing among countries. It is therefore difficult for any guidelines to fulfil all requirements or expectations of individual practitioners. However, the EAUN Guidelines Group aims to ensure that every nurse and health care professional will gain some benefit from using these guidelines. In different countries, and even in different areas within the same country, job titles differ within the specialty. For the purpose of this document, we refer to all nurses who are working with intravesical instillation as specialised nurses.

2. Methodology

The EAUN Guidelines Working Group for intravesical instillation have prepared these guidelines to help nurses assess evidence-based management and incorporate the recommendations into their clinical practice. These guidelines are not meant to be prescriptive, nor will adherence to them guarantee a successful outcome in all cases. Ultimately, decisions regarding treatment and care must be made on a case-by-case basis by health care professionals after consultation with their patients and colleagues, and using their clinical judgement, evidence-based knowledge, and expertise. The Working Group consists of a multidisciplinary team of nurse specialists, including Susanne Vahr (Chair), Willem De Blok, Bente Thoft Jensen, Nora Love-Retinger, Bruce Turner and Giulia Villa, as well as urologist Jan Hrbáček (see Chapter 15).

2.1 Literature search

The information offered in these guidelines was obtained through a systematic literature search and a review of current procedures undertaken in various member countries of the EAUN.

A search of the medical literature was conducted using Medline (Ovid SP), (1946 to November 2014), Embase (Ovid SP) (1974 to November 2014), CINAHL (1982 to November 2014), Cochrane Central Register of Controlled Trials and the Cochrane Health Technology Assessment databases (from inception to November 2014).

Both medical subject headings (MeSH) and free-text terms, as well as variations of root words, were searched. Key terms related to “non-muscle invasive bladder cancer” were combined using the set operator AND key terms related to “bladder instillation” AND key terms related to “mitomycin or BCG”. MeSH terms included non muscle invasive bladder cancer, bladder tumor, bladder neoplasms, bladder cancer, bladder carcinoma, transitional cell carcinoma, carcinoma in situ; mitomycins, mitomycin, mitomycin C, BCG vaccine; bladder irrigation, therapeutic irrigation, intravesical drug administration, and administration, intravesical.

Non-English-language studies, animal or *in vitro* studies, conference proceedings, and paediatric studies were excluded.

The search was based on PICO questions formulated by the Working Group. (Appendix 14.11)

2.2 Limitation of the search

Limitations:

- English language
- Adults

The search results were not limited to randomised controlled trials (RCTs), controlled clinical

trials, meta-analyses or systematic reviews. In all databases, output was limited to human studies, adults aged ≥ 19 years, 1946 to July 2013, and English-language publications. Additional searches were not limited to any level of evidence (LE), and EU, USA and national regulations were also used.

Exclusion criteria during search:

- Painful bladder syndrome

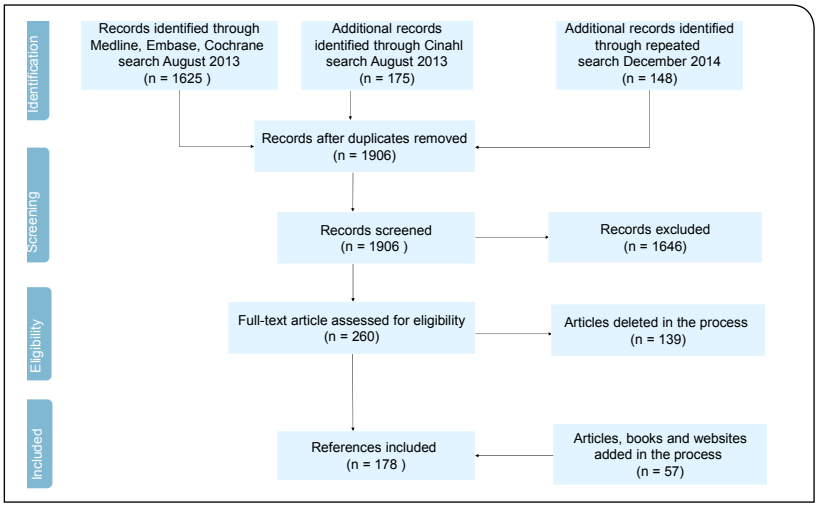
Exclusion criteria when selecting the abstracts:

- Treatment planning
- Tumour recurrence
- *In vitro* studies
- Studies comparing effects of treatment with MMC/BCG with those of other chemotherapy neoadjuvant medication, thermo chemotherapy, and electromotive drug approach.

2.3 Search results

The initial search was done in August 2013 by Yuhong (Cathy) Yuan, Research Associate at McMaster University, Hamilton, Ontario, Canada, and repeated in December 2014, which resulted in:

Flowchart 1. Literature search "Intravesical instillation"



It was a policy decision to restrict the search in the way described, although the Group was aware that more complex strategies were possible, and would be encouraged in the context of a formal systematic review. In the process of working with the articles, new references were found and added to the reference list, if they were relevant to the topic and cited in the text.

2.4 Disclosures

Members of the Working Group have provided disclosure statements of all relationships that might be a potential conflict of interest. This information is stored in the EAU database. This guidelines document was developed with the financial support of Medac and BD (Becton, Dickinson & Co).

The EAUN is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

2.5 Limitations of the document

The EAUN acknowledges and accepts the limitations of this document. It should be emphasised that the current guidelines provide information about treatment and care of individual patients according to a standardised approach. The information should be considered as providing recommendations without legal implications. The intended readership is practising urology nurses and nurses working in a related field throughout Europe. Cost-effectiveness considerations are best addressed locally and therefore fall outside the remit of these guidelines.

2.6 Review process

The Working Group included some topics that are not only applicable to intravesical instillation, but decided to include them because they make the guidelines more complete. A blinded review was carried out by specialist nurses, urologists in various European countries and the USA, a patient representative and a representative of a local occupational health and safety organisation. The Working Group revised the document based on the comments received and included relevant references received (also from after the search period). A final version was approved by the EAUN Board and the EAU Executive responsible for EAUN activities.

2.7 Rating system

The recommendations provided in this document are based on a rating system modified from that produced by the Oxford Centre for Evidence-based Medicine (OCBM) in 2011. [3] External data extractors recruited from the EAU used the EAU data-extraction system for critical assessment of the papers identified.

Whenever possible, the Working Group graded treatment recommendations using a three-grade system (grade of recommendation; GR A–C) and inserted levels of evidence to help readers assess the validity of the statements made. The aim of this practice is to ensure a clear transparency between the underlying evidence and the recommendations given. This system is further described in Tables 1 and 2.

Some of the literature was not easy to grade. However, if the Working Group thought that the information would be useful in practice, it was ranked as LE 4 and GR C. Low-level evidence indicated that no higher level evidence was found in the literature when writing the guidelines, but cannot be regarded as an indication of the importance of the topic or recommendation for daily practice.

The literature used in these guidelines included qualitative research, but because there is no systematic ranking for these types of studies, the qualitative studies were all graded LE 4.

The recommendations in these guidelines are based on synthesis of evidence from the articles.

The Working Group aims to develop guidelines for evidence-based nursing, as defined by Behrens (2004): "Integration of the latest, highest level scientific research into the daily nursing practice, with regard to theoretical knowledge, nursing experience, the ideas of the patient and available resources". [4] The Working Group based the text on evidence whenever possible, but if evidence were missing, it was based on best practice.

Four components that influence nursing decisions can be distinguished: personal clinical experience of the nurse; existing resources; patient wishes and ideas; and results of nursing science. [4] This statement implies that, although literature is important, the experience of nurses and patients is also necessary for decision making. Consequently, it is not only the written guidelines that are relevant for nursing practice.

Table 1. Level of evidence (LE)

Level	Type of evidence
1a	• Evidence obtained from meta-analysis of randomised trials
1b	• Evidence obtained from at least one randomised trial
2a	• Evidence obtained from one well-designed controlled study without randomisation
2b	• Evidence obtained from at least one other type of well-designed quasi-experimental study
3	• Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies, and case reports
4	• Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 2. Grade of recommendation (GR)

Grade	Type of evidence – Nature of recommendations
A	• Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	• Based on well-conducted clinical studies, but without randomised clinical trials
C	• Made despite the absence of directly applicable clinical studies of good quality

3. Terminology (definitions)

3.1 Intravesical instillation

Intravesical instillation is a procedure by which fluids are slowly introduced into the bladder and allowed to remain there for a specific length of time before being drained, voided or withdrawn. It is performed to expose the tissues of a given area to the solution.

Intravesical instillation is drug administration into the urinary bladder via a catheter. This procedure allows drug delivery to the urothelium with reduced systemic side effects compared with oral or parental drug delivery. [5] The procedure is also referred to as bladder instillation, intravesical treatment, intravesical therapy. These guidelines use the term intravesical instillation.

3.2 Intravesical chemotherapy

Intravesical chemotherapy aims to eradicate any surviving cancer cells in the bladder mucosa (so-called "chemoresection" of the tumour), and in case of immediate postoperative instillation, to destroy any floating tumour cells left behind by TUR-BT and prevent them from implantation.
Mitomycin C (MMC) is a chemotherapeutic agent that inhibits DNA synthesis in tumour cells. MMC decreases the recurrence rate from 54% to 38%, but has no impact on the risk of progression. [6] There are other intravesical chemotherapeutic agents apart from MMC. Doxorubicin, epirubicin and thiotepa are used in some countries and no superiority of one drug over the others has been demonstrated. [1,7]

3.3 Intravesical immunotherapy

Immunotherapy aims to eradicate disease by provoking or enhancing the host immune response.

BCG is a live attenuated strain of Mycobacterium bovis. When instilled into the bladder, it triggers an immune response in the mucosa that eventually kills cancer cells. Bacteria in the suspension attach to the tumour cells and are absorbed. Consequently, immune cells such as granulocytes, macrophages and lymphocytes move into the tissue as a part of the inflammatory reaction, leading to tumour elimination. The less differentiated (i.e., more aggressive) the tumour, the more sensitive it is to BCG. [8]

A Cochrane meta-analysis of 1,901 patients with Ta-T1 tumours comparing MMC vs. BCG found BCG more efficient in preventing recurrence, but having no effect on survival and progression. [9] According to a meta-analysis from 2002, BCG reduced recurrence rates by 32% and prolonged time to recurrence from 1-2 to 2-4 years. BCG decreased the odds of progression of Ta, T1 and Tis disease from 13.8 to 9.8% during follow-up of 2.5 years, when compared

with TUR-BT alone or TUR-BT plus other intravesical treatment – provided that maintenance therapy was given. [10]

4. Indications and contraindications, alternatives

4.1 Indications for intravesical instillations

From the prognostic viewpoint, NMIBC falls into one of three categories: low risk (LR), intermediate risk (IR) and high risk (HR) for progression and for recurrence according to the European Organization for Research and Treatment of Cancer (EORTC) criteria.

Table 3. Risk categories of NMIBC
Adapted from: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2014 (Table 8).[1]

Category	Definition
LR	A primary solitary Ta G1 lesion < 3 cm with no associated carcinoma *in situ* (CIS) in the bladder.
IR	Tumours fall between LR and HR categories.
HR	Tumour classified as stage T1, or high-grade (or G3), or associated with CIS in the bladder or multiple large recurrent Ta G1–2 tumours (in this case, all of the characteristics must be present).

