Yorkshire Palliative Medicine Clinical Guidelines Group

Guidelines on the management of bleeding for palliative care patients with cancer

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Overall objective: To provide evidence-based guidance for the management of bleeding in cancer patients within specialist palliative care.

Search strategy: Medline, CINAHL and Embase databases were searched with the help of an experienced librarian using MESH terms for cancer, neoplasm, the generic and trade names for individual drugs and haemorrhage or site-specific areas for haemorrhage. Searches were limited to papers published in English relating to human adults up until March 2008. References obtained were hand searched for additional materials relevant to this review. Additional searches were also conducted for NICE and SIGN guidelines, Cochrane databases, Clinical Knowledge Summaries and publications from associated Royal Colleges. The bulletin board of palliativedrugs.com and palliative medicine textbooks were also reviewed for expert advice.

Level of evidence: Evidence regarding medications included in this review has been graded according to criteria described by Keeley [2003] on behalf of the SIGN research group (see appendix 4).

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Competing interests: None declared

Disclaimer: These guidelines are the property of the Yorkshire Palliative Medicine Clinical Guidelines Group and are intended for qualified, specialist palliative medicine professionals as an information resource. They should be used in the clinical context of each individual patient's needs and reference to appropriate prescribing texts / literature should also be made. The Clinical Guidelines Group takes no responsibility for any consequences of any actions taken as a result of using these guidelines.

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General principles of bleeding management

1.1 Introduction

Haemorrhage can be a highly distressing symptom for patients, carers and health professionals. It can present in a variety of ways, from occult bleeds causing anaemia over weeks to months, to overt external bleeding from particular anatomical sites, e.g. haemoptysis, haematuria etc. Estimates of the incidence of bleeding range between 6 and 14% of patients with advanced cancer (Periera et al 2000, Regnard & Makin), and is the immediate cause of death in around 6% of cases (Regnard & Makin).

Early recognition of patients thought to be at significant risk of bleeding can lead to effective treatment and future care planning.

1.2 Identification of patients at risk of haemorrhage

The increased risk of bleeding in cancer patients can be attributed to a number of causes:

1. Local infiltration of blood vessels by tumour

Bleeding may have been the patient's initial presenting symptom, with many patients continuing to show signs of haemorrhage throughout their illness. The risks of bleeding increase as tumours progress and metastasise, for example lung tumours over 10cm in diameter (whether primary or metastatic) are thought to carry a significant risk of haemorrhage unless treated (Oxford Textbook of Palliative Medicine p251). An increase in the frequency or severity of bleeds should lead to further investigation and management planning.

There may be anatomical or radiographic evidence of tumour in close proximity to a major blood vessel where direct infiltration can lead to a sudden bleed. Warning signs of visible pulsations in malignant wounds, or a sudden increase in pain should prompt a swift assessment of the patient.

2. Cancer treatments such as radiotherapy, chemotherapy or surgery

The myelosuppressive effects of chemotherapy and radiotherapy can result in thrombocytopenia and an increased bleeding tendency. In addition, newer agents such as Bevacizumab have direct effects on tumour angiogenesis, with recognised complications of bowel perforation and delayed healing after surgery (Electronic medicines compendium).

Local inflammation around surgery or radiotherapy sites also result in an increased risk of bleeding.

3. Systemic complications of cancer

The liver synthesises clotting factors, with vitamin K necessary in the production of factors II, VII, IX and X. Liver disease, biliary obstruction or bowel problems such as small bowel resection can lead to deficiencies in clotting factors and an increased bleeding tendency.

Some patients may have an underlying coagulopathy due to the illness itself e.g. hepatic involvement, or its treatment. Disseminated Intravascular Coagulation (DIC) is seen in many forms of cancer, with chronic (low grade) DIC often being asymptomatic. This condition can lead to acute DIC with both thrombotic and haemorrhagic symptoms. For further advice on the management of DIC, see appendix I.

Thrombocytopenia and platelet dysfunction is also commonly seen in haematological malignancies and other conditions such as thrombotic thrombocytopenic purpura due to cancer or chemotherapy.

4. Drug treatments such as anticoagulants or non-steroidal anti-inflammatory agents

There are many drugs that interfere with platelet function, and these are summarised in Appendix 3. Use of anticoagulants such as warfarin and low molecular weight heparin will also increase bleeding risk.

5. Concurrent illness, including infection

Local infection within tumour cavities can also increase the risk of bleeding. If infection is suspected antibiotic therapy should be considered in order to reduce this risk, and also help alleviate other symptoms of infection such as pain.

1.3 Most appropriate place of care

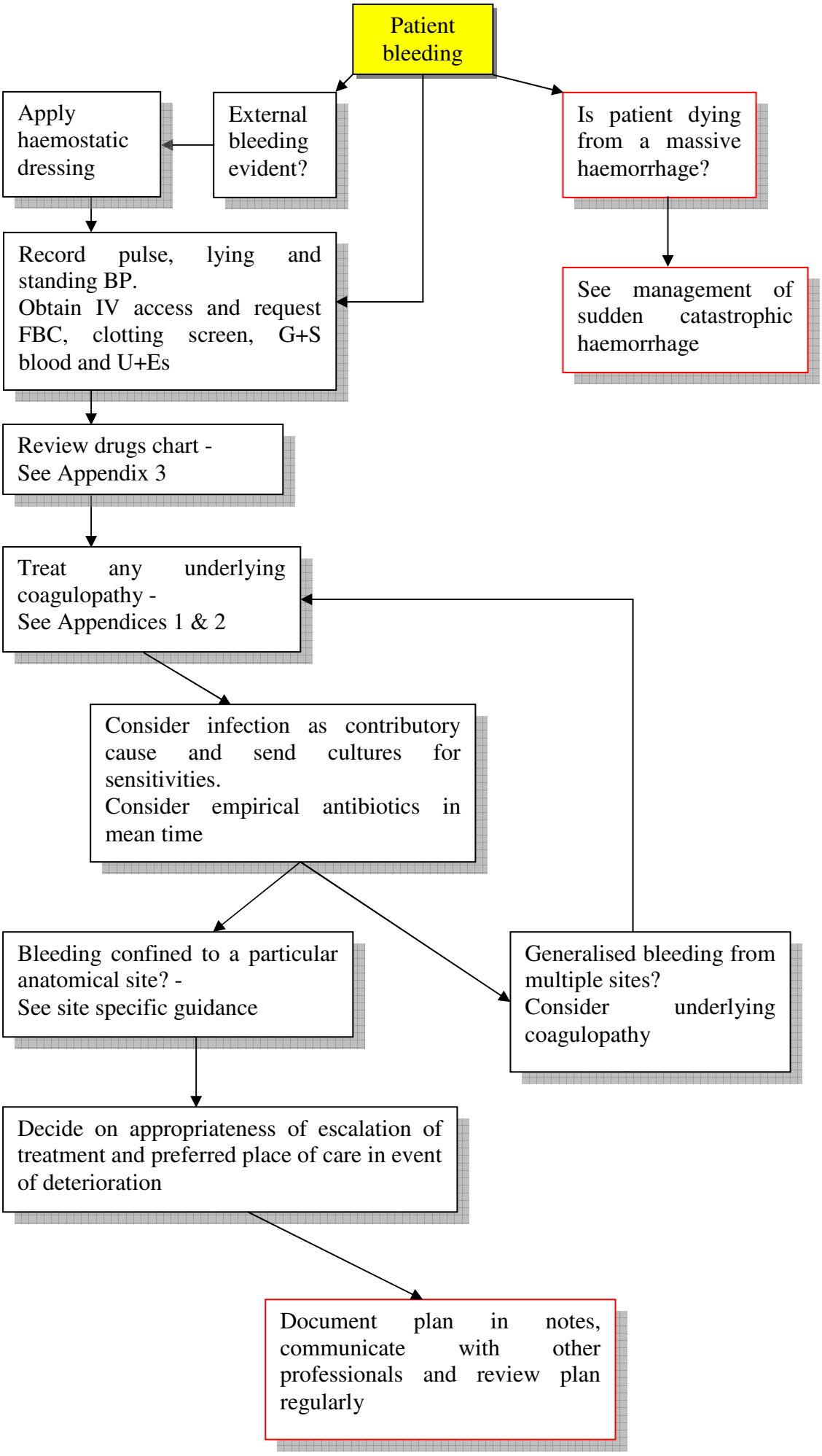
In the event of severe haemorrhage, or if the risk of a bleed is thought to be significant, a decision should be made regarding the most appropriate place of care for the patient. Depending on where the patient is, discussion may be needed to reach an informed decision about possible treatment options. Facilities for highly specialised interventions (e.g. specialist surgery, radiotherapy or interventional radiology) may not be available in smaller centres. Equally it may not be appropriate for patients at the end of life to be subjected to transfer to another site for interventions that may not confer significant survival benefit or add to their quality of life. Decisions regarding what is required to manage a patient's bleeding problem should be made at an early stage, so that clinical teams can act appropriately in the patient's best interests.

It may also be appropriate to discuss what should be done in the event of a cardiac arrest, and the decision regarding resuscitation status clearly documented in the patient's notes.

1.4 A general approach to the management of bleeding in cancer patients

The following steps are a suggested means of assessing a patient receiving palliative care who presents with bleeding. It should only be used as a guide and is not comprehensive. The treating team should seek expert advice if required and individualise treatment where appropriate.

1. Where is/are the site(s) of bleeding?
    a. For external bleeding: apply a dressing to reduce bleeding and protect the wound from trauma and infection. See section 3.7 on bleeding wounds for guidance on dressings.
2. How large is the bleed? Consider the following:
    a. Pulse, lying and standing BP (a postural blood pressure drop is often the first sign of blood loss)
    b. FBC, X-match/G+S, clotting, U+E (to check for dehydration, and a disproportionately high urea may suggest a gastrointestinal bleeding source). Consider securing IV access at this point.
    c. Fluid resuscitation to maintain blood pressure and vital organ perfusion. Indications may include a positive 'shock index' where the pulse rate (in beats per minute) is greater than the systolic blood pressure (in mmHg).
    d. For massive catastrophic haemorrhage, see section 4.1
3. Are there any reversible local or systemic causes?
    a. Review medications and consider stopping any drugs that adversely affect clotting (see appendix 3).
        - For patients on anticoagulant drugs for deep venous thrombosis (DVT) or a pulmonary embolus (PE), an overall assessment of likely risks versus benefit on continuing treatment needs to be made and ideally communicated with the patient.
    b. Where there appears to be bleeding from a number of different sites, consider an underlying coagulopathy and whether this should be corrected (may need to consult a local haematologist for advice).
    c. If infection is thought to precipitate haemorrhage, consider wound swabs and cultures for microbiological identification of pathogens and antimicrobial sensitivities
4. Are there any immediate local measures that can be used?
    a. See site specific guidance for management of local bleeding in section 3.
5. Decide on most appropriate place of care for the patient, both now and in the event of deterioration.
6. Regularly review the treatment plan and ensure that planned management is documented and communicated clearly to all staff involved in the patient's treatment.


Patient bleeding
External bleeding evident?
Apply haemostatic dressing
Is patient dying from a massive haemorrhage?
See management of sudden catastrophic haemorrhage
Record pulse, lying and standing BP.
Obtain IV access and request FBC, clotting screen, G+S blood and U+Es
Review drugs chart - See Appendix 3
Treat any underlying coagulopathy - See Appendices 1 & 2
Consider infection as contributory cause and send cultures for sensitivities.
Consider empirical antibiotics in mean time
Bleeding confined to a particular anatomical site? - See site specific guidance
Generalised bleeding from multiple sites? Consider underlying coagulopathy
Decide on appropriateness of escalation of treatment and preferred place of care in event of deterioration
Document plan in notes, communicate with other professionals and review plan regularly

Use of interventional services

2.1 Surgery

Removal of bleeding tissue or surgical ligation of vessels that supply it is a technique that has been used for many years. This is often technically difficult due to the abnormal anatomy of tumours, and has the associated risks of general anaesthesia in ill patients. Due to the invasive and risky nature of this technique, consideration of its use should be reserved for those patients at a very early stage of their disease, or who have exhausted other options such as pharmacological treatment, radiotherapy, and where vascular interventional radiology (see below) is not possible.

2.2 Radiotherapy

The use of external beam and internal radiotherapy in management of bleeding in cancer patients can be highly effective. Single fractions of external beam radiotherapy for haemoptysis can achieve control in 80% of patients, often with little planning time required. Other sites effectively controlled by radiotherapy include skin, vagina, rectum and bladder. (Please refer to site-specific guidance for further details). When treatment is with palliative intent, fractionation regimens are kept short in order to minimise disruption to the patient, and moderate doses are used to ensure that the burdens of treatment-related toxicity are outweighed by the potential benefits.

Limitations to this technique include anatomical site (some areas are less amenable to the side effects of radiotherapy), previous exposure to radiotherapy at the effected site and the proximity of radiotherapy services from the patient.

2.3 Vascular Radiology

The deliberate occlusion of arteries (embolisation) with either particles (e.g. polyvinyl alcohol), mechanical devices (e.g. coils) or liquids (e.g. glue, alcohol) can be used as palliative treatment to control haemorrhage, pain, reduce tumour bulk and lower hormone production in hormone-secreting tumours (Oxford Textbook of Palliative Medicine p283). Embolic therapy has been used to treat haemorrhage from a number of tumour sites throughout the body, often with excellent results. There are potential limiting factors to embolic treatment, such as the site and extent of tumour infiltration, inability to catheterise the tumour supply selectively, potential end organ damage, etc. These are often patient specific and will require discussion with the vascular interventional radiologist and patient.

Prior to considering treatment, any available cross-sectional imaging should be reviewed with a vascular interventional radiologist, with regard to the clinical problem being addressed. Pre-procedure laboratory investigations

include assessment of serum creatinine and clotting. Any coagulopathy should be corrected as the procedure is performed via an arterial puncture of the femoral, brachial or radial artery. The patient should be fasted for at least 4 hours but should remain well hydrated (with either clear oral fluids or, if necessary, intravenous fluids) to reduce the risk of contrast induced nephropathy and prevent the potential effects of tumour lysis. The patient should be able to lie flat for the procedure (1-2 hours).

There are potential risks and side-effects of embolisation. Puncture site related complications include bruising/haematoma, bleeding or vessel occlusion. Any embolisation procedure may be associated with the post-embolisation syndrome. This includes varying degrees of pain at the site of embolisation, nausea/vomiting and flu-like symptoms. These are related to tissue ischaemia/necrosis and may last for several days following embolisation. The patient should, therefore, have adequate peri- and post procedure analgesia, possibly via a patient controlled analgesia syringe (PCAS). Although not the primary aim of embolisation, there is the potential for critical ischaemia of organs at or adjacent to the site of treatment. In addition to the potential complications outlined above, there will be additional risks specifically related to the proposed site of embolisation.

