PERCUTANEOUS BLEOMYCIN FOR SCLEROTHERAPY OF LOW-FLOW VASCULAR MALFORMATIONS

DRUG PROTOCOL©

DOCUMENT SUMMARY/KEY POINTS

- Clinical indications for use of percutaneous bleomycin in sclerotherapy
- Dosing guidelines
- Maximal lifetime cumulative dose of 300,000 international units
- Precautions for use including obtaining baseline chest radiography, monitoring total lifetime cumulative dosage, avoiding high-flow and high FIO_2 oxygen use, and avoiding adhesive tapes during anaesthesia.
- Patients treated with bleomycin should avoid smoking, activities requiring extra oxygen such as scuba diving, and notify their treating doctors prior to future general anaesthesia procedures.

CHANGE SUMMARY

- This is a new document

READ ACKNOWLEDGEMENT

- Medical, pharmacy, and nursing staff who care for patients being treated with percutaneous bleomycin are required to read and acknowledge the document.

Note: Separate Practice Guidelines may be required to cover all aspects of management.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st August 2024	**Review Period**: 3 years
Team Leader:	VMO – Interventional Radiologist	**Area/Dept**: Medical Imaging CHW

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Introduction / Background

Bleomycin is a non-ribosomal peptide that induces DNA strand breaks and inhibits DNA synthesis. It acts as an anti-biotic and an anti-neoplastic agent.

In Australia, we utilize the European pharmaceutical measurement (Ph. Eur.) which measures bleomycin in international units (IUs). 1000 IUs (Ph. Eur.) is equivalent to 1 U in USA pharmaceutical measurements (USP). It is routinely utilized in the treatment of squamous cell carcinoma, lymphoma, testicular carcinoma, and as intra-pleural therapy for malignant pleural effusion[1].

In lower doses, intra-lesional bleomycin is an effective and commonly used sclerosant agent for the treatment of low-flow vascular malformations (venous malformations[2] and lymphatic malformations[3]), inducing damage to the underlying vascular endothelium to causes fibrosis and reduction of the malformation.

Registered Use

As per the ARTG: Squamous cell carcinoma of the skin, head and neck, and oesophagus (primary indication), squamous cell carcinoma of the larynx, penis and uterine cervix, squamous cell carcinoma of the bronchus (response infrequent), choriocarcinoma and embryonal cell carcinoma of the testis, advanced Hodgkin's disease and other lymphomas and mycosis fungoides. The use of bleomycin in vascular anomalies is off-label.

Indications in treatment of paediatric vascular anomalies

Indications (off-label) for bleomycin use in paediatric vascular anomalies:

- Venous malformations: Percutaneous sclerotherapy
- Lymphatic malformations (macrocystic, microcystic, and mixed): Percutaneous sclerotherapy
- Veno-lymphatic malformations: Percutaneous sclerotherapy

Specific patient groups most likely to benefit

Patients undergoing percutaneous sclerotherapy with intra-lesional injection of sclerosant, for the treatment of low-flow vascular malformations (venous and lymphatic malformations) involving locations in which post-operative swelling should be minimized, including but not limited to:

- Adjacent to the airway
- Orbital and periorbital tissues
- Tongue
- Infratemporal and temporal fossae
- Lips and oral cavity, Nose, Submandibular and sublingual spaces
- Mediastinum
- Digits
- Involving or adjacent to the genitalia
- Axillae

Contraindications

- Prior anaphylactic reaction to bleomycin
- Known pulmonary restrictive lung disease, moderate to severe lung function impairment, or active lung infection
- Severe renal impairment
- Previous treatment of malignancy using bleomycin
- Patient age < 12 months is a relative (but not a total) contraindication for bleomycin sclerotherapy. Use of bleomycin for sclerotherapy should be delayed until after the age of 12 months where possible.