Table 4. Intravesical treatment according to tumour risk category

Category	Treatment
LR	One single immediate postoperative instillation of chemotherapy is considered sufficient adjuvant treatment. Immediate means preferably within 6 h of TUR, but definitely no longer than 24 h after surgery.
IR	One immediate postoperative instillation should be followed by 1 year of maintenance chemotherapy or maintenance BCG (see Chapter 5).
HR	Full-dose intravesical treatment with BCG for 1–3 years is indicated. [1]

4.2 Contraindications for intravesical instillations

Intravesical chemotherapy is contraindicated in cases of gross haematuria requiring irrigation, and/or any suspicion of extra- or intraperitoneal bladder perforation. Extravasation of chemotherapy may lead to serious adverse events. [1]

Pregnancy is not an absolute contraindication to MMC administration according to the summary of product characteristics (SPC) [11], but given the relatively small benefit of the

instillations, the decision to give intravesical chemotherapy during pregnancy is on a case-by-case basis. Breastfeeding should be discontinued during MMC treatment. [11]

Intravesical administration of BCG is contraindicated in patients with gross haematuria, after traumatic catheterisation, for 2 weeks after TUR-BT, and in patients with a symptomatic urinary tract infection (UTI). [1] Asymptomatic bacteriuria is not a contraindication. [12] Other contraindications include active tuberculosis, hypersensitivity to BCG, previous radiotherapy of the bladder, pregnancy and lactation. [13] There is evidence that BCG therapy may be safe in immunocompromised patients. [14] BCG administration is not recommended during pregnancy, although relevant data are lacking. [13]

4.3 Alternatives to MMC and BCG

None of the following treatments is recommended as standard by the current EAU Guidelines and they should be regarded as investigational: intravesical administration of MMC and gemcitabine, paclitaxel, docetaxel, BCG and interferon (IFN)-α, and thermochemotherapy. [15]

5. Care pathway

5.1 Common treatment schedules

Many different chemotherapy and BCG schedules have been described; the following schedules are in common use.

Chemotherapy (MMC): one single immediate postoperative instillation; or immediate postoperative instillation followed by 6 weekly instillations and then, if cystoscopy is negative, monthly instillations for a period of 1 year. [16] (See Chapter 4 for indications)

BCG: there is no immediate postoperative instillation of BCG. Administration should not start sooner than 2 weeks after TUR-BT and consists of 6 weekly instillations: induction course followed by 3 weekly instillations (maintenance) at 3, 6, 12, 18, 24, 30 and 36 months, provided that cystoscopy and cytology are negative. This schedule was established by a Southwest Oncology Group trial. [17] The dwell time is 1-2 h. [18] Maintenance in IR tumours stops after 12 months. [1] BCG is not superior to MMC unless at least 1 year of maintenance is completed. [1] Maintenance MMC is better than non-maintenance BCG. [18]

The first cystoscopy is performed at 3 months after the standard 6-week induction. In patients who are disease free, 3 weekly instillations are given 1 week after cystoscopy, and then maintenance continues as described above. [19]

5.2 Resistance to intravesical treatment

Patients who fail intravesical chemotherapy and experience disease relapse can benefit from BCG instillations. In the case of BCG failure, however, radical cystectomy is the safest treatment option. Recent evidence suggests that immunotherapy, chemotherapy, and combination therapy can yield responses in selected cases after BCG treatment failure. [1]

6. Safety

All antineoplastic agents are potentially hazardous and must be handled with caution. Although the risks of BCG and MMC are different (an attenuated vaccine and a cytotoxic agent), both are on The National Institute for Occupational Safety and Health (NIOSH) Alert List as hazardous drugs. They have the potential to cause carcinogenic, developmental or reproductive toxicity or organ injury. [20,21]

6.1 European safety regulations

The European Agency for Safety and Health at Work (EU-OSHA) aims to reduce any risk of mutagenic exposure to the population. [22] European regulations are in force in the individual EU Member States. Each Member State is responsible for developing local regulations based on the below mentioned EU directive. This implies that local rules for safety must be followed. In the US, Healthcare Workers Safety Guidelines exist under a regulatory body called the Occupational Safety and Health Administration (OSHA).

The European Council issued a directive in which the minimum of safety measurements were stated to protect workers from exposure to carcinogenic toxins. [23]

The Directive makes the following recommendations (Article 5):

1. Reduce sources of exposure
   ✓ Use closed systems
2. Evacuation of carcinogens at source by local extraction or general ventilation
   ✓ Clean rooms with biological safety cabinet (BSC) or isolators
3. Individual protection measure (personal protective equipment)
   ✓ Use of gloves, gowns, masks, protective clothing

Prevention of exposure is the highest goal to reach in working with hazardous medication.

6.2 Risk factors and exposure

Both BCG and MMC are potential health risks to all persons exposed to them during handling. There is no permissible exposure level set for these hazardous drugs. [24] Analysis of occupational exposure of health care workers to these drugs has shown that oncology nurses have the highest exposure rate. Oncology nurses exposed to carcinogenic agents have an increased incidence of leukaemia and other cancers, as well as genetic mutations noted in their urine because of accidental exposure to carcinogenic agents. [25–31]

Employers must assess the risk of handling antineoplastic and biological drugs and take suitable precautions to protect employees by identifying the hazards, and deciding who might be harmed and how. Exposure during handling of BCG and MMC may be through skin or eye contact, skin absorption, inhalation of aerosols and drug particles, ingestion, and needle stick injuries during the following activities:

- Drug preparation
- Drug administration
- Handling patient waste
- Transport and waste disposal
- Cleaning spillages

People at risk of contamination:
- Transporters of the medication before and after preparation
- Pharmacists/pharmacy assistants
- Nurses/nurses' assistants
- Operating room theatre technicians
- Doctors
- Cleaning personnel
- Handlers of waste
- Handlers of linen/bedding
- Patients
- Family members/people close to the patient

6.2.1 Risks during drug preparation/reconstitution

Spillage of medication often occurs at the connection points of syringes, tubes (such as infusion sets) and urinary catheters.

When preparing medication that needs to be reconstituted, there is the possibility of spillage due to difficulty when introducing a needle into the vial and instilling fluid/diluent. The risk of over-pressure from the additional fluid can lead to aerosolisation of the medication and pose an increased risk to the person preparing MMC and BCG. [32]

Fig. 1 Aerosolisation of the medication when introducing a needle into the vial
(Courtesy: CareFusion)

To reduce risk during drug preparation Closed System Transfer Devices (CSTD) are available to help prevent contamination.

Fig. 2a Equipment for reconstitution with a CSTD

Fig. 2b Dissolved BCG

Fig. 2c Syringe BCG using a CSTD
(Courtesy: W. De Blok – BD PhaSeal shown)

6.2.2 Risks during drug administration

The risk of spillage during instillation can occur as follows:

- Connection of the system of administration of the prepared medication due to the possibility of the medication in contact with the outside of the container due to spillage during preparation.
- After removal of the catheter due to possible spillage of medication remaining within the catheter, or the patient's inability to retain the medication for the prescribed dwell time, or incontinence.

To reduce risk during drug administration, a closed system is preferable. [33] Closed administration systems are available to connect the syringes or bags containing the medication to the catheter, both with and without luer lock tips.
Both intermittent and indwelling catheters may be used. In the case of a catheter without a luer lock, an adaptor can be used to connect the catheter with the administration system. By folding an absorbent pad around the catheter and the whole administration system before removal of the catheter, the risk of skin exposure and contamination of the environment will be reduced considerably.

Fig. 3a Before BCG instillation

Fig. 3b Performing BCG instillation

Fig. 3c-d-e-f Retrieving catheter after BCG instillation in folded pad and dispose of in hospital waste bin.
(Courtesy: W. De Blok)

When performing MMC installation additional PPE is required.

6.2.3 Risks when handling patient waste

All material that has been exposed to medication used in intravesical instillation should be considered as contaminated and disposed of in accordance with local and hospital regulations, in a container specifically used for chemotherapeutic waste. [21]

Single use

- Disposables
- Syringes
- Tubing
- Packaging material
- Catheters
- Cleaning tissues
- Absorbent pads
- Incontinence pads
- Protective material (e.g., gloves)

Reusables

- Linen contaminated with MMC or BCG or excreta from patients who have received intravesical instillations in the past 2 days is a potential source of occupational exposure. Linen soiled with blood or other potentially infectious materials, as well as excreta, must also be managed as contaminated material. Linen contaminated with MMC or BCG should be placed in specially marked impervious laundry bags. The laundry bag and its contents should be prewashed, and then the linens added to other laundry for a second wash [21,22,34] Normal washing procedures are sufficient to remove both MMC and BCG. [35]
- The mattress of the gurney or bed used during the intravesical instillation should be protected from contamination by protective absorbent pads. [35]

6.2.4 Risks during transportation

During transportation, drug contamination might occur due to damage of the vial/container or contamination of the exterior of the package after preparation. During transportation, the handling personnel must be aware of the content and the risks involved. In accordance with local regulation, a sign/label can be used. Mellinger (2010) also stated that for those present in the same room where hazardous drugs are stored or used, special signage should be used. [35] This is not a European standard yet; therefore, signage should be based on local regulations.

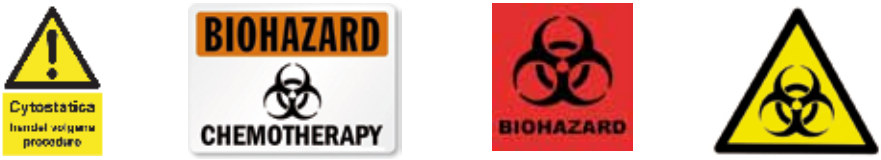


Fig. 4a, 4b, 4c, 4d Examples of warning signs

6.2.5 Cleaning and management of spillages

Periodic cleaning of work surfaces and areas with appropriate deactivation agents before and after each patient encounter should be part of the established practice of each clinic/hospital.

Deactivation agents are listed on the Material Safety Data Sheet for each manufacturer [36], for example, TICE recommends the use of a tuberculocidal disinfectant. [37]
Medac advises that spillage of BCG-Medac solution should be treated with a disinfectant with proven activity against mycobacteria. [38]

Clean-up of small spills

Safety procedures should be in place in any area involved with handling hazardous drugs. Small spills are considered to be < 5 ml.

- Spills < 5 ml or < 5 g outside a BSC should be cleaned up immediately by personnel wearing gowns, double latex gloves, and splash goggles. If latex gloves are against national regulations or in cases of allergies of health care worker and/or patient chemotherapy nitrile/neoprene gloves should be used.
- Liquids should be removed with absorbent gauze pads, and solids should be wiped with wet absorbent gauze. The spill areas should then be cleaned 3 times using a detergent

solution followed by clean water.
- Any broken glass fragments should be picked up using a small scoop (never the hands) and placed in a sharps container. The container should then go into a hazardous drugs disposal bin, along with used absorbent pads and any other contaminated waste.
- Contaminated reusable items, for example, glassware and scoops, should be treated as outlined above under Reusables. [22]

Clean-up of large spills
- Large spill areas should be isolated, avoiding aerosolisation of the drug.
- Spills should be handled by personnel properly trained in the handling of hazardous material.
- Cover liquid spills with an absorbent pad/sheet.
- Protective apparel, including respirators, should be used as with small spills when there is any suspicion of airborne powder or that an aerosol has been or will be generated.
- All contaminated surfaces should be thoroughly cleaned three times with detergent and water. All contaminated absorbent sheets and other materials should be place in a disposal bag for hazardous drugs. [22]

6.3 Health care workers safety

Risk prevention strategies are mandatory and should start by using instillation methods that minimise risk of contamination. Kastango et al. [39] stipulates that the lowest risk in complexity, and in number of aseptic manipulations, is by making use of pre-mixed compounded sterile preparations. The use of totally enclosed systems where practicable, carries the lowest risk for health care workers and patients. [22]

When performing intravesical instillations, healthcare workers should use protective equipment that protects them against contamination with medication.