Due to the often complex nature of the clinical problem, careful patient selection is important, and advice should be sought from a vascular interventional radiologist to weigh up the risks and benefits of any proposed intervention.

2.4 Endoscopy

Endoscopic treatment has proven to be effective in haemorrhage from the upper GI tract, lungs and bladder. Endoscopic procedures have also been used for bleeding from the lower GI tract, although this is more challenging (Periera, 2004). This approach has the added benefit of direct visualisation of the bleeding site, and the possibility of performing both diagnostic biopsies and therapeutic interventions. Bleeding sites may be injected, cauterised by heat or by laser coagulation.

For haemoptysis the bronchoscopist may perform ice-cold saline lavages, use balloon tamponade, laser phototherapy or apply topical thrombin or fibrinogen to the bleeding site. For haematuria the urologist may use cystoscopy when bladder irrigation has failed in order to inspect the bladder lining and treat any local haemorrhage.

Limitations to its use are local availability of these services, which are largely confined to hospitals and the ability of the patient to withstand the procedure, often with only light sedation (except in the case of cystoscopy).

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Site specific guidelines

Interventions for head and neck cancer-associated bleeding

General measures

For bleeding from superficial lesions affecting the scalp or skin of the head and neck, please refer to management of bleeding wounds in section 3.7

Many areas of the head and neck affected by cancer may be amenable to further chemotherapy or radiotherapy to reduce the size and vascularity of the tumour. As a result early consideration of these treatments in consultation with an oncologist is recommended.

Interventional radiology

There are various reports on the use in arterial embolisation to treat bleeding from head and neck cancer. Wong et al review a series of 17 patients with severe epistaxis due to nasopharyngeal cancer, all treated by arterial embolisation. Kim et al report 4 patients successfully treated with carotid artery stents to prevent sudden life threatening haemorrhage, and Del Pero reports a rare case of a vertebral artery aneurysm successfully treated by embolisation some 35 years after radiation therapy for a laryngeal cancer. All reports suggest a low incidence of side effects and complications. [all level 3]

Systemic treatment

Where the site of bleeding is not readily accessible to local therapies, systemic treatment should be used to reduce bleeding. Tranexamic acid is suggested to reduce bleeding by Dean and Tuffin in a series of patients, which included 2 patients with head and neck cancer [level 3].

Local treatment

a)Nasopharynx

In a Cochrane review on management of recurrent epistaxis in children, local cautery with a silver nitrate stick is recommended, despite this being painful at times [level 1++]. This is also suggested by the authors of the Oxford Handbook of Palliative Medicine [level 4] (Oxford Handbook Palliative Care (OHPC) p402).

De Lange et al conducted a prospective RCT looking at hypotensive anaesthesia with 2ml of 1% adrenaline packed into the nasal cavity, with or without 100ml cocaine, for management of Le Fort 1 osteotomies. Blood loss was significantly less in the cocaine treatment arm, with systemic absorption of cocaine reduced by adrenaline causing further local vasoconstriction. A survey by De at al of ENT surgeons in 2003 showed cocaine still being used in routine practice in nasal and sinus procedures by 61% of respondents. Eleven percent of respondents felt that they had experienced complications attributed to cocaine toxicity at some time, with CNS excitability, arrhythmias, tachycardia, and hypotension/hypertension. No death was thought to be directly attributable to cocaine toxicity, although it was not specified if this was used in combination with adrenaline [level 3].

Regnard suggests for anterior nasal bleeds, packing with a ribbon gauze soaked with 1% alum, or consideration of a bismuth/iodine pack kept in-situ for 3 days [level 4]. For posterior bleeds, referral to an ENT surgeon for direct packing under observation +/- diathermy is recommended [level 4].

Other suggestions are for nasal packing with calcium alginate rope (e.g. Kaltostat) or with a ribbon soaked in 1:1000 adrenaline (epinephrine) [level 4] (OHPC p402).

b)Oropharynx

Both Regnard and the Oxford Handbook of Palliative Medicine suggest using sucralfate suspension for bleeding from the oropharynx. Two grams of sucralfate suspension in 10ml is given BD as a mouthwash [level 4]. Also suggested is a solution of tranexamic mouthwash using 5g of injectable vials mixed with 50ml warm water and used BD (OHPC p403) [level 4]

Rowlands et al report the use of nebulised adrenaline in a patient with heavy oropharyngeal haemorrhage from a recurrent tonsillar cancer. Five millilitres of 1 in 1000 adrenaline was given in 5ml of 0.9% saline QDS for 5 days following fluid resuscitation. The bleeding stopped and the patient was discharged home 4 days later. This case series also included 2 patients with post tonsillectomy bleeds treated effectively this way when topical adrenaline soaked on gauze was not feasible. No side effects were reported, including cardiac toxicity or bronchospasm. [level 3]

Summary recommendations

Treatment in most care settings

1. For general bleeding from a number of anatomical sites, or where the bleeding site is not easily accessible to local therapy, consider use of oral tranexamic acid (1g TDS)
2. For bleeding from the nasopharynx
   - Use silver nitrate sticks for localised bleeding in accessible sites
   - Use haemostatic packing kept in site until bleeding controlled (usually a few days). If no commercial preparations kept locally use gauze soaked in 1% alum.
   - Cautious use of gauze soaked in 1:1000 adrenaline (beware of rebound bleeding once removed)
3. For bleeding in the oropharynx
   - Use tranexamic acid mouthwash (5g in 50ml warm water BD), or
   - Use sucralfate suspension mouthwash (2g/10ml suspension BD)
   - Consider topical 1 in 1000 adrenaline soaked on gauze for bleeding in localised and accessible sites
   - Consider nebulised adrenaline (5ml 1% adrenaline with 5ml 0.9% saline QDS) for bleeding in less accessible bleeding sites

Treatment in hospital

4. Seek advice from oncologist for possibility of further palliative chemo- or radiotherapy.
5. If service available, consider use of interventional radiology for (potential) bleeds from major blood vessels

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Haemoptysis

One third of patients with lung cancer experience haemoptysis and 3% suffer fatal bleeds, often without warning (Twycross R and Wilcock A, 2001). Death is generally due to suffocation and not exsanguination. Massive haemoptysis is most likely with squamous cell carcinoma, especially if it causes cavitation with necrosis of vessels within the tumour bed. Metastatic lung cancers can also bleed, most commonly with breast, colorectal, renal or melanoma primary tumours. Chest infection and pulmonary embolism may also present with haemoptysis in cancer patients.

Evidence

There is a paucity of evidence-based treatment recommendations for haemoptysis in the literature. A review article looking at evidenced-based clinical practice guidelines for palliative care in lung cancer did not mention any systemic interventions for haemoptysis (Kvale et al, 2007)

Anti-Fibrinolytic Agents:

i. Tranexamic acid

A pilot study evaluating the effect of tranexamic acid and the related anti-fibrinolytic agent aminocaproic acid included 3 patients with haemoptysis due to lung cancer (Dean A and Tuffin P, 1997). All 3 patients experienced cessation of bleeding within 1-4 days without any recurrence. Patients received tranexamic acid 1.5 mg initially, followed by 1g tds for a week after cessation of bleeding.

ii. Etamsylate (Ethamsylate)

Expert opinion advocates 500mg qds for haemoptysis (Twycross R and Wilcock A, 2001).

In conclusion, limited evidence regarding use of antifibrinolytic agents was identified. However, these drugs are worth a trial as anecdotal evidence supports their use and they are effective in reducing bleeding in cancer patients from other sites.

Corticosteroids

Anecdotal evidence supports the use of dexamethasone in the management of haemoptysis. Little evidence is available on route of administration, dose or length of course (Coucher et al, 1990) [Level of evidence 4]. Expert opinion advocates dexamethasone 2-4 mg (Twycross R and Wilcock A, 2001).

Nebulised Adrenaline

Expert opinion suggests using 1mg in 1ml of 1 in 1000 epinephrine diluted to 5ml in 0.9% N saline and nebulised up to four times a day (Twycross R and Wilcock A, 2001). [level 4]

Pressins

This group of drugs work as vasoconstrictors and are widely used in other types of bleeding e.g. oesophageal varices. One case series examined the use of parenteral **terlipressin** in 20 patients with severe haemoptysis. Dosing information was not described but the treatment was described as a 'total success' in 14/20 and a partial success (defined as 30% reduction in the initial haemoptysis) in a further 5/20 (Ramon et al, 1989).

A second group presented a case report of recurrent haemoptysis treated with aerosolised **ornipressin** at a dose of 5IU nebulised in 2ml of normal saline. They concluded it was a safe and effective method of treating mild to moderate haemoptysis (Anwar et al, 2002). The same group published a case series of three patients treated with nebulised **vasopressin** (Anwar et al, 2003) and a review paper (Anwar et al, 2005). In the first case, a 53 year old man with colon cancer with bone, liver and lung metastases had recurrent haemoptysis (50-100ml) and dyspnoea. He was treated with aerosolized vasopressin (five units [1ml] of ornithine-8-vasopressin in 1-2ml normal saline) and his haemoptysis stopped. Two days later he had recurrent haemoptysis which responded well to the same treatment. The second case was a 72 year old man with carcinoma of the tongue and hypopharynx and lung metastases. He was having haemoptyses consisting of approximately 30mls of fresh blood. One dose of vasopressin was effective at controlling his bleeding. However, he had two further episodes of haemoptysis within 2 days and was therefore given aerosolized vasopressin bd for four days with good effect. The third case was a 49 year old man with chondrosarcoma of the pelvic girdle and extensive lung metastases. He was having recurrent haemoptyses of 30-40ml. Aerosolized vasopressin tds controlled his haemoptysis [Level of evidence 3].

Recombinant Factor VIIa

Activated factor VIIa acts as a cofactor in the conversion of factor X to Xa in the final step of the intrinsic pathway of coagulation. Activated Xa converts prothrombin to thrombin and hence fibrinogen to fibrin to promote blood clotting.

Case reports detail the use of recombinant activated factor VIIa in pulmonary haemorrhage or haemoptysis [Level of Evidence 3]. In the most recent, a 25 yr old man with a relapsed extragonadal germ cell tumour was bleeding from pulmonary metastases 24 hours after administration of epirubicin and cisplatin. Platelets and coagulation were normal and treatment with oxygen, iv furosemide and iv tranexamic acid had failed to stop the bleeding. He was given factor VIIa at a dose of **100mcg/kg** iv and showed

improvement in arterial blood gases in 5 hours, was ambulant without oxygen the next day and was discharged 4 days later (Wheater MJ et al, 2008).

A second case was a 48 year old man with diffuse alveolar haemorrhage 1 month after allogenic stem cell transplantation. He was thrombocytopenic but had normal blood clotting. Treatment with corticosteroids, antibiotics, platelets and ventilation had failed to control the bleeding. Factor VIIa was give two hourly at a dose of **90mcg/kg iv** and after 2 doses the haemoptysis rapidly subsided (Pastores et al, 2003).

A third case was a 49 year old man with acute leukaemia with massive pulmonary haemorrhage due to suspected invasive aspergillosis. Platelet count was 8 x 10 9/L, with normal clotting and multiple platelet transfusions and tranexamic acid had earlier failed to control haemoptysis. He was given a single dose of **90mcg/kg factor VIIa** with platelet transfusions and the bleeding promptly stopped. Despite this, his conscious level deteriorated and he died 4 days later after a suspected intracerebral bleed (Maijer et al, 2000).

Although activated factor VIIa may have been useful in these very specific life-threatening scenarios, it is difficult to translate that into recommending use in our patient population. A single dose costs approximately £5000 and it can only be given intravenously under the recommendation of a Haematology Specialist.

INTERVENTIONAL TECHNIQUES

Radiotherapy

External beam radiotherapy has been shown to decrease haemoptysis caused by lung cancer, with control occurring in up to 80% of patients. A single fraction of 10Gy has been shown to be as effective as multiple fractions in this setting, which permits re-treatment if required (Pereira J and Phan T, 2004). **Brachytherapy** (endobronchial radiation), in which a fine catheter is placed at the tumour site during bronchoscopy and after-loaded by remote control with a radio-active source can also be helpful in haemoptysis. Success rates of >80% are quoted in the literature and the procedure can be carried out as a day case.

Diathermy or **cryotherapy** can be used for any endoscopically available site if they are available. However, cryotherapy requires a rigid bronchoscope and general anaesthetic to pass the liquid nitrogen probe and multiple treatments may be required.

LASER therapy requires rigid bronchoscopy and a general anaesthetic so is less appealing for a palliative patient group.

Haemoptysis is also amenable to **vascular embolisation**, provided the patient is stable enough to undergo such a procedure. Early referral to a vascular interventional radiologist is recommended (Kawaguchi T et al, 1996, Marshall and Jackson, 1997).

Summary recommendations

Treatment in most care settings

Try to rule out a pulmonary embolism (PE) before embarking on the following:
1. Oral tranexamic acid (1g TDS) and/or etamsylate (500mg QDS)
2. Consider oral steroids (2-4mg dexamethasone OD)
3. Consider nebulised adrenaline (1ml of 1 in 1000 adrenaline with 4ml 0.9% saline QDS)
4. Consider nebulised orlipressin / vasopressin (5IU in 2ml 0.9% saline prn)

Hospital Setting

1. Refer for radiotherapy or brachytherapy
2. Consider embolisation or bronchoscopy
3.Consider use of recombinant factor VIIa (need to liaise with a haematologist)

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Upper Gastrointestinal bleeding

Introduction

Upper gastrointestinal (GI) haemorrhage is a life threatening emergency with a mortality rate of approximately 7%. However, there is a lack of evidence about the frequency of symptomatic GI bleeding in patients with advanced cancer. An Italian group carried out a longitudinal study to assess frequency of and risk factors for GI bleeding in patients with advanced cancer (Mercadante et al 2000). Of 800 consecutive patients who were referred to a home palliative care programme over a 2 year period, 2.25% had GI bleeding. This was significantly higher than in the general population where the incidence of hospitalisation with acute GI bleeding was 1 per 1000 (0.01%). Patients with liver cancer and hepatic metastasis represented a group at higher risk of GI bleeding and use of non-steroidal anti-inflammatory drugs and steroids were also associated with bleeding. This survey also indicated that GI bleeding in patients with a poor performance status was associated with a poor prognosis. [Level of evidence 3]

Causes of GI Bleeding in Palliative Care Patients

Systemic

- coagulopathy

Local

- Infection
  - candidiasis
  - H.pylori
- Ulceration
  - stress ulcers
  - drug induced - NSAIDS, steroids, SSRIs
  - alcohol
  - radiotherapy / chemotherapy
- Variceal Haemorrhage / portal hypertensive gastropathy
  - portal hypertension
    - cirrhosis
    - liver / porta hepatis infiltration by tumour
    - portal vein obstruction / thrombosis
- Tumour bleeding
- Other

Severity of Haemorrhage in Upper GI bleeding

It can be difficult to assess the magnitude and risk of death to the patient of an episode of GI bleeding. One scale used in the acute setting is the Rockall Score which gives a percentage risk of mortality (see table).

