Anticoagulant and antithrombotic therapy
Haematopoietic Stem Cells Transplantation

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Anticoagulant and antithrombotic therapy

Broadly speaking, antiplatelet medications are of greater efficacy in the prevention of arterial thrombosis and of less value in the prevention of venous thromboembolism (VTE). Thus, antiplatelet agents, such as aspirin, clopidogrel &, increasingly, ticagrelor, are the drugs of choice in acute coronary events and in ischaemic cerebrovascular disease.

warfarin and other anticoagulants are favoured in VTE and management of atrial fibrillation .

In some extremely prothrombotic situations, such as coronary artery stenting, a combination of anticoagulant and antiplatelet drugs is used .

Newer agents allow predictable anticoagulation without the need for frequent monitoring and dose titration.
Although warfarin remains the mainstay for oral anticoagulation, newer oral anticoagulants (dabigatran, rivaroxaban, edoxaban and apixaban), which can be given at fixed doses with predictable effects and no need for monitoring, have now been approved for the prevention of perioperative VTE, the Treatment of established VTE and the prevention of cardioembolic stroke in patients with atrial fibrillation.

Heparins

Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) act by binding via a specific pentasaccharide in the heparin molecule to antithrombin. **Fondaparinux** is a synthetic pentasaccharide, which also binds antithrombin and has similar properties to LMWH. These agents enhance the natural anticoagulant activity of antithrombin .

Heparin/LMWH/Fondaparinux(Indications)

- Prevention and treatment of VTE
- Percutaneous coronary intervention
- Post-thrombolysis for MI
- Unstable angina pectoris
- Non-Q wave MI
- Acute peripheral arterial occlusion
- Cardiopulmonary bypass
- Haemodialysis and haemofiltration

LMWHs augment antithrombin activity against factor Xa.For the licensed indications, LMWHs are at least as efficaciousas UFH but have several advantages:

- LMWHs are nearly 100% bioavailable and so produce reliable dose-dependent anticoagulation.
- LMWHs do not require monitoring of their anticoagulant effect (except possibly in patients with very low body weight and with glumerular filtration rate below 30ml/min.

- LMWHs have a half-life of around 4 hours when given subcutaneously, compared with 1 hour for UFH. This permits once-daily dosing by the subcutaneous route, rather than the therapeutic continuous intravenous infusion or twice-daily subcutaneous administration required for UFH.
- While rates of bleeding are similar between products, the risk of osteoporosis and heparin-induced thrombocytopenia is much lower for LMWH.

UFH is, however, more completely reversed by protamine sulphate in the event of bleeding and at the end of cardiopulmonary bypass, for which UFH remains the drug of choice .

In some situations,UFH is still favoured by some clinicians, though there is little evidence that it is advantageous, except when rapid reversibility is required. UFH is useful in patients with a high risk of bleeding, e.g. those who have peptic ulceration or who may require urgent surgery.

It is also favoured in the treatment of life-threatening thromboembolism, e.g. major pulmonary embolism with significant hypoxaemia, hypotension and right-sided heart strain.

In this situation, UFH is started with a loading intravenous dose of 80 U/kg, followed by a continuous infusion of 18 U/kg/hr initially.
The level of anticoagulation should be assessed by the APTT after 6 hours and, if satisfactory, twice daily thereafter. It is usual to aim for a patient APTT that is 1.5–2.5 times the control time of the test. Monitoring of UFH treatment by APTT is notwithout difficulties and other assays, such as the specific anti-Xa assay calibrated for measurement of UFH, provides more accurate guidance.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin therapy, caused by induction of anti-heparin/PF4 antibodies that bind to and activate platelets via an Fc receptor. This results in platelet activation and a prothrombotic state, with a paradoxical thrombocytopenia.

HIT is more common in surgical than medical patients (especially cardiac and orthopaedic patients), with use of UFH rather than LMWH, and with higher doses of heparin. Some adenovirus vector-based SARS-CoV-2 RNA vaccines have been associated with a similar condition characterised by venous thrombosis (often cerebral) and paradoxical thrombocytopenia.