6.3.1 Personal protective equipment (PPE)

Gloves

Long, thick chemotherapy approved gloves that cover the gown cuff are recommended for use with hazardous drugs. Gloves with little or no powder are preferred because the powder can absorb contaminating substances. [22]

Nitrile or natural rubber latex gloves (where in use) are preferred. Vinyl gloves are inappropriate because of their increased permeability. For extended exposure to chemotherapeutic drugs, double gloving, use of thicker gloves, and frequent changes of gloves increases the protection they afford. [40]

Gowns

Protective disposable gowns made of lint-free, low-permeability fabric, with a closed front, long sleeves, and elastic or knitted closed cuffs should be worn. The cuffs should be tucked under the gloves. If double gloves are worn, the outer glove should be over the gown cuff and the inner glove should be under the gown cuff. When the gown is removed, the inner gloves should be removed last. Gowns and gloves in use in MMC or BCG preparation areas should

not be worn outside those areas. [22]

Respiratory protection
A BSC is essential for the preparation of hazardous drugs. If a BSC is not available, a NIOSH-approved respirator appropriate for the hazard must be worn to afford protection until the BSC is instilled. [22]

Eye and face protection
Whenever splashes, sprays, or aerosols of hazardous drugs are generated that can result in eye, nose, or mouth contamination, chemical-barrier face and eye protection must be used. Eyeglasses with temporary side shields are inadequate protection. Eyewash facilities should also be available.

6.3.2 Pregnant health care workers

Reproductive effects associated with occupational exposure to antineoplastic agents are well documented. Several studies of nurses found a significantly high proportion of adverse pregnancy outcomes when exposure to antineoplastic agents occurred during pregnancy. The nurses involved in these studies usually prepared and administered the drugs. [22]

When giving MMC instillation it is advised that pregnant or lactating workers should not do the following:

- Prepare antineoplastic agents
- Perform intravesical instillations
- Clean up after spills
- Handle cytotoxic waste
- Take care of patients with heavy perspiration
- Handle patient waste

Pregnant or lactating workers are allowed to take care of patients being treated with antineoplastic agents if they do not come in contact with urine, stools or vomit. They can also change linen if no visible contamination is seen. [30]

6.4 Patient safety

6.4.1 Care instructions

Skin contact
Intravesical agents should not be allowed to come in contact with the patient's skin. If this does happen with MMC, the skin should be cleaned with water and soap. Contact with the eyes should also be handled by prolonged (15 min.) flushing with water. A physician should always be notified. The same procedures apply to contact with BCG and washing with soap and water is sufficient.

Hand washing is advised after passing urine.

Toileting
Toilets are where the risk of contamination after preparation and administration of

chemotherapeutic agents is highest. [178] High urinary urgency and incontinence are additional reasons for toilet contamination after intravesical instillation. In some countries, it is advised to flush the toilet twice with the lid closed, However, there is no evidence to support this precaution. When the toilet is used by more persons, cleaning with normal detergent and water is advised.

Contamination of clothes
Normal washing of clothes is safe enough to deal with MMC and BCG contamination. [35,41]

For further information on side effects, resuming normal activities, voiding and medication, see Section 8.5.

6.4.2 Pregnant patients
Pregnancy within 6 months after the therapy is not advised. Breast feeding during therapy with MMC or BCG is contraindicated. [11,13,42]

6.4.3 Fertility
Patients treated with BCG can show marked changes in sperm quality. [43,44] Some patients have sperm counts below oligospermia levels.

It is advised to use protective contraception (e.g. condoms) during sexual intercourse or to refrain from intercourse for 1 week after treatment, because excreta can remain in the body of patients undergoing BCG-therapy. [13]

For detailed information on cleaning procedures and material see Appendix 14.1

Recommendations	LE	GR
Employers must assess the risk of handling antineoplastic and biological drugs and take suitable precautions to protect employees by identifying the hazards, and deciding who might be harmed and how.	4	C
Health care workers involved in the preparation and administration of intravesical instillation medication should always follow local and hospital safety procedures to prevent exposure of patients and personnel to hazardous medication.	4	C
Instillation medication should be prepared in a pharmacy or BSC to prevent exposure.	4	C
To reduce risk of exposure during drug administration, a closed system is recommended. [33]	3	B
To reduce risk of exposure during drug preparation and administration personal protective clothing should be worn in accordance with local and hospital safety procedures. [21,22,26–31,40,45]	3	B
All material that has been exposed to medication used in intravesical instillation should be considered as contaminated and disposed of in accordance with local and hospital regulations, in a container specifically used for chemotherapeutic waste.	4	C

Reusable materials and furniture at risk of being contaminated during the intravesical instillation should be protected by protective absorbent pads.	4	C
All personnel handling, transporting and cleaning materials used for intravesical instillations must be properly trained on the content and the risks involved.	4	C
Nurses should educate patients and care givers how to deal with the risk of exposure during and after the intravesical instillation.	4	C
Nurses should advise patients not to become pregnant within 6 months after the treatment with BCG or MMC.	4	C
Pregnant or lactating health care workers taking care of patients being treated with antineoplastic agents (MMC) should follow local guidelines when preparing or administering the drugs, clean spillage or waste and prevent contact with the patient's urine, stools, vomit or heavy perspiration.	4	C

7. Nurse education prior to instillation

Regardless of the expertise of the nurse administering the treatment, there are pre-requisites that are important to ensure that a universal standard of education, understanding and competence is possessed by all to maintain patient and nurse safety.

In compliance with the Hazard Communication Standard, all personnel involved in any aspect of the handling of MMC or BCG (physicians, nurses, employees involved in receiving, transport or storage) must receive information and training to appraise them of the hazards of the drugs present in the work area. Such information should be provided at the time of an employee's initial assignment to a work area where the drugs are present. The employer should provide annual refresher information and training. [22]

The nurse specialist administering intravesical treatment needs to be trained and assessed by a competent practitioner according to local guidelines. It is also important that the nurse specialist remains up to date with the skill to maintain competence.

It is also a pre-requisite that the nurse is assessed to be competent in urethral catheterisation. [46]

The decision to initiate intravesical treatment should be made by the urological surgeon or at the multidisciplinary team meeting. In countries where specialist nurses have a license to prescribe medication, it remains good practice for the decision to initiate intravesical treatment to be made in consultation with the urologist and multidisciplinary team.

Table 5. Nurse education for bladder instillation

Maintain knowledge/skill in:	Rationale
Bladder cancer pathway	To ensure other elements of treatment/ investigation take place as required
Indication for treatment	To ensure the patient meets requirements for treatment To ensure the treatment is beneficial for the patient To help the patient understand the benefits of treatment for their disease
Data supporting use of treatment	To help the patient understand the benefits of treatment
Importance of counselling the patient regarding the treatment	To help ensure concordance and compliance
Pharmacokinetics and pharmacodynamics of the agent being used	The nurse should have an understanding of any medication that they administer to a patient To help the patient understand how the treatment works and how it affects their disease

Contraindications of treatments	To maintain patient safety
The physical and health hazards of MMC and BCG in the work area and the measures employees can take to protect themselves from these hazards	To maintain patient safety To maintain nurse safety To maintain safety of others/environment
Management of spillages	To maintain patient safety To maintain nurse safety To maintain safety of others/environment
Anatomy and physiology of the urinary tract	To understand the effect of treatment on the urinary tract To understand urinary tract side effects To comply with requirements for catheterisation
Competent in urethral catheterisation	To ensure safe and effective administration of the treatment and reduce risk of side effects
Side effects of the agent being used	To help patients manage side effects To help improve concordance and compliance To identify side effects that require further management To counsel the patient effectively
Dose/schedule	To ensure the treatment is administered in a timely fashion
Personal protective equipment to be used when performing intravesical instillation	To maintain nurse safety To maintain safety of others/environment
The carcinogenic potential and reproductive hazards of these drugs	To understand the importance of avoiding drug exposure, especially early in pregnancy, so that they can make informed decisions about the hazards involved

Recordkeeping

The competent practitioner who educates the nurse should make training records including the following information:

- Dates of the training sessions;
- Contents or a summary of the training sessions;
- Names and qualifications of the persons conducting the training; and
- Names and job titles of all persons attending the training sessions.

Training records should be maintained for three years from the date on which the training occurred. [22]

The training document in appendix 14.7 is available as printable Word file on the EAUN website, page: Nursing guidelines.

Recommendations	LE	GR
Nurses should maintain a universal standard of education, understanding and competence in relation to intravesical therapies	4	C
All staff involved in handling hazardous drugs must receive training on the hazards	4	C
Nurse specialist administering intravesical therapies needs to be trained and assessed by a competent practitioner	4	C
In countries where nurses have a licence to prescribe medication the decision to initiate intravesical therapies should be made by the multi-disciplinary team	4	C
Training records should be maintained	4	C

8. Principles of management of nursing interventions

Before starting the intravesical instillation, some general aspects should be considered. In this chapter we describe aspects related to patients, medication used, and administration procedures.

8.1 Patient assessment

Prior to initial and subsequent administration of intravesical therapy, the patient should be assessed before and after all instillations with regard to:

- Overall health status
- Specific urological health status
- Ability to understand the procedure
- Ability to comply with the treatment plan
- Understanding treatment complications

8.1.1 Pre-procedure

Assessing the patient prior to commencing each intravesical therapy aims to:

- Highlight any potential risks or complications from treatment
- Identify any individual patient requirements that may affect compliance, concordance and efficacy of treatment
- Help manage patient expectations
- Highlight any aspects requiring specialist referral or further assessment

The common problems of patient assessment are highlighted below.

A common tool for undertaking nursing assessment is using a model of nursing care such as the Roper, Logan and Tierney Activities of Daily Living model of nursing assessment. [47] This assessment is undertaken at the outset of treatment and highlights the normal situation for patients and identifies the changes that occur during their illness.

8.1.2 Common problems identified during assessment

Maintaining a safe environment		
Finding	**Nursing solution**	**LE**
Inability to mobilise to/from toilet	Consider indwelling catheter with clamp/ valve for dwell time	4
Neurological impairment	Consider keeping patient in clinic for dwell time	4
History of traumatic/difficult catheterisation causing urethral bleeding	Catheterise with extra care, use more lubricant than usual, consider alternative catheter, or more experienced personnel	4
Communication		
Finding	**Nursing solution**	**LE**
Inability to understand rationale for treatment	Provide explanation and written information	4
Memory or mental health problems	Ensure carer available or keep patient in hospital/clinic for whole dwell time	4
Inability to understand the importance of holding urine for dwell time	Consider indwelling urethral catheterisation with clamp/valve for dwell time	4
Eating, drinking and smoking		
Finding	**Nursing solution**	**LE**
Unable/unwilling to restrict fluid intake prior to instillation	Advise that restricting fluid intake may help to maintain intravesical therapy for desired time [48]	3
Unwilling to drink excess fluid after dwell time	Advise increased fluid intake after dwell time may help eliminate intravesical therapy agents from bladder and reduce risk of side effects	4
Current smoker	Inform that smoking has been shown to reduce the efficacy of BCG immunotherapy [49,50]	2a
Elimination		
Finding	**Nursing solution**	**LE**
Lower urinary tract symptoms (LUTS)	Assess LUTS with International Prostate Symptom Score (IPSS) prior to treatment	4
Storage symptoms	Consider management of storage symptoms which are likely to worsen during treatment (e.g. anticholinergics, containment products) [51]	4

Obstructive symptoms (affecting elimination of intravesical therapy)	Consider post-micturition bladder scan to ensure intravesical therapy agents are eliminated from the bladder In patients with residual urine, consider blockers, 5α-reductase inhibitors, intermittent self-catheterisation, and surgical management	4
Signs/symptoms of UTI	Send urine for culture and withhold treatment	4
Urinary incontinence	Consider containment products or indwelling urethral catheterisation for dwell time.	4
Controlling body temperature		
Finding	**Nursing solution**	**LE**
High fever (> 38.5°C)	Discuss with doctor and consider interruption of treatment	4

8.1.3 Informed consent

In some centres the patient may be asked to sign a consent form, whereas in other centres, verbal consent may be obtained, depending on local regulations. It is important that before administering treatment, the nurse is confident that the patient has been informed regarding the benefits and risks of intravesical instillation.

