Itch

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Abstract

Itching (pruritus) is a distressing symptom of many skin diseases, as well as systemic, neurological or psychosomatic disorders. Itching is the sensation defined as the reflex or desire to scratch the skin. Chronic itching has a similar impact on the quality of life as chronic pain. The pathophysiology of itch is implicated in the mechanisms and pathways that are described for pain. Itch is caused by a number of inflammatory chemical mediators in the skin and blood, with involvement of peripheral, as well as central neural mechanisms. Some dermatoses, such as atopic dermatitis, urticaria and lichen planus, are characterized by itch. Itching can be associated with systemic diseases, including renal failure, hepatic disorders, thyroid dysfunction, infections, haematological malignancy and solid tumours. The treatment should be directed at the underlying cause, guided by the history, clinical examination and laboratory findings. Treatments include topical corticosteroids, oral antihistamines, opioid antagonists and phototherapy. The management can be complex and no single therapy is consistently effective. This article summarizes the common causes of itching, including those associated with a rash, with normal skin or skin that has the signs of scratching. Common systemic causes of itch are also discussed with possible treatment options.

Keywords antihistamine; atopic; dermatoses; haematological; hepatic; itch; pruritus; renal; thyroid; urticaria

What's new?

- Recent studies show a high incidence and burden of itch in the general population
- Recent data from the International Forum on the Study of Itch suggest that structural questionnaires in addition to visual analogue scales are useful in the assessment of itch
- New mediators have been implicated in itch; therefore combination therapies are important
- New guidelines on management of urticaria recommend up to four times the usual daily dosage of non-sedative H_1 antihistamines
- New European guidelines recommended gabapentin for the treatment of pruritus associated with chronic renal disease and neuropathic chronic pruritus
- Antidepressants may be helpful in treatment due to their sedative properties, although precise mechanisms are still unclear

Introduction

Itching (pruritus) is a frequent symptom of many dermatoses and systemic diseases, as well as some neurological and psychological disorders. Itch is the sensation that leads to reflex scratching of the skin to relieve it, just as pain elicits the withdrawal reflex to remove the cause. It may be acute or chronic (lasting more than 6 weeks) and is an extremely distressing symptom that can be disabling and can impair quality of life.[1] Each patient with itch has to be considered individually as the origins of the symptom are numerous. A recent study showed a high burden of chronic pruritus in the general population.[2]

Pathophysiology of itch

The pathophysiology of itch is complicated and multifactorial. Itching is caused by a number of complex factors including chemical mediators in the skin and blood. Involvement of peripheral and central neural mechanisms is similar to the pathways described for pain.[3,4] Unmyelinated nerve fibres for itch and pain both originate in the skin with information being conveyed centrally by two distinct systems. However, both use the same peripheral nerve bundle and spinothalamic tract.[5] A number of different types of stimuli can induce itch. Histamine is still the most well-known mediator but other factors include prostaglandins, proteinases, opiates, neuropeptides (substance P), neurotrophins (nerve growth factor) and cytokines (interleukin (IL)-2, IL-31). This explains why not every itch is relieved by antihistamines and why no single therapy is consistently effective.[6,7]

Classification of itching

A useful clinical approach for patients with chronic pruritus is the clinical classification of itch by the International Forum on the Study of Itch (IFSI).[8] The IFSI classification draws a clinical distinction between patients with itch, depending on whether their skin is normal, primarily inflamed (dermatoses) or associated with lesions secondary to scratching. The underlying disease process can be masked due to excoriations. Chronic itching can result from dermatological and systemic diseases. Itching is present in all patients with certain dermatoses, such as atopic dermatitis, urticaria and lichen planus. Patients with systemic diseases, such as primary biliary cirrhosis, chronic renal failure and Hodgkin's disease, can also present with itch. In patients where no identified underlying disease is detected, the term pruritus of unknown origin is used. The IFSI has recently provided invaluable data on the use of visual analogue scales (VAS) as an assessment tool in routine examinations, although more disease- and population-specific questionnaire validation is recommended for future studies.[9]

Other clinical classifications have been proposed in the past, based on the understanding of peripheral and central origins of itch. The four categories proposed were pruritoceptive itch (due to inflammation), neuropathic itch (post-herpes zoster), neurogenic itch (itch of cholestasis) and psychogenic itch (delusional parasitophobia). This classification is also clinically relevant and informative as to the pathomechanisms of pruritus.

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Causes of itch

Common dermatoses characterized by itch

The commonest inflammatory dermatoses causing itch include eczema, urticaria, lichen planus, scabies and immunobullous disorders (e.g. dermatitis herpetiformis). Psoriasis can also be associated with itch. To establish the diagnosis, a skin biopsy may be necessary, with histology, and in some cases direct immunofluorescence (as in immunobullous disorders or autoimmune disease) (Table 1).

Dry skin (xerosis) can be itchy, especially in the elderly (senile pruritus, asteatotic eczema), and can result from decreased function of the stratum corneum, polypharmacy or underlying disease (e.g. hypothyroidism).

Urticaria is an example of a cutaneous disease characterized by or associated with itch. It may be spontaneous, inducible and intermittent (Table 2). The history and assessment of the patient is very important as there may be no rash when the patient is seen. Urticaria is managed according to the assessment of the patient by history, clinical examination, and physical or laboratory tests. It can be acute (less than 6 weeks) or chronic (more than 6 weeks). Non-sedating H_1 antihistamines are the preferred treatment for symptomatic relief and current European guidelines suggest increasing the dosage by up to four times the recommended dosage.[10] H_2 receptor antagonists (ranitidine, cimetidine) can be used as well. Montelukast may be used off licence in some individuals with urticaria. Further treatments include immunomodulatory agents such as prednisolone, ciclosporin, methotrexate, mycophenolate mofetil or dapsone. The latest treatment for urticaria unresponsive to second-line treatment is the biologic immunoglobulin E (IgE) receptor antagonist, omalizumab, anti-IgE.