Clinical features

Patients present, typically 5–14 days after starting heparin treatment, with a fall in platelet count of more than 30% from baseline. The count may still be in the reference range. The patient may be asymptomatic, or develop venous or arterial thrombosis and skin lesions, including overt skin necrosis.

Affected patients may complain of pain or itch at injection sites and of systemic symptoms, such as shivering, following heparin injections.

Patients who have received heparin in the preceding 100 days and who have preformed antibodies may develop acute systemic symptoms and an abrupt fall in platelet count in the first 24 hours after re-exposure.

Investigtiaons

The pre-test probability of the diagnosis is assessed using the 4Ts scoring system. This assigns a score based on:

- the Thrombocytopenia
-the Timing of the fall in platelet count
-the presence of new Thrombosis
-the likelihood of anoTher cause for the thrombocytopenia.

Individuals at low risk need no further test. Those with intermediate and high likelihood scores should have the diagnosis confirmed or refuted using an anti-PF4 enzyme-linked immunosorbent assay (ELISA).

Management

Heparin should be discontinued as soon as HIT is diagnosed and an alternative anticoagulant that does not cross-react with the antibody should be substituted.

Argatroban (a direct thrombin inhibitor) and danaparoid (a heparin analogue) are licensed for use in the UK. Fonaparinux is not licensed for this indication but can also be used. In asymptomatic patients with HIT who do not receive an alternative anticoagulant, around 50% will sustain a thrombosis in the subsequent 30 days. Patients with established thrombosis have a poorer prognosis.

Coumarins

Coumarins inhibit the vitamin K-dependent post-translational carboxylation of factors II (prothrombin), VII, IX and X in the liver .

This results in anticoagulation due to an effective deficiency of these factors. This is monitored by the INR, a standardised test based on measurement of the prothrombin time .

Warfarin anticoagulation typically takes more than 3–5 days to become established, even using loading doses. Patients who require rapid initiation of therapy may receive higher initiation doses of warfarin.

A typical regime in this situation is to give 10 mg warfarin on the first and second days, with 5 mg on the third day; subsequent doses are titrated against the INR.

Patients without an urgent need for anticoagulation (e.g. atrial fibrillation) can have warfarin introduced slowly using lower doses. Low-dose regimens are associated with a lower risk of the patient developing a supratherapeutic INR, and hence a lower bleeding risk.

The duration of warfarin therapy depends on the clinical indication, and while treatment of deep vein thrombosis (DVT) or preparation for cardioversion may require a limited duration, anticoagulation to prevent cardioembolic stroke in atrial fibrillation or from heart valve disease is long-term.

The major problems with warfarin are:

- a narrow therapeutic window
- metabolism that is affected by many factors
- numerous drug interactions.

Major bleeding is the most common serious side-effect of warfarin and occurs in 1–2% of patients each year.
Fatal haemorrhage, which is most commonly intracranial, occurs in about 0.25% per annum.

There are scoring systems that predict the annual bleeding risk and these can be used to help compare the risks and benefits of warfarin for an individual patient .

Bleeding risk score

-Several bleeding risk scores exist for different indications for anticoagulation
-The validation of most bleeding risk scores has been poor
-Many risk factors for thrombosis are also risk factors for bleeding
-HAS BLED is the best validated score for patients with atrial fibrillation.
Following anticoagulant-related bleeding, reassessment of bleeding and thrombosis risk is indicated
-In many cases, patients benefit from recommencing anticoagulants after bleeding

Bleeding risk score*

- Age > 65 yrs (1 point)
- Previous gastrointestinal bleed (1 point)
- Previous stroke (1 point)
- Medical illness (1 point)