8.2 Preparation of bladder instillation medication

BCG should not be prepared in areas where intravenous drugs are prepared, because nosocomial infections have been reported in patients receiving parenteral drugs which were prepared in areas in which BCG was prepared. [52]

Procedure

Follow the manufacturer's package insert (SPC) for proper preparation of MMC and BCG.

Dosage

Dose range for MMC is 20–60 mg. The most frequent dose currently is 40 mg.
Dose of BCG is based on the number of CFUs (colony forming units), which depends on the specific BCG strain and varies between 1 to 8 x 10^8 and 10^9 CFUs. In clinical practice, milligram dosages are often used (range 40-120 mg, depending on the strain). [53]

Recommendation	LE	GR
BCG should not be prepared in areas where intravenous drugs are prepared. [52]	3	B

8.3 Medication pre-procedure

Anticholinergics
If the patient has a pre-existing storage symptoms anticholinergics may be effective if suitable. [54] Caution must be used in patients with conditions that could be aggravated by this medication, for example, angle-closure glaucoma, benign prostatic hyperplasia, and cardiac disease. If anticholinergics are ineffective or contraindicated, β-agonists may be used. A study by Johnson et al. (2013) found no benefit in using oxybutynin routinely as prophylaxis against urinary symptoms during bacillus Calmette-Guérin therapy. [55]

Analgesics
There is no contraindication for non-steroidal anti-inflammatory agents.

Alkalising agents
Urinary alkalisation decreases degradation of MMC. Increasing urine pH from 5 to 7 has an estimated improvement factor of 1.6. In certain cases, a patient can be prescribed sodium bicarbonate (1.3 g) in the evening prior to, and an additional dose on the day of instillation to increase urine pH and maximise efficacy. [54]

Antibiotics
There is no evidence that concurrent use of antibiotics decreases the efficacy of BCG or MMC, but if a patient is being treated with antibiotics, starting bladder instillation should be discussed with the prescribing physician.

Diuretics
When patients are prescribed diuretics as part of their regular medication, the need to refrain from taking prescribed diuretics must be verified with the patients' urologist, because this is a patient-specific issue. Instruct the patient to minimise fluid intake in the hours before treatment to minimise urine production during treatment. [56] (LE 4) This may also assist the patient with the ability to hold the instilled medication for the prescribed dwell time.

8.4 Administration of intravesical instillation

Information on how the instillation can be performed in a safe and appropriate way is shown in a table in Appendix 14.1.

8.4.1 Positioning of the patient

The anatomy of the empty bladder allows the wall of the bladder to make contact with the intravesical medication, and the patient should be encouraged to mobilise as usual. In some hospitals and clinics, after the drugs are instilled, the patient is rotated side-to-side every 15 min. to enhance contact of the drug with the entire bladder mucosa. In the product description (SPC) of BGC Tice, patients are advised to rotate after instillation, whereas staying mobile is advised in SPC of BCG Medac. [21,57] However, there is no evidence to support these practices.

8.4.2 Cleaning of the meatus

Routine daily personal hygiene is all that is needed to maintain meatal hygiene. [58-62] Trials of various cleaning agents, such as chlorhexidine and saline, have failed to reduce bacterial growth rate, therefore, soap and water is sufficient to achieve effective meatal cleaning. [6,63,64]

8.4.3 Instillation equipment

Fig. 5a Equipment for BCG instillation
(Courtesy: W. De Blok)

Fig. 5b Equipment for MMC instillation

8.4.3.1 Catheter type and size

Where possible an intermittent catheter should be used. Some considerations for the choice of catheter for the intravesical instillation are listed:

- The smallest size possible should be used, to prevent causing pressure and injuring urethral tissue [62] and to prevent too rapid instillation.
- Hydrophilic catheters decrease the risk of discomfort, trauma and post-catheterisation infection. [65–67]
- Luer lock catheters reduce the risk of spillage by maintaining a closed system. Some intermittent catheters have the luer lock end integrated, whereas indwelling catheters need an adaptor attached before the instillation procedure. Some of the MMC and BCG products in “ready to use packaging” are equipped with the luer lock system.

- First choice for instillation is an intermittent catheter; an indwelling catheter should only be placed when there is a clear indication. It should not stay in place longer than necessary. [62]

Fig. 6a and 6b Luer lock catheter and syringe with mitomycine

(Courtesy: W. De Blok)

Recommendations	LE	GR
In intravesical instillations an intermittent catheter with the smallest size possible should be used [62]	4	C
In intravesical instillations a luer lock catheter is recommended to reduce risk of exposure	4	C
If possible choose a hydrophilic catheter to reduce risk of discomfort, trauma and infection [65–67]	3	B
Use 10-15 ml of lubricants when a non-hydrophilic catheter is used [62,68]	2a	B

8.4.3.2 Lubricant

For non-hydrophilic catheters, 10–15 ml of lubricant with lidocaine and chlorhexidine should be used. [62,68] This dose does not significantly reduce the efficacy of BCG therapy.

Safety precautions

BCG

Atraumatic catheterisation is essential for the safe instillation of BCG. Major complications can appear after systemic drug absorption. Thus, contraindications for BCG intravesical instillation should be respected. BCG is contraindicated:

- during the first 2 weeks after TUR-BT;
- in patients with macroscopic haematuria;
- after traumatic catheterisation;
- in patients with symptomatic UTI.

[1] (LE: 3)

MMC
Nurses should observe urine before the treatment and contact the physician in case of gross haematuria.

8.4.4 Ability of the bladder to hold medication

There is no evidence to support that reduced bladder capacity decreases the effectiveness of intravesical therapy. The total volume of either drug solution is < 60 ml and therefore should be tolerated by any bladder capacity. Factors that may assist patients with reduced bladder capacity to retain these medications for the prescribed dwell time include:

- minimising the volume of the drug solution to be instilled to increase the concentration in the urine, and therefore, facilitate diffusion across the urinary mucosa; [54]
- treating with anticholinergics.

8.4.5 Post-operative administration of MMC

The most favourable time for postoperative instillation of MMC is within 6 h after TUR-BT.

The rationale for immediate postoperative instillation is:

- prevention of implantation of circulating tumour cells in the bladder;
- chemoresection of any residual tumour cells. [1]

In a meta-analysis of 18 RCTs (with 3,103 patients), 37% of patients receiving a single dose of MMC chemotherapy immediately after TUR-BT experienced recurrence, compared to 50% of those who had undergone TUR-BT alone. [7] This means that 7 patients need to be treated to avoid 1 recurrence. Some authors consider this number an underestimation. [6]

The dwell time was 1 h in most studies (range: 25–120 min.). Although recent RCTs have failed to show significant benefit of a single postoperative instillation, the above meta-analysis reported a pooled relative risk of recurrence of 0.67 (95% confidence interval: 0.56–0.79). [7] If a T1, TIS or Ta high-grade tumour is suspected, the benefit of immediate instillation is not supported by consistent evidence and remains only an option. [69]

In a study by Kaasinen et al. (2002) [70] administration of the first postoperative instillation later than on Day 0 was associated with > 2-fold relative risk of recurrence in multivariate analysis. [70]

8.4.6 Dwell time

MMC
Efficacy of intravesical MMC chemotherapy is relative to the duration of exposure and drug concentration at the tumour site. Dilution of the MMC solution by urine production occurs within 5 min. of instillation.[71] Although dwell time is still subject to debate, recurrence rates are lower with an increase in dwell time from 30 to 60 min. [72] Systemic drug absorption is not affected by extended exposure to MMC. The dwell time that is commonly practised is 1-2 h. Longer periods are not recommended due to dilution of the drug concentration over time as urine is transported into the bladder.

8.5 Patient education

Why

No identified studies have demonstrated that patient education affects quality of life, outcomes, side effects or increased treatment compliance. However, the purpose of education is to empower patients and/or caregivers to enable them to have more control and ease problem solving related to intravesical instillation. A fundamental role of nursing is patient education. Before any intravesical therapy begins, patients need to be informed about the mechanism of action of their therapy and any side effects that may occur. Schedules and post-procedural follow-up are included in this education. Education needs to be directed to patients and caregivers. The communication skills and attitudes of health care professionals are instrumental in promoting confidence in completing the procedure and can promote long-term compliance.

Who

Health professionals need to communicate the procedure to the patient. When patients are discharged, caregivers and those living with the patients require instructions on the precautions needed at home.

When

To decrease anxiety about the treatment, it is important to instruct patients about the necessary steps of the procedure that they are about to undergo. Upon discharge, patients need to know where and when to void, including proper handling of any spilled urine. After discharge, it is important that patients are counselled regarding signs of local and systemic skin reactions, and notify their physicians if any of these unforeseen changes occur. [73]

Where

Teaching should take place in the clinic prior to any treatment.

How

The educator should assess the best method of learning for each individual patient (i.e. verbal instruction, booklets, or digital information). All verbal information should be reinforced with written information that the patients and caregivers can keep and consult.

What

The following topics should be discussed

- Medications to avoid/delay prior to instillation (see Section 8.3)
    - Antibiotics
    - Diuretics
- Fluid intake management
    - Prior to each treatment, fluids should be restricted to maximise the concentration of the drug in contact with the bladder wall. Patients should refrain from fluid intake for 8 h prior to instillation.[74] This minimises urine production during therapy and increases the ability of patients to retain the agent for the prescribed dwell time; usually 2 h.
    - Upon treatment completion on any day, patients should be instructed to increase

fluid intake to flush out any remaining agent from the bladder.

- Voiding post-procedure
  - Upon completion of the prescribed dwell time, patients should void directly into the toilet, and male patients should sit when voiding. This is to limit splashing and contact of surfaces with residual agents.
  - The toilet should be flushed twice, with the lid in the closed position if available, after each void.
  - It is common practice in some countries to advise patients undergoing BCG therapy that 250 ml of bleach/hypochlorite should be poured into the toilet and remain there for 15 min before flushing. However, no evidence has been found to support this.
  - Hands should be thoroughly washed after voiding.
  - In the case of MMC therapy, due to the possibility of contact dermatitis, patients should be instructed to wash their genitalia after voiding. [34]
- The most common side effects associated with BCG (see Section 9.2)
- The most common side effects associated with MMC (see Section 9.3)
- Urinary tract irritation is a common reaction to all agents. This may be due to chemical cystitis and not a bacterial infection. Patients should be informed of the signs and symptoms of UTI. (see checklist in appendix 14.2)
- Launder any clothing that may be contaminated with these agents, due to spillage or incontinence, separately from other clothing.
- Instruct patients that they may resume normal activity, including health maintenance, diet and exercise for a healthy lifestyle.
- In patients who are sexually active, instruct them to use barrier/protective mechanisms during intercourse (i.e. condoms) or to abstain from intercourse for 1 week after treatment.
- Alcohol should be avoided due to its diuretic effect.

For easy reference, a checklist is provided, which is intended to assist health care professionals to check whether all the information that needs to be given to the patients has been provided.