Classification and common causes of pruritus

Dermatological
Most inflammatory dermatoses — *Atopic dermatitis, lichen simplex, lichen planus, urticaria, drug hypersensitivity, scabies, xerosis, mycosis fungoides*
Systemic
Hepatic — *primary biliary cirrhosis, biliary obstruction, cholestasis during pregnancy, hepatitis B and C*
Renal — *chronic renal failure, dialysis*
Endocrine — *hypothyroidism*
Malignancies — *lymphoma, myeloma, central nervous system tumours*
Haematological — polycythaemia rubra vera, paraproteinaemia, iron deficiency
Neurological
Multiple sclerosis, brachioradial pruritus, notalgia paraesthetica, post-herpetic neuralgia
Psychogenic/psychosomatic
Parasitophobia
Mixed
Co-existence of several diseases
Other
Pruritus of undetermined origin

Table 1

Classification of urticaria

Spontaneous urticaria
Acute urticaria — *Spontaneous weals <6 weeks*
Chronic urticaria — *Spontaneous weals >6 weeks*
Inducible urticaria
Physical Urticaria:
Acquired cold urticaria — *Cold air, water, wind*
Delayed pressure urticaria — *Vertical pressure, weals arising 3–8 hours later*
Heat urticaria — *Localized heat*
Solar urticaria — *ultraviolet or visible light*
Dermographic urticaria, urticaria factitia — *Mechanical shearing forces, weals arising after 1–5 minutes*
Vibratory urticaria, angioedema
Other types of urticaria
Cholinergic urticaria — *Increase of core body temperature*
Exercise-induced anaphylaxis, urticaria — *Physical exercise*
Contact urticaria
Aquagenic urticaria — *Water*

Table 2

Itch and systemic disease

Systemic diseases are frequently associated with itching which can precede the diagnosis of the underlying disease.[11]

Pruritus in liver disease

Itching can be a feature of primary biliary cirrhosis, cholestasis (induced by drugs, mechanical obstruction, amyloidosis[12]), hepatitis B, hepatitis C and alcoholic liver disease.[13] Successful treatments include opiate antagonists, bile salt-binding agents, hepatic enzyme inducers and ultraviolet B (UVB) phototherapy.

Pruritus in renal disease

Itch is commonly seen in patients with chronic renal disease, especially those undergoing dialysis. The pathogenesis of itch due to uraemia is unknown, but metabolic factors have been implicated (calcium, magnesium, parathyroid hormone, histamine, and tryptase), as well as dysfunction of peripheral or central nerves involved with opioid receptors.[14] Dry skin is also associated with chronic renal failure. Chronic renal failure patients may be treated with erythropoietin, opioid antagonists, thalidomide, parathyroidectomy or UVB phototherapy.[15]

Itching in metabolic/endocrine disease

A significant number of patients with endocrine disorders (e.g. thyroid disease, diabetes mellitus) report itching. In hypothyroidism the itch is often associated with dry skin. In diabetes there can be localized anogenital pruritus, which may be caused or exacerbated by mucocutaneous candidiasis. But it is unclear whether diabetes is responsible for generalized pruritus without a rash.

Pregnancy

Itching in pregnancy can be due to polymorphic eruption of pregnancy, pemphigoid gestationis, intrahepatic cholestasis or

atopic eruption of pregnancy.[16] These are treated with topical or systemic glucocorticoids and antihistamines. Delivery may alleviate symptoms, but in some cases the itching can persist after childbirth.

Haematological disorders

Iron deficiency or iron overload (haemochromatosis) can present with pruritus, as can haematological disorders. Polycythaemia rubra vera can be associated with aquagenic pruritus. Other myeloproliferative disorders may also cause itching.

Itching in malignancy

A number of different malignancies can present with pruritus.[17] Lymphoproliferative disorders are often associated with itch, which may be secondary to toxic by-products or allergic reactions that can directly affect neurones or the brain. Hodgkin's lymphoma leads to itching without a rash, which could be secondary to peptidases, bradykinin, histamine release or increased IgE concentration. Carcinoid syndrome may lead to flushing, diarrhoea, cardiac symptoms and itching.

Infectious diseases

Infections such as hepatitis can cause itch. HIV disease can result in itch with purpuric, papular and folliculitic lesions.[18] Some infestations, such as scabies or lice, cause generalized itching with widespread evidence of scratching (excoriations). Scalp, finger webs and clothing seams should be closely examined.

Drug-induced itching

In most cases of drug reactions the itch is associated with a rash, such as urticarial lesions, morbilliform lesions, dryness or phototoxicity. In some cases, only scratch marks are seen, as in cholestasis due to the oral contraceptive pill and phenothiazines. Opiates appear to act centrally and on mast cells, inducing histamine release and itch.

Neuropathic and psychogenic itching

Multiple sclerosis, cerebral infarctions and brain tumours can all lead to itching. Neurological itch may also be secondary to compression of nerves or spinal damage, as in brachioradialis pruritus and localized chronic itching (following herpes zoster infection). Somatoform pruritus is defined as itching where psychiatric and psychosomatic factors play a critical role in the inflammation, intensity, aggravation or persistence of itching.[19]

Assessment and investigations

History

A detailed history of the itch is important, including its duration, onset, frequency, time-course and whether it is localized or generalized. Factors that alleviate or exacerbate itch should be documented, as well as any previous skin disorders or history of atopy. The presence of a rash, the severity and effect on quality of life should be assessed. A full medical, drug and social history is essential.

Investigation

Dermatoses with rash: examination of the skin in generalized pruritus should include the finger webs, nails, scalp and mucosae. Dermographism should be elicited, as well as signs of scratching, such as excoriations, purpura or bruising. Evidence of chronic scratching may present as lichenification or pigmentary changes.[20] Dermatoses causing itch can be localized or generalized (Table 3).

Generalized itching without rash: this can be extremely challenging. A wide variety of disorders are associated with itch, although in many cases no single cause may be identified. Underlying causes should be looked for in the history, examination and tests of these patients to detect a treatable systemic disease. Often the itch can predate evidence or diagnosis of the underlying cause. If no cause for itch can be found (pruritus of unknown origin), psychological disorders, such as anxiety, neuroses and parasitophobia, should be considered.

Management of itching

While the diagnosis can be difficult to establish, investigation of the underlying cause is important so that the most appropriate and successful therapeutic intervention may be given. Several topical, systemic and physical treatments are available.[21,22] General measures can be beneficial in both primary dermatoses and where the itch is secondary to an underlying cause. These include avoiding heat, allergens and certain drugs, as well as use of emollients and cooling menthol preparations. Soap substitutes and moisturizers prevent loss of water from the skin and form a barrier to irritants. Systemic treatments include oral

Investigation of common causes of itching

History
Establish history of pruritus or rash, identify associated systemic disorders, past medical history including psychiatric disorders, drug history, allergies, family history. Itch may occur without a rash.

Examination
There may be evidence of skin disease or signs of systemic disorders should be looked for, examine all areas - finger webs (scabies), scalp (lice, fungal infection) and mucosae. Look for evidence of urticaria (wheals) symptomatic dermographism, cholinergic urticaria (small inducible papules) and cold urticaria (ice cube test), should be tested for when suspected from the history.

Baseline investigations
Full blood count, erythrocyte sedimentation rate, iron, serum ferritin, renal function, liver function, thyroid function, blood glucose, chest X-ray

Other investigations where appropriate
Calcium, serum electrophoresis and urine test, stool for ova, cysts and parasites, HIV testing, hepatitis B, hepatitis C, cancer screening, serum C-reactive protein, autoantibodies, antinuclear factor

Diagnostic investigation
Skin biopsy, histopathology and consider direct immunofluorescence

Questionnaire assessment
Visual analogue scales, quality of life measurements

Table 3

antihistamines (urticaria), and are effective in breaking the itch–scratch cycle (atopic dermatitis) due to their sedative properties.