Recent myocardial infarction

Renal failure

Anaemia

Diabetes mellitus

Score: annual rate of major haemorrhage

0=3%

1 -2=12%

4–3=30-48%

Coumarins (warfarin) indications

• Prevention and treatment of VTE • Arterial embolism • AF with specific risk factors for stroke • Mobile mural thrombus post-MI • Extensive anterior MI • Dilated cardiomyopathy • Cardioversion • Ischaemic stroke in APS • Mitral stenosis & mitral regurgitation • with atrial fibrillation	INR 2.5
• Recurrent venous thrombosis while on Warfarin • Mechanical prosthetic cardiac valves Rivaroxaban5	INR 3.5

Management of warfarin includes strategies for over-anticoagulation and for bleeding:

• If the INR is above the therapeutic level, warfarin should be withheld or the dose reduced. If the patient is not bleeding, it may be appropriate to give a small dose of vitamin K either orally or intravenously (1–2.5 mg), especially if the INR is greater than 8.

• In the event of bleeding, withhold further warfarin.

Minor bleeding can be treated with 1–2.5 mg of vitamin K IV.

Major haemorrhage should be treated as an emergency with vitamin K 5–10 mg slowly IV, combined with coagulation factor replacement .

This should optimally be a prothrombin complex concentrate (30–50 U/kg) that contains factors II, VII, IX and X; if that is not available, fresh frozen plasma (15–30 mL/kg) should be given.

Anticoagulations Contraindications

1. Recent surgery, especially to eye or central nervous system
2. Pre-existing haemorrhagic state, e.g. advanced liver disease,haemophilia, thrombocytopenia
3. Pre-existing structural lesions, e.g. peptic ulcer
4. Recent cerebral or gastrointestinal haemorrhage
5. Uncontrolled hypertension
6. Cognitive impairment
7. Frequent falls

Direct oral anticoagulants

The direct oral anticoagulants (DOACs) are specific inhibitors of key proteases in the common pathway and offer an alternative to coumarins in the management of VTE and the prevention of stroke and systemic embolism in patients with atrial fibrillation. Dabigatran inhibits thrombin while rivaroxaban, apixaban and edoxaban inhibit Xa .

The key features of these drugs include the fact that they are efficacious in fixed oral doses, have a short half-life of around 10 hours, achieve peak plasma levels 2-4 hours after oral intake, have very few drug interactions and all are Moderately dependent on renal function for their excretion.

An initial perceived drawback was the lack of specific reversal agents for these drugs but idarucizumab is a monoclonal antibody now available for the reversal of dabigatran, and andexanet alfa, a site-inactivated Xa molecule, is close to licensing for the reversal of apixaban and rivaroxaban .

DOACs are now licensed for the prevention of VTE following high-risk orthopaedic surgery (except edoxaban), the acute management and prevention of recurrence of VTE and the prevention of stroke and systemic embolism in patients with atrial fibrillation with risk factors. Dosing is standard across a range of conditions, but is affected by extremes (low and high) of body weight and impaired renal function. The general perception is that in these indications they are at least as efficacious as dose-adjusted coumarin and probably associated with less clinically significant bleeding.

Rivaroxaban

-Prevention and treatment of VTE

- Atrial fibrillation with risk factors for stroke

- Post acute coronary syndrome

-Symptomatic coronary artery disease and peripheral vascular disease

Dabigatran etexilate

-Prevention and treatment of VTE

-Atrial fibrillation with risk factors for stroke

Apixaban

-Prevention and treatment of VTE

-Atrial fibrillation with risk factors for stroke

Edoxaban

-Treatment of VTE

-Atrial fibrillation with risk factors for stroke

(INR = international normalised ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; VTE = venous thromboembolism

HAEMATOPOIETIC STEM CELLS TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) is a medical procedure in the fields of hematology and oncology, most often performed for patients with certain cancers of the blood or bone marrow , such as multiple myeloma or leukemia. In these cases, the recipient's immune system is usually destroyed with radiation or chemotherapy before the transplantation. .

Transplantation of haematopoietic stem cells (HSCT) has offered the only hope of ‘cure’ in a variety of haematological and non-haematological disorders .

As standard treatment improves, the indications for HSCT are being refined and extended, although its use remains most common in haematological malignancies.