The checklist for patient information can be found in: Appendix 14.2: Checklist for patient information

Recommendations	LE	GR
Before any intravesical therapy begins, nurses need to inform patients and care givers about the therapy, fluid intake, safety precautions that should be taken and any side effects that may occur.	4	C
The educator should assess the best method of learning for each individual patient.	4	C

9. Complications and side effects

9.1 Catheter associated bacteriuria

Insertion of a catheter outside an operating theatre is a risk factor for developing bacteriuria. Bacteriuria is acquired at a rate of 1–3% per catheterisation. [75]
Aseptic technique must be used when inserting the catheter before instillation. To minimise the risk of cross-infection health care professionals should be constantly aware of their hand hygiene. [46]

Recommendations	LE	GR
Aseptic technique should be used when inserting the catheter before intravesical instillation [75–77]	3	B
Health care professionals should be constantly aware of their hand hygiene and observe protocols on hand hygiene [75,76]	1b	A

9.2 Side effects of MMC

The high molecular weight of MMC results in low absorption, therefore, it does not usually cause systemic toxicity. However, local toxicity is more common, resulting in chemical cystitis, allergic rash, and palmar or genital desquamation from contact dermatitis. [57]

9.2.1 Side effects

Local side effects: chemical cystitis

Administration of cytotoxic chemotherapy into the bladder can induce an array of irritative voiding symptoms. Most of the adverse effects occur during the first 6 months of therapy. [78] These side effects may be treated symptomatically:

- dysuria
- frequency
- urgency
- suprapubic discomfort
- gross haematuria
- pelvic pain

The above symptoms are collectively referred to as chemical cystitis. [73,79–83] The incidence of chemical cystitis is ~10%, and the prevalence of symptoms is 1–25%. [73]

There are other severe local side effects of intravesical chemotherapy [73,80,81,84,85]:

- transmural and extravesical fat necrosis
- bladder wall ulceration and calcification

Systemic side effects

- Intravesical chemotherapy can cause skin toxicity, both by direct contact and systemic

exposure following absorption through the bladder epithelium. An estimated 9% of patients develop some type of cutaneous side effect. Common manifestations of skin reactions include a generalised rash, along with dermatitis of the hands and feet or genitalia. Other reported symptoms include eruptions of the face, trunk, or chest, vulvar dermatitis, and palpable purpura of the lower extremities. [73,80,82,86,87]

Long-term complications

- Benign chronic ulcers at the resection site have been described and are attributed to the effect of impaired healing from chemotherapy. Calcification, fibrosis, reduced bladder volume, and reduced bladder compliance are less common. [73,80,83,88,89]

9.2.2 How to reduce risk of side effects of MMC

One of the first factors to be considered is the risk of drug absorption, which may result in systemic toxicity. Although some factors that affect drug absorption may be under the control of the operating surgeon (such as surgical technique and depth of resection), others are strictly related to the physical properties of the drug. Such properties include molecular weight, concentration, and liphophilicity. Others factors that may increase absorption include drug dwell time and bladder wall integrity. [73]

Other strategies to help reduce discomfort during treatment include ensuring that the bladder is empty before drug instillation, and ensuring meticulous haemostasis at the end of resection to prevent accumulation of blood clots that may occlude the catheter and exacerbate the symptoms. [73] A novel technique has been proposed to improve patient comfort during intravesical instillation of MMC. Some of the pain associated with perioperative instillation results from the rigid resistance of a clamped catheter, and it is proposed to maintain the chemotherapeutic agent in the bladder without clamping. By elevating the urine bag 1 m above the supine patient, MMC can be retained in the bladder by hydrostatic pressure. [73,90]

The most important method to reduce the incidence of necrosis and ulceration is to establish meticulous haemostasis after tumour resection and perform intraoperative cystography if there is any suspicion of bladder injury. [73]

9.2.3 How to manage side effects of MMC

Intraperitoneal extravasation: initial management comprises immediate evacuation of the drug, followed by confirmation by cystography. Exploratory laparotomy is required to confirm evacuation of the drug and repair of the defect. [73,91]

Extraperitoneal extravasation: management involves catheter drainage, but it is also essential to perform imaging to evaluate fluid collection, abscess formation, fistula formation, or bowel obstruction. Fluid collections should be drained and culture-directed antibiotics initiated. [73,91]

Chemical cystitis: symptoms are usually self-limiting and require no further treatment in the perioperative setting. Agents such as phenazopyridine and anticholinergics can be used in difficult cases. Powdered opium and belladonna alkaloid suppositories can also be used during instillation to provide relief of bladder spams and discomfort, and to help with

retention of the intravesical agent. [73]

Skin toxicity: in most cases, cutaneous side effects resolve after removal of the causative agent. Antihistamines and corticosteroids are useful for those who develop generalised urticaria. [73,86]

Myelosuppression: management is usually supportive. Blood products may be given in severe cases of myelosuppression, but the incidence of severe myelosuppression is low. [73]

Recommendation	LE	GR
To ensure that the bladder is empty before instilling BCG or MMC and ensure meticulous haemostasis at the end of bladder tumour resection [73]	3	C

Side effects of MMC [73,86,91]			
MMC – local	**Nursing solution**	**LE**	**GR**
Chemical cystitis	- Treat these side effects symptomatically. - Agents such as phenazopyridine and anticholinergics can be used in more bothersome cases. - Powdered opium and belladonna alkaloids in a suppository form can also be used during instillation to provide relief of spams and discomfort, and to help with retention of the intravesical agent	3	C
MMC – systemic	**Nursing solution**	**LE**	**GR**
Skin toxicity	- Remove exposing agent - Use antihistamines and corticosteroids	3	C
Myelosuppression	- Blood products may be given in severe cases	3	C
Intraperitoneal extravasation	- Call the doctor for immediate evacuation of the agent followed by cystography	3	C
Extraperitoneal extravasation	- Fluid collections should be drained with a catheter - Initiate antibiotic prophylaxis	3	C

9.3 Common side effects of BCG

Intravesical BCG is associated with more side effects compared to intravesical chemotherapy. [1] The most common side effects of BCG treatment are increased urinary frequency, dysuria and urgency. These effects are reported in > 90% of patients receiving therapy. [92] In a study by EORTC, 20% of patients treated for 3 years with BCG stopped treatment due to local or systemic side effects. [93] However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases. [1] Maintenance therapy is not associated with an increased risk of side effects compared with induction. [1] Major complications can appear after systemic absorption of BCG. Thus, contraindications to intravesical instillation of BCG should be respected. [1]

9.3.1 Side effects

The most common side effects of intravesical instillation of BCG are:

- cystitis [1,94–104]
- haematuria [1,94,95,97,99,101,102,105,106]
- symptomatic granulomatous prostatitis [1,95,99,101,102,106–111]
- epididymo-orchitis [1,95,101,102,106,112–116]

Rare local side effects are listed in Appendix 14.3.

The most common systemic side effects of intravesical instillation of BCG are:

- general malaise, fever [1,94,97,99–102,104–106,117–120]
- allergic reactions [1,95,97,101]

Less common side effects are: arthralgia and/or arthritis [1,102,106,121–125] and BCG sepsis [1,94,95,102,103,106,126–131]

Rare systemic side effects are listed in Appendix 14.3.

In four of five studies with toxicity data, BCG-associated cystitis was significantly more frequent than MMC-associated cystitis (53.8% vs 39.2%). [98]

9.3.2 How to reduce risk of side effects of BCG

In a pilot study a sequential administration of 40 mg of hyaluronic acid reduced local side effects of BCG. [132] Further studies are needed.
Prophylactic ofloxacin (a fluoroquinolone antibiotic) decreased the incidence of moderate to severe adverse events associated with BCG, which are primarily associated with patient dropout. Compliance with induction and maintenance therapy may be improved by adjuvant ofloxacin therapy. However, long-term comparative studies with other preventive strategies must be done to confirm these initial findings with compliance and recurrence-free survival as the primary end points.[133] Ciprofloxacine is now more widely used.

9.3.3 How to manage side effects of BCG

Management of side effects after BCG should reflect their type and grade. Recommendations for individual situations are provided by the International Bladder Cancer Group (IBCG). [95]

No significant differences in toxicity are detected according to dose (one-third dose vs full dose) or duration (1 yr. vs 3 yr.) of BCG treatment. Neither reducing the dose nor shortening the duration of maintenance decreased the percentage of patients who stopped treatment because of side effects. [134,135]

Recommendations	LE	GR
Dose reduction to 1/3 of the usual dose for the reduction of side effects is no longer recommended. [134,135]	1b	A

10. Patient Quality of Life (QoL)

10.1 Impact of intravesical instillations on the patient reported outcome

Introduction
NMIBC considerably affects a patient's daily life for different reasons. Increased recognition of impairment related to cancer treatment reveals a growing interest in patient-reported outcomes (PROs). PROs are defined as perceived current health status as expressed by health-related quality of life (HRQoL) or treatment satisfaction. [136,137] The term HRQoL was introduced to distinguish between general QoL and the current level of functioning as it is perceived by patients.

The limited evidence base for PROs in bladder cancer is due to limited RCTs, no preprocedural baseline assessments, and longitudinal data to evaluate the impact on patient QoL over time. In addition, there was no validated instrument specific to bladder cancer until recently introduced by EORTC.

Examples of tools to assess QoL are shown in appendix 14.5.

General HRQoL status
Early attempts to determine HRQoL found that patients with high-risk NMIBC and CIS had significantly worse body functioning and therefore worse HRQoL compared with the general population. [138,139] A prospective study of Japanese men showed that general health perception was severely impaired in patients with NMIBC and CIS compared with sex- and age-matched controls, using the validated SF-36 questionnaire (see Appendix 14.5, table 6). The most severe impairment was observed in the overall global health score regardless of primary or recurrent disease. [139]

Symptoms as predictors of HRQoL
Psychological distress and physical symptoms of patients are intense at the time of diagnosis of bladder cancer, however these symptoms are transient. Global HRQoL improves during follow-up with maintenance therapy using topical BCG. [139]

Unlike other early-stage urological malignant diseases, such as localised renal cancer and prostate cancer, patients with NMIBC frequently exhibit urinary tract symptoms. These symptoms may be partly responsible for the initial impairment in addition to cancer diagnosis, however not documented.

Overtime factor
Patients' HRQoL is considered to be affected by loss of their autonomy in daily life. A five year follow up study of 76 NMIBC patients showed that autonomy and other sociodemographic factors (such as old age and comorbidities) were determinants of QoL [140] although not compared to normal population. Moreover, the patient's family situation is expected to have

a critical impact on emotional and social well-being, although this is not well documented in NMIBC. [141]
According to the definition HRQoL is a multi-dimensional construct. Domains such as social function, role and emotional functions are associated with working status and reported to be severely impaired after the first cycle of BCG. Physical function is impaired further after the second or third TUR-BT. [139,142] HRQoL gradually returns to initial levels during follow-up, even with tumour recurrence in long-term survivors. [140,141] It is speculated that patients undergoing frequent TUR-BT (≥ 4 times) may accept bladder cancer as part of their daily lives, and may not be suffering from this disease to the same degree as before due to the over-time factor. [139]
A prospective RCT of the efficacy, safety and impact on HRQoL comparing a conservative pathway with an alternative maintenance strategy of BCG documented that there was no difference in function or symptom scales at 14 months follow-up after randomisation. [143]

Regardless of limited long term evidence regarding HRQoL even patients with tumour recurrence are reported to return to initial levels. [139–141] No evidence was found describing whether MMC or BCG is superior regarding impact on HRQoL. [144]

Conclusion
Patients experience a high impact on HRQoL at the time of diagnosis but often experience a gradual return to initial HRQoL status when undergoing frequent TUR-BT and instillation therapy.

Recommendations	LE	GR
When assessing patients before treatment predictors for intermittent loss of HRQoL such as autonomy in daily life, comorbidities, older age and family situation should be assessed. [140]	3	B
The multi-professional team should Inform, educate, comfort and motivate NMIBC and CIS patients regarding treatment impact on global health and when to expect to regain initial HRQoL status. [139,142]	3	B
Patients should be informed pre-procedure that: • Most patient will regain initial HRQoL status within one year. [139] • Most domains included in global HRQoL will return to initial levels except from physical function within one year. [145] • Social function, role and emotional functions, which are also associated with working status, are most severely impaired at the first cycle of BCG. [139]	 3 2a 3	 B B B

11. Documentation

11.1 What needs to be documented

When a patient starts intravesical instillation the following data must be collected and documented:

- Name of patient
- Date of birth
- Medication agent
- Dose prescribed
- Mode of administration
- Date of administration
- Initials of the doctor and nurse (and verification nurse)
- Side effects/reactions to earlier treatment

Local policy may differ from the above.