Table 2 The Rockall scoring system[1]

Variable	Score 0	Score 1	Score 2	Score 3
Age (years)	<60	60–79	>80	–
Shock	None	Pulse >100 beats/min; normal blood pressure	Pulse >100 beats/min; systolic blood pressure <100 mm Hg	–
Co-morbidity	None	–	Cardiac; gastrointestinal cancer; other major co-morbidity	Renal failure; liver failure; disseminated malignancy
Diagnosis	Mallory-Weiss tear; no lesion, no SRH	All other diagnoses	Malignancy of the upper gastrointestinal tract	–
Major SRH	None or dark spots	–	Blood in the upper gastrointestinal tract, adherent blood clot, visible or spurting vessel	–

SRH, stigmata of recent haemorrhage.

Table 3 Rockall score, re-bleeding, and mortality[1]

Risk score	No	% Re-bleed	% Mortality
0	144	5	0
1	281	3	0
2	337	5	0.2
3	444	11	3
4	528	14	5
5	455	24	11
6	312	33	17
7	267	44	27
>8	190	42	41

Treatment of Haematemesis in Palliative Care

Non-interventional Measures

1. Gastric acid lowering drugs: PPIs
   H2 Receptor antagonists
2. Sucralfate
3. Octreotide
4. Pressins
5. Tranexamic Acid / Epsilon Aminocaproic Acid
6. Etamsylate
7. Thalidomide
8. Drugs that affect the clotting cascade: Thrombin
   Vitamin K
   Recombinant Factor VII
9. Systemic steroids

Interventional Measures

- Radiotherapy
- Radiology
    - Ultrasound-guided radiofrequency ablation
    - Embolisation
    - Intra-arterial steroid injection
- TIPSS - Trans-jugular Intrahepatic Portal-Systemic Shunt (if portal hypertension)
- endoscopic
    - laser
    - clip
    - banding of varices
    - radiofrequency ablation
    - injection of
        - adrenaline
        - thrombin
        - gelatin
        - acrylate
        - terlipressin
        - ethanol
- cryotherapy

The focus of these guidelines will be on the evidence for non-interventional management of GI bleeding. For some general guidelines on referring for radiotherapy or embolisation, please see chapter 2.

Evidence for Non-Interventional Measures

1. Gastric Acid Lowering Drugs: Proton Pump Inhibitors and H2 Receptor Antagonists

The stability of a blood clot is low in an acid environment. Acid suppressing drugs therefore have the potential to optimise clot formation and reduce the risk of re-bleeding. It is crucial that the pH does not fall below 6 and this can only be practically achieved by continuous Proton Pump Inhibitor (PPI) infusion.

A systematic review of 4 Randomised Controlled Trials (RCTs) (total n=1512) of **PPI** (oral or iv) vs **H2 receptor antagonist** or placebo in patients with **acute haemorrhage of unknown aetiology** (prior to endoscopy) found **NO** difference in mortality / rebleed rate / need for surgery (Dorwood et al, 2006). The only significant difference was in stigmata of recent bleed at endoscopy: 20/110 (18%) pts on PPI had stigmata vs 41/112 (36%) on placebo (p=0.003). This Cochrane review included a study using omeprazole 80mg stat IV, then 40mg IV TDS for 24hrs, then 40mg BD orally for up to 3 days (Daneshmend et al). [Level of Evidence 1]

A double-blind RCT was subsequently carried out looking at **pantoprazole** vs **ranitidine** for **prevention of ulcer rebleeding** (Jenson et al, 2006). 150 patients were randomised to either pantoprazole (80mg IV plus 8mg/hr x 72hrs) or ranitidine (50mg IV plus 6.25mg/hr x 72 hrs). This trial was stopped early because of slow recruitment but showed an arithmetic, but not significant difference in ulcer rebleeding. [Level of Evidence 2]

A further systematic review of 24 RCTs looked at **PPIs** vs control (some = placebo, some = **H2 antagonist**) in **acute peptic ulcer bleeding** (Leontiadis et al, 2006). Of 4373 patients with active peptic ulcer bleeding, PPI treatment was found to reduce rebleeding (odds ratio 0.49, 95%CI= 0.37-0.65) and surgery (odds ratio 0.61, 95%CI =0.48-0.78), but not all cause mortality. [Level of Evidence 1]

A smaller study (n = 143) compared the effectiveness of **rabeprazole** vs **cimetidine** at **preventing bleeding from an ulcer created by endoscopic submucosal dissection of early gastric cancer** (Uedo et al, 2007). Prophylactic treatment was started the day before the procedure and continued for 8 weeks after. Patients were given either rabeprazole 20 mg orally or cimetidine 800mg orally before the procedure, then intravenously for 2 days, then orally again. PPI treatment was found to prevent bleeding more effectively than H2 antagonists. Size of the main tumour and a scar in the tumour were independent predictors for bleeding. [Level of evidence 2]

A further small RCT (n= 144) compared the H2 antagonist **cimetidine** and **sucralfate** in the **prophylaxis of gastrointestinal tract bleeding** in patients admitted to a general hospital ward (Grau et al, 1993). Patients with respiratory failure, heart failure, sepsis, stroke (haemorrhagic or thrombotic), liver failure, renal insufficiency, treated with steroids or anticoagulated were all included. Those with a history of or evidence of treatment for upper GI symptoms were excluded. The patients were randomised to receive either cimetidine 800mg at night or sucralfate solution 1G every 6 hours and were examined daily for evidence of GI bleeding (stools were examined for occult blood loss). Gastrointestinal bleeding was found to occur in the same proportion in both groups (approx 3 %). In a previous inpatient study this group had shown that the rate of GI bleeding in untreated inpatients was 25%. [Level of evidence 2-]

A small RCT (n = 90) looked at the effect of **oral antacid** treatment in patients with **acute upper gastrointestinal haemorrhage** (Kittang et al, 1982). Patients received 20mls of 'balanced' antacid or placebo every 2 hours (while they were awake) for 7 days. They underwent endoscopy on the day of admission and on day 7. Patients with oesophageal varices, gastric cancer , Mallory-Weiss tears, or where bleeding source could not be identified, were excluded. Those anticoagulated or on H2 antagonists were also excluded. The incidence of continuous bleeding or rebleeding in the two groups was not significantly different. [Level of evidence 2]

Conclusion

There is some evidence supporting the use of PPIs and H2 antagonists in reducing rebleeding and the need for surgery in patients with peptic ulceration as a cause of upper GI bleeding. However, PPIs do not appear to have any impact on mortality in this setting. There is no evidence regarding the efficacy of gastric acid suppressing drugs in reducing bleeding in patients with a GI malignancy. However, the population of patients receiving palliative care has multiple risk factors for peptic ulceration and patients with upper gastrointestinal bleeding should therefore be treated with a proton pump inhibitor.

2. Sucralfate

A double-blind RCT (n = 168) compared **antacid** and **sucralfate suspension** for acute **upper gastro-intestinal haemorrhage** (Charoenwat, 1996). They included patients presenting with acute upper GI haemorrhage due to gastric ulcer, duodenal ulcer or gastritis (all pts had endoscopy to determine cause of bleeding in the first 24 hours). Patients with coagulopathy or cancer as direct source of bleeding were excluded. Participants were given sucralfate solution 2g vs Aluminium/Magnesium solution 30ml 2 hourly via nasogastric tube. At endoscopy 72 hours after admission, 10.7% of patients receiving sucralfate vs 17.9% receiving antacid had stigmata of recent bleeding (p=0.05). This study did not assess drop in haemoglobin, mortality or operation rates.
[Level of Evidence 2-]

A Case report of a 78 year old woman with duodenal adenocarcinoma found symptomatic benefit using a combination of oral **famotidine 20mg nocte** and **sucralfate 1g BD** (Gonzales RF et al, 1998). The patient had complained of early satiety, nausea, anorexia, abdominal pain and fatigue and had a haemoglobin of 7.9 g/dl, despite ferrous sulphate tds. All symptoms except fatigue resolved and her haemoglobin level rose to 10.1 g/dl over 5 months without transfusion. [Level of Evidence 3]

Another case report of an 83 year old woman with inoperable gastric carcinoma who had anaemia, haematemasis and melaena found benefit from using **sucralfate 2g BD** orally (Regnard et al, 1990). The patient had required 10 units of packed cells in the two months between diagnosis and starting sucralfate, and only 3 units following commencement of sucralfate. Her bleeding was stable enough to enable transfer to a nursing home for continuing care. [Level of Evidence 3]

In conclusion, there is limited evidence to support the use of sucralfate in GI haemorrhage.

3. Somatostatin and Octreotide

Somatostatin and its analogue octreotide are theoretically attractive because they reduce mesenteric (splanchnic) arterial flow and suppress gastric acid and pepsin secretion (Sanaki et al, 2005). They also suppress angiogenesis and activate platelet aggregation in vitro. Possible side effects include hypoglycaemia, thrombocytopenia, heart block and severe liver failure in those with cirrhosis and heart failure.

A meta-analysis, including data on 1829 patients from 14 trails, compared **somatostatin** (or octreotide in 2 of the trials) with **H2 antagonists** and placebo in the management of **acute non-variceal upper gastrointestinal haemorrhage** (Imperiale, 1997). Bleeding from cancer was an exclusion criteria in most of the studies included in the analysis. The relative risk for continued bleeding or rebleeding was 0.53 in favour of somatostatin. Number needed to treat was quoted as 5. This suggests that somatostatin (or octreotide) significantly reduces the risk for continued bleeding and the need for surgery, but these results were obtained from heterogenous studies. When stratified for the underlying cause of bleeding, the effectiveness of somatostatin was limited to **peptic ulcer bleeding**, although a trend for non peptic ulcer causes of bleeding was shown.

The 2 trials involving octreotide had divergent conclusions (Masaki, 2005 and Lamb, 2005). An investigator-blinded study concluded that octreotide had no effect on any outcome related to upper GI bleeding, whereas a non-investigator-blinded study concluded that octreotide stopped peptic ulcer haemorrhage and decreased transfusion requirement, need for aggressive management and length of stay in hospital. [Level of evidence 1-]

A double blind RCT (n = 630) looked at **somatostatin** in the treatment of **haematemesis and melaena** (Somerville et al, 1985). Patients in the treatment arm received an initial bolus of 250 micrograms, followed by a 72 hour infusion providing 250 micrograms of somatostatin per hour. There was a non-significant reduction of rebleeding in the somatostatin treated group. [Level of evidence 2 +]

A single case report quotes the use of **octreotide** in the palliative treatment of a 66 yr old man with unresectable gastric adenocarcinoma (Sanaki et al, 2005). He had continued to bleed despite IV omeprazole and blood transfusion and was greatly bothered by passing melaena stools. He refused endoscopy and surgical intervention, so was given a trail of intravenous octreotide (100microgram bolus followed by continuous infusion of 25 micrograms per hour). Melaena resolved within 2 days of starting treatment, but recurred 2 days after stopping octreotide (one day after resuming eating) [Level of evidence 3]

Another case report used **octreotide** as an adjunct to embolisation in the management of recurrent bleeding from upper gastrointestinal metastases (Lamb et al, 2005). A 69 year old man with metastatic renal cell carcinoma presented with a massive GI bleed. OGD and angiography confirmed metastasis on the posterior gastric wall which was embolised. Despite this, he

went on to have 10 further episodes of severe upper GI bleeding in 18 months, despite lansoprazole 30mg BD and five further embolisation procedures. He was given octreotide 50mg SC BD and in the next 23 months before death, had only one further episode of bleeding which settled spontaneously without needing transfusion. [Level of Evidence 3]
A further case report looked at a **somatostatin analogue** in occult gastrointestinal bleeding (Tamaggno et al, 2004). An 84 year old man with GI bleeding and anaemia of undiagnosed aetiology needed repeated transfusions despite tranexamic acid and a PPI. He was given "long acting octreotide" 10mg IM 4-weekly**.** After this, he had no further bleeding and a stable haemoglobin level until the somatostatin analogue was stopped after the 3rd injection. Consequently, he restarted the long acting octreotide and had no further bleeding and a stable haemoglobin level for the 6 months of follow up. [Level of Evidence 3]

A Cochrane review of 21 trials (2588 patients) of **somatostatin/analogue** vs placebo in patients with **acute or recent bleeding from oesophageal varices** found **no** significant reduction in mortality (Gotzshe et al 2005). The only significant finding was that the need for blood transfusion corresponded to half a unit of blood saved per patient in the treatment group.
[Level of Evidence 1]

In conclusion, there is weak evidence supporting the use of somatostatin or octreotide in upper gastrointestinal haemorrhage. The main evidence for benefit is again when bleeding is due to peptic ulcer disease. There is some evidence in case reports of the successful use of octreotide in palliative care patients, where more invasive interventions are not appropriate.

4. Pressins

Hypovolaemic shock can be resistant to fluid resuscitation because ischaemic reperfusion leads to accumulation of vasodilatory metabolites which may also be resistant to catecholamines (hypovolaemic shock results in acidosis which inactivates catecholamines). There may be vasopressin (ADH) deficiency in hypovolaemic shock, so treating with vasopressin causes fluid retention in the kidney and thus vasoconstriction (Sharma and Setlur, 2005).
Pressins work in variceal bleeding because they cause systemic vasoconstriction which increases blood pressure and they also reduce portal vein flow/pressure due to splanchnic arteriolar constriction (Soderland et al, 1987). Side effects include colic, loose/frequent stools, nausea (common) and worsening liver function in cirrhotic patients (due to reduced perfusion).
They can also cause ischaemia, leading to claudication, portal thrombosis, or rarely gangrene. Long term peripheral IV administration of vasopressin can cause tissue necrosis.

A Cochrane meta-analysis of 20 studies (n = 1609) using **terlipressin** for **acute oesophageal variceal haemorrhage** (Ioannou et al 2003) showed a statistically significant reduction in all cause mortality compared with placebo (RR = 0.66, 95% confidence intervals 0.49-0.88). There was no

statistical difference in outcomes between terlipressin and somatostatin or terlipressin and endoscopic treatment. No significant difference was found between terlipressin and any of the comparison groups in the number of adverse events that caused death or withdrawal of medication. [Level of Evidence 1]

A case series (Sharma and Setlur, 2005) looked at the use of **Vasopressin** in **haemorrhagic shock in 2 cancer patients**. The first was a 61 year old lady with peri-ampullary carcinoma who sustained an intra-operative laceration of the portal vein which resulted in hypotension resistant to fluid resuscitation to a CVP of 14 and norepinephrine. She improved with an infusion of vasopressin and dobutamine. The second patient was a 53 year old man with gastric carcinoma who was had 2 litres of haematemasis on day 7 post- operatively. He was resuscitated after cardiac arrest with blood transfusion, fluids, epinephrine and dobutamine infusions but remained hypotensive. His blood pressure finally responded to vasopressin. Both cases received vasopressin at a dose of 0.04 Units/minute. [Level of Evidence 3]

A case report detailed the use of IV **vasopressin** at home to control GI bleeding (Davis et al, 1997). A 51 year old man with uncontrolled upper GI bleeding due to metastases from leiomyosarcoma had been maintained on IV vasopressin via central venous catheter in ITU, but wanted to go home. The patient was given a GTN patch to prevent angina and his haemoglobin improved from 6.7g/dL to 9.5g/dL over the 100 days he was treated at home. He did not require transfusion and had no further major haemorrhage in that time. [Level of Evidence 3]

In conclusion, case report evidence supports the use of vasopressin in upper GI bleeding in cancer patients, but the best evidence supports its use in variceal bleeding. Its use is limited in the palliative setting by the need for iv administration and potentially serious side effects.