Precautions

- **Pulmonary fibrosis:**
  - The maximum safe lifelong cumulative dose of bleomycin is 300,000 international units, above which the patient is at progressive risk of developing bleomycin-induced pulmonary fibrosis[1]. This treatment complication is well reported in the management of malignancy using bleomycin.
  - Bleomycin-induced pulmonary fibrosis can result in a permanent reduction in lung function.
  - The typical doses used in treatment of malignancy are 10,000 – 15,000 international units per dose, once to twice per week[1].
  - The typical dosage used for percutaneous sclerotherapy of paediatric low-flow vascular malformations is 500 - 1000 international units/kg/session to a maximum of 15,000 international units/session[4]. However, typically doses of up to 5000 international units/session are utilized, administration is far less frequent, and the medication is administered into a focal malformation rather than directly into the systemic circulation. These lower doses and methods of administration are associated with a negligible risk of developing bleomycin-induced lung toxicity.
  - Two separate meta-analyses[5, 6] of studies using lower dose protocols as described above for the treatment of low-flow vascular malformations (n=1121[5] and n=1135[6] patients respectively), identified no cases of pulmonary fibrosis.
  - Based on extreme rarity of pulmonary fibrosis from bleomycin sclerotherapy at the low doses described above, routine baseline lung function testing with spirometry appears to have little role or benefit in this clinical scenario.
  - Baseline chest X-ray with regular monthly follow-up chest X-rays are routinely undertaken when using bleomycin in the treatment of malignancy[1].
  - **Baseline chest X-ray and repeat follow-up chest X-rays prior to each subsequent sclerotherapy session** are to be undertaken for any patients receiving bleomycin sclerotherapy for low-flow vascular malformations.

- No single predictive monitoring test for bleomycin-induced pulmonary toxicity has been identified[1]. Frequent physical examinations should be undertaken. Cough, basal rales, and pleuritic chest pain are frequent first signs of toxicity. Dyspnoea is usually the first symptom. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related.
- The cumulative lifetime dose of bleomycin received should be closely monitored and assessed by the prescribing doctor on PowerChart prior to any new doses being prescribed. The cumulative dose on eMR is accessible via PowerChart using the Discern Analytics 2.0 tab (see Appendix A).

- **Pneumonitis:**
  - Rare cases of severe acute/subacute pneumonitis have been described in children who received low doses of bleomycin for sclerotherapy[7-9].
  - Some cases have responded well to supportive ventilation and corticosteroid therapy[8, 9].
  - Treating teams should be aware of this rare but potential complication and early management should be instituted in suspected cases.
- **Oxygen therapy:**
  - The risk of pulmonary toxicity is increased in patients treated with bleomycin who receive high concentrations of oxygen, particularly over prolonged periods[1].
  - During anaesthesia and in post-procedure recovery, FIO_2 concentration should be maintained at approximately that of room air (21-25%).
- **Tape precautions:**
  - Hyperpigmentation and erythema are well described in patients receiving bleomycin therapy, particularly in skin regions in which adhesive tapes have been used[10].
  - Use of non-adhesive tapes and avoidance of adhesive dressings or adhesive ECG leads during anaesthesia, surgery, and aftercare is recommended.
  - These precautions should be discussed with parents and anaesthesia team members prior to commencing the procedure.
  - Parents, anaesthetic team staff, and nursing staff should be notified to avoid adhesive tapes and dressings for 7 days post-administration of bleomycin.
- **Infants**:
  - Patient age < 12 months is a relative (but not a total) contraindication for bleomycin sclerotherapy. Use of bleomycin for sclerotherapy should be delayed until after the age of 12 months where possible.
- **Long-term precautions:**
  - **Smoking**: Patients should avoid smoking if they have received bleomycin.
  - **High-oxygen activities**: Patient who receive bleomycin at doses used for chemotherapy in malignancy are advised to avoid activities in which there are high-oxygen use such as scuba diving. Whilst the lower doses used in sclerotherapy may

not warrant such an approach, patients and families should seek advice from a respiratory physician before undertaking scuba diving or similar activities.

- **General anaesthesia**: Patients and families should notify their treating doctors of their prior bleomycin treatment before undergoing general anaesthesia.

Presentation

- Bleomycin 15,000 international units vial power for injection OR
- Bleomycin 5000 international units in 5mL sodium chloride 0.9% Baxter prefilled syringe

Dose

- 500 – 1000 international units/kg/session, to a maximal dose of ≤ 15,000 international units[4].
- Maximum safe dose in a single session is 15,000 international units.
- Maximum safe cumulative lifetime dose of bleomycin is 300,000 international units[1].
- Treatment sessions should be separated by a minimum of 3-4 weeks[4].