The type of HSCT is defined according to the donor and source of stem cells:

- **In allogeneic HSCT,**

the stem cells come from a donor– either a related donor (usually an HLA-identical **sibling) or a closely HLA-matched volunteer unrelated donor (VUD).**

- **In an autologous transplant,**

the stem cells are harvested **from the *patient and stored in the vapour phase of liquid*** **nitrogen until required.**

Stem cells can be harvested from the bone Marrow or from the blood

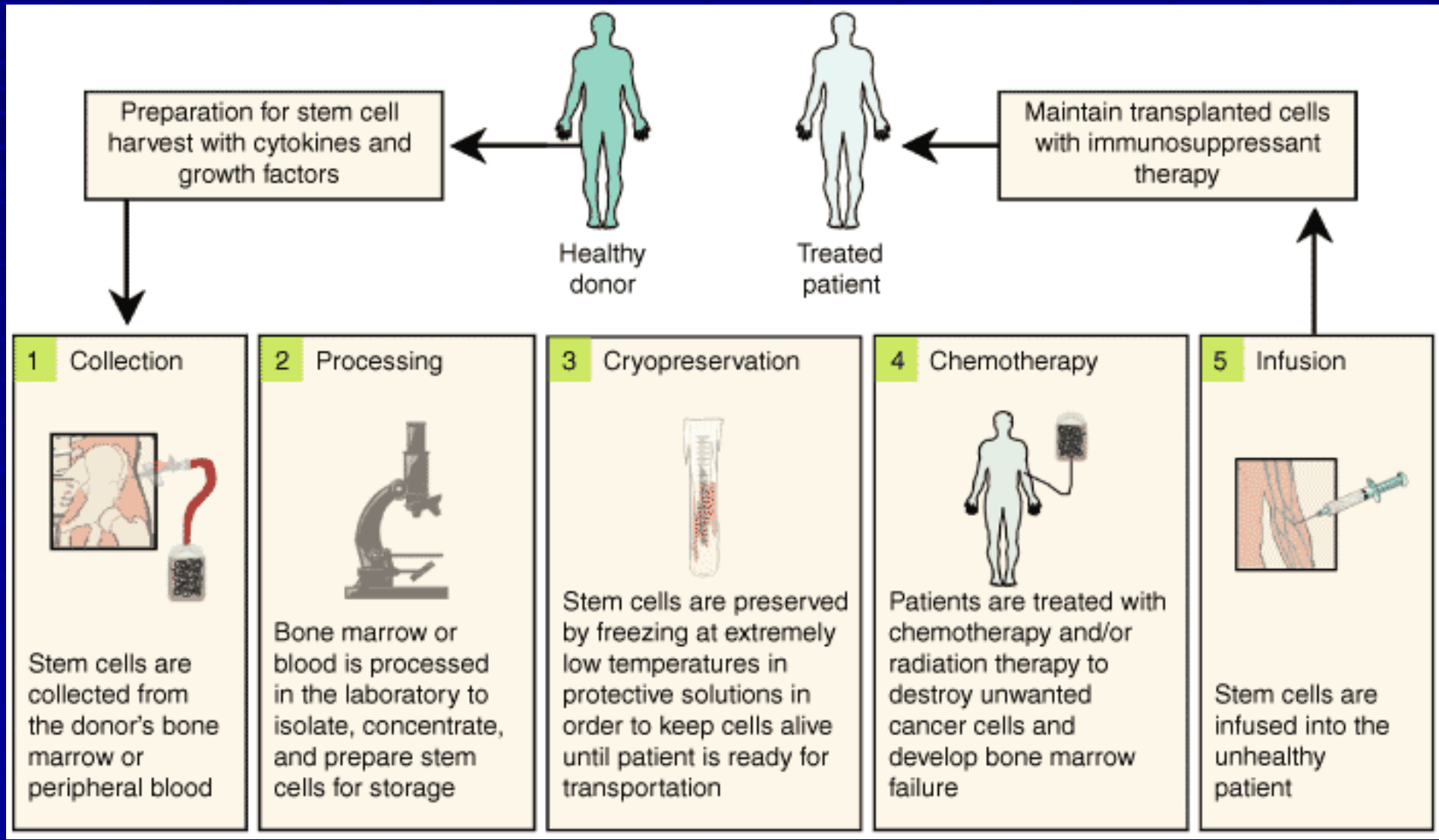
Indications for allogeneic haematopoietic stem cell transplantation