If topical treatments and antihistamines are not successful, further treatment options include immunosuppressants, such as prednisolone and ciclosporin for inflammatory diseases. Tricyclic (doxepin) and other antidepressants may be useful, but the precise mechanism is not known and they may act through an antidepressant or antineuralgic effect. Paroxetine and other selective serotonin re-uptake inhibitors (SSRIs) may also be helpful. Other neuromodulatory agents, such as gabapentin and pregabalin, have recently been found to be safe and effective in treating itch associated with chronic renal disease and neuropathic chronic pruritus. Phototherapy is useful in itching associated with malignancy and pruritus of unknown origin (Table 4).[23]

Treatment of itch

Common topical treatments

Emollients

Reduce trans-epidermal water loss by improving barrier function.

Aqueous cream, emulsifying ointment, white soft paraffin, hydrous wool fat

Other topical lotions

Calamine, menthol, capsaicin

Topical corticosteroids

Use in corticosteroid-sensitive inflammatory conditions such as eczema

1% hydrocortisone (mild), clobetasone butyrate (Eumovate®)(moderate), betamethasone valerate (Betnovate®) (potent), clobetasol propionate (Dermovate®) (very potent)

Systemic treatments

Antihistamines

Reduce itch in some conditions associated with histamine release or can act as sedative agents to reduce the itch–scratch cycle; H_1 antihistamine and H_2 receptor blockers can be helpful in some conditions, such as urticaria

Chlorphenamine, loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine

Immunosuppressants

Consider in inflammatory disorders

Prednisolone, ciclosporin

Antidepressants

May be effective by antihistaminic, antidepressant or antineuralgic effect.

Tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs)

Other neuromodulatory agents

In chronic renal failure and liver disease

Gabapentin

Opiate (μ receptor) antagonist – naltrexone

Physical treatments

Phototherapy

Used in itching associated with malignancy. Useful in patients with pruritus of unknown origin

Ultraviolet (UV) A, psoralen UVA

Table 4

Conclusion

Itch is often extremely distressing, affecting the patient's quality of life. Successful management of the itching patient relies on a thorough clinical history, examination, investigation and diagnosis. This allows treatment to be directed towards the underlying cause, resulting in symptomatic relief.[24] Itch can be due to an underlying skin disease or systemic disorder, but in some cases its origin remains unknown. Even when a diagnosis has been established it can be a difficult symptom to treat. No single therapeutic agent is consistently successful in treating itch. Recent advances in mechanisms underlying this common symptom may identify novel targets for future therapy.[25] ◆

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Haematological emergencies

This article presents emergency management from scenarios across haematology. These have been prepared by the individual contributing authors but assembled here for direct reference.

Sickle cell emergencies[1]

Acute vaso-occlusive sickle crisis (VOC)

VOC is a common reason for admission among patients with sickle cell disease. Supportive treatment includes:

- *Analgesia* — rapid and effective pain relief; NICE guidelines recommend[2] adequate analgesia within 30 minutes of presentation. Opioids are often required.
- *Hydration* — ideally oral, or intravenous when necessary.
- *Oxygenation* — if oxygen saturation is less than 94% breathing room air.
- *Anti-microbials* — if there is concern about an intercurrent infection.

Acute chest syndrome

Acute chest syndrome usually presents with pain and hypoxia (should be managed by or with support from a clinical haematologist). Management comprises:

- *Oxygen* — supplementary oxygen aiming to keep oxygen saturation over 94%.
- *Analgesia* — see acute VOC crisis management above.
- *Antibiotics* — broad-spectrum agents with cover for lower respiratory tract infection.
- *Transfusion* — consider and discuss with all patients; if haemoglobin is less than 60 g/litre simple top-up transfusion is used aiming for haemoglobin (Hb) of 100 g/litre, but in patients with severe disease or Hb over 90 g/litre exchange transfusion may be necessary, aiming to decrease HbS to less than 30%.
- *Hydration* — good hydration is mandatory with close monitoring of fluid status to avoid fluid overload.
- *Early referral for consideration of ventilation support* — is essential.

Acute stroke

Acute stroke should be managed by or with support from a clinical haematologist. All sickle cell patients presenting with new neurological symptoms require urgent assessment. Where a stroke is suspected, confirm urgently with an MRI scan of brain if possible. Treat with urgent exchange transfusion, aiming to decrease the HbS to less than 30%. Once exchange complete, admit to a stroke unit/ward for joint management by haematologist and stroke team. There is no evidence of the efficacy of aspirin or thrombolysis but these can be considered if there are no contraindications. Following a stroke there is a high risk of recurrence so long-term transfusion should be offered as secondary prevention.

Infections and sepsis

The risk of infection is increased in part because of hyposplenism, which develops during childhood. All sickle patients should be given life-long prophylactic phenoxymethylpenicillin from presentation, and offered vaccination against pneumococcus, *Haemophilus influenza* B, meningitis C and seasonal influenza. It is important to have a low threshold for treatment with antibiotics when a patient presents with signs and symptoms of infection.

Priapism

A sickle patient with priapism lasting more than 2 hours should be referred urgently for urological assessment. Initial management is as for a presentation with acute VOC crisis, ensuring good analgesia and hydration. Urological management may comprise an α-adrenergic agent, such as etilefrine, or aspiration of blood from the penile vasculature (corpus carvenosum), with or without irrigation with a dilute solution of phenylephrine. Emergency surgery may be required. Exchange blood transfusion may be considered if urological measures are not wholly successful.

Splenic sequestration and acute aplasia secondary to erythrovirus (parvovirus) B19

Both of these conditions require prompt recognition and management with transfusion. Patients with an aplastic crisis are usually reticulocytopenic and may give a history of a preceding viral illness. Patients with splenic sequestration (usually children) present with anaemia in the presence of an enlarging spleen.

Acute pulmonary embolism (PE)

This involves prompt recognition of the possibility of this diagnosis and appropriate imaging; a suggested algorithm is summarized in Figure 1.

Immune thrombocytopenic purpura (ITP)[3]

Marked bleeding (usually gastrointestinal, urogenital or neurological) will need urgent management to control the bleeding and increase the platelet count. Platelet transfusions will be effective only for a short period; in severe uncontrolled bleeding they may need to be given twice daily (or more frequently), and are usually best combined with intravenous (IV) immunoglobulins (up to 1 g/kg/day) and high-dose IV methylprednisolone (500 mg/day for 2—3 days if needed). Anti-platelet agents (aspirin and clopidogrel) should be stopped and tranexamic acid (an antifibrinolytic agent) given either IV or orally at a dose of 1 g up to 4-hourly considered. Consider emergency splenectomy, rituximab or thrombopoietin agonists if there is no response to initial treatment.