5. Tranexamic Acid

The Cochrane Library has a protocol for “Tranexamic Acid for upper gastrointestinal bleeding” but no review to date.

An RCT (n=775) of all patients admitted with **upper GI bleeding** (haematemasis, melaena or both), compared placebo vs **cimetidine** 400mg vs **tranexamic acid 1g** (Barer et al, 1983). All patients had upper GI endoscopy within 24 hrs after randomisation and treatments were all given iv qds for 48hrs and then orally for 5 days. Results were analysed on both an intention to treat basis and after exclusion of 99 patients with wrong diagnosis, more pressing medical problems, needing immediate surgery, cancer and varices. Tranexamic acid resulted in clinically and statistically significant reduction in mortality, but no statistically significant change in re-bleeding or operation rate overall. [Level of Evidence 1] See table below.

	Absolute mortality (%)	
	Intention to treat	After exclusions
Placebo	13.5	11
Cimetidine	7.7	8
Tranexamic acid	6.3 (p=0.0092)	4

A small RCT (n = 43) compared placebo (n=22) vs **tranexamic acid** (n=21) 2g via naso-gastric tube for 48 hrs in patients presenting with **haematemasis/melaena and shock** (Berggvist D, 1980). No difference was found in transfusion or operation frequency but mortality was found to be lower in the treatment group (12.3 vs 22.7) but no p values reported.
[Level of Evidence 2-]

An early RCT compared **tranexamic acid** (1g IV +1g oral TDS for 48hrs, then 1g oral for 72hrs) against placebo in reducing upper GI haemorrhage (Biggs et al, 1976). Tranexamic acid reduced operation rate and transfusion at days 4-6 and non-significantly reduced mortality. [Level of Evidence 2-]. See table below

	N	Operation rate (%)	Transfusion rate days 1-3	Transfusion rate days 4-6	Mortality (%)
Tranexamic Acid	103	7	no difference	tranexamic acid group lower; exact figures not given	2
No tranexamic acid	97	21			4
p value		not provided		<0.05	>0.05

A letter describing another early RCT (n=150) comparing **tranexamic acid** (1.5g TDS orally) and placebo in patients admitted with **upper GI tract bleeding** (excluding "those with conditions known to be fatal") found a significant response in reducing the need for blood transfusion (Cormack F et al, 1973). The authors also found that treatment was unlikely to fail if a barium meal carried out in the treatment group before hospital discharge was negative. Urine was checked in 10 patients to ensure tranexamic acid was absorbed orally in the presence of an upper GI bleed. A value of 57% oral bioavailability was obtained. [Level of Evidence 2+] See table below.

	N	Initial blood transfusion (%)	Repeat transfusion (%)	repeat Tfx after excluding bleeding from oesophageal varices and hiatus hernias(%)	Treatment failure if subsequent Ba meal negative (%)	Death (%)
Tranexamic Acid	**76**	49	20	11	0	4
Placebo	**74**	50	27	27	23	4
p value			>0.05	<0.05	<0.05	

Another early RCT (n=149) compared **tranexamic acid** (n=76) (1g IV for ≤3/7 then 1.5g o QDS for ≥4/7) and placebo (n= 73) in patients admitted with **haematemasis/melaena and hypovolaemic shock** requiring ITU admission (Enggvist A et al, 1979). There was a trend towards less need for surgery with tranexamic acid but this was not statistically significant. [Level of Evidence 2] See table below.

	surgery (%)	**death (%)**	**blood transfusion**	**Complications**
Tranexamic acid	13	14	overall no significant difference	2 post-op PEs, 2 pre-op MIs
Placebo	25	16		2 cerebral infarcts (one pre- /one post-op)
p value	>0.05			

More recently, a pilot study in 20 consecutive **dialysis patients with major upper GI bleeds** (36 episodes of bleeding) compared **tranexamic acid** and placebo (Sabovic et al, 2003). Endoscopy was performed in all cases and sclerotherapy carried out where possible. The treating physician decided whether or not to give tranexamic acid in a particular episode (initial dose of 20mg tranexamic acid IV then 10mg/kg/48hrs orally for 4 weeks with dose adjustment for renal function). The patients underwent heparin-free dialysis for the 1st week, then low-heparin dialysis for 2 weeks. All patients had PPI and antacids for ≥1 month. Tranexamic acid significantly reduced early and late rebleeding, need for repeated endoscopy and requirement for blood transfusion in this patient group. [Level of Evidence 1] See table below.

	n=	**Early re-bleeding**	**Early and late rebleeding**	**Repeated endoscopic procedures**	**Units of blood transfused**
Tranexamic Acid	16	0	1	1	1.37 +/- 1.31
No tranexamic acid	20	6	8	8	2.65 +/- 1.53
p value		0.02	0.02	0.02	0.01

Finally, a RCT (n=154) compared **tranexamic acid** (1g 4 hrly x 3 days then 1.5g 6hrly x 3 days) and placebo in patients with **gastric and duodenal bleeding** at endoscopy (Von-Holstein CC, 1987). All patients also received antacid 2 hourly via nasogastric tube and they also received cimetidine or ranitidine if they had a peptic ulcer. Patients with gastric cancer and renal failure were excluded. Tranexamic acid significantly reduced the need for blood transfusion and emergency surgery. [Level of Evidence 1] See below.

	N	**Units blood transfused (%)**					**Rebleeding (%)**	**Emergency surgery (%)**	**Death (%)**	**Complications (%)**
		0	**1-2**	**3-4**	**5-6**	**>6**				
Placebo	**82**	34	18	17	12	18	26	18	5	0
Tranexamic Acid	**72**	34	26	28	6	6	14	4	3	DVT = 1 Superficial thrombophlebitis=3
P value	**-**	**0.018**					0.097	**0.01**		

Conclusion

Tranexamic acid appears to be effective in reducing rebleeding, need for repeat endoscopy and blood transfusion in patients with acute upper GI bleeding. However, many of the above studies excluded patients with cancer as a cause of bleeding, so efficacy in the palliative setting is not known.

EPSILON AMINOCAPROIC ACID (EACA)

A retrospective case series (n = 77)/ regression analysis looked at transfusion requirement in patients prescribed EACA for thrombocytopenic haemorrhage, defined as platelets < 75 (Kalmadi et al, 2006). EACA was started in a dose of 4g/day and could be titrated according to response over 8 days. A complete response was defined as cessation of all bleeding and a partial response as clinical reduction of bleeding, with a reduction of >50 % in red cell transfusion compared with the previous 3 days. Overall, 66% of patients achieved complete response and 17% a partial response. Requirement for platelet transfusion fell (from a mean of 1.5 units plts/day to 1 unit/day, $p<0.0001$). The average dose of EACA required was 6g/day. Adverse effects included 7 patients with abnormal LFTs (all abnormal before EACA), 3 GU clots, 1 atrial fibrillation, 1 orthostatic hypotension and 1 nausea (the latter 2 both responded to dose reduction). [Level of Evidence 2-]

6. Etamsylate

The only evidence reported is a double-blind cross-over RCT (n=18) in fit 19-25 year olds which found that etamsylate 500mg had **no** impact on aspirin-induced bleeding after 48 hours of administration (Daneshmend et al, 1989).

7. Thalidomide

Thalidomide is postulated to reduce bleeding by reducing levels of vascular endothelial growth factor (VEGF). Another possible mechanism is mediated by increasing messenger RNA degradation causing a reduction in TNFα levels.

A case series (n=6) of **patients with recurrent intestinal bleeding** (3 with undiagnosed cause of bleeding, 3 with Crohns's disease), refractory to standard treatment were given **300mg thalidomide daily** (reduced to 50-100mg daily after 6-9 months) (Bauditz et al, 2004). The mean transfusional requirement prior to treatment was 56 units of packed cells over 24 weeks. Bleeding stopped in all pts within 2 weeks of starting thalidomide and there was no further need for transfusions in the 33 month follow-up. In patients with an undiagnosed cause of bleeding transfusion requirement fell from a mean of 3.1 transfusions/month to zero.

A further case report describes a 59 year old man with cholangiocarcinoma causing extra hepatic portal vein obstruction (Karaieha MA et al, 2006). He had clipped varices but also had portal hypertensive gastropathy. The patient required 30units of packed cells over 35 days despite terlipressin, propranolol, sucralfate, tranexamic acid and omeprazole at maximum doses. He was not candidate for TIPPS. He was commenced on **thalidomide 100mg daily** and thereafter needed only 1 unit of blood in the next 5 days, then none for a further 7 months.

A review article cites the 2 articles above, and discusses the use of **thalidomide** in 2 other single case reports of patients with hereditary haemorrhagic telangiectasia and angiodysplasia as the causes of bleeding (Generali and Cada, 2007).

8. Drugs affecting the clotting cascade

Thrombin

A very early placebo-controlled trial (Edmunds E, 1953) looked at 22 patients presenting with **gastro-duodenal bleeding** given **liquid thrombin solution** via nasogastric tube. **No** difference in outcome was found between treatment and control groups. The authors comment that at gastric pH < 6.5, thrombin's action is impeded (and at pH <4.3 thrombin is destroyed) so buffering solution needs to be given to ensure appropriate pH in all patients! [Level of Evidence 2-]

Another Case report looked at 2 patients with metastatic ulcers in the upper GI tract which bled despite endoscopic injection. Bovine collagen/thrombin suspension was mixed with the patients' centrifuged blood, then injected via endoscope, resulting in cessation of overt GI bleeding and marked reduction in transfusion requirements (Milkes et al, 2002). [Level of Evidence 3]

Vitamin K

A Cochrane review looked at RCTs describing the efficacy and safety of Vitamin K for **upper gastrointestinal bleeding in patients with liver disease** (Marti-Cajaval A J et al, 2005). There were no RCTs published! [Level of Evidence = 1]

Recombinant Factor VII

A case report described the use of recombinant factor VII in a 59 yr old man with a **bleeding duodenal ulcer** (Volt et al, 2000). He was treated with an H2 antagonist, but had re-bled the day following admission and so required surgery. Post- operatively bleeding continued to be a problem and he had 2 further laparotomies. Fibrinogen and platelet count dropped and he was given fresh frozen plasma and platelet infusions as well as multiple units of packed

cells. Bleeding persisted despite administration of tranexamic and then octreotide. He was then given **activated recombinant factor VII** (90 micrograms/kg every 2 hours for 21 hours). Bleeding was controlled and the patient was transferred for gastro-duodenal artery embolisation.
The patient was treated with factor VII despite an intact haemostatic system but the effects of octreotide cannot be excluded, as treatments overlapped. The authors hypothesize that the infused factor VII bound to tissue factor on the cell surface of the ulcer and initiated haemostasis. [Level of evidence 3]

9. Systemic steroids

A single case report describes a 53 year old woman with haemorrhagic gastritis secondary to radiotherapy for cholangiocarcinoma (Tsay et al, 2006). The patient experienced intermittent haemorrhagic shock despite epinephrine spray & injection, sucralfate and lansoprazole. She was given **Prednisolone 40mg daily** which was subsequently tailed down to a maintenance dose of 5mg daily. After 2 days, no further bleeding occurred for 5 months. [Level of Evidence 3]

EVIDENCE FOR INTERVENTIONAL MEASURES

Cryosurgery

A Japanese study looked at cryosurgical treatment for **ano-rectal cancer patients** (Yamamoto et al, 1989). Cryosurgery produces a sharply demarcated volume of necrotic tissue, which sloughs off over several days.
Patients were divided into 3 categories: those who had cryosurgery for palliation (no previous surgery) with symptoms such as bowel obstruction or bleeding, those who had recurrent tumour after previous surgical excision and patients who had excisional surgery with adjunctive cryosurgery.
Bleeding and pain were controlled in the first 2 groups of patients. Post procedure bleeding was not noted in this series. [Level of evidence 3]

Embolisation

Embolisation was reported to be effective in a case report of a 71 yr old man with a poorly differentiated adenocarcinoma of the sigmoid colon and liver metastases. Despite surgical excision of the primary tumour, he presented with **haematemesis and melaena** and was found to have a bleeding posterior ulcer at endoscopy (histologically metastatic adenocarcinoma). He was transfused and treated with tranexamic acid but continued to bleed. Further surgery was not felt to be an option and he was treated with radiotherapy. He continued with daily melaena and so was referred for trans-catheter arterial embolisation. Selective embolisation was carried out in the hope that reduction of the perfusion pressure in the duodenal vessels would lead to reduction of bleeding. The treatment was

effective, there was no further bleeding until death and pain also was reduced. [Level of evidence 3]

SUMMARY OF EVIDENCE FOR NON-INTERVENTIONAL TREATMENT OF UPPER GI BLEEDING IN PALLIATIVE CARE PATIENTS (LEVEL OF EVIDENCE IN SQUARE BRACKETS)

PPIs and H2 antagonists

Cochrane review of PPIs vs control for upper GI bleeding prior to endoscopy [1] found **no difference** compared with placebo or H2 antagonist except slightly lower rate of stigmata of recent bleed on OGD. This review was not specific for cancer patients.

Sucralfate

One randomised controlled trial (RCT) using 2g 2hrly found reduced stigmata of recent bleed on OGD at 72 hrs [1] Again, this was not specific to cancer patients.

Case reports x 2 found reduced blood loss in patients with malignant upper GI lesions [3]

Octreotide

Cochrane review in variceal bleeding found no difference in mortality but a small difference in transfusion requirements (0.5 units per pt)

Case reports x3 (2 in cancer) showed marked reduction in bleeding and need for transfusion [3]

Pressins

Cochrane review of terlipressin in variceal bleeding [1] found statistically significant reduction in mortality compared with placebo (RR = 0.66), no difference between terlipressin and somatostatin analogues/endoscopic treatments and no difference in adverse events that caused death / drug cessation

Case report x1 and case series (n=2) of marked reduction in bleeding and transfusion with use of 0.04 units/min of vasopressin

Tranexamic Acid

RCTs x 7 [1] which suggest lower mortality, lower rates of need for surgery and lower transfusion rates in some cases when treated with tranexamic acid compared with placebo.