A scheme for MMC and BCG instillation can be found in Appendix 14.1: Procedures for intravesical instillation

11.2 Examples of documentation

Examples of documentation can be found in Appendix 14.8: Examples documentation for MMC and BCG instillation

12. Glossary and abbreviations

Glossary

- Mutagenic effects — Changes in the genetic information of cells
- Carcinogenic effects — Tumour causing
- Antineoplastic — Antitumour

Abbreviations

- BSC — Biological safety cabinet
- BCG — Bacillus Calmette-Guérin
- CIS — Carcinoma *in situ*
- EORTC — European Organisation for Research and Treatment of Cancer
- LR — Low risk
- HR — High risk
- IR — Intermediate risk
- MMC — Mitomycin C
- NMIBC — Non-muscle invasive bladder cancer
- OSHA — Occupational Safety and Health Administration
- SPC — Summary of Product Characteristics
- TUR-BT — Transurethral resection of bladder tumour
- UTI — Urinary tract infection

13. Figure reference list

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14. Appendices

14.1 Procedures for intravesical instillation

Example protocol for intravesical instillation of MMC using an intermittent catheter

No.	Activity	Section in these guidelines
1	Prepare room - place a gurney/trolley/bed in the room - place warning sign outside room - bring risk disposal bin inside room - place risk disposal bag for bed linen in the room - place hazard box /accident kit outside the room Materials needed: - medication with appropriate connector - catheter (luer lock) - 3-way luer lock valve - 3-ml saline syringe to flush out the medication after administration - required PPE: chemotherapy approved gloves, gown, mask and goggles - 2 absorbent pads for use on the bed - incontinence protection material - meatal cleaning set (catheter set if applicable) - wash cloths and towel	 6.2.4 6.2.3 6.2.5 6.2.5 8.4.3-6.1–6.2.2 6.3.1 - 6.2.3 6.2.3 6.1 - 6.4.1 8.4.2 6.3.1
2	Asses patient: - check ID - check informed consent - check if the patient understood the instructions - assess whether the patient has haematuria	Chapter 8
3	Prepare bed: place 1 pad beneath the buttocks of the patient to absorb any spillage	6.2.3
4	Prepare medication as described by manufacturer if ready to use package (use gloves when handling the medication)	6.2.1 - 6.2.2
5	Or: collect medication from the pharmacy department	6.2.1
6	Check the prescription, ID patient, and cross check	
7	Place all needed items within reach	
8	Connect the medication to the luer lock connector of the valve with 3 ml saline	6.1
9	Ask the patient to assume supine position	
10	Place the second absorbent pad with 1 corner of the pad beneath the genital area with 2 corners draped over the legs	6.2.3

11	Clean the meatus	8.4.2
12	Insert the catheter into the bladder	
13	Drain the bladder with the catheter until it is completely empty, and collect the drained urine if needed for culture or other purposes	
14	Connect the syringe, valve and medication to the luer lock end of the catheter	6.1 - 6.2.2 - 8.4.3
15	Open the valve, open the final connectors to the medication device, and let the medication go into the bladder without any extra pressure (gravity alone)	
16	Turn the valve to the position of the 3-ml saline syringe	
17	Expel residual medication out of the catheter by inserting the saline	6.1
18	Fold the 2nd absorbent pad around the catheter and gently remove the catheter from the patient into the folded pad. Maximal protection from spillage is obtained.	6.2.3
19	Throw away the folded pad with the catheter into the risk disposal bin	6.2.5
20	Dispose of the gloves into the risk disposal bin	6.2.5
21	Put on new gloves	6.3.1 - 6.2.3
22	Help the patient with cleaning of the genital area	6.4.1
23	Offer the patient incontinence protection (also to take home) and help with dressing if needed.	6.1 - 6.4.1
24	Check if the patient understood the instructions before leaving: after dwell time, urinate sitting down; flush the toilet twice with the lid closed; clean the genitalia after each voiding; and wash hands after the whole procedure.	6.1 - 6.4.1
25	Remove contaminated material (which has been in open contact with the medication) and dispose of in the correct bag or bin	6.2.5
26	Clean any non-disposable items with detergent and water	6.1 - 6.2.5 - 6.3.1

Example protocol for intravesical instillation of BCG using an intermittent catheter

No.	Activity	Section in these guidelines
1	Prepare room - place a gurney/trolley/bed in the room - place warning sign outside room - bring risk disposal bin inside room - place risk disposal bag for bed linen in the room - place hazard box /accident kit outside the room Materials needed: - medication with appropriate connector in order to reach a closed system - catheter (luer lock) - 3-way luer lock valve - 3-ml saline syringe to flush out the medication after administration - required gloves: nitrile or neoprene - 2 absorbent pads for use on the bed - incontinence protection material - meatal cleaning set (catheter set if applicable) - wash cloths and towel	 6.2.4 6.2.3 6.2.5 6.2.5 8.4.3-6.1–6.2.2 6.3.1 - 6.2.3 6.2.3 6.1 - 6.4.1 8.4.2 6.3.1
2	Asses patient: - check ID - check ID - check if the patient understood the instructions - assess whether the patient has haematuria	Chapter 8
3	Prepare bed: place 1 pad beneath the buttocks of the patient to absorb any spillage	6.2.3
4	Prepare medication as described by manufacturer if ready to use package	6.2.1 - 6.2.2
5	Or: collect medication from the pharmacy department	6.2.1
6	Check the prescription, ID patient, and cross check	
7	Place all needed items within reach	
8	Connect the medication to the luer lock connector of the valve with 3 ml saline	6.1
9	Ask the patient to assume supine position	
10	Place the second absorbent pad with 1 corner of the pad beneath the genital area with 2 corners draped over the legs	6.2.3
11	Clean the meatus	8.4.2
12	Insert the catheter into the bladder	
13	Drain the bladder with the catheter until it is completely empty, and collect the drained urine if needed for culture or other purposes	

14	Connect the syringe, valve and medication to the luer lock end of the catheter	6.1 - 6.2.2 - 8.4.3
15	Open the valve, open the final connectors to the medication device, and let the medication go into the bladder without any extra pressure (gravity alone)	
16	Turn the valve to the position of the 3-ml saline syringe	
17	Expel residual medication out of the catheter by inserting the saline	6.1
18	Fold the 2nd absorbent pad around the catheter and gently remove the catheter from the patient into the folded pad. Maximal protection from spillage is obtained.	6.2.3
19	Throw away the folded pad with the catheter into the risk disposal bin	6.2.5
20	Dispose of the gloves into the risk disposal bin	6.2.5
21	Put on new gloves	6.3.1 - 6.2.3
22	Help the patient with cleaning of the genital area	6.4.1
23	Offer the patient incontinence protection (also to take home) and help with dressing if needed.	6.1 - 6.4.1
24	Check if the patient understood the instructions before leaving: after dwell time, urinate sitting down; flush the toilet twice with the lid closed; clean the genitalia after each voiding; and wash hands after the whole procedure.	6.1 - 6.4.1
25	Remove contaminated material (which has been in open contact with the medication) and dispose of in the correct bag or bin	6.2.5
26	Clean any non-disposable items with alcohol	6.1 - 6.2.5 - 6.3.1

Example protocol for postoperative intravesical instillation of MMC

No.	Activity	Reference in guidelines
1	Prepare room - place a gurney/trolley/bed in the room - place warning sign outside room - bring risk disposal bin inside room - place risk disposal bag for bed linen in the room - place hazard box /accident kit outside the room Materials needed: - medication with appropriate connector - catheter (luer lock) - 3-way luer lock valve - 3-ml saline syringe to flush out the medication after administration - required PPE: chemotherapy approved gloves, gown, mask and goggles - 2 absorbent pads for use on the bed - incontinence protection material - meatal cleaning set (catheter set if applicable) - wash cloths and towel	 6.2.4 6.2.3 6.2.5 6.2.5 8.4.3 - 6.1 - 6.2.2 6.3.1- 6.2.3 6.2.3 6.1 - 6.4.1 8.4.2 6.3.1
2	Asses patient: - check ID - check informed consent - check if the patient understood the instructions - assess whether the patient has gross haematuria - assess whether there are clots blocking bladder drainage; if so, postpone the instillation - assess whether the patient has signs of bladder spasm; if so, decide whether anti-cholinergic medication should be prescribed	Chapter 8
3	Prepare bed: place 1 pad beneath the buttocks of the patient to absorb any spillage	6.2.3
4	Prepare MMC as described by manufacturer of ready-to-use package (use gloves when handling)	6.2.1 - 6.2.2
5	Or: collect medication from the pharmacy department	6.2.1
6	Check the prescription, ID patient, and cross check	
7	Place all needed items within reach	
8	Connect the medication to the luer lock connector of the valve with 3 ml saline	6.1
9	Ask the patient to take assume supine position	
10	Place the second absorbent pad with 1 corner of the pad beneath the genital area and underneath the catheter, with 2 corners draped over the legs	6.2.3

11	Connect the syringe, valve and medication to the luer lock end of the catheter	8.4.3 - 6.1 - 6.2.2
12	Open the valve, open the final connectors to the medication device, and let the medication go into the bladder without any extra pressure (gravity alone)	
13	Turn the valve to the position of the 3-ml saline syringe	
14	Expel residual medication out of the catheter by injecting the saline	6.1
15	Clamp the catheter to ensure the dwell time of the MMC	8.4.6
16	Avoid as much as possible opening the closed and contained system of the catheter and all its attachments. Any opening of the connections risks contamination.	6.1 - 6.2.2
17	Ensure that there is no leakage of medication alongside the catheter; if so, use incontinence pad to absorb it	6.1
18	In case of a bladder spasm that expels the medication, assess whether there is still any residual medication and try to avoid the spasms by use of anti-cholinergic medication	8.3
19	After the dwell time is completed and if the catheter can be removed, follow the instructions below	
20	Fold the 2nd absorbent pad around the catheter	6.1
21	Empty the catheter balloon and gently remove the catheter from the patient into the folded pad. This ensures maximal protection from spillage.	6.1
22	Throw away the folded pad with the catheter and all attachments into the risk disposal bin; note that all urine is also regarded as contaminated	6.2.3
23	Dispose of the gloves into the risk disposal bin	6.2.5
24	Put on new gloves	6.3.1 - 6.2.3
25	Help the patient with cleaning the genital area	6.4.1
26	Offer the patient incontinence protection (also to take home) and help with dressing if needed.	6.1 - 6.4.1
27	Check if the patient understood the instructions before leaving: after dwell time, urinate sitting down; flush the toilet twice with the lid closed; clean the genitalia after each voiding; and wash hands after the whole procedure.	6.1 - 6.4.1
28	Remove contaminated material (which has been in open contact with the medication) and dispose of in the correct bag or bin	6.2.5
29	Clean any non-disposables with detergent and water	6.1 - 6.2.5 - 6.3.1

14.2 Checklist for patient information

- Most common side effects associated with BCG (see Section 9.2)
- Most common side effects associated with MMC (see Section 9.3)
- Medications to avoid/delay prior to instillation visit
    - Antibiotics
    - Diuretics
- Fluid intake management
- Voiding post-procedure
- Irritative symptoms of the urinary tract may be due to cystitis or UTI. Instruct the patient on the signs and symptoms of a UTI.
    - Burning on urination
    - Frequency/urgency
    - Painful voiding
    - Foul smelling urine
    - Cloudy/dark urine
    - Fever and/or chills
    - Haematuria
- Laundering of contaminated clothing
- Resuming normal activity, including health maintenance, diet and exercise
- Sexual activity

