Stone’s Plastic Surgery Facts

A Revision Guide
Fourth Edition
To my family
## Contents

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Preface to the fourth edition

I remember buying the first edition of *Plastic Surgery: Facts* by Christopher Stone. I was not alone in appreciating the easy-to-read format, and the fact that it was born out of the author’s revision notes made it all the more useful for those of us studying for our own exit examinations in plastic surgery.

I had the privilege of taking over the project for the previous (third) edition. The production of each new edition has added a large amount of new information. I focused on arranging the material for clarity and readability, and also to follow the syllabus of the Intercollegiate Surgical Curriculum Programme as closely as possible – the chapter layout is based on the Key Topics. There is also the excellent e-LPRAS resource that I have had the privilege of being able to contribute to.

Obviously, discussion of everything on the plastic surgery syllabus is not possible in a book of this size, nor is this intended to be the scope of this book. Each revision takes a great deal of time and effort; however, I was greatly encouraged to continue updating this book by the feedback from plastic surgery trainees. I was gratified to hear their comments and their appreciation of the philosophy of the book – it is very dense with information and deep insights. It is most useful after some prior reading of the subject.

The book has been thoroughly updated to include new materials including the surgical management of lymphoedema, the eighth edition of the 2018 Staging for Melanoma, updates in melanoma management such as PD1 protein inhibitors and inclusion of newer flaps such as the SCIP and MSAP. I have expanded the scope of the book somewhat to cover materials relevant to the US board exam. The article summaries have been a favourite feature of the book and have been retained and updated. Every reference has been rechecked and reviewed. I hope that new readers find this book useful.
Taking the board exams marks the finale of a long training journey. During the preparation, it will probably be the last time you dive in deep to the whole broad spectrum of plastic surgery. It is during this time your general concept and understanding of plastic surgery is organised and stored as part of your knowledge. After this period of in-depth studying, you will be most likely to focus on a single or a couple of subspecialties in plastic surgery. At this time, your knowledge of that subspecialty field will continuously grow and expand, whilst the rest of the general knowledge stays dormant. My current work focuses on reconstruction of trunk and lower extremity, and the experience accumulated from this work allows me to evolve and provide new ideas and approaches. However, when a patient walks through the door, it is your job to notice the clues other than the subspecialties you focus on. This is when your fundamental knowledge of plastic surgery kicks in to observe the patient as a whole and not to miss obvious or hidden clues. That is why this opportunity to build your fundamentals and organise your thoughts and knowledge on plastic surgery is important as this will be the foundation of your future practice.

Dr Tor Chiu practices a wide spectrum of plastic surgery in one of the most prestigious training facilities in Hong Kong. His experience from the United Kingdom and Hong Kong allows him to have a wide exposure to plastic surgery, and lets him adapt to the new trends in this field. By training residents, he understands what is more essential in today’s practice and how the fundamentals of plastic surgery evolve. He has added these new trends in this book, which gives you the opportunity to study and organise new topics as well as current knowledge in plastic surgery.

This book will help you develop and organise your knowledge in plastic surgery. It will guide you in your board exams; most of all, it will help you build your fundamentals in plastic surgery, which you can take along with you in your journey as a clinician.

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Wound care

A. WOUNDS AND WOUND HEALING

I. WOUND HEALING AND TISSUE TRANSPLANTATION

WOUND HEALING

Wound repair proceeds through several stages that overlap somewhat:

- Inflammation (haemostasis, then increased vascular permeability and cell infiltration)
- Proliferation (re-epithelialization, fibroplasia)
- Remodelling (maturation)

INFLAMMATORY PHASE (DAYS 0–6)

Haemostasis - this phase is immediate, short-lived (lasting minutes) and characterised by vasoconstriction and coagulation. Haemostatic cascades lead to the formation of a thrombin–platelet plug (clot) that is adherent to type II collagen exposed by endothelial disruption. This clot has several functions:

- The fibrin acts as a scaffold for incoming cells and concentrates cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factors (TGF), α and β at the site.
- It traps more platelets to perpetuate the cycle.
- Fibrin is an essential component of wound healing.
- It releases chemotactic factors such as interleukin 2 (IL-2), tumour necrosis factor (TNF)-α, TGF-β.

Inflammation – this phase (lasting 3–5 days) is defined by the vasodilation (due to inflammatory mediators such as histamine, kinins, complement), increased vascular permeability and cell infiltration. Cells clear debris and initiate the proliferative phase; close regulation is needed to avoid overactivity (SIRS) or underactivity (chronic wounds – wounds that do not heal in an orderly set of stages in a timely manner, usually within 3 months; these are characterised by persistently elevated levels of matrix metalloproteinases, MMPs).