Bleeding in haemophilia A and B[4]

Prompt assessment and treatment of bleeding problems in patients with inherited bleeding tendencies leads to a better outcome. In the acute period, trough factor levels of 60—70% are desirable. Trauma results in the need for immediate access to factor concentrate replacement, aiming for levels of ≥100%; trauma to the head, neck or abdomen is the most dangerous and challenging. Head injuries and neck trauma should always be managed as life threatening, with a low index of suspicion for intracranial bleeding. Symptoms and signs may take some time to develop. Reference to the patients bleeding disorder card (which identifies their diagnosis and specific product usage) is helpful, but expert advice from a haemophilia

Taken with permission, from the freely downloadable app for iPhone, iPad and Android (type Thrombosis into the App Store) detailing all the Thrombosis guidelines at Guy's & St Thomas' NHS Foundation Trust, London.

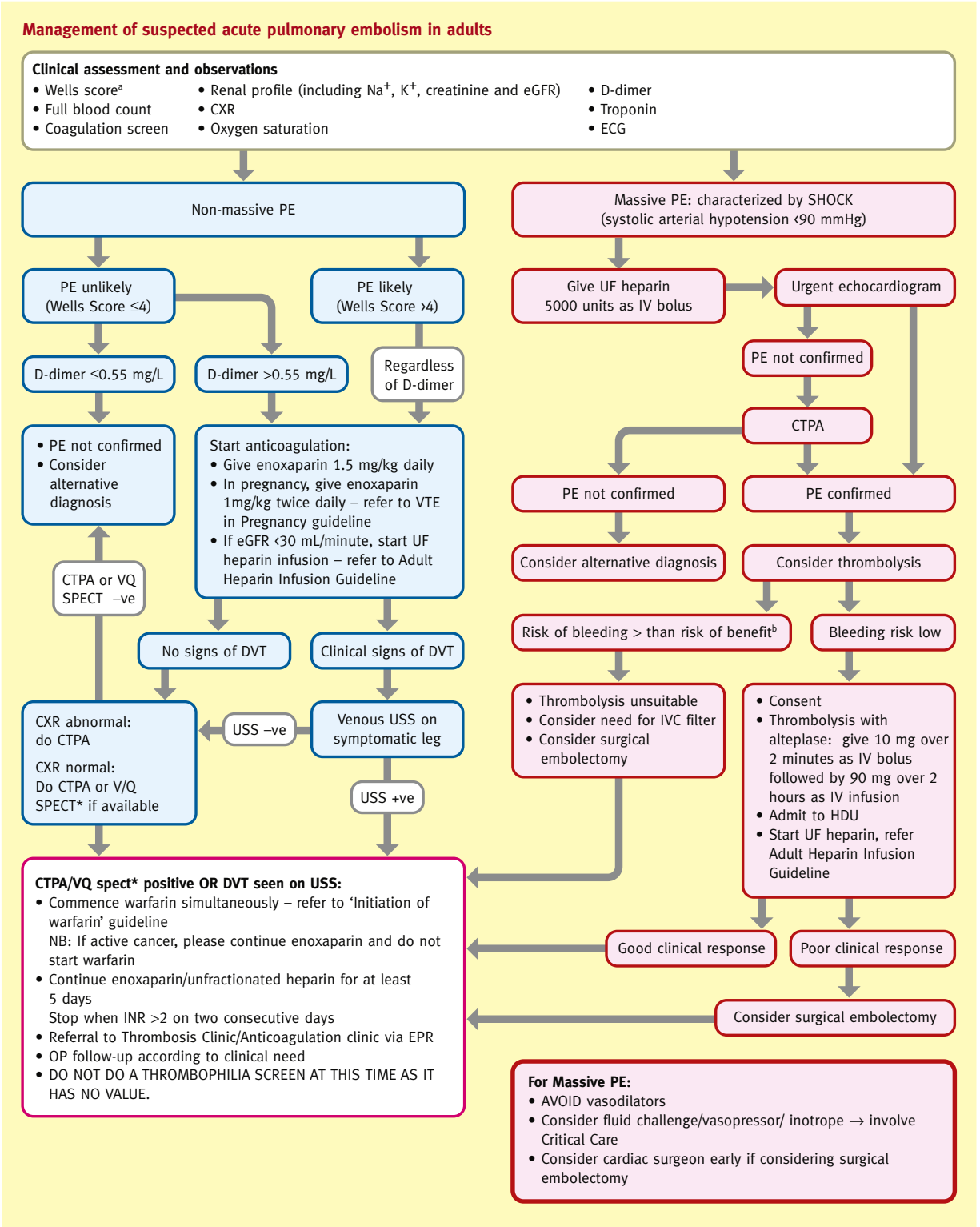

Figure 1 Reproduced by kind permission of the Thrombosis & Thromboprophylaxis Committee of Guy's & St Thomas' NHS Foundation Trust. (See also appendix A, B and C).

specialist is essential. Standards of care for emergency situations and UK guidelines can be found at www.ukhcdo.org/UKHCDOguidelines.htm.[5]

Disseminated intravascular coagulation (DIC)[6,7]

These patients may present with bleeding or thrombosis or have deranged coagulation in the absence of either bleeding or thrombosis. The most important aspect of management of DIC is to remove the causative factor and treat underling infections. If the patient is bleeding, they should also receive fresh frozen plasma (FFP), which contains almost all clotting factors and inhibitors. Standard doses of 15 ml/kg should be given initially but patients may require more. Platelet transfusions should be used if the platelet count is less than 50×10^9/litre, to maintain a target of $75–100 \times 10^9$/litre, depending upon the severity of the bleeding. Fibrinogen concentration should be raised if less than 1.0 g/litre using fibrinogen concentrates or cryoprecipitate.

If thrombosis is extensive, heparin therapy is sometimes given. Following initial replacement therapy, any further treatment should be guided by the clinical and laboratory response with the following suggested threshold values: platelets over 50×10^9/litre, fibrinogen over 1.0 g/litre and the maintenance of the prothrombin time (PT) and activated partial thromboplastin time (APTT) less than 1.5 times the mean control. There is no need to restore these variables to normal in the absence of bleeding unless the patient is due to have an invasive procedure.

Management of acute transfusion reactions

All patients should be transfused in clinical areas where they can be directly observed to allow prompt detection and immediate management of acute reactions. If the presumed transfusion reaction is severe or life threatening, the transfusion must be discontinued with immediate assessment.