Epsilon Aminocaproic Acid

Case series (n=77) [3] of patients with GI bleeding in the context of thrombocytopenia found 66% achieved complete cessation of bleeding and 17% had marked reduction in bleeding.

Etamsylate

RCT x 1 - No evidence to suggest improvement in GI bleeding [1]

Thalidomide

Case report x 1 (cancer pt) and case series (3/6 pts with undiagnosed cause of bleeding) [3] all experienced cessation of bleeding while on treatment (min 100mg daily)

Thrombin

RCT x1 found oral thrombin was no different to placebo (n=22) [1]

Systemic steroids

Case report of oral prednisolone markedly reducing bleeding from radiotherapy induced gastritis [3]

Vitamin K

Systematic review found no RCTs looking at use in upper GI bleeding in liver disease [1]

SUGGESTED TREATMENT ALGORITHM FOR UPPER GIT BLEEDING

Treatment in most care settings

1. proton pump inhibitor (oral or IV)
2. oral tranexamic acid (1g QDS po initially)
3. oral sucralfate (2g BD po)
4. consider iv/im octreotide/somatostatin
5. consider oral thalidomide (?100-300mg daily)

Hospital Measures

1. consider definitive treatment of tumour (if not already exhausted)
2. refer for radiotherapy provided the patient is well enough to tolerate it
3. consider referral for arterial embolisation or cryotherapy
4. consider iv pressins (need central line if used long-term)

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PPIs

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Management of Rectal Bleeding in Palliative Care

Introduction

Rectal bleeding can be due to the cancer itself (intraluminal tumour) or to co-existing GI pathology e.g. IBD, gut pathogens causing bloody diarrhoea, angiodysplasia, diverticular disease, polyps, rectal fissure/haemorrhoids etc. Management of rectal bleeding should be directed at treating the underlying cause if appropriate.

Radiotherapy can cause or exacerbate rectal bleeding. Radiation proctitis can occur after any form of pelvic radiotherapy, especially after prostatic and cervical treatment. Acute proctitis is usually self-limiting and can last up to 3 months. A chronic form can present months or years after the radiation exposure (median time 8 to 12 months) and is the result of obliterative endarteritis, submucosal fibrosis and new vessel formation. There can be associated non-healing mucosal ulceration. The incidence is unknown as there are no clearly defined diagnostic criteria. It usually presents with rectal bleeding (amongst other symptoms) which can range from mild to life-threatening. Tissue biopsy may be inconclusive and the diagnosis may have to be made by excluding any co-existing disease and the presence of recurrent tumour.

A Cochrane review of non-surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis (including palliative radiotherapy) was conducted in 2001 and the search extended to April 2007 in its current update (Denton et al). This is a difficult subject area to draw conclusions about owing to the lack of diagnostic criteria, and variability in treatment modalities studied in a non-systematic way with different outcome parameters.

Oral treatments for rectal bleeding

1. Tranexamic acid

A case series by Dean and Tuffin on cancer patients with bleeding complications includes one patient with PR bleeding due to a rectal tumour. She was treated with oral tranexamic acid 1.5g initially and then 1g TDS. Her bleeding improved after 3 days and stopped completely after 5 days with no recurrence. There appeared to be no complications from this treatment. [level 3]

Topical Treatments for Rectal Bleeding

1. Tranexamic Acid

A single case report exists of a 61-year old man with prostate cancer and rectal bleeding (McElligott et al). Colonoscopy was used to investigate the source of bleeding and Prednisolone suppositories found to be unhelpful. Tranexamic acid 5g in 50 ml warm water was given as an enema twice daily. Bleeding was

substantially reduced 'in a few days' and 'virtually stopped' by day 10. Enemas were then reduced to one/day then used on alternate days. Stopping enemas caused recurrence of bleeding. Control was achieved using thrice weekly enemas for over 3 months
[Level of evidence: 3]

2. Sucralfate (complex of a disaccharide polysulphate and aluminium)

A case study (Farncombe, 1993) describes a 76- year old man with rectal cancer who was bleeding due to perineal recurrence. Sucralfate paste (produced by mixing tablets with KY jelly) was applied locally to the area at the first sign of ooze and application repeated twice daily for 2 more days. If bleeding stopped, the regime was discontinued and then sucralfate was used on a prn basis. In this case, bleeding was controlled for 6 months with application required 2-4 times a week. The patient was able to easily apply the paste as the area was accessible.
[Level of evidence: 3]

A prospective, double-blind RCT of oral sulfasalazine plus rectal steroids versus rectal sucralfate included 37 patients, mostly with a history of cervical cancer (Kochhar et al, 1991). Patients were excluded if they had used steroids in the last 2 weeks and baseline characteristics were both clinical (including bleeding) and endoscopic. Patients were randomised to receive either rectal prednisolone and oral sulfasalazine or rectal sucralfate suspension 2g bd with oral placebo. Sucralfate showed a statistically significant greater clinical improvement over a 4 week treatment period. No difference was identified between the two arms with respect to endoscopic criteria.
[Level of evidence: 1+]

Another study looked at 26 patients with rectal bleeding due to proctitis (Kochhar et al, 1999). 10 patients had moderate bleeding (defined as 8-14 episodes/week) and 16 had severe bleeding (15 or more episodes/week). All patients were given a 20 ml enema of 10% rectal sucralfate suspension twice daily until PR bleeding stopped or failure of treatment was acknowledged. A 'good' response was defined as bleeding severity improving by 2 grades and was seen in 20 patients at 4 weeks, 22 at 8 weeks and 24 at 16 weeks. Two patients needed surgery due to a poor response and there were no treatment related complications.
[Level of evidence: 2-]

3. Thalidomide

A case report describes a 78 year-old woman with history of cervical cancer and rectal bleeding secondary to radiation proctitis which was colonoscopically diagnosed (Craanen et al, 2006). Topical mesalazine, steroid enemas, epsilon-aminocaproic acid had all been unsuccessful in stopping the bleeding. Thalidomide was commenced at 50-100 mg/day (no further dose details). Three weeks later the patient's haemoglobin had remained stable after the last transfusion. No blood transfusions were needed at 3 month follow up. The paper doesn't comment on whether the patient remained on the thalidomide.

[Level of evidence: 3]

4. Hyperbaric oxygen therapy for chronic radiation proctitis

Hyperbaric oxygen (HBO) is thought to have an angiogenic effect. By stimulating collagen formation at the wound edges it elevates local tissue oxygen levels and allows re-epithelialisation to occur. Limitations to this include local availability.

Interventional techniques for Rectal Bleeding

- Evidence for treatments requiring endoscopy, general anaesthetic or sedation are listed below
- Actual availability of these procedures is dictated by local expertise, patient preference and patient suitability.

1. Alum solution

A single case report describes a 71-year old man with rectal carcinoma and uncontrolled bleeding (Paes et al, 1986). Gauze soaked in a 1% solution of alum was packed into the rectum under general anaesthetic and left in situ for 3 days. A one-week respite from bleeding resulted. The procedure was repeated and the patient remained free from bleeding for at least 3 months.
[Level of evidence: 3]

2. Fibrin glue

- A topical adhesive consisting of fibrinogen concentrate that is activated by the addition of thrombin and calcium chloride
- A sticky coagulum is produced rapidly when the constituents are mixed
- Reproduces the final stage of the coagulation cascade and so its action is not dependent on the body's clotting mechanisms
- First used 40 years ago as an anastomotic sealant for nerves

A single case report exists of a 76-year old woman with highly vascular pelvic hemangiopericytoma and rectal bleeding treated with intrarectal fibrin glue (Soweld et al, 1997). The patient had a 20-year history of disease and operations, resulting in recurrent tumour invading her 10cm rectal stump. Six sessions of Nd:YAG laser treatment had not helped. Fibrin glue was instilled into the rectal stump endoscopically using a Foley catheter. The patient noted a single episode of minor ooze after 1 month and further fibrin was applied. She then remained free of bleeding for remaining 5 months of life
[Level of evidence: 3]

3. Formalin

- Topical formalin is thought to act by protein cross-linking and superficial coagulation of tumour neovasculature

A single case report exists of a 44 year-old woman who developed severe rectal bleeding 3 weeks after commencing neoadjuvant chemo radiotherapy for rectal adenocarcinoma 2cm from anal verge (Zbar et al, 2005). Local suture and diathermy in theatre were unsuccessful at stopping the bleeding. Solution of 4% formalin on gauze was then applied to the tumour edge for 10 minutes. Immediate visible slowing down of bleeding resulted and the procedure was repeated for another 10 minutes and bleeding stopped. The patient developed anal pain and fever 48 hours later but no perforation was found. No mention is made of whether bleeding ever recurred.
[Level of evidence: 3]

Another case series of 2 patients describes the successful use of topical formalin (Kelly et al, 2002) Patient A had rectal bleeding secondary to locally advanced rectal cancer.
Examination under anaesthesia was followed by infusion of 4% formalin via Foley catheter. Bleeding apparently stopped but no further details are given. Patient B had rectal bleeding secondary to recurrent bladder cancer and underwent the same treatment with formalin. No further bleeding was seen within 3 months of follow-up
[Level of evidence: 3]

4. Laser therapy

Usually Nd:YAG (generates infra-red light) treatment, transmitted via an endoscope. Bowel preparation is therefore needed and patients may need GA/sedation. The procedure can be administered repeatedly. Potential complications include bleeding, perforation, stenosis, fistulae, with literature quoting a 5-10% complication rate.
This technique can be used for tumour-related bleeding and bleeding secondary to radiation proctocolitis.

5. Argon Plasma Coagulation

Also used for tumour-related bleeding and bleeding secondary to radiation proctitis, but may be better suited to larger surface areas of bleeding. It is given via an endoscope but may not need sedation and is a quick treatment that may need to be repeated. It probably has lower complication rates than the Nd:YAG treatment.

6. Cryosurgery

A Japanese study looked at cryosurgical treatment for **anorectal cancer patients** (Yamamoto et al, 1989). Cryosurgery produces a sharply demarcated volume of necrotic tissue, which sloughs off over several days.

Patients were divided into 3 categories: those who had cryosurgery for palliation (no previous surgery) with symptoms such as bowel obstruction or bleeding, those who had recurrent tumour after previous surgical excision and patients who had excisional surgery with adjunctive cryosurgery.
Bleeding and pain were controlled in the first 2 groups of patients. Post procedure bleeding was not noted in this series.
[Level of evidence 3]

7. Arterial embolisation

Gady et al describe a case series of 10 patients who underwent selective arterial embolisation for lower GIT bleeding, including one cancer patient. Ischaemic complications have been quoted as being as high as 22% following this procedure, but not all cases may be clinically significant. It is suggested that bleeding from a surgical anastamosis is not treated in this way due to a limited collateral blood supply and high risk of ischaemia. Discussion of each case with an interventional vascular radiologist is advised. See section 2.3 for further advice on patient selection. [Level 3]

8. Radiotherapy

Bleeding from the sigmoid colon and rectum is usually easier to localise, and treatment can be delivered by external beam or internal brachytherapy. Here response rates can be as high as 85%, but previous radiotherapy to this area may limit further treatment. (OTPM p252) As with most forms of radiotherapy treatment, bleeding may take a few weeks to subside and so should not be used on its own when urgent relief is required

Summary of treatment recommendations

Treatment in most care settings:

- Oral tranexamic acid (1g TDS)
- Rectal sucralfate (2g suspension or 2g tablets mixed with aqueous jelly BD)
- Rectal tranexamic acid (5g injectable vials mixed with 50ml warm water as enema BD)
- Consider oral thalidomide (?50-100mg daily initial dose)

Additional treatment in specialised centres:

- Consider radiotherapy to tumour sites where an immediate effect is not required, and patient has not had maximum radiotherapy to this site previously
- Consider referral for endoscopy (for laser treatment, cryotherapy, argon plasma coagulation, or application of formalin, alum packs or fibrin glue), where the patient is fit enough to tolerate procedure
- There may be a role for interventional radiology in selected cases of bleeding resistant to other measures. Consultation with an vascular interventional radiologist is recommended
- For radiation proctitis hyperbaric oxygen therapy may be useful, but is time consuming and limited by local availability

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Bleeding in the renal tract

Introduction

Bleeding can occur from any part of the renal tract, the primary sites being kidney, bladder and prostate.

It can occur as a result of

1. Tumour – either primary or metastases
2. Drug treatment
3. Oncological intervention eg chemotherapy with alkylating agents such as cyclophosphamide or radiotherapy for pelvic/lower gastrointestinal malignancies.
4. Infection
5. Stones
6. Urethritis
7. Benign prostatic hypertrophy

It is a significant cause of morbidity and mortality

Recurrent bleeding due to carcinoma of the prostate may occur in up to 45% of patients (Tomlinson 1977)

Incidence of haemorrhagic cystitis after cyclophosphamide treatment has been described as being as high as 68% (majority of studies 2-40%).

Radiation cystitis – Approx 20% of patients treated with pelvic radiation have bladder complications. In one study 9% of patients who received full dose radiation suffered haemorrhage. Haematuria may develop months to years after treatment

Methods of treating haematuria are based on source of blood loss, severity of haemorrhage and performance status of patient:

Grading system for bladder haemorrhage- Mitcheson and Schiff 1985

Mild	No acute drop in haematocrit and controlled with simple measures
Moderate	Gradual decrease in haematocrit requiring ≤6units packed cells
Severe	Acute drop in haematocrit requiring >6 units packed cells

Oral treatments

Conjugated oestrogens

Liu et al report a series of five patients with severe haemorrhagic cystitis due to radiation or cyclophosphamide treated with oral or IV oestrogen. Three patients received diethylstilbestrol 5mg PO OD with macroscopically normal urine after 4-7 days. Two patients received 1mg/kg IV for 2 days, followed by 5mg PO OD thereafter, where urine became marcoscopically normal after 1-3 days.