14.3 Rare side effects of BCG

Rare local side effects

- Penile granuloma [146–149]
- Bacteriuria [150]
- Bladder ulcer and calcifications [95,104,109,120,151,152]
- Contracted bladder [95,106]
- Ureteral obstructions [95,101,104,106]
- Urinary incontinence [102]
- Extravesical granuloma [104]
- Prostatic abscess [153]
- Renal abscess/mass [106,154,155]
- Suprarenal mycotic aortic aneurysm [117,118,156]
- Contact dermatitis [95,102,106,120,157]
- Ischemic colitis [99]
- Femoral artery aneurysm [158]
- Ruptured abdominal aortic aneurysm [158]
- Pelvic and inguinal abscess [159]
- Granulomatous pyelonephritis [160]

Rare systemic side effects

- Pneumonitis, hepatitis [60,94,102,103,105,106,118,126,129,161–168]
- Granulomatous hepatitis and choroiditis [169,170]
- Myelosuppression [95,106]
- Decrease in the sperm count [43]
- Headache [102]
- Aortoduodenal fistula [169]
- Vertebral osteomyelitis, epidural abscess, cerebral tuberculoma [171]
- Acute renal failure, interstitial nephritis [172]
- Bilateral cervical lymphadenitis and chorioretinitis [173]
- Reiter's syndrome (pain, limitation of the cervical spine, synovitis of the right knee) [165]
- Persistent high-grade fever (> 38.5°C for > 2 days) [1,97,99,101,102,118]

14.4 Management options for side effects associated with intravesical BCG

Management options for side effects associated with intravesical BCG [95,100,174,175]

Management options for local side effects (modified from IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: a. Postpone the instillation b. Perform a urine culture c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: d. With positive culture: antibiotic treatment according to sensitivity e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary)
	If symptoms persist [100]: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [174]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.

Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs
	If no/partial response, proceed to corticosteroids, high-dose quinolones or anti-tuberculosis drugs [175]
Persistent high-grade fever(> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with ≥ two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-TURB (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

BCG = bacillus Calmette-Guérin; IBCG = International Bladder Cancer Group; NSAID = non-steroidal anti-inflammatory drug; TURBT = transurethral resection of bladder tumour

Table 7.1 from: Non-Muscle-Invasive Bladder Cancer (Ta, T1 And Cis) - Limited Text Update April 2014, page 23. [1]

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BLS24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Have you had pain or a burning feeling when urinating?	1	2	3	4
38. Did you have a fever?	1	2	3	4
39. Did you feel ill or unwell?	1	2	3	4
40. Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
41. Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4
43. Did you worry about the results of examinations and tests?	1	2	3	4
44. Did you worry about possible future treatments?	1	2	3	4
45. Did you have a bloated feeling in your abdomen?	1	2	3	4
46. Have you had flatulence or gas?	1	2	3	4

Please go on to the next page

ENGLISH

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
49. **For men only:** Did you have difficulty gaining or maintaining an erection?	1	2	3	4
50. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4
Please answer the following 4 questions only if you have been sexually active during the past 4 weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
51. Have you felt uncomfortable about being sexually intimate?	1	2	3	4
52. Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
53. To what extent was sex enjoyable for you?	1	2	3	4
54. **For Women only:** did you have a dry vagina or other problems during intercourse?	1	2	3	4

Table 6. Health-related quality-of-life instruments used in bladder cancer studies

General health-related quality-of-life instruments
• **BDI** Beck Depression Inventory • **FLZ** Fragenzur zur Lebenszufriedenheit Module (German) • **HADS** Hospital Anxiety and Depression Scale • **MLDL** Munich Life Dimension List (German) • **PMS** Profile of Mood States • **SF-36** Medical Outcomes Study 36-Item Short Form • **SIP** Sickness Impact Profile
Cancer-specific instruments
• **EORTC QLQ-C30** European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire • **FACT-G** Functional Assessment of Cancer Therapy - General
Bladder-cancer-specific instruments
• **EORTC QLQ-BLS24** European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire – Bladder Cancer Superficial • **EORTC QLQ-BLM30** European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire – Bladder Cancer Muscle Invasive • **FACT-BL** Functional Assessment of Cancer Therapy – Bladder Cancer • **FACT-VCI** Functional Assessment of Cancer Therapy – Vanderbilt Cystectomy Index

[176]

14.6 Example of Competency document

European Association of Urology Nurses

Intravesical instillation - Competency Document

Name_____ Title_____

Performance Criteria			
Please place a check mark to indicate completion of competency as applicable for the employee's role. (√ = Completed/Passed)			
Competency	**Method of Evaluation**	**Learner's signature**	**Assessor's Name/Date**
Understands the clinical pathway, indication for use and pharmacokinetics of the agents	**Discussion**		
Demonstrates safety in handling of agents	**Performance**		
Demonstrates proper use of personal protective equipment (PPE)	**Performance**		
Demonstrates Patient Identification Process	**Performance**		
Demonstrates proper procedure for urethral catheterisation	**Performance**		
Verbalises management and reporting of:			
Extravasation	**Discussion**		
Hypersensitive reaction	**Discussion**		
Adverse drug reaction	**Discussion**		
Spillage of agent	**Discussion**		
Documentation	**Discussion**		

These competencies are reviewed and discussed annually.

	Print Name	**Signature**	**Date**
Reviewer:			
Reviewer:			
Employee:			

A printable PDF of this form will be available on the EAUN website, page: Nursing guidelines

A printable PDF of these forms will be available on the EAUN website, page: Nursing guidelines

Guideline for bladder instillation – Training Document

The aim of this document is to complement the EAUN Evidence-based Guidelines for Best Practice in Health Care in "Intravesical instillation with mitomycin C or bacillus Calmette-Guérin in non-muscle invasive bladder cancer".

These pages can be downloaded to ensure that the practitioner has written evidence of assessment and competence in the various aspects of intravesical therapy.

The documentation should be kept in a safe place in case it should be required in the future.

Using the performance levels below, the practitioner should achieve at least Level 3 on 20 patients before undertaking the procedure independently.

Performance Levels Results	
Level 0	Cannot perform this activity in the clinical environment but knows the key principles involved.
Level 1	Can perform this activity with constant supervision and some assistance.
Level 2	Can perform this activity with some supervision and assistance.
Level 3	Can perform this activity satisfactorily without supervision or assistance at an acceptable speed.
Level 4	Can perform this activity satisfactorily with more than acceptable speed and quality of work.
Level 5	Can perform this activity satisfactorily with more than acceptable speed and quality of work and with initiative and adaptability to special problem situations.

14.7 Example of Training document

Performance criteria			
Competency	**Competence level**	**Assessor's signature**	**Learner's signature**
Describe anatomy of the lower urinary tract			
Outline physiology of the lower urinary tract			
Undertake urethral catheterisation			
Describe bladder cancer treatment pathway			
Describe indications for intravesical therapy			
Ability to counsel patients regarding intravesical therapy (prior to instillation)			
Ability to counsel patients regarding intravesical therapy (during instillation			
Ability to counsel patients regarding intravesical therapy (post-instillation)			
Determine appropriateness of referral for treatment			
Demonstrate understanding of how the drugs work			
Demonstrate understanding of the drug hazards			
Demonstrate understanding of the management of spillages			
Demonstrate understanding of the management of waste			
Describes personal protective equipment required			
Explain side effects and their management			
Describe the dose/schedule of administration			
Ensure pre-procedure patient preparation is met (e.g., urinalysis)			
Apply infection control procedures			
Position patient correctly			
Protect privacy and dignity			

Maintain communication with patient			
Mix the drug correctly with all the required equipment			
Assess patient's needs following the procedure			
Ensure patient is aware how to deal with any complications after discharge			
Assess patient's fitness for discharge			
Discard all used equipment appropriately			
Record details of the procedure in patient record			
Recognise when help is needed			
Aware of keeping up to date with procedure			

Assessor's signature: Assessor's name:	Designation:
Assessor's signature: Assessor's name:	Designation:
Assessor's signature: Assessor's name:	Designation:

Record of learning

Date	Case No.	Trainer	Observed	Performed	Level

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Declaration of competency to administer intravesical therapy

I confirm that I have assessed ……(name) to be competent at Level .. at administering intravesical therapy independently.

I am competent at undertaking this procedure independently.

I expect the named practitioner to maintain their knowledge and skills in this procedure or to undertake a period of re-training and competency assessment if this should lapse.

Assessor's name: ……..….

Assessor's signature: ……

Designation: …….. Date: ……....

I confirm that I have the necessary knowledge and skills to undertake this procedure independently.

I have been assessed as competent practitioner.

I will maintain my knowledge and skills in this area and if they lapse I will seek a period of re-training and assessment.

Learner's name: ……..……

Learner's signature: ……..….

Designation: …… Date: …….

14.8 Examples of Documentation for MMC and BCG instillation

BCG weekly instillations

BCG Instillation

Name: _____

Date of birth: _____

	WEEKLY INSTILLATION						
DATE							CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION
TREATMENT NUMBER	1	2	3	4	5	6	
SIGNATURE							
BLOOD TESTS							
NORMAL							
ABNORMAL – APPROVED BY PHYSICIAN							
URINE DIPSTICK							
NORMAL							
ABNORMAL – APPROVED BY PHYSICIAN							

- Remember to document the findings in the patient chart.
- See the local guideline about BCG instillation.
- Remember to hand out the patient information about BCG instillation.

A printable PDF of this form will be available on the EAUN website, page: Nursing guidelines

BCG every 4th week instillation

BCG Instillation

Name: _____

Date of birth: _____

	INSTILLATION EVERY 4TH WEEK												
DATE				CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION			CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION			CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION			CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION
TREATMENT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	
SIGNATURE													
BLOOD TESTS													
NORMAL													
ABNORMAL – APPROVED BY PHYSICIAN													
URINE DIPSTICK													
NORMAL													
ABNORMAL – APPROVED BY PHYSICIAN													

- Remember to document the findings in the patient chart.
- See the local guideline about BCG instillation.
- Remember to hand out the patient information about BCG instillation.

A printable PDF of this form will be available on the EAUN website, page: Nursing guidelines

MMC weekly instillations

Mitomycin Instillation

Name: _____

Date of birth: _____

	WEEKLY INSTILLATION								
DATE									CYSTOSCOPY 4 WEEKS AFTER LAST INSTILLATION
TREATMENT NUMBER	1	2	3	4	5	6	7	8	
SIGNATURE									
BLOOD TESTS									
NORMAL									
ABNORMAL – APPROVED BY PHYSICIAN									
URINE DIPSTICK									
NORMAL									
ABNORMAL – APPROVED BY PHYSICIAN									

- Remember to document the findings in the patient chart.
- See the local guideline about mitomycin instillation.
- Remember to hand out the patient information about mitomycin instillation.