- Neutrophils
  - Within 12 hours of wounding, cells appear in the wound, attracted by chemotaxins including fibrin degradation products (FDPs), complement proteins, IL-1s, TGF-β, TNF-α, platelet factor 4 (PF4) and PDGF. Translocation of marginating neutrophils (at 24–48 hours) through capillary endothelium and basement membrane is facilitated by collagenase.
  - Neutrophils produce inflammatory mediators and cytokines, and remove debris; the response and population decline after a few days, whereupon the function of debris removal is taken over by macrophages. Neutrophils are not essential for wound healing.
- Macrophages arrive after 48–96 hours and begin to phagocytose debris and release cytokines and growth factors, thus coordinating and promoting healing. They are vital to wound healing.
- Fibroblasts become the dominant cell type 1 week after injury, with a key role in the production of collagen. TGF-β promotes migration and proliferation of dermal fibroblasts.
- T-lymphocytes migrate into wounds after the macrophages (at 5–7 days) and persist for up to 1 week – a reduced response may lead to inferior wound healing. Their primary role seems to be to mediate in fibroblast recruitment and activation.
- Keratinocytes – differentiated cells are converted to immature cells that migrate over the wound surface.

PROLIFERATIVE PHASE (4 DAYS TO 3 WEEKS)

Re-epithelialisation begins within hours of wounding with migration of marginal keratinocytes over the matrix due to loss of contact inhibition, staying beneath the eschar. There is a phenotypic conversion of differentiated
keratinocytes into non-polarised cells expressing basal cytokeratins similar to cultured cells; increased mobility comes from dissolution of anchoring junctions and realignment of the cortical actin cytoskeleton to form lamellipodia. Cells stop migrating when they form a contiguous layer (contact inhibition). As the basement membrane is reconstituted, the cells are induced to adopt their previous morphology and form anchoring junctions with fibronectin. A moist environment increases the rate of (re-)epithelialisation.

- **Epidermal growth factor (EGF)** – mRNA levels increase rapidly after wounding to promote re-epithelialisation. Abnormalities of EGF expression are thought to impair wound healing; glucocorticoids suppress EGF expression in cutaneous wounds but have less effect on EGF receptor levels.
- **Growth-related oncogene α** (GRO α), originally called ‘melanocyte growth-stimulating activity’ due to its mitogenic activity on melanocytes, is also a chemoattractant for neutrophils that is more potent than IL-8. Both GRO α and IL-8 stimulate keratinocyte proliferation in vitro; both are maximally expressed on day 1 after injury and subside after wound closure.

**Fibroplasia** – there is an influx of fibroblasts over the fibronectin scaffold; they are activated by PDGF and TGF-β. These cells synthesise type III collagen, which with ongoing neovascularisation forms granulation tissue. Wound tensile strength increases during the fibroblastic phase.

- **Activin** is strongly expressed in wound skin. Overexpression in transgenic mice improves wound healing and enhances scar formation; activin A has been implicated in stimulating formation of granulation tissue whilst activin B mRNA has been localised to hyperproliferative epithelium at the wound edge.
- Secretion of glycosaminoglycans (GAGs) such as hyaluronic acid (HA), chondroitin sulphate and dermatan sulphate, which become hydrated to form an amorphous ground substance within which fibrillar collagen is deposited.
- **Zinc, vitamins A (retinoids) and C** are also required for normal collagen synthesis.

**Angiogenesis** – low oxygen tension in the wound leads to secretion of vascular endothelial growth factor (VEGF); MMPs degrade the extracellular matrix (ECM) to facilitate the passage of newly formed vessels.

**REMODELLING PHASE (3 WEEKS TO 18 MONTHS)**

The ECM appears to modulate fibroblast activity through changes in composition during healing. When fibronectin initially predominates, fibroblasts actively synthesise HA and collagen, but in a maturing wound, when collagen becomes abundant, fibroblast proliferation and collagen production then cease – irrespective of any stimulation by TGF-β. At this point, the wound becomes a relatively acellular scar. This phase ends with the formation of the final scar.

- **Collagen remodelling.** Residual fibroblasts mature into myofibroblasts and form cell–matrix and cell–cell contacts that contract the wound (scar contracture). Type III collagen is gradually replaced by type I collagen by the activity of MMPs released by macrophages, keratinocytes and fibroblasts, slowly returning to the normal type I/III ratio of 3:1.
- **Peak wound tensile strength** is achieved at ~60 days and is a maximum of ~80% of unwounded skin strength.
- **Vascular maturation.** The abundant capillaries regress.

**CYTOKINES AND GROWTH FACTORS**

**Cytokines**

Cyto, from Greek *kyttaro*, which means ‘cell’, and kines, from Greek *kinisi*, which means ‘movement’.

Cytokines are small molecules (peptide, protein or glycopeptide) that are secreted predominantly by immune cells (mostly lymphocytes and macrophages) and affect the behaviour of other cells. They are important in cell-to-cell signalling and mediate in protective and reparative processes and also regulate cell growth and maturation. Interferon α (IFN-α) was the first cytokine to be discovered in 1957.