- Neoplastic disorders affecting stem cell compartments (e.g. leukaemias)
- Failure of haematopoiesis (e.g. aplastic anaemia)
- Major inherited defects in blood cell production (e.g. thalassaemia, immunodeficiency diseases)
- Inborn errors of metabolism with missing enzymes or cell lines

Allogeneic HSCT

Healthy bone marrow or blood stem cells from a donor are infused intravenously into the recipient, who has been suitably ‘conditioned’. The conditioning treatment (chemotherapy with or without radiotherapy) is ‘myeloablative’ or, increasingly, ‘nonmyeloablative’.

Myeloablative conditioning destroys malignant cells and immunosuppresses the recipient, as well as ablating the recipient’s haematopoietic tissues.


Preparation for stem cell harvest with cytokines and growth factors
Healthy donor
Treated patient
Maintain transplanted cells with immunosuppressant therapy
1 Collection
Stem cells are collected from the donor's bone marrow or peripheral blood
2 Processing
Bone marrow or blood is processed in the laboratory to isolate, concentrate, and prepare stem cells for storage
3 Cryopreservation
Stem cells are preserved by freezing at extremely low temperatures in protective solutions in order to keep cells alive until patient is ready for transportation
4 Chemotherapy
Patients are treated with chemotherapy and/or radiation therapy to destroy unwanted cancer cells and develop bone marrow failure
5 Infusion
Stem cells are infused into the unhealthy patient

Reduced intensity conditioning (non-myeloablative) relies on intense immunosuppression to provide ‘immunological space’ for transplanted stem cells.

The infused donor cells ‘home’ to the marrow, engraft and produce enough erythrocytes, granulocytes and platelets for the patient’s needs after about 2–4 weeks.

During this period of aplasia, patients are at risk of infection and bleeding, and require intensive supportive care , It may take several years to regain normal immunological function and patients remain at risk from opportunistic infections, particularly in the first year.

An advantage of receiving allogeneic donor stem cells is that the donor's immune system can recognise residual recipient malignant cells and destroy them. This immunological 'graft-versus-disease' effect is a powerful tool against many haematological tumours and can be boosted post-transplantation by the infusion of T cells taken from the donor: so-called donor lymphocyte infusion (DLI).

Considerable morbidity and mortality are associated with HSCT.

The best results are obtained in:

1-patients with minimal residual disease

2- in those under 20 years of age who have an HLA-identical sibling donor

However, reduced-intensity conditioning (RIC) has enabled treatment of older or less fit patients, in whom the majority of haematological malignancies occur. In this form of transplantation, rather than using very intensive myeloablative conditioning, which causes morbidity from organ damage, relatively low doses of chemotherapy drugs, such as fludarabine and cyclophosphamide or busulfan, are used in combination with antibodies such as alemtuzumab (which targets CD52 on mature lymphoid cells) or anti-thymocyte globulin (ATG) to immunosuppress the recipient and allow donor stem cells to engraft.

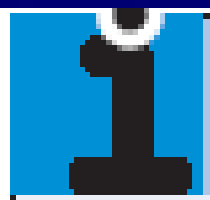
The emerging donor immune system then eliminates malignant cells via the ‘graft-versus-disease’ effect, which may be boosted by the elective use of donor T-cell infusions posttransplant.
Such transplants have produced long-term remissions in some patients with acute leukaemia and myelodysplastic syndromes aged 40–65 years, who would not previously have been considered for a myeloablative allograft

Complications

The risks and outcomes of transplantation depend upon several patient- and disease-related factors.