- Stop and disconnect the blood pack and giving-set immediately (but *do not* discard).
- Maintain venous access with sodium chloride 0.9%, commence resuscitation.
- Take samples for full blood count, renal and liver function tests, blood cultures, coagulation screen, repeat compatibility testing, DAT, LDH and assessment of urine for haemoglobin.
- Check identification details between the patient, their identity band and the blood component.
- Consider key/additional features:
  - Fever and shock without anaphylaxis – ? ABO mismatched transfusion? bacterial sepsis.
  - Dyspnoea without shock – ? TRALI vs TACO – check O_2 sats or blood gases and CXR.
  - Dyspnoea/stridor with shock - ?severe allergic reaction or anaphylaxis.
- Seek early support and advice from critical care and haematology teams.

Table 1

Bleeding during anticoagulant treatment[8]

Emergency management of haemorrhage comprises supportive treatment, transfusion, stopping anticoagulant therapy and urgent reversal of anticoagulation. Clinical assessment of the patient to ascertain the degree and site of bleeding is imperative in addition to monitoring coagulation and full blood count to determine the extent of bleeding. Reversal of anticoagulation is summarized in Table 1, page 238, *Medicine* 2013; **41**(4).

For elective procedures where cessation of anticoagulation is required, the risk of bleeding must be balanced against the thrombotic risk of the procedure and the consequences of reversal for the patient. Patients deemed to have a high risk of perioperative thromboembolism (e.g. recent thrombosis, or a metallic mitral valve) require bridging anticoagulant therapy with shorter-acting anticoagulants. Low-molecular-weight heparin (LMWH) is used as a bridging agent perioperatively. In these circumstances it is wise to discuss management with a haematologist.

Massive haemorrhage[9]

Definitions of massive blood loss vary (e.g. loss of one blood volume within a 24-hour period, 50% blood volume loss within 3 hours, loss of 150 ml/minute) but these may be difficult to apply in the acute situation. Hospitals must have local major haemorrhage protocols and all medical, nursing, laboratory and support staff should know where to find the major blood loss protocol in relevant areas and be familiar with its contents, supported by training and regular drills. This must include a strategy to ensure that red cells and components are readily available in life-threatening bleeding. The patient must have a correctly labelled blood sample for pre-transfusion testing before Group O emergency blood is administered.

Good communication is essential between all teams involved in the management of patients. The switchboard can play a key role in initial alert of key members, followed by contact of further teams as needed. These might include the senior clinician in the relevant clinical area, an anaesthetist/intensive care unit (ITU) team, a senior nurse/midwife, the transfusion laboratory and other laboratories (haematology and coagulation, biochemistry), the clinical haematologist on call, radiology (including interventional radiology), and porters/other support staff. There should be a designated team leader coordinating management, who should also nominate a specific member of the team to communicate with the laboratory staff throughout the incident.

FFP used early may pre-empt the development of significant coagulopathy. While traditional wisdom recommends use of FFP to maintain PT and APTT at a ratio of less than 1.5 times normal, in practice there are often significant delays in the availability of laboratory-based coagulation testing. Studies investigating the use in massive haemorrhage of early FFP in a ratio of 1:1 with red cells are largely retrospective, often in the military situation and are limited by the effect of survivor bias, so this approach is not routinely recommended. An empirical approach involves the administration of FFP early in the resuscitation process at a dose of 15–20 ml/kg (pragmatically four units FFP with six units red cells) and before coagulation investigation results are known (although baseline tests should have been taken). If possible, further treatment should be guided by results of laboratory-

based (e.g. PT/APTT) or near-patient (e.g. thromboelastography (TEG) or thromboelastometry (ROTEM)) tests of coagulation.

Fibrinogen supplementation should be given if fibrinogen concentration falls below 1.5 g/litre or as guided by TEG/ROTEM. Cryoprecipitate is given at a standard dose of two five-unit pools. Fibrinogen concentrate is currently not licensed in the UK but is used extensively in Europe as an alternative to cryoprecipitate at a dose of 3–4 g. One unit of platelets should be administered when the platelet count falls below 75×10^9/litre, or 100×10^9/litre in complex trauma (especially with head injury). Aim to maintain platelet count over 50×10^9/litre, or over 75×10^9/litre if there is active bleeding.

Adult trauma patients with, or at risk of, major haemorrhage, in whom antifibrinolytics are not contraindicated, should be given tranexamic acid as soon as possible after injury, in a dose of 1 g over 10 minutes followed by a maintenance infusion of 1 g over 8 hours. The use of tranexamic acid should be considered in non-traumatic major bleeding where there is no contraindication.[10]

Acute blood transfusion reactions

The differential diagnosis of a severe, life-threatening transfusion reaction includes acute haemolytic reactions (usually due to ABO-incompatible transfusion), bacterial transfusion-transmitted infection, anaphylaxis, transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). The British Committee for Standards in Haematology (BCSH) has produced a guideline for the investigation and management of acute transfusion reactions (see Figure 1, *Medicine* 2013; **41**(4): pages 242–247).

Acute haemolytic reaction is most commonly due to human error with transfusion of ABO-incompatible red cells, which react with the patient's anti-A or anti-B antibodies. Activation of complement causes rapid destruction of the transfused red cells in the circulation (intravascular haemolysis) and triggers the release of inflammatory cytokines. The patient quickly becomes shocked and develops acute renal failure and DIC.

Transfusion of a blood component contaminated by bacteria is a rare event seen in particular with platelet components that are stored at 22–24 °C, rather than red cells. Bacterial screening of platelets is now carried out throughout the UK and has reduced the risk of such events. The transfusion of a contaminated pack can produce rapid onset of fever (usually >2°C above baseline), rigors and hypotension, which may be initially indistinguishable from an acute haemolytic reaction or severe allergic reaction.

Severe allergic or anaphylactic reaction can result in severe hypotension or shock associated with wheeze (bronchospasm), stridor or swelling of the face, limbs or mucous membranes (angioedema), and urticarial. It is most commonly reported with plasma-rich components such as platelets or FFP but can occur with red cells. This reaction requires immediate intervention to ensure the airway is patent and the administration of adrenaline (epinephrine) according to the UK Resuscitation guidelines.

Transfusion-related acute lung injury (TRALI) is caused by antibodies *in the donor blood* reacting with the patient's neutrophils sequestered in the lungs, causing leakage of plasma into the alveolar spaces. Most cases present within 2 hours of transfusion (maximum 6 hours), with severe dyspnoea and cough with frothy pink sputum, often associated with hypotension and occasionally fever and rigors. Chest X-ray shows bilateral nodular shadowing. TRALI is often confused with acute heart failure due to circulatory overload. Treatment is supportive, with high-concentration oxygen therapy and ventilatory support, and corticosteroid therapy is not effective.

Transfusion-associated circulatory overload (TACO) presents with acute or worsening pulmonary oedema within 6 hours of transfusion with respiratory distress, tachycardia, raised blood pressure and evidence of positive fluid balance. TACO is a significant cause of morbidity and mortality due to blood transfusion. The haemovigilance scheme, SHOT (serious hazards of transfusion), received 71 reports of TACO in 2011, contributing to death in two patients and responsible for 24 cases of major morbidity.