Duration of treatment

- Most patients require multiple staged sclerotherapy procedures, separated by 4 - 12 week periods, over a duration of 12 - 18 months.
- Some patients may have intermittent procedures over several years
- Monitoring and recording of the cumulative bleomycin dose must be undertaken in the medical records

Authorised Prescribers

- Interventional radiologists and interventional neuroradiologists
- Paediatric surgeons or plastic surgeons involved in the care of paediatric vascular anomalies

Place in therapy in relation to alternatives

- Bleomycin, when used as a sclerosant via intra-lesional injection, causes significantly less swelling, pain, skin necrosis, and nerve injury then other sclerosant agents for low-flow vascular malformations including ethanol[11], sodium tetradecyl sulfate[6], and doxycycline.
- As a result, bleomycin is of greatest utility, compared to other sclerosant agents, when treating low-flow vascular malformation regions of the body in which swelling should be minimized (e.g. adjacent to the airway, orbit, tongue, lips, axillae, genitalia, digits).

Preparation and Administration

- Intra-lesional injection of dissolved bleomycin sulfate under imaging-guidance.
- Please refer to the Paediatric Injectable Medicines Handbook (PIMH) for details on medication preparation.
- At CHW and SCH please contact the Department of Pharmacy Sterile Suite giving 2 business days notice to organise either ordering of a pre-filled syringe or manufacture of the medication.
- All staff handling the syringe should wear impermeable gloves and eye protection, and utilize standard cytotoxic medication precautions for transport, handling, and disposal. Please refer to the SCHN Practice Guideline for '**Hazardous Medication: Administration and Handling**' via the ePolicy website of the SCHN intranet[12]:
- The contents of the syringe, up to the amount of the pre-planned dose, are to be administered via intra-lesional injection under imaging guidance by an interventional radiologist or paediatric surgeon with experience in the management of vascular anomalies.
- The dose of bleomycin is to be prescribed in PowerChart and visible in the MAR (Medication Administration Record). After administration, the proceduralist who administered the medication is to sign off the administration in the PowerChart MAR (with co-signature by a witness who is a medical doctor or registered nurse present during the procedure).
- The cumulative dose will be monitored in the eMR via PowerChart using the Discern Analytics 2.0 tab (see Appendix A). Prescribing doctors must assess the cumulative lifetime dose on PowerChart prior to prescribing any new doses.

Safety and Patient Monitoring

- **Baseline chest X-ray and repeat follow-up chest X-rays prior to each subsequent sclerotherapy session** are to be undertaken for any patients receiving bleomycin sclerotherapy for low-flow vascular malformations.
- Based on the extreme rarity of pulmonary fibrosis from bleomycin sclerotherapy at the low doses described above, routine baseline lung function testing with spirometry appears to have little role or benefit in this clinical scenario.
- The maximum safe lifelong cumulative dose of bleomycin is **300,000 international units**, above which the patient is at progressive risk of developing bleomycin-induced pulmonary fibrosis[1].
- No single predictive monitoring test for bleomycin-induced pulmonary toxicity has been identified[1]. Frequent physical examinations should be undertaken. Cough, basal rales, and pleuritic chest pain are frequent first signs of toxicity. Dyspnoea is usually the first symptom. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related.
- The cumulative lifetime dose of bleomycin received should be closely monitored and recorded in the patient's medical documentation.

- **Oxygen precautions:** During anaesthesia and in post-procedure recovery, FIO_2 concentration should be maintained at approximately that of room air (21-25%).
- **Tape precautions:** Use of non-adhesive tapes and avoidance of adhesive dressings or adhesive ECG leads during anaesthesia, surgery, and aftercare is recommended. Patients should be closely monitored for the development of hyperpigmentation under prior sites of tape administration or development of flagellate dermatitis. *Parents, anaesthetic team staff, and nursing staff should be notified to avoid adhesive tapes and dressings for 7 days post-administration of bleomycin.*
- **Pregnancy - Category D:** Bleomycin has caused, is suspected to have caused or may be expected to cause, an increase incidence of human foetal malformations or irreversible damage[1]. It may also have adverse pharmacological effects. Safe use of bleomycin in pregnant women has not been established. Patients of child-bearing age are required to have a pregnancy test prior to the commencement of the procedure. Such a pregnancy test is also required by the Department of Medical Imaging prior to any procedures involving the use of X-rays (including sclerotherapy). Sexually active patients will be counselled regarding the teratogenic effects of bleomycin during the informed consent process.
- **Lactation:** It is not known whether bleomycin is excreted in breast milk. Due to the potential for serious adverse effects in infants, it is recommended that breastfeeding is discontinued prior to administration of bleomycin sulfate to the mother[1].
- **Cytotoxic/hazardous agent handling precautions**:
  - Bleomycin is primarily excreted in the urine.
  - Serum levels are undetectable at 72 hours post administration when given intravenously[1].
  - With intra-lesional administration for sclerotherapy, there is evidence of systemic absorption and a terminal elimination half-life of 111.6 (+/- 37.75) minutes[13].
  - The SCHN Practice Guideline for '**Hazardous Medication – Administration and Handling**' should be followed at all times during preparation, transport, handling, administration, disposal, and for handling of patient waste[12].
  - As a general rule (as per the guideline above for Hazardous Medication), **a 7-day excretion protection period for hazardous agents should be observed**, This means, from the commencement of hazardous medication treatment staff should wear appropriate PPE when handling patient bodily fluids until 7 days post the last hazardous medication[12].