In general, 25% die from procedure related complications, such as infection and GVHD, and there are remains a Sinificant risk of the heamatological malignancy relapsing.

The long term survival of patients undergoing allogeneic HSCT in Acte lueukaemia around 50%.



Complications of allogeneic HSCT

Early

- Anaemia
- Infections
- Bleeding
- Acute GVHD
- Mucositis – pain, nausea, diarrhoea
- Liver veno-occlusive disease

Late

- Chronic GVHD
- Infertility
- Cataracts
- Secondary malignancy

(GVHD = graft-versus-host disease)

Graft-versus-host disease

GVHD is caused by the cytotoxic activity of donor T lymphocytes that become sensitised to their new host, regarding it as foreign.

This may cause either an acute or a chronic form of GVHD.

Acute GVHD occurs in the first 100 days after transplant in about one-third of patients. It can affect the skin, causing rashes, the liver, causing jaundice, and the gut, causing diarrhoea, and may vary from mild to lethal.

Prevention includes HLA-matching of the donor, immunosuppressant drugs, including methotrexate, ciclosporin, alemtuzumab or ATG. Severe presentations are very difficult to control and, despite high-dose glucocorticoids, may result in death.

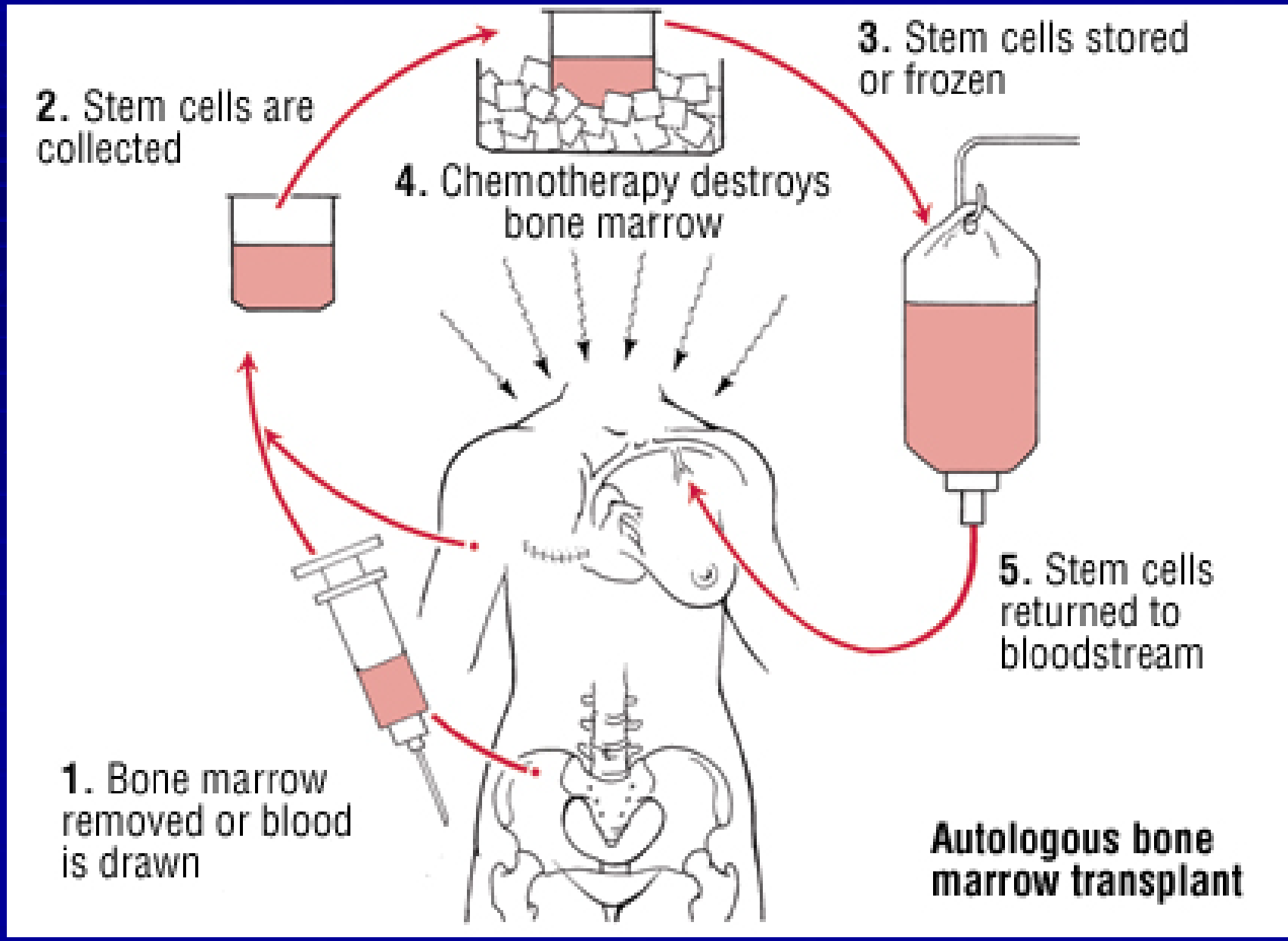
Chronic GVHD may follow acute GVHD or arise independently; it occurs later than acute GVHD. It often resembles a connective tissue disorder, although in mild cases a rash may be the only manifestation.