A printable PDF of this form will be available on the EAUN website, page: Nursing guidelines (Forms adapted from forms used in a Danish hospital)

14.9 Example of Side effect questionnaire

Side-effect Questionnaire

European Association of Urology Nurses

Name: _____

ID: _____

Day of treatment: _____

Treatment nr: _____ Dwell-time: _____ minutes

1. How often did you have to void after treatment (frequency)?

- ☐ Normal
- ☐ More than normal
- ☐ Every other hour
- ☐ Once every hour
- ☐ Several times every hour

2. When were your voiding normally again?

- ☐ Normal all the time
- ☐ In six hours
- ☐ In twelve hours
- ☐ In twenty-four hours
- ☐ Two days later
- ☐ Three days later
- ☐ More than three days later

3. Chills?

- ☐ No
- ☐ Yes

4. Fever?

- ☐ No
- ☐ Yes Temperature: _____ °C

5. Nausea?

- ☐ No
- ☐ Yes

6. Dysuria?

- ☐ No
- ☐ Yes If yes, for how long?
  - ☐ About six hours
  - ☐ About twelve hours
  - ☐ About twenty-four hours
  - ☐ For two days
  - ☐ For three days
  - ☐ More than three days later

7. Haematuria?

- ☐ No
- ☐ Yes For how many days: _____

8. When were you back to normal after the treatment?

- ☐ After six hours
- ☐ After twelve hours
- ☐ After twenty-four hours
- ☐ After two days
- ☐ After three days
- ☐ After more than three days

9. Any other symtoms that you would like to discuss?

_____

_____

_____

_____

A printable PDF of this form will be available on the EAUN website, page: Nursing guidelines
(Adapted from a form used in the Sahlgrenska University Hospital in Sweden)

14.10 Example of Safety guidelines for cleaning and handling hazardous drugs

Instructions for cleaning spills of liquid hazardous waste

- For information about the hazards of the spilled drug, contact the area pharmacy or use the pharmacy-sponsored Micromedex web page.
- Whenever possible, spills of liquid hazardous drugs will be handled by employees in the area of the spill.
- Employees may call 911 to contact OESO for telephone advice or assistance cleaning up the spill. OESO will respond to large spills that are beyond the capacity of employees in the vicinity of the spill.

Equipment needed:

Chemotherapy/hazardous drug spill kit (available from Pharmacy Store Room at 22 22 2), including:

- Tyvek gown or coveralls
- Shoe covers
- Splash goggles
- 2 pairs chemotherapy tested disposable gloves
- Absorbent pads
- Scoop with detachable scraper for collecting glass fragments
- 2 5-gallon plastic waste disposal bags
- One Ziploc bag for returning contaminated splash goggles to pharmacy
- Hazardous drug waste labels

1. Alert nearby persons about the spill.
2. If the spilled drug got on anyone's skin, eyes, or clothing, see supplemental info information below (*).
3. Prevent risk of additional skin contact with the spilled drug.
4. Obtain chemotherapy/hazardous drugs spill kit.
5. Put on safety goggles and double gloves from kit. If spill involves more than 5 mL or covers more than one square foot (or, for smaller spills, at the discretion of the person cleaning the spill), put on Tyvek gown and shoe covers (or coveralls) from kit. Tuck sleeves into the outer gloves.
6. If there are broken glass fragments, use the detachable scraper to carefully "sweep" them or other sharps into the scoop. Place these sharps in a needle box.
7. Use the absorbent pads to gently cover and wipe up the spilled material. If additional absorbent material is needed, use plastic lined blue pads (chux) or other available materials. Place used absorbent in one of the clear 5-gallon bags from the spill kit.
8. Clean the area thoroughly with water. Disposable materials used in this step should go into the open bag from the spill kit.
9. Clean the area three times using a detergent solution, then rinse. (Housekeeping

can be called in for this step only.)

10. Place any contaminated hospital linens in a hospital laundry bag.
11. Place other (personal) contaminated clothing in a sealed plastic bag. If it will be laundered, double bag for transport, then wash twice before combining with other laundry. If it will be discarded, place it in the open bag from the spill kit.
12. Remove the shoe covers (if used) and outer pair of gloves. Place these into the open bag from the spill kit.
13. Remove the goggles and place them into the open bag from the spill kit. (Alternately, goggles may be washed and reused.)
14. Close the open waste bag (by knotting or using twist tie or tape), then place it into the second clear 5-gallon bag from the spill kit.
15. Remove the Tyvek gown (or coveralls) and inner gloves. Place these into the second bag from the spill kit. Close the outer bag.
16. Wash hands thoroughly.
17. **Read carefully for proper waste disposal** (Improper disposal can mean large fines):

Nursing & Medical Research : If the drug is listed below, determine a location where the bag can be left for a few days without being moved or thrown in the trash. Contact the Occupational and Environmental Safety Office (OESO) at 11 11 11 to arrange for waste pick-up. Be prepared to give the name of the drug, location of the waste bag, and the name and telephone number for a responsible person who will be available during business hours. Fill in the blanks on the "Hazardous Drug Waste" labels and put them on the bag, then put bag in location described to OESO.

<u>These are the drugs that must be treated as described above:</u>

- Chlorambucil (Leukeran)
- Cyclophosphamide (Cytoxin)
- Daunorubicin (Daunomycin, Cerubidine)
- Melphalan (Alkeran)
- Mitomycin (Mitomycin C, Mutamycin)
- Streptozocin (Zanosar, Streptozotocin)
- Uracil mustard (Uramustine, U-8344)
- Arsenic Trioxide
- Diethylstilbestrol

<u>If the drug is not on the above list</u>, put the knotted bag of spill waste directly into a biohazard container (WITHOUT labels).

18. Call the Pharmacy Store Room at 22 22 22 to obtain a replacement chemotherapy/ hazardous drug spill kit.
19. Nursing staff should bag and label any contaminated pumps and send to Pharmacy.
20. Follow reporting procedures in the supplemental info below(**).

SUPPLEMENTAL INFORMATION

For Employees Cleaning up Spills of Hazardous Drugs

***Obvious contamination of gloves, clothing, skin or eyes will be treated as follows:**

a. Remove contaminated gloves or clothing (if applicable).
b. Wash the affected skin area with soap (not germicidal cleaner) and lukewarm water. For eye exposure, immediately flush the affected eye with water or isotonic eyewash (or normal saline) for at least 15 minutes.
c. For direct skin or eye contact,

- Obtain medical attention as soon as possible. Employees should go to Employee Occupational Health and Wellness or the Emergency Dept.
- Fill out the appropriate incident report form and submit as follows:
- Employees who are exposed must fill out a Report of Work-Related Injury/Illness and send to Employee Health.

- If patient injury occurs, notify Pharmacy Quality Improvement (pager 111-1111) and Risk Management (pager 111-2222) immediately.
- If a visitor is exposed, notify Risk Management.

Inform the appropriate area manager.

****Reporting Requirements for ALL Incidents During Patient Treatment:**
Any drug spill during patient treatment should be documented in the Safety Reporting System.

About these instructions and when they should be used:
These instructions are provided with hazardous drugs spill kits so that, whenever possible, spills of LIQUID hazardous drugs can be handled by employees in the area of the spill. Hazardous drugs are those marked “Chemotherapy” or “Hazardous drug” by the pharmacy.

Additional Information:

- For information about the hazards of the spilled drug, contact the area pharmacy or use the Pharmacy-sponsored Micromedex web page. Ask for or look for a Material Safety Data Sheet (MSDS) on the drug.
- It is not necessary to report hazardous drug spills to the Occupational and Environmental Safety Office (OESO) unless hazardous waste pickup is required. However, employees may call 911 to contact OESO for telephone advice or assistance cleaning up the spill. **OESO will respond to large spills that are beyond the capacity of employees in the vicinity of the spill.** If you call 911, tell the dispatcher there is a hazardous drug spill and give a number where you or someone else in your work area can be reached. Please make sure someone is available to answer the telephone and talk with the Spill Responder from OESO.

Hazardous Drug Spill Training is Available through OESO’s Training Website

Adapted from a Safety guidelines document of the Occupational & Environmental Safety Office of Duke University, www.safety.duke.edu

14.11 PICO questions

According to the Centre for Evidence Based Medicine (CEBM), "one of the fundamental skills required for practising EBM is the asking of well-built clinical questions. To benefit patients and clinicians, such questions need to be both directly relevant to patients' problems and phrased in ways that direct your search to relevant and precise answers."

A well-built clinical foreground question should have 4 components. The PICO model is a helpful tool that assists you in organizing and focusing your foreground question into a searchable query. Dividing into the PICO elements helps identify search terms/concepts to use in your search of the literature.

- P = Patient, Problem, Population (How would you describe a group of patients similar to you? What are the most important characteristics of the patient?)
- I = Intervention, Prognostic Factor, Exposure (What main intervention are you considering? What do you want to do with this patient? What is the main alternative being considered?)
- C = Comparison (Can be None or placebo.) (What is the main alternative to compare with the intervention? Are you trying to decide between two drugs, a drug and no medication or placebo, or two diagnostic tests?)
- O= Outcome (What are you trying to accomplish, measure, improve or affect? Outcomes may be disease-oriented or patient-oriented.) [177]

The following questions were defined by the EAUN Working Group:

- PICO 1: Are there factors in nursing competence that predict untoward effects of bladder instillation therapy with mitomycin C or BCG (Bacillus Calmette-Guérin)?
- PICO 2: In bladder instillation treatment with mitomycin C or BCG, would the use of specific types or size of catheter or specific catheter material or lubricant have an influence on the safety of the patient?
- PICO 3: In bladder instillation treatment with mitomycin C or BCG, would the use of protective equipment compared to no protective equipment have an influence on the safety of nurses and patients?
- PICO 4: What is the effect of bladder instillation therapy in NMIBC (non-muscle invasive bladder cancer) patients with co-morbidities of the bladder (e.g., diabetes mellitus, neurogenic, atonic bladder or reduced bladder contractibility?)
- PICO 5: In patients with reduced ability to empty the bladder (e.g., people with diabetes or neurogenic, atonic bladder or low bladder contractibility) is there a difference in adverse effects after bladder instillation compared to people with no reduced ability to empty the bladder?
- PICO 6: Are there aspects related to the preparation of the bladder instillation medication (mitomycin C or BCG) that influence the safety of patients, cleaning personnel and health care worker?
- PICO 7: In patients with a reduced storage ability of the bladder would the intravesical administration of mitomycin C or BCG be less effective?
- PICO 8: Does patient positioning during dwell time of the bladder instillation therapy

with mitomycin C or BCG impact the outcome of the procedure or treatment

- PICO 9: What evidence is there that delay of treatment affects bladder cancer outcome or side effects (delay from TURB (TUR/TUR-BT) (Transurethral Resection of Bladder) to initiating bladder instillation treatment with mitomycin C or BCG) in NMIBC patients.
- PICO 10: Does the dwell time of the bladder instillation therapy with mitomycin C or BCG impact side effects or QoL or outcome of the bladder cancer treatment in NMIBC patients?
- PICO 11: In NMIBC patients, what is the effect of patient education and adherence on quality of life, bladder cancer outcome and side effects of bladder instillation therapy with mitomycin C or BCG?
- PICO 12: Do NMIBC patients treated with bladder instillation therapy with mitomycin C or BCG that receive patient education have a better adherence to the treatment?
- PICO 13: What are the adverse effects of not following instructions on the place of voiding after bladder instillation and other precautions taken on the safety of the patient and relatives?
- PICO 14: In patients treated with bladder instillation therapy (mitomycin C or BCG) for NMIBC will reducing the adverse effects of therapy influence adherence/compliance to/ with the treatment?
- PICO 15: In patients treated with bladder instillation therapy (mitomycin C or BCG) for NMIBC will reducing the adverse effects of therapy influence their quality of life?

15. About the authors

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Works as a Clinical Nurse Specialist, Urological Department, Rigshospitalet, University Hospital of Copenhagen, Denmark.

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Worked on and chaired the Evidence-based Committee for > 12 years and produced a significant portion of the Policy and Procedure Manual at the Center which is updated every 3 years. Significant guidelines she has written include:

- CAUTI (Catheter Associated Urinary Tract Infection) Prevention Guidelines
- Patient Education for the Care of a Continent Urinary Diversion
- Care of the Indwelling Foley Catheter
- Safe Handling of Intravesicle Cidofovir
- Intermittent Catheterization

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