Elderly patients are at particular risk and many have predisposing medical conditions such as heart failure, renal impairment, hypoalbuminaemia and fluid overload. Treatment includes stopping the transfusion and administering oxygen and diuretic therapy, with careful monitoring and specialist support if required. The risk of TACO is reduced by careful pre-transfusion assessment of predisposing factors, prescription of appropriate volume and flow rate and adequate monitoring during the procedure.

Large mediastinal mass[11]

Patients with large mediastinal masses may present acutely with airway compromise and/or superior vena cava obstruction and require urgent therapy for symptom relief. Wherever possible, diagnostic tissue must be obtained before treatment to allow an accurate diagnosis and definitive treatment plan. Surgical decompression is almost never indicated as non-Hodgkin's lymphoma is likely to respond promptly to appropriate chemotherapy with clinical improvement within hours. If there are delays in administering definitive chemotherapy once diagnostic tissue has been obtained, corticosteroid therapy can be started (e.g. prednisolone 100 mg daily). Measures may need to be taken to protect the airway in the short term.

Hypercalcaemia[12]

Hypercalcaemia, defined as a corrected serum calcium higher than 2.6 mmol/litre, is a presenting feature in up to 30% of patients with myeloma but may also occur in other malignancies and endocrine conditions. It can be asymptomatic but more often presents with one or more of the following symptoms: fatigue, nausea, vomiting, anorexia, abdominal pain as a consequence of constipation or rarely pancreatitis, polyuria and thirst, bone aches, muscle weakness, cardiac arrhythmias, confusion and, rarely, coma. In addition to the raised serum calcium, renal impairment and a shortened QT interval on ECG can be detected.

Treatment requires measures to reduce serum calcium acutely as well as appropriately directed chemotherapy. Mild hypercalcaemia (2.6–2.9 mmol/litre) will often respond to rehydration with oral and/or IV fluids (sodium chloride 0.9%). Moderate/severe hypercalcaemia (>2.9 mmol/litre) requires patients to be hydrated more aggressively. Fluid overload is a risk and a loop diuretic, which may additionally aid calcium excretion, may be necessary. It is routine to give an IV bisphosphonate. Zoledronic acid (4 mg over 15 min) or disodium pamidronate (90 mg over 90 minutes) are the

bisphosphonates of choice. Zoledronic acid had demonstrated superiority for the treatment of hypercalcaemia of malignancy in a trial of predominantly solid tumour patients. Dose reduction is required in renal impairment. Normalization of serum calcium is achieved by 4 days in 50% of patients whereas poorly responsive patients may need further bisphosphonate therapy. The use of corticosteroids or calcitonin should be considered in poorly responsive hypercalcaemia.

Cord compression

Spinal cord compression is a medical emergency and requires prompt diagnosis and management to prevent irreversible damage and paralysis. It occurs in up to 5% of myeloma patients and is the result of bony or soft tissue expansion of myeloma or vertebral collapse. Presenting features depend on the site, extent and rate of development of the lesion, and include sensory disturbance or loss in distribution areas below the lesion (sensory level), reduction of power in the limbs, difficulty walking and sphincter disturbance. Treatment with dexamethasone 8 mg twice daily should be commenced on suspicion of spinal cord compression and directed investigations undertaken urgently. MRI scanning is the imaging modality of choice but if this is unavailable or not tolerated computed tomography can be used. Bone-associated cord compression may be best managed by surgical decompression and/or stabilization and should be discussed with a neurosurgical/orthopaedic team as appropriate to local availability. Soft tissue compression is more often amenable to local radiotherapy and discussion with a clinical oncology team is urgently recommended.

Neutropenic sepsis[13]

This is an emergency that occurs commonly either in the presentation or during the course of treatment of patients with leukaemia and other haematological malignancies. It is defined as the occurrence of temperature of 38°C or higher in a patient who has a neutrophil count less than 0.5×10^9/litre and may be associated with a systemic inflammatory response (neutropenic sepsis) and evidence of end-organ decompensation such as hypotension, renal failure, hypoxia (septic shock). Patients should be advised to monitor their temperature whilst ambulant or at home and contact their treating hospital (usually the treating haematology team) immediately if they are unwell or have temperature of over 38°C. Immediate blood cultures from central venous catheters as well as peripheral blood cultures should be followed by parenteral broad-spectrum antibiotics — to cover *Pseudomonas* and Gram-negative bacteria as per the local protocol — as soon as possible with a suggested door-to-needle time of under 1 hour. Where a catheter-related infection is suspected, vancomycin may be added. For patients undergoing chemotherapy who attend an emergency service it would be prudent to assume neutropenia and administer antibiotics whilst awaiting confirmatory blood tests. For continued neutropenic sepsis, further antibiotics may be added based on culture results, or changed to second line if sepsis persists beyond 48 hours.

Hyperleucocytosis

The presence of a high white cell counts, usually over 100×10^9/litre, particularly in acute myeloid leukemia (AML) (rarely in acute lymphoblastic leukaemia (ALL)), may cause symptoms such as dyspnoea, headaches or confusion. This may be confirmed by finding papilloedema or retinal haemorrhage on fundoscopy, and/or chest X-rays that show pulmonary infiltrates. Early management includes cytoreduction with either chemotherapy (hydroxycarbamide or induction chemotherapy) or leukapheresis. Blood transfusions may worsen these symptoms and should be either withheld or given cautiously whilst attempting to reduce the white cell burden.

Acute promyelocytic leukaemia (APML)

APML should be suspected in any leukaemia presenting with bleeding manifestation. All-trans-retinoic acid (ATRA) should be commenced immediately whilst attempting to confirm the diagnosis morphologically, cytogenetically or, rarely, using the PML antibody test. Frequent monitoring of the haemogram, particularly the platelet count and coagulation profile including fibrinogen, with correction of any abnormalities in order to maintain platelet count over 50×10^9/litre ($>100 \times 10^9$/litre if intracranial bleed) and fibrinogen over 150 mg/dl is necessary. Treatment of APML with ATRA/arsenic or ATRA/idarubicin or all three results in excellent long-term remission.

Tumour lysis syndrome (TLS)

TLS is defined by the presence of at least two of the following criteria:

- laboratory — abnormal serum zinc, potassium, phosphate or calcium at presentation or a 25% change in value
- clinical — presence of renal dysfunction, seizures, or cardiac arrhythmias/arrest.