Chronic GVHD is usually treated with glucocorticoids and prolonged immunosuppression with, for example, ciclosporin. Chronic GVHD results in an increased infection risk. However, associated with chronic GVHD are the graft-versus-disease effect and a lower relapse rate of the underlying malignancy

Autologous HSCT

This procedure can also be used in haematological malignancies.

The patient's own stem cells from blood or marrow are first harvested and frozen. After conditioning myeloablative therapy, the autologous stem cells are reinfused into the blood stream in order to rescue the patient from the marrow damage and aplasia caused by chemotherapy.


2. Stem cells are collected
3. Stem cells stored or frozen
4. Chemotherapy destroys bone marrow
5. Stem cells returned to bloodstream
1. Bone marrow removed or blood is drawn
Autologous bone marrow transplant

Autologous HSCT may be used for disorders that do not primarily involve the haematopoietic tissues, or for patients in whom very good remissions have been achieved.
The most common indications are lymphomas and myeloma.
The preferred source of stem cells for autologous transplants is peripheral blood (PBSCT).

these stem cells engraft more quickly, marrow recovery occurring within 2–3 weeks.
There is no risk of GVHD and no immunosuppression is required. Thus autologous stem cell transplantation carries a lower procedure related mortality rate than allogeneic HSCT at around1- 5%, but there is a higher rate of recurrence of malignancy because the anti-malignancy effect is solely dependent on the conditioning chemotherapy with no ‘graft-versus-disease’ effect.

Infections during recovery from HSCT

Infection	Time after HSCT	Management
Herpes simplex	0–4 wks (aplastic phase)	Aciclovir prophylaxis and therapy
Bacterial, fungal	0–4 wks (aplastic phase)	As for acute leukaemia ( ) – antibiotic and antifungal prophylaxis and therapy
Cytomegalovirus	5–21 wks (cell-mediated immune deficiency)	Antigen screening in blood (PCR) and pre-emptive therapy (e.g. ganciclovir)
Varicella zoster	After 13 wks	Aciclovir prophylaxis and therapy
Pneumocystis jirovecii	8–26 wks	Co-trimoxazole
Encapsulated bacteria	8 wks to years (immunoglobulin deficiency, prolonged with GVHD)	Prophylaxis and revaccination

Prognosis

Prognosis in HSCT varies widely dependent upon:
disease type
stage
stem cell source
HLA-matched status (for allogeneic HCST)
and conditioning regimen.
A transplant offers a chance for cure or long-term remission if the inherent complications of graft versus host disease, immuno-suppressive treatments and the spectrum of opportunistic infections can be survived. In recent years, survival rates have been gradually improving across almost all populations and sub-populations receiving transplants.

THANK YOU