Four patients remained asymptomatic on 1.25mg conjugated oestrogen per day, but one patient still had intermittent haematuria despite 10mg/day. Complications such as thromboembolism were not observed. [level of evidence 3]

Skubitz provides a case report of a 60 year old man with a retroperitoneal mass (leiomyosarcoma) invading both kidneys, admitted for continuous bladder irrigation and as haematuria cleared was commenced on 5mg diethylstilboestrol (DES) /day. For following 3 weeks on DES there was no further haematuria. DES was stopped and 3 days later he developed gross haemturia which resolved within 24hrs of DES being restarted. [level of evidence 3]

Oral / Topical Fibrinolytic inhibitors

Dean and Tuffin report a series of 16 patients with tumour associated bleeding. Five patients reported had haematuria. Two patients had prostate cancer, two patients had bladder tumours and one patient had a melanoma. All had normal coagulation profiles. Four patients were given 1.5g tranexamic acid followed by 1g TDS PO, and advised to continue for 7 days after cessation of bleeding. One patient received 5g Aminocaproic acid, with 1g QDS PO after. The average time to improvement was 2 days, with average cessation of bleeding after 4 days. Four patients had effective control of bleeding, but one patient had a less severe recurrence on day 6. [level of evidence 3]

Singh and Laungani report 37 patients with intractable bladder haemorrhage given intravesical aminocaproic acid (ACA) following a cystoscopy and removal of clots. 200mg of ACA was diluted in 1L 0.9% saline and infused continually until 24h after the bleeding stopped. Thirty four of the thirty seven responded, with 32 patients responding within 48 hours. [level of evidence 3]

However**,** as these drugs prolong the dissolution of fibrin deposits already formed, macroscopic haematuria is a contraindication for their use because of the risk of clot formation with resultant obstruction and colic. This is particularly true if bleeding is from the upper renal tract. Local specialist advice is to use with caution in patients with severe haematuria only. The consequences of a patient developing clot retention whilst outside of a hospital with specialist urology services must be considered [level 4]

Schultz reports three cases of obstruction developing in patients with thrombocytopenia secondary to haematological malignancy with microscopic haematuria, suggesting that this should be a relative contra indication. [level of evidence 3]

Sodium pentosanpolysulphate

Parson reports a series of 5 patients with radiation-induced cystitis treated with 100mg TDS PO of sodium pentosanpolysulphate. Bleeding subsided on average 4-7 days later. It is thought to act by coating the bladder lining. [level of evidence 3]. However this drug has not been approved for its licensed use in the treatment of interstitial cystitis in the UK, and therefore availability is limited.

5α-reductase inhibitors

Hochberg and Barnaby et al. both suggest the use of 5α-reductase inhibitors in patients with prostate cancer with haematuria. It is suggested that tumours that cause haematuria must encroach on the transition zone or bleed from coexisting benign prostatic enlargement, and so 5 ARI's may help. [level of evidence 3 , 4]

Bladder instillations / irrigation

Aluminium Salts

Alum (either aluminium ammonium sulphate or aluminium potassium sulphate) acts as an astringent leading to protein precipitation on the irrigated surface. 1% solution is used – diluted in sterile distilled water. As its pH is 4.5 salts precipitate if you try to neutralise the pH. As a result it cannot be combined with local anaesthesia, as the anaesthesia is rendered useless.

Arrizabalaga et al report 15 patients with massive haematuria (13 due to bladder cancer) who were irrigated for an average of 21 hours (range 3-48h). Ten patients had a complete response, 2 a partial response requiring further treatment and 3 patients either did not respond of had intolerable side effects. [level of evidence 3]

Thompson et al report 2 patients with haematuria due to prostate cancer treated with 1% alum solution. Both responded within 24 hours, but one required further irrigation after a re-bleed the following day. [level of evidence 3]

Ostroff and Chenault report 6 cases of massive bladder haemorrhage that "All responded, albeit over various periods, with cessation of haematuria". In these patients bladder biopsies taken 1 month later showed no histological change in the bladder mucosa from the alum treatment. [level of evidence 3]

Side effects of alum treatment include vesical tenesmus and spasms and suprapubic pain. These can be effectively managed with antispasmodic drugs. In addition, there is the risk of systemic absorption causing CNS toxicity (one case report by Kavoussi et al recommending not exceeding a rate of 3g/hour and extra caution in patients with renal failure – level of evidence 3). This can cause speech disorders, dementia and seizures in severe cases.

Silver Nitrate

Kumar and Wrenn report a series of 9 children with cyclophosphamide or radiation induced bladder haemorrhage treated with 10-15 minute instillations of 0.5 – 1% silver nitrate solution following a cyctoscopy. Variable results are poorly reported. [level of evidence 3]

Raghavaiah and Soloway report a case of silver nitrate salts obstructing the right collecting ducts and left vesico-ureteric junction following irrigation. The authors recommend performing a cystogram to exclude vesicoureteral reflux, avoid using silver nitrate on an extensively ulcerated bladder as precipitation of salts more likely, and avoid saline irrigations after instillation for fear of precipitating silver chloride. [level of evidence 3]

Intravesical Formalin

Formalin precipitates cellular proteins of the bladder mucosa and has occluding and fixative actions on telangiectatic tissue and on small capillaries. It is instilled under general or spinal anaesthesia.

Complications include a small contracted bladder, urinary incontinence, vesicourerteric reflux, ureteric strictures, acute tubular necrosis, fistulas, VUJ obstruction

In trials to date multiple concentrations of formalin have been used with variable lengths of instillation times and volumes. Concentration appears to be linked most closely with complication rate i.e. higher concentrations give higher number of complications.

Success rates between 80-100% are seen in patients with bladder cancer, post radiation cystitis or cystitis secondary to cyclophosphamide therapy. Given the potential serious complications however it should be reserved for those with severe intractable haematuria in whom all other treatment options have been exhausted. [all level of evidence 3]

Intravesical prostaglandins

Cyclophosphamide and ifosphamide are used in haematological malignancies and some solid tumours. It results in acreolin (a hepatic metabolite) being excreted in the urine which causes haemorrhage, oedema, ulceration and necrosis of the urothelium. Adequate hydration during therapy and use of oral Mesna reduce the local toxic effects on the bladder.

Prostoglandins have been used to treat haemorrhagic cystitis secondary to cyclophophamide and ifosphamide therapy and the mechanism of action is thought to be that of a cytoprotective, encouraging platelet aggregation, inducing vasoconstriction and smooth muscle contractions in mucosal and submucosal blood vessels.

Advantages of prostaglandins include overall good tolerance, no significant toxicity or anaesthetic requirement, easy bedside administration, no significant problem in patients with VUR and no precipitate to block catheters. Disadvantages include cost and a high percentage of bladder spasms

Sodium hyaluronate

Sodium hyaluronate is a glycosaminoglycan present on the bladder mucosa which serves as an important protective substance against uroepithelial damage. Miodosky et al report a series of 7 patients with haemorrhagic cystitis following stem cell transplantation treated with intravesical sodium hyaluronate (40mg in 50ml), instilled for 20mins. Five patients had a complete response (4 in first 7 days) and 1 had partial response. [level 3]

Intravesical Ozone therapy

There is one case report of a patient with radiation induced haematuria following treatment for prostate cancer treated with ozonated water instillations. Instillations were given for 30 minutes alternate days, with macroscopic haematuria stopping after one week. It is thought to work by altering the pro-oxidant/antioxidant balance. [level 3]

Other treatments

Embolisation

Transarterial-angioembolisation (TAE) of the internal iliac artery or super selective embolisation of small tributaries (bladder) or renal artery (kidney) can be performed under local anaesthesia and has a good success rate (92% in one case series) (Makie et al 2007)

The commonest complication is gluteal pain and post embolisation syndrome is pain and fever related to tissue necrosis after embolisation. This usually responds well to simple analgesics and antibiotics. Rarer complications depend on the type of embolic material used. Consultation with an interventional vascular radiologist is recommended.

Radiotherapy

Radiotherapy has proven benefits in controlling haemorrhage in cancers arising from the renal tract. This treatment is usually reserved for patients who have not received previous radiotherapy treatment to this area, but additional doses may occasionally be possible to palliate symptoms in some cases.

Moderate doses may be given over shorter periods of time, with invasive bladder cancer haemorrhage being treated as effectively with 21Gy over 3 fractions than 35Gy in 10 fractions. Even single fractions can improve symptoms in frail patients. (Oxford Textbook of Palliative Medicine (OTPM))

Haemorrhage from renal cell carcinomas may also benefit from local radiotherapy, but due to the poor tolerance of normal kidney to the effects of treatment, renal function in the affected kidney is likely to decline. Therefore ensuring the remaining kidney is functioning well before embarking in this treatment is essential (OTPM p251).

It is recommended that discussions are held with a medical oncologist about feasibility of using this approach to control haemorrhage.

Hyperbaric oxygen

HBO is thought to reverse the vascular radiation-induced pathophysiology caused by radiation (i.e. progressive obliterative endarteritis of the small blood vessels), resulting in cellular hypoxia. No papers were identified for management of haematuria for causes other than radiation cystitis.

Bevers, amongst others, reports a case series of 40 patients with severe haematuria from radiation cystitis, where local tumour recurrence had been excluded on cystoscopy. Twenty sessions lasting 90 minutes of 100% hyperbaric oxygen resulted in complete response in 75% (no further haematuria), 17% with a partial response and 7.5% with no response. It was not thought that this treatment promoted cancer growth. It is difficult however to extrapolate these findings to other causes of haematuria.

Local availability of hyperbaric oxygen also limits its use in management of bleeding from the renal tract.

Summary of guidance for bleeding from the renal tract

In hospital settings:

1. Kidney	Embolisation of Renal artery Nephrectomy	
2. Bladder	Radiotherapy	
	Embolisation Internal iliac artery or branches of	
	Oral Tranexamic acid (use with caution due to risk of clot retention. Intravesical tranexamic acid via 3-way catheter is preferable) Oestrogens (Sodium pentosanpolysulphate if available)	
	Intravesical	Tranexamic acid Aluminium salts (beware of systemic toxicity) Prostaglandins (for cyclophosphamide induced haemorrhage) Sodium hyaluronate Formalin (GA or sedation required) Silver nitrate (beware of precipitating salts)
Also consider:		
	Systemic	Hyperbaric oxygen therapy for radiation induced cystitis
	Surgery	Radical cystectomy
3. Prostate	Oral	Fibrinolytic Inhibitors 5 α-reductase inhibitors
	Radiotherapy	
	TURP	

In hospice / home settings:

Always consider transfer to a hospital for above measures if possible

Bladder	Oral tranexamic acid (risk of clot retention) Oral oestrogens ?Intravesical instillations
Prostate	Oral tranexamic acid 5 α-reductase inhibitors

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VAGINAL BLEEDING

Introduction

Vaginal bleeding from gynaecological pelvic malignancy may occur from untreated primary cervical, vaginal or endometrial cancer or from vagi-pelvic recurrence once primary surgery and/or radiotherapy is completed.

In cervical cancer, vaginal bleeding is a common presenting feature (56-76%) and is associated with tumour size. The cause of bleeding may be related to erosion of vessels by the tumour or from radiation injury which often also affects the rectum or bladder (Lin et al). Profuse haemorrhage can occur with minimal stimuli especially if tumours are proliferative and bleed easily. Bleeding can also complicate up to 1/3rd of genital fistulas resulting from cervical cancer and its treatment (Emmert C and Kohler U).

Massive vaginal haemorrhage is relatively rare. In one study 35/1683 (2%) of cases of cervical cancer presented with massive bleeding requiring packing, transfusion and radiotherapy (Kraiphibul et al). In addition, the incidence of massive haemorrhage from cervical tumour is decreasing, largely because of cervical screening programmes and the consequent decreasing incidence of bulky tumours (Lin et al).

Uncontrollable haemorrhage from extensive pelvic malignancy or treatment complications can be managed supportively with fluid resuscitation, transfusion of blood or clotting factors or Vitamin K. Direct compression (vaginal packing) and bed rest can also be useful, as can styptics (drugs that check bleeding).

Radiotherapy is very effective at stopping bleeding, either externally or using intra-cavity techniques to target the bleeding site.

Large vessel pelvic haemorrhage may be treated surgically by ligation of the pelvic arteries. Smaller vessel haemorrhage can be treated with angiographic embolisation of the affected artery by interventional radiologist. Even with more invasive procedures, haemostasis is often sub-optimal due to the development of collateral circulations.

EVIDENCE

LOCAL INTERVENTIONS

1. Tranexamic acid

One entry describes the use of tranexamic acid as a vaginal pessary on the bulletin board of Palliativedrugs.com (level of evidence 4). The patient in question had recurrent carcinoma of the ovary and bleeding from the vaginal vault. Oral tranexamic acid had originally helped but was becoming less effective over time. The patient could not tolerate vaginal packing and was awaiting radiotherapy. The author used a 500mg tablet of tranexamic acid crushed in KY jelly and inserted using a vaginal applicator from a Canesten pessary pack. This settled the bleeding and the patient went on to use whole tranexamic acid tablets inserted in the same way which enabled her to reduce the oral dose of tranexamic acid. The haemostatic effect was maintained prior to definitive treatment with radiotherapy.

Use of IV tranexamic acid 5ml on a gauze swab applied to the bleeding area in a patient with bleeding recurrent vulval carcinoma is also discussed in the correspondence to the above thread. Other replies suggested the use of topical haemostatic sponges (Spongistan) inserted per vaginally which absorb blood and promote clotting; calcium alginate dressings, local application of aminocaproic acid (from an IV ampoule) or thrombin solution. Cautery with a silver nitrate stick or compression with a dressing soaked in silver nitrate solution were other suggestions [level of evidence 4]

2. Acetone

Patsner et al describe the use of topical acetone in 2 patients with life-threatening vaginal bleeding from recurrent gynaecological cancer (1 cervical and 1 endometrial). The patients had received maximal therapeutic radiotherapy and had extensive pelvic collateral vessels, precluding embolisation.

In the cervical cancer patient, a 4 x 4 cm gauze pad soaked in acetone was pushed to the apex of the vagina through a speculum and stopped bleeding after a 2L vaginal bleed, allowing the patient to be stabilised haemodynamically before the pad was removed 4 hours later. No further vaginal bleeding occurred before death 4 months later. The patient complained of a painful burning sensation but otherwise tolerated the procedure well. [Level of evidence 3]

The patient with recurrent endometrial carcinoma was loosing approximately 1L of blood per vagina over 24hrs, necessitating multiple blood transfusions. An acetone-soaked laparotomy pad was packed against the vaginal tumour under general anaesthetic and stopped the bleeding. The pad was removed at the bedside the following day under sedation with no bleeding recurrence until death 4 months later.

Acetone causes reversible damage to mucous membranes after topical application for 90 minutes. It probably acts as an astringent when applied to

tumour masses and causes moderate to severe pain or a sensation of intense heat. It is thus best given under general anaesthetic, providing the patient is stable enough. On the plus side, it is inexpensive, readily available, easy to use and works immediately.

3. Formaldehyde

Fletcher et al report a case series of 2 women treated with formaldehyde-soaked gauze pads for intractable vaginal bleeding. Neither woman had a cancer diagnosis, one was bleeding from a hydatidiform mole and the other from post-partum lacerations. They applied 20ml of 10% formaldehyde to 6 gauze packs and inserted them per vaginally, leaving them in situ for up to 59 hours before removing them. In both cases, bleeding abated within hours of applying the packs and one case went on to have a second uncomplicated vaginal delivery. The authors suggest that this treatment is more an adjunct to definitive treatment e.g. resuscitation with blood products or chemotherapy and should be used as a last resort when conventional packing is unsuccessful [Level of evidence 3].

There is limited discussion of toxicity, except to say that the squamous cell lining of the vagina makes it more durable and systemic absorption is not thought to reach potentially toxic levels. Other authors have reported the use of a 4% formaldehyde instillation to stop intractable vaginal bleeding.