Adverse effects

- **Bleomycin-induced pulmonary fibrosis**, with a progressive increase in risk in patients receiving a cumulative lifetime dose greater than 300,000 international units. No cases of this serious complication have been described across two large meta-analyses of studies utilizing bleomycin at low doses for sclerotherapy of low-flow vascular malformations[5, 6].

- **Acute/subacute pneumonitis**
- **Skin:** Hyperpigmentation, flagellate dermatitis, urticaria, pruritis – particularly in regions affected by adhesive tapes or dressings.
- **Anaphylactic and anaphylactoid reactions**

Significant drug interactions

- **Cisplatin:** Cisplatin-induced renal function impairment may result in delayed clearance and bleomycin toxicity even at low doses. An increased incidence of bleomycin-induced pulmonary toxicity has been observed when these two agents are administered as part of an antineoplastic treatment regimen. Dosage reduction may be required.
- **Digoxin:** Serum levels of Digoxin may be reduced and its actions may be decreased. It is thought that drug-induced alterations of the intestinal mucosa may be involved in the reduced GI absorption.
- **Phenytoin:** Serum concentrations of phenytoin may be decreased due to decreased absorption or increased metabolism of Phenytoin.

Management of complications

- **Management of anaphylaxis:** Resuscitation equipment and medication should be readily available as anaphylactoid reactions have occurred. Stop injection immediately if severe anaphylactoid reaction or haemodynamic instability occurs and start treatment. Notify the medical officer urgently.
- **Acute/subacute pneumonitis:** Some cases have responded well to supportive ventilation and corticosteroid therapy[8, 9].
    - Treating teams should be aware of this rare but potential complication and early management should be instituted in suspected cases.
- **Pulmonary fibrosis:** No single predictive monitoring test for bleomycin-induced pulmonary toxicity has been identified[1]. Frequent physical examinations should be undertaken. Cough, basal rales, and pleuritic chest pain are frequent first signs of toxicity. Dyspnoea is usually the first symptom. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related.
- **Hyperpigmentation or flagellate dermatitis:** Dermatology team consultation is recommended for further advice.

Consent for administration of bleomycin

- Informed written consent for the percutaneous administration of bleomycin for the purposes of sclerotherapy will be obtained by the interventional radiologist or surgeon undertaking the procedure, with the patient and/or primary caregiver/guardian, as part of the consent process for the interventional procedure.
- This process will include a discussion of the nature and rationale for the procedure, the alternative sclerotherapy agents available (e.g. sodium tetradecyl sulfate, doxycycline), the advantages and disadvantages of each agent, and the potential complications of bleomycin use for sclerotherapy (as discussed above).
- The necessary safety precautions when utilizing bleomycin for sclerotherapy (discussed above) and the rationale for these precautions should be discussed.

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Appendix A: Monitoring cumulative lifetime dosage for bleomycin

- The cumulative lifetime dose of bleomycin administered must be assessed by the prescribing doctor prior to any new prescriptions of bleomycin, to ensure that the cumulative dose not exceed 300,000 international units.
- The cumulative dose can be assessed in the eMR via PowerChart using the Discern Analytics 2.0 tab.
- Following the opening of this module, double-click on the ‘Recent Reports’ folder.
- Then, double-click on the ‘Cytotoxic Cumulative Dose Report’ tab.
- Enter the patient’s medical record number (MRN) when requested.
- Then click on either the ‘ALL’ box for all cytotoxic medications or the ‘Bleomycin’ box for bleomycin only.
- Ensure that ‘Report’ is selected within the Output section.
- Then click the ‘Execute’ tab at the bottom of the page.
- A summary of the doses of bleomycin previously administered as well as the cumulative lifetime dose will appear on the screen.
- If the cumulative lifetime dose of bleomycin is approaching 300,000 international units (i.e. greater than 200,000 international units), do not prescribe any further doses of bleomycin but instead seek advice from the Oncology team.