Ideally, TLS should be prevented and anticipated rather than treated. It is prevented by aggressive hydration, maintaining diuresis and use of allopurinol or, in high-risk cases, rasburicase (not to be used in glucose-6-phosphate dehydrogenase-deficient patients). Treatment includes attention to electrolyte abnormalities, consideration for dialysis and use of allopurinol or rasburicase. ◆

Appendix. Additional data for Figure 1

Management of suspected acute pulmonary embolism in adults protocol

A: Wells score	3
• Clinical signs of a DVT	
• Alternative diagnosis less likely than a PE	3
• Previous DVT or PE	1.5
• Recent surgery or immobilization	1.5
• Heart rate >100 beats/minute	1.5
• Cancer	1
• Haemoptysis	1

Clinical probability: add up individual scores and check the following:

- Score > 4 — PE likely. Consider diagnostic imaging.
- Score 4 or less — PE unlikely. Consider D-dimer to rule out PE

B: Consider bleeding risks for thrombolysis

- Hypersensitivity to the active substance or to any of the excipients of alteplase:
  - Arginine
  - Dilute phosphoric acid
  - Polysorbate 80
- Known bleeding diathesis
- Patients taking oral anticoagulants (e.g. warfarin)
- Suspected/recent intracranial haemorrhage/stroke/sub-arachnoid haemorrhage or CNS damage or surgery
- Recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- Severe uncontrolled arterial hypertension
- Bacterial endocarditis, pericarditis
- Acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
- Neoplasm with increased bleeding risk
- Severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Recent major surgery or significant trauma

NB: Decision for individual patient depends on individual risk benefit analysis.

C: VQ Spect

- Similar sensitivity for diagnosing patient as CTPA
- Lower radiation dose to breast tissue

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The blood in systemic disease

Ted Gordon-Smith

Abstract

Haematological changes are common in systemic disease. Anaemia of chronic disease (ACD) occurs in inflammatory conditions where persistent cytokine release takes place. Autoimmune cytopenias may accompany systemic immune disorders, lymphomas and virus infections including human immunodeficiency virus (HIV) and Epstein–Barr virus (EBV). Autoimmune cytopenia and ACD may precede the diagnosis of the underlying disease. Liver disease causes coagulation defects through loss of clotting factors but also a procoagulant thrombotic state if protein C becomes deficient first. Neutrophilia occurs in acute bacterial infections; anaemias may be triggered by particular infections.

Keywords anaemia of chronic disease; erythropoietin; hepcidin; liver disease; secondary polycythaemia

Knowledge of the haematological abnormalities of systemic disease aids diagnosis and management. Anaemia is the most common accompaniment, and immune cytopenias occur with some virus diseases and B-cell lymphomas. Lymphomas are more common in immunodeficient disorders (Table 1).

Anaemia of chronic disease

Anaemia of chronic disease (ACD) is the most common anaemia in hospitalized patients. It occurs in chronic inflammation, including infections, connective tissue diseases and malignancy (Table 1), whenever there is an acute phase response, particularly via the cytokines including interleukin-6 (IL-6).[1] A similar anaemia has been recognized in congestive heart failure and type 1 diabetes mellitus without significant renal failure. ACD presents as normocytic, normochromic anaemia (rarely haemoglobin (Hb) <9.0 g/dl) associated with low serum iron and reduced transferrin saturation (reduced total iron-binding capacity), and normal or elevated serum ferritin, and may be evident before any underlying disease causes symptoms. Hypochromic and microcytic change may occur due to impaired release of iron from the reticuloendothelial system, requiring distinction from true iron deficiency anaemia (IDA). In malignancy, other causes of anaemia, such as tumour infiltration of bone marrow and bleeding, may further reduce Hb concentration.

Pathogenesis

Hepcidin is a polypeptide produced in the liver that impairs iron release from macrophages and intestinal enterocytes by binding to and internalizing ferroportin, the major route of iron delivery to transferrin from within the cells.[1,2] It is upregulated by IL-6 and is a key mediator of ACD. Increased hepcidin decreases serum iron and hence its availability for erythropoiesis.

Management

ACD does not respond to iron therapy, which may increase the risk of infection by making iron available to bacterial pathogens.[3] Recombinant human erythropoietin (rhEpo) will raise the Hb but increases beyond total 10–12 g/dl are associated with increased risk of thrombosis.[4–6] In chronic renal failure treated with dialysis, the anaemia responds to rhEpo and iron supplements.[4,5] New therapies directed towards the hepcidin–ferroportin system are under investigation.[6,7]

Malignancy

Anaemia is common in cancer patients, contributes to fatigue and has many causes (Table 1). ACD occurs commonly in patients with necrotic tumours. Disseminated malignancy often produces leucoerythroblastic anaemia or microangiopathic haemolytic anaemia (MAHA) (Table 2, Figure 1). The combination is highly suggestive of disseminated malignancy with marrow involvement. Autoimmune haemolytic anaemia (AHA) is a frequent feature of lymphoma and occasionally other cancers, and benign ovarian cysts.

Renal disease

Anaemia is principally caused by low erythropoietin concentration, which can be corrected by rHuEPO therapy,[8] although full restoration of Hb carries a risk of cardiovascular events.[6] Other causes of anaemia include reduced red blood cell (RBC) survival, iron deficiency (blood loss during haemodialysis and frequent blood sampling), and bleeding as a result of defective platelet function, folate deficiency (chronic haemodialysis), hyperparathyroidism or aluminium toxicity.

HIV infection

Haematological manifestations

The introduction of highly active anti-retroviral therapy (HAART) has greatly changed the spectrum of haematological disorders seen in human immunodeficiency virus (HIV) infection (Table 3). Some, like the primary central nervous system (CNS) lymphoma and Kaposi sarcoma, are AIDS-defining late manifestations of HIV and are rarely seen where screening and early HAART are in place. Others, in particular the immune cytopenias, may still present before HIV is diagnosed and HIV serology should be part of the investigation. Unlike most HIV-associated lymphomas, Hodgkin's disease (HD) has increased since the introduction of HAART; EBV is incorporated in the genome in 90% or more of HIV-HD cases and it may be that this accounts for the finding.[9]

Summary

Anaemia is frequent in chronic disease. ACD must be distinguished from IDA. Autoimmune cytopenias may presage lymphomas, chronic lymphocytic leukaemia or systemic lupus erythematosus. Treatment of the underlying disease together