4. Thrombin

Phelan et al describe the use of thrombin-soaked gauze tamponade as part of a series of steps taken to treat life-threatening uterine haemorrhage in a patient with AML. The uterus was packed with a thrombin-soaked pad under general anaesthesia. However, the patient ultimately needed bilateral uterine artery embolisation to stop her bleeding. [Level of evidence 3]

5. Sucralfate paste

Regnard suggests the use of topical sucralfate paste for vaginal bleeding in his flow diagram on the management of bleeding in advanced cancer. However, this evidence is not referenced [Level of evidence 4].

SYSTEMIC INTERVENTIONS

1. Anti-fibrinolytic drugs

There is substantial evidence for the use of oral tranexamic acid and etamsylate in reducing vaginal bleeding from non-malignant causes e.g. dysfunctional uterine bleeding. A landmark paper on **tranexamic acid** and ‘intense genital bleeding’ was reported when tranexamic acid first became available in 1966 (Kobayashi). The authors looked mainly at patients with bleeding from functional uterine bleeding (no cancer patients). They graded the amount of vaginal bleeding on a scale of 0-4 and the response to tranexamic acid as poor/good/remarkable or dramatic. Of 51 patients, 53% achieved complete haemostasis and 71% achieved a substantial reduction in bleeding within 24 hrs. There was no apparent dose – response effect (patients receiving

1g tranexamic acid daily did not have better reduction in bleeding than those receiving 2g/day). However, patients receiving the 2g/day dose were more likely to get complete haemostasis (69% vs 39%). No side effects were reported in this study. [Level of evidence 3]

The reported use of oral haemostatic drugs in the treatment of gynaecological cancer patients with vaginal bleeding is more limited:-

A case series evaluating the effect of tranexamic acid and the related anti-fibrinolytic agent aminocaproic acid included 1 patient with PV bleeding due to cervical cancer (Dean A and Tuffin P, 1997). The patient experienced cessation of bleeding within 4 days with no recurrence on a maintenance dose of tranexamic acid of 1g tds [Level of evidence 3],

A case report describes a pregnant 30 yr old woman diagnosed with acute promyelocytic leukaemia at 34 weeks gestation presenting with vaginal bleeding (Sugawara et al). Labour was induced and a healthy boy delivered but the patient developed disseminated intravascular coagulation. Vaginal bleeding persisted for 15 days despite the use of heparin and anti-leukaemic therapy. The vaginal bleeding was finally stopped by the use of tranexamic acid 3g/day iv which was needed for 10 days before the patient's condition stabilised [Level of evidence 3].

2. Recombinant Factor VII

Sajdak et al used **recombinant factor VII** to treat bleeding from endometrial and vaginal malignant tumours in patients without pre-existing coagulation factor deficiency. In this case series of 2 patients, 10 -21 micrograms/kg of Novoseven was infused intravenously when conventional treatment had failed to arrest bleeding (tranexamic acid, etamsylate and packing). Bleeding slowed and stopped within hours of a single infusion. One patient was given a repeated dose 24 hours later and both were subsequently discharged with no recurrence of bleeding. Factor VII at supraphysiological doses is postulated to accelerate or facilitate haemostasis in large bleeding areas after malignant transformation [Level of Evidence 3].

INTERVENTIONAL TECHNIQUES

1. Radiotherapy

Radiotherapy can control vaginal bleeding by rapid shrinkage of the tumour and sealing of the oozing vasculature by fibrosis, promoting scar formation and mucosal healing. Both external and intra-cavity radiotherapy have been used for haemostasis, which usually stops within 12-48 hours after treatment.

Biswal analysed a case series of 20 patients with cervical cancer presenting with heavy vaginal bleeding and treated with either external beam (5 Gy in 1# to 20 Gy in 5#) or intra-cavity (30 Gy to tumour surface) radiotherapy to achieve haemostasis. A complete response (cessation of bleeding) was seen in

6/20 patients with a further 12 described as having a partial response (60-80%). [level of evidence 3]

The patients were subsequently treated with radical radiotherapy and compared to a group of controls of cervical cancer patients not presenting with bleeding. There was a significant survival difference between the 2 groups, with patients presenting with bleeding having a much poorer prognosis. Late bowel and bladder morbidity in the bleeding group was significant at 15% (Biswal et al). [Level of evidence 2-]. The authors comment that infiltrative tumours may take longer to stop bleeding because they invade the vascular spaces and erode tumour neovasculature. They are also less radio-responsive and hence failure rate for radiotherapy is higher.

Large dose hypofractionated regimes are thought to be superior to conventional radiotherapy for haemostatic purposes. Kraiphibul at el describe haemostasis in 63% of cervical cancer patients presenting with massive haemorrhage within 3 fractions of 3-6 Gy and 97% within 5 fractions. Complications included diarrhoea (mild), cystitis and proctitis. [level of evidence 3]

Hoskin and Blake describe complete resolution of vaginal bleeding from pelvic tumour in relapsed ovarian cancer in 8 patients treated with 8Gy in 2# of radiotherapy on consecutive days. They comment that such treatment can be given after previous radiotherapy, has few side effects and causes minimal disruption. It should be considered prior to topical treatments, whose efficacy has not been evaluated in the context of a clinical trial [Level of evidence 3].

2. Arterial Embolisation

Lin et al present a case report followed by a review of the literature on arterial embolisation as a treatment of massive pelvic haemorrhage [level of evidence 3]. They quote two cases series of 23 and 12 patients respectively who developed intractable or life-threatening haemorrhage due to pelvic neoplasms. Gelfoam particles or metal embolisation coils were used and initially stopped bleeding in all patients. However, 41% of patients had recurrent bleeding within 2 weeks requiring secondary embolisation and others developed complications such as fistulae or bladder symptoms (thought to be more due to tumour progression than the procedure itself).

The authors suggest that arterial embolisation should be the method of choice in life-threatening pelvic haemorrhage from a gynaecological cancer **if the service is available**. Adjuvant care should include prompt fluid and blood product resuscitation and definitive local or systemic treatment to the primary lesion once haemostasis has been achieved.

McQuillan et al report 2 cases of arterial embolisation, one with a less positive outcome. The first was a lady with metastatic uterine carcinoma with gross vaginal bleeding post chemo radiotherapy. She underwent a successful embolisation procedure which reduced her vaginal bleeding to a manageable level. The second patient had recurrent cervical carcinoma and presented with

profuse rectal bleeding post chemo radiotherapy. Her rectal bleeding ceased after embolisation, but she experienced worsening leg pain and was found to have an ischaemic leg. She also developed a recto-vaginal fistula which resulted in a defunctioning colostomy 3 weeks after the embolisation. The authors postulate that the embolisation probably further compromised the blood supply to her already pre-existing claudication of her leg and suggest that reduce pelvic blood supply possibly also precipitated tumour necrosis and fistula formation from her pre-existing rectal involvement of the tumour. They suggest that suitable patients suitable for the procedure need to be carefully selected. [level of evidence 3]

CONCLUSION

There is very little evidence-based practice for any topical or oral intervention for vaginal bleeding in cancer patients.

A pragmatic approach would be to try simple local measures such as vaginal packing and the commonly available oral haemostatic agents e.g. tranexamic acid before considering more interventional approaches such as radiotherapy or angiography (if appropriate in the clinical context).

The more unorthodox and unevaluated suggestions detailed above should be considered only once the more familiar measures have been exhausted.

SUGGESTED ALGORITHM FOR TREATMENT OF VAGINAL BLEEDING

For most treatment settings

1. vaginal packing/tampon
2. trial of oral tranexamic acid (1g TDS)
3. consider topical application of tranexamic acid (500mg tablet crushed with aqueous jelly or 5ml vial soaked on gauze) or sucralfate (2g in 10ml suspension)

For Hospital Setting

5. consider definitive treatment of tumour (if not already exhausted)
6. refer for radiotherapy provided the patient is well enough to tolerate it
7. arterial embolisation if available and with careful selection of suitable patients
8. for life-threatening haemorrhage, consider topical acetone or formaldehyde

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Bleeding Wounds

Summary of management of bleeding wounds

In general there is a poor level of evidence for the management of bleeding malignant wounds, limited to case series and expert opinion. Despite there being a relatively large number of articles on this subject, most are either not referenced (and therefore expert opinion), or refer to only a few key texts (which are often expert opinion).

The following is a guide, based on these articles, with references cited below.

Consider antibiotics if signs or symptoms of infection as infected wounds are more likely to bleed. For all patients consider the appropriateness of radiotherapy, chemotherapy, cauterisation or embolisation.

- Minimize trauma during dressing changes by cleaning gently with irrigation and using non-adherent dressings (Level 4).
- Some brands of alginate (Kaltostat, Sorbsan) claim to have haemostatic properties that can be used to control minor bleeding (Level 4). Alginate dressings are manufactured from the calcium salt of an alginic acid polymer derived from brown seaweed. It is claimed that calcium ions that are released into the wound from the dressing activate platelets, which results in haemostasis. These dressings are not licensed as haemostatic dressings.
- To control profuse bleeding, use Adrenaline soaked gauze, 1 in 1000 (1mg in 1ml) applied with pressure for 10 minutes. This causes local vasoconstriction, but may also cause ‘rebound’ bleeding once these effects wear off. Care should be taken to avoid ischaemic necrosis (Level 4). An alternative is Tranexamic acid 500mg in 5ml soaked into gauze and applied with pressure for 10 minutes (Level 4).
- Sucralfate can be applied topically to help slow capillary ooze. To apply it, a paste is made of Sucralfate 1-2g, which is then crushed with water-soluble gel. The resulting mixture is adherent and can be applied to the bleeding site once or twice daily. (Level 4).
- Consider oral Tranexamic acid or Etamsylate to stop the bleeding and prevent further future bleeding (Level 4). This can be discontinued 1 week to 10 days after bleeding stops. Restart if bleeding recurs.

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MANAGEMENT OF CATASTROPHIC BLEEDING IN ADVANCED CANCER PATIENTS

INTRODUCTION:

Although many patients may be at risk of a major haemorrhage, catastrophic bleeding is actually rare. Reliable data regarding the incidence of major haemorrhage within palliative care units is not available.

If the blood volume loss is substantial enough the patient may become unconscious such that little action may be needed to ease patient suffering. However, when a patient does have a major haemorrhage, it can be a very distressing for family and staff.

This guidance refers to situations where there is felt to be no definitive treatment available to halt haemorrhage. **Please refer to the other sections of these guidelines to ensure therapies to reduce bleeding risk, or stop haemorrhage, have been considered appropriately.**

ADVANCE CARE PLANNING:

Multidisciplinary assessment, identification and discussion of those at risk of major haemorrhage should facilitate advance care planning in case of a major event occurring.

Risk Assessment

Patients potentially at risk include:

- Site of cancer eg. head and neck, haematological
- Presentation with bleeding eg. haemoptysis in lung cancer
- Co-existing disease eg. gastrointestinal bleeding, liver failure, oesophageal varices
- Smaller warning bleeds
- Local infection at the tumour site
- Clotting abnormalities
- On potentiating drugs eg. heparin, enoxaparin

** For those identified as high risk for major bleeding, a plan should be individualised, reviewed and clearly documented **

Who needs to be informed?

Discussion with patients and relatives may cause unnecessary anxiety and concern. There should be careful assessment of how beneficial this may be for a particular individual. However, it is good practice to offer patients/families the opportunity to discuss any worries or concerns they may have about the mode of death.

In some situations it is advisable to discuss the risk of major haemorrhage:

- If it is raised by the patient or family

- If knowledge about the risk allows the patient/family to change their behaviour in a helpful manner
- If there have been warning bleeds
- If there are special circumstances which make it valuable for the the family to know eg. children in the home

Communicate risk and care plan to healthcare professionals involved eg. primary care team (medical & nursing) and out-of-hours service providers (handover form).

What action should be taken?

- Stop anticoagulants and antiplatelet drugs (including NSAIDs) where possible.
- Refer to bleeding guidelines to determine if any specific treatments may benefit.

Consider:

- Preferred care setting – available level of care
- If an inpatient, offer a side room where possible
- If at home, provide telephone numbers for emergency assistance
- Ensure a supply of dark sheets/towels is available along with other equipment: gloves, aprons, plastic sheet or incontinence pad, clinical waste bags.
- Plan for who will clean up after an event and how to contact them
- Prescription and preparation of crisis medication (not always appropriate/available – see below)

IN THE EVENT OF AN ACUTE BLEED:

- Stay calm and if possible summon assistance
- Ensure that someone is with the patient at all times
- If possible nurse patient on their side to keep airway clear
- Stem/disguise bleeding with dark towels/sheets
- Apply pressure to the area if bleeding from external wound with adrenaline soaks if available
- Administer crisis medication if available (see below) which can be repeated after 10minutes if needed.

* REMEMBER patient support & non-drug interventions may be more important than crisis medication *

AFTER THE EVENT:

- Offer de-briefing to the whole team
- Ongoing support as necessary for relatives/staff members
- Disposal of clinical waste appropriately

Crisis Medication:

If medication is felt to be appropriate it needs to be rapid in onset and readily available.

If nursing staff are available quickly (within minutes) 24h/day:

Drug	Route *	Dose	Rate of onset
Midazolam (pre-drawn up if possible)	IV (if existing access)	10mg	2-3minutes
	IM (preferably deltoid[$])	10mg	5-15minutes

* The subcutaneous route is inappropriate due to peripheral shut down and unpredictable absorption.

[$] IM injection should be given proximally and deltoid muscle has greater blood supply than gluteal muscle.

Notes:

If the patient is already on large background doses of midazolam or other benzodiazepines, but still not adequately sedated during catastrophic bleeding they may need larger doses of midazolam in proportion with the background dose.

Specific local policy would be required if an individual unit authorises registered nurses to administer crisis medication in line with above guidelines but in the absence of a medical prescription in the event of a sudden unexpected major haemorrhage [#].

[#] The Nursing and Midwifery Council acknowledge that it may be necessary to administer a named medicine in an identified clinical situation according to specific written instructions.

If domiciliary setting or nursing staff not available quickly:

Drug	Route	Dose	Rate of onset
Diazepam	PR	10mg	5-15mins
Midazolam	Buccal	10mg(1ml) – note unlicensed, special order.	15min
Lorazepam	Sublingual	4mg (1ml)	5mins

References:

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   Level 4
3. Protocol for Management of Acute Terminal Haemorrhage in a Hospice Setting. A. Hunter, Northern Deanery, October 2004 (unpublished).
   Level 4
4. Guidance for Healthcare Staff for Managing Catastrophic Haemorrhage. North Cumbria Palliative Care Service Crisis Management Guidance Group, 2005 (accessed on www.palliativedrugs.com RAG panel).
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6. Arbogast D. What you need to know about managing a carotid artery rupture – Prepare yourself to handle this sudden dramatic bleeding. Nursing; 2001; 31, 8: p32cc1-5.
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    Level 3-4

MANAGEMENT OF A MAJOR CATASTROPHIC BLEED IN ADVANCED CANCER PATIENTS

Risk Assessment

Patients potentially at risk include:

- Site of cancer eg. head and neck, haematological
- Presentation with bleeding eg. haemoptysis in lung cancer
- Co-existing disease eg. gastrointestinal bleeding, oesophageal varices
- Smaller warning bleeds
- Local infection at the tumour site
- Clotting abnormalities
- Drugs eg. heparin, enoxaparin

Is the patient at risk of a major life-threatening bleed?

Yes

No → Reassess as appropriate

Advance Care Plan

- Stop anticoagulants and antiplatelet drugs where possible.

Consider:

- Who needs to be aware of risk? – patient, family, carers, other healthcare professionals?
- Preferred care setting – available level of care
- Equipment: dark sheets/towels, gloves, aprons, plastic sheet or inco pad, clinical waste bags.
- Plan for who will clean up after an event and how to contact them
- Prescription and preparation of crisis medication (not always appropriate/available) * see overleaf

If an inpatient: offer a side room where possible

If at home: provide telephone numbers for emergency

IN THE EVENT OF AN ACUTE BLEED:

- Stay calm and if possible summon assistance
- Ensure that someone is with the patient at all times
- If possible nurse in recovery position to keep airway clear
- Stem/disguise bleeding with dark towels/sheets
- Apply pressure to the area if bleeding from external wound with adrenaline soaks if available
- Administer crisis medication if available (see overleaf) which can be repeated after 10minutes if needed.

* REMEMBER patient support & non-drug interventions may be more important than crisis medication *

After the Event

- Offer de-briefing to the whole team
- Ongoing support as necessary for relatives/staff members
- Disposal of clinical waste appropriately

Crisis Medication

If nursing staff are available quickly (within minutes) 24h/day:

Drug	Route *	Dose	Rate of onset
Midazolam (pre-drawn up if possible)	IV	10mg	2-3minutes
	IM (preferably deltoid)	10mg	5-15minutes

* The subcutaneous route is inappropriate due to peripheral shut down and unpredictable absorption.

Note: If the patient is already on large background doses of midazolam or other benzodiazepines, but still not adequately sedated during catastrophic bleeding they may need larger doses of midazolam in proportion with the background dose.

If domiciliary setting or nursing staff not available quickly:

Drug	Route	Dose	Rate of onset
Diazepam	PR	10mg	5-15mins
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Appendix 1 – Use of blood products to manage bleeding

Haematological factors that contribute to bleeding should be corrected where appropriate. These factors include:

1. Thrombocytopenia.
   This may be due to reduced production (e.g. chemotherapy, marrow infiltration), splenic pooling or increased consumption (e.g. DIC)

2. Abnormal platelet function.
   This can be caused by drugs (see appendix 3), renal failure and haematological disorders such as AML and multiple myeloma.

3. Altered clotting factors.
   This may be due to consumption of clotting factors such as DIC, or reduced synthesis e.g. in metastatic liver disease, or use of anticoagulants such as warfarin.

Management of thrombocytopenia

Spontaneous bleeding is rare with platelet counts above 20 x 10^9/l, and most severe bleeds occur when counts are below 5 to 10 x 10^9/l. Traumatic bleeds can occur however with counts less than 40 x 10^9/l, and abnormal platelet function may increase the bleeding tendency further. (Oxford Handbook of Palliative Care (OHPC) p 400)

Platelet transfusion should be considered for bleeding that is distressing, where the platelet count is less than 50 x 10^9/l. Its effects last only a few days, and are therefore only a short term measure unless repeated transfusions are proposed. A single unit of platelets should raise the platelet count by 6 – 10 x 10^9/l, and an adult transfusion usually contains 4 units. The patient should be grouped for ABO compatibility and the unit given at room temperature over 30 minutes.

Clotting factor abnormalities

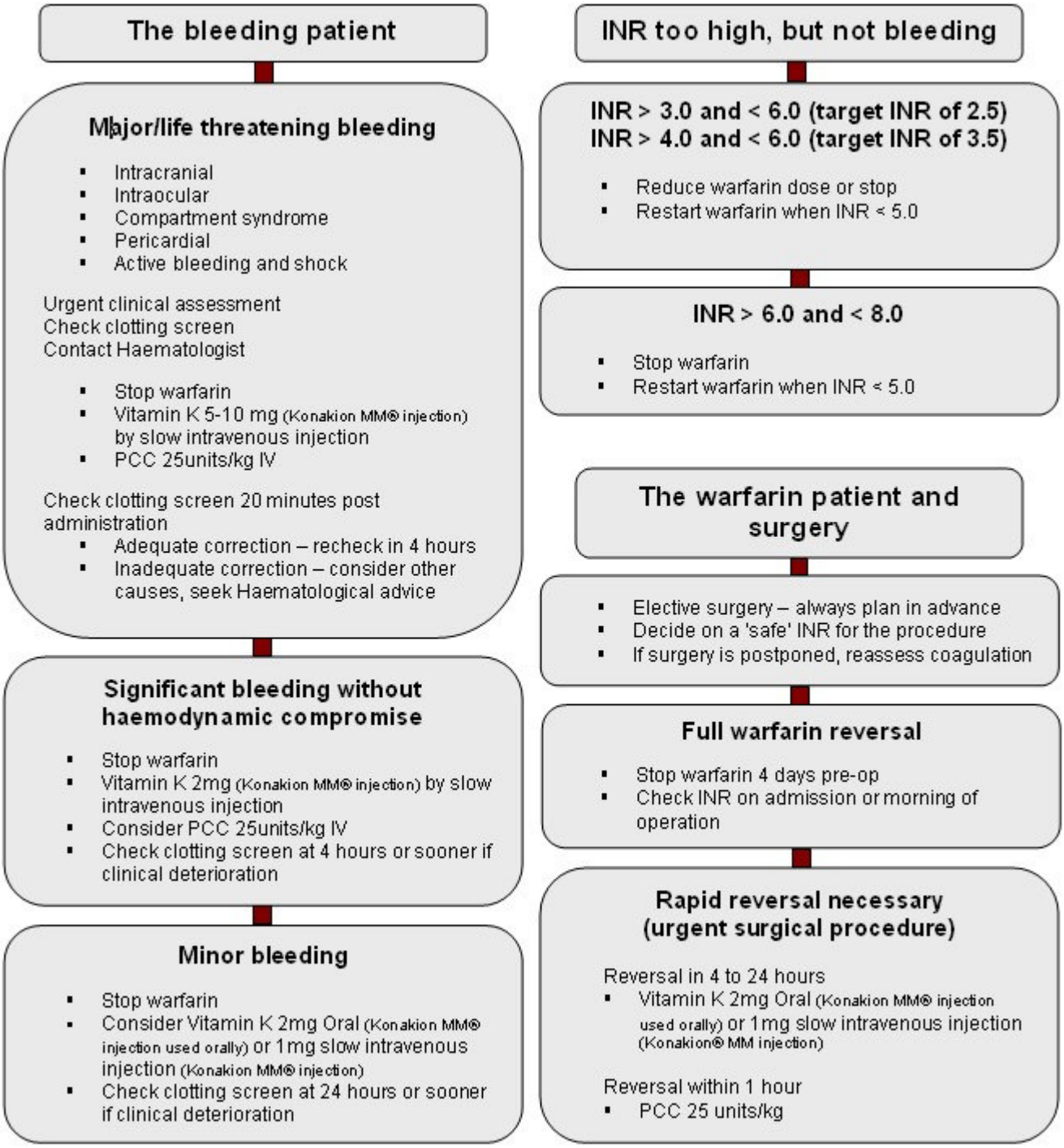
Close liaison with a haematologist is recommended for bleeding due to a consumptive coagulopathy such as DIC, which can present with both thrombotic and haemorrhagic symptoms. Low grade (chronic) DIC is seen more commonly in cancer patients, and may present with symptoms of a DVT, PE or migratory thrombophlebitis. Treatment should be with a low molecular weight heparin, following laboratory confirmation of the diagnosis (OHPC p 401).

Acute DIC is seen less commonly in cancer patients. This presents with the activated coagulation system forming thrombi that cause end organ failure and bleeding as a result of the consumption of clotting factors. This can lead to gangrene of the extremities, purpura and bleeding from areas of trauma. A diagnosis of DIC is made clinically, confirmed by raised D-dimers, Prothrombin Time (PT) and a reduced Clauss fibrinogen level. There may also be a

thrombocytopenia and signs of Micro-Angiopathic Haemolytic Anaemia (MAHA) on blood film. Treatment involves use of Fresh Frozen Plasma (FFP), cryoprecipitate and platelet transfusions under supervision from a haematologist.

Occasionally palliative care patients may require blood products such as FFP for liver disease, treatment of coagulopathies following massive blood loss or red cell transfusions and for rapid correction of warfarin overdoses (see appendix 2 below). Cryoprecipitate is also used where fibrinogen levels are low, such as in DIC or dysfibrinogenaemia. (OHPC p 402)

Appendix 2 - Leeds Teaching Hospitals Flowchart for the management of warfarin reversal



Note:
1. PCC - Prothrombin Complex Concentrate (e.g. Beriplex®, Octaplex®)
2. **Subcutaneous** vitamin K (at the same dose) can be given when IV access is difficult, but it has a slower onset of action and is thought to be less effective than IV use (Periera)[1].
3. When INR > 8.0 with no bleeding - stop warfarin and give 0.5 to 2.5mg oral vitamin K if risk factors for bleeding present.[1]

[1] Periera J, Phan T. Management of bleeding in patients with advanced cancer. Oncologist 2004 9;561-570

Appendix 3 – Drugs and conditions that affect platelet function

Examples of platelet related factors influencing bleeding

- Number of platelets (leukaemia and ITP)
- Inherent platelet function
- Disease effects on platelet function (e.g. uraemia)
- Advanced age, bleeding history, general bleeding diatheses
- Rate of fall in platelet levels - an acute process suggests immune-mediated thrombocytopenia or platelet aggregation whereas a slow decline suggests marrow suppression

Non Drug causes for thrombocytopenia

- Alcoholism, Acute hepatitis, Splenomegaly
- HIV status
- Sepsis, DIC, TTP, HUS, SLE
- Uraemia
- Recent or excessive blood transfusion
- Leukaemia, other haematological diseases
- Viral infections (infectious mononucleosis, varicella, rubella)
- Hyperthyroidism

Identifying drug induced thrombocytopenia

- Take an accurate Drug History
- Agents commonly associated with thrombocytopenia should be sought first, then a more extensive review for associations may be conducted
- A temporal relationship between the start of an agent and onset of the disorder must be established.
- Review recent anti-cancer chemotherapy exposure
- Further information available from http://www.medscape.com/viewarticle/409521_print and your local Pharmacy Medicines Information Service

Examples of individual drugs/classes of drugs affecting bleeding

1. Aspirin

- Aspirin in high doses for several days can reduce prothrombin concentrations and prolong the prothrombin time.
- Contributes to bleeding problems initiated by other factors, including aspirin's local irritant effects on epithelial cells.
- Inhibits platelet aggregation. Low dose (around 40mg per day) effects both cyclo-oxygenase isoenzymes and inhibits platelet thromboxane A2 formation. (NB Low dose wont inactivate prostacycline which is a general inhibitor of platelet aggregation)

- Effect in platelet is irreversible and persists for the lifetime of the platelet (10 days)

2. Coumarin anticoagulants

- Warfarin , Phenindione – Vitamin K antagonists

3. SSRIs

- SSRIs have in rare cases been reported to produce bruising, bleeding, prolonged bleeding time, increased prothrombin time, and other haematological disturbances
- Suggested mechanism of these adverse effects is reduced granular storage of serotonin in platelets, leading to disturbances of platelet function (especially in predisposed patients with mild underlying platelet disorders).
- Alternative mechanism is increased capillary fragility.
- Some patients appear to have a pre-existing susceptibility.

4. Anti – epileptics

- Valproate - Thrombocytopenia, platelet dysfunction and altered coagulation are not uncommon in patients taking valproate (severe hemorrhagic complications are rare).
- Carbamazepine – rash/leukopaenia/ thrombocytopenia recognised

5. Beta-lactam antibiotics

- Use may result in impaired haemostasis and bleeding
- Direct inhibition of the hepatic production of vitamin K-dependent clotting factors from antibiotics with a non-substituted *N*-methylthiotetrazole (NMTT) side chain – (**not used in the UK**) and alterations in the intestinal flora, with subsequent reduction of microbial supply of vitamin K, have been implicated
- Platelet dysfunction - occurs primarily with the broad-spectrum penicillins, but the NMTT cephalosporins, notably moxalactam (withdrawn from clinical use) have also been implicated
- Monitoring of bleeding time should be considered in patients at risk

6. Nicorandil

- Possibly effects platelet aggregation by increasing intracellular platelet cyclic GMP levels. Theoretical effect on bleeding

7. NSAIDS

- Reported to cause thrombocytopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia . Thrombocytopenia is generally mild and reversible and has a low case-fatality rate, but deaths from bleeding have been reported, particularly with indometacin, oxyphenbutazone, and phenylbutazone
- Ibuprofen was associated with the lowest risk of gastrointestinal toxicity; diclofenac, naproxen, and possibly indometacin were intermediate, while piroxicam and in particular azapropazone had much higher risks. The differences appeared to be due to the fairly low dosage of ibuprofen; there were also dose–response relations for naproxen and indometacin.
- Least toxic compound should be selected and start treatment with low dosages and review efficacy after a short trial period.
- Parenteral and rectal administration of NSAIDs does not spare the stomach.
- COX2 Inhibitors: Platelets have only the COX-1 isoform for generating thromboxane to precipitate platelet aggregation. Therefore, selective COX-2 inhibitors have no effect on platelet aggregation or bleeding time (They might increase the risk of thromboembolic cardiovascular events because of preferential inhibition of endothelial prostacyclin synthesis without corresponding inhibition of platelet thromboxane synthesis)

Haematemesis

8. Tetracyclines

- Oesophageal ulcers have been described in association with oral doxycycline or tetracycline

9. Theophylline

- In two elderly patients hematemesis was thought to have been due to a local irritant action of aminophylline . Oesophageal ulceration can result from tablets that were taken with insufficient fluid and/or while lying down

Haemoptysis

10. Iron tablets

- Case report of aspiration leading to haemoptysis

11. Nebulised amphotericin

- Case report of nebulised amphotericin when given at same time as platelet transfusions potentially causing haemoptysis

Appendix 4 – Grading of evidence

Evidence identified as relevant to this review was graded according to published criteria developed for the purpose of creating clinical guidelines. A summary of these criteria is included below.

Level	Criteria
1++	High-quality meta-analyses, systematic reviews of RCTs, OR RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, OR RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, OR RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies OR high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

From: Keeley PW. Clinical guidelines. *Palliat Med* 2003; **17**: 368-74

Appendix 5 - List of contributors and acknowledgements

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