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Pathogenesis	Causes	Examples
ACD (see text)	Chronic infections	*Bacterial/fungal*: endocarditis, osteomyelitis, tuberculosis, bronchiectasis, abscess, chronic urinary tract infection *Viral*: HIV infection
	Connective tissue disorders	Rheumatoid arthritis,[10,11] SLE, inflammatory bowel diseases, polymyalgia rheumatica, giant cell arteritis, scleroderma
	Malignant disease	Necrotic tumours (e.g. renal cell carcinoma), metastatic carcinoma, lymphoma, myeloma
	Other conditions	Congestive heart failure, ischaemic heart disease, type 1 diabetes mellitus
Iron deficiency anaemia	Blood loss	Gastrointestinal and gynaecological tumours, oesophageal varices, hiatus hernia, drug therapy (aspirin, NSAIDs, corticosteroids)
Haemolytic anaemias	Immune	SLE, lymphomas (B-cell tumours), ovarian cysts, viruses (EBV, HIV), drug induced
	Fragmentation haemolysis (Figure 1a, Table 2)	Cardiac haemolysis (paravalvular/paraprosthetic leak), carcinoma (particularly mucin-secreting tumours), vasculitis (particularly renal), haemolytic uraemic syndrome, meningococcal sepsis
	Intravascular haemolysis	*Liver disease*: Wilson's disease, Zieve's syndrome
Leucoerythroblastic (Figure 1b,Table 2)	Bone marrow (BM) infiltration	Malignant infiltration of BM (metastases), granulomatous disease in BM
Bone marrow depression	Pure red cell aplasia	Thymoma; drug induced (e.g. azathioprine); erythrovirus (parvovirus) B19 (in presence of haemolytic anaemia)
	Aplastic anaemia	Anorexia nervosa; chemotherapy; idiopathic drug induced; hepatitis; chemotherapy/radiotherapy
Macrocytosis	Folate/B_{12} deficiency	Alcoholic liver disease; HIV; ileocaecal tuberculosis; drug induced (zidovudine; chemotherapy)
Polycythaemia	Excess erythropoietin	Renal cell carcinoma (ACD more common), uterine myoma, cerebellar haemangioblastoma
Thrombocytopenia	Immune	Viruses (HIV, EBV, measles); CLL, B-cell NHL; rarely carcinoma (ovarian, lung)
	TTP/HUS	Disseminated carcinoma; HIV; *Escherichia coli* O157 infection
Coagulopathy	Haemorrhagic	Chronic liver disease (factor II, VII, IX deficiency) DIC: Sepsis/severe infection; carcinoma; obstetric complications Renal disease (platelet dysfunction in uraemia)
	Thrombotic	Chronic liver disease (protein C, protein S deficiency) Carcinoma: VTE, Trousseau's syndrome Anti-phospholipid syndrome

ACD, anaemia of chronic disease; BM, bone marrow; CLL, chronic lymphocytic leukaemia; DIC, disseminated intravascular coagulopathy; EBV, Epstein—Barr virus; HIV, human immunodeficiency virus; HUS, haemolytic uraemic syndrome; NHL, non-Hodgkin's lymphoma; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; VTE, venous thromboembolism.

Table 1

Features of leucoerythroblastic anaemia and microangiopathic haemolytic anaemia

	Leucoerythroblastic anaemia	Microangiopathic haemolytic anaemia
Features	Presence of granulocytic and erythrocytic precursors in peripheral blood; anaemia not always present; platelet count usually normal, but may be raised or occasionally low	Mild-to-moderate haemolysis with reticulocytosis, fragmented RBCs, free haemoglobin in plasma and urine, and urine haemosiderinuria; can be associated with disseminated intravascular coagulation, resulting in thrombocytopenia and coagulation disorder
Pathogenesis	Occurs when normal marrow environment disrupted by fibrosis, tumour metastases or granuloma; accompanies extramedullary haemopoiesis	Abnormalities of microvascular microcirculation caused by tumour, vasculitis or fibrin strands deposited in infection, resulting in physical disruption of RBCs; haemolysis is intravascular
Systemic associations	Metastatic carcinoma of bone marrow; granulomatous disease on marrow (tuberculosis, fungal); myelofibrosis	Malignant disease (e.g. mucin-secreting adenocarcinoma of stomach, breast); vasculitis (particularly involving kidney); infection (meningococcal sepsis); haemolytic uraemic syndrome

RBCs, red blood cells.

Table 2

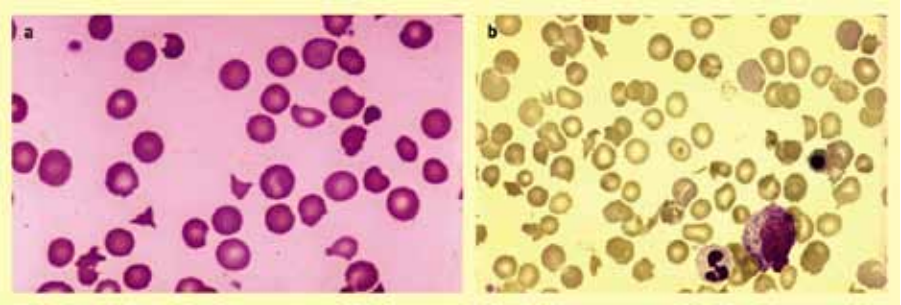

Figure 1 (**a**) Microangiopathic haemolytic anaemia — fragmented red blood cells, spherocytes. (**b**) Microangiopathic haemolytic anaemia with leucoerythroblastic changes.

Haematology of HIV infection

Complication	Causes	Associations	Management
Anaemias	ACD	Common, exacerbated by secondary infections	HAART and antibiotics
	Nutritional	B_{12} deficiency (20—30%); IDA and folate deficiency common	Replacement, HAART
	Drug induced	Less common with HAART; gancyclovir; hepatitis C treatment	Dose adjustment, replacement
	Autoimmune	$DAGT^{+}$ HA	Corticosteroids, IvIg
		Pure red cell aplasia	Ciclosporin
Thrombocytopenia	Autoimmune	ITP	Corticosteroids, splenectomy
		TTP/HUS	HAART, plasma exchange
Malignancy	Lymphomas	NHL/Burkitt-like primary central nervous system	HAART standard treatment
		lymphoma (late complication: AIDS-defining)	HAART + chemotherapy
		Hodgkin's disease (often extranodal)	+/− radiotherapy
		Hodgkin's disease in HIV + EBV (less commonly extranodal)	HAART, standard treatment. Not affected by HAART
	Gammopathies	Oligo-, polyclonal hyper-IgG without immunodeficiency or	HAART
		Bence Jones protein myeloma	HAART + standard treatment

ACD, anaemia of chronic disease; EBV, Epstein—Barr virus; HIV, human immunodeficiency virus; IDA, iron deficiency anaemia; ITP, idiopathic thrombocytopenic purpura; HUS, haemolytic uraemic syndrome; IgG, immunoglobulin G; IvIg, intravenous immunoglobulin; NHL, non-Hodgkin's lymphoma; TTP, thrombotic thrombocytopenic purpura.

Table 3

with judicious use of Epo may improve ACD. Malignancies, particularly lymphomas, are a high risk in immunocompromised conditions such as HIV. ◆

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Practice points

- In older patients anaemia of chronic disease (ACD) may indicate the presence of underlying chronic disease
- Iron status in any anaemia should be assessed to distinguish ACD from iron deficiency anaemia
- Transfusion is rarely indicated in ACD
- Immune cytopenias raise the possibility of underlying autoimmune disease, lymphoma or HIV infection