Cytokines tend to be pleiotropic (affects many different cells) and redundant (many do the same thing); they can be synergistic or antagonistic. One can try to classify them broadly according to their function:

- **Non-specific (innate) immunity and inflammation** – mostly made by macrophages, mast cells and endothelium.
  - Chemokines (chemotaxis)
  - TNF and IL-1
  - IFN-γ and IL-12 (chronic inflammation)
  - Specific (acquired/adaptive) immunity – most are made by T-helpers (TH) cells.
  - IFN-γ and IL-5 (cell activation)
  - IL-2 and IL-4 (lymphocyte proliferation)
  - Haematopoiesis – made by endothelium, macrophages, etc.
- **Colonising factors causing haematopoietic cell proliferation**
Tumour necrosis factor-α

TNF-α is released by macrophages/monocytes when stimulated by pathogens, tumour cells and toxins. It appears at wound sites 12 hours after wounding and peaks at 72 hours.

- Mediates in chemotaxis of inflammatory cells.
- Up-regulation of cellular adhesion molecules on endothelium.
- Other effects on collagen synthesis; may impair wound healing if it persists at high levels beyond natural peak, and excess TNF-α is associated with multisystem organ failure.

Interleukin-1

Interleukins (ILs) are cytokines, classically made by leucocytes that act on other leucocytes. Interleukin-1 (IL-1) is produced by macrophages/monocytes as well as keratinocytes at wound sites. It is detectable at wound sites after 24 hours, peaking around day 2 with levels rapidly declining thereafter.

- Neutrophil activation and chemotaxis
- Increased collagen synthesis and keratinocyte maturation
- Similar action to TNF-α; also activates T helper cells
- High levels in chronic non-healing wounds; also called endogenous pyrogen and causes fever

Interleukin-2

Interleukin-2 is produced by T lymphocytes.

- Sustains the post-injury inflammatory response via T-cell activation
- Promotes fibroblast infiltration at wound sites

Interleukin-6

Interleukin-6 is released by macrophages/monocytes, polymorphs and fibroblasts.

- Promotes stem cell growth and B- and T-cell activation, and mediates in hepatic acute phase protein synthesis
- Stimulates fibroblast proliferation
  - High IL-6 increases scarring and high systemic levels have been described as a marker of wound severity in major burns and a poor prognostic indicator (Modi S, Indian J Med Microbiol, 2014).
  - Low IL-6 in elderly patients with impaired wound healing and at scar-less foetal wound sites

Interleukin-8

Interleukin-8 is released by macrophages and fibroblasts at wound sites.

- Neutrophil chemotaxis, adhesion and activation
- Promotes keratinocyte maturation and migration
- High levels in patients with psoriasis and low levels at foetal wound sites

Interferon γ

Interferons interfere with viral replication. Interferons α and β are type 1 and interferon γ is type 2. Interferon γ is produced by T-helper cells primarily, but also by Tc and macrophages. It has many functions in both specific and non-specific immunity.

- Macrophage and polymorph activation
- Mediates in wound remodelling; reduces wound contraction
- Possible role for decreasing scar hypertrophy but may decrease wound strength

Interleukin-4

Interleukin-4 is produced by T-cells, mast cells and B-lymphocytes.

- Promotes B-cell proliferation and IgE-mediated immunity and inhibits the release of pro-inflammatory cytokines by macrophages.
- Promotes fibroblast proliferation and collagen synthesis at wound sites.
- High levels are found in patients with scleroderma

Interleukin-10

Interleukin-10 is produced by activated macrophages and T-cells; it has mostly inhibitory actions.

- Inhibits production of pro-inflammatory cytokines at acute wound sites
- Persistently high levels at chronic wound sites, e.g. venous ulcers; contributes to impaired wound healing

Growth factors

Growth factors are polypeptides whose primary role is in regulation of cell growth and maturation.

Platelet-derived growth factor

PDGF is released from platelet α granules and by macrophages.

- Recruitment and activation of immune cells and fibroblasts in the early post-injury phase.
- Later stimulates the production of collagen and GAGs; reduced levels are found in non-healing wounds.
- Three isomers of PDGF (2 polypeptide chains ‘A’ and ‘B’):
  - AA – elevated at acute wound sites
  - BB – most useful clinically, used for chronic and diabetic ulcers (Regranex®, see below)
  - AB

Transforming growth factor β

TGF-β is released by macrophages, platelets and fibroblasts; it has mostly inhibitory actions.

- Blocks macrophage activation; inhibits the action of other cytokines on neutrophils and endothelium.
• Fibroblast maturation, collagen and proteoglycan synthesis.
• Inhibition of proteases.
• There are three isomers – TGF-β1, TGF-β2 and TGF-β3.
  • TGF-β1 and TGF-β2 are associated with hypertrophic and keloid scarring, and neutralising antibodies decrease scarring at rat wound sites (Shah M, J Cell Sci, 1994).
  • Low TGF-β levels at foetal wound sites.
  • TGF-β3 shown to decrease scarring.
  • Ratio of TGF-β1 and β2 – TGF-β3 determines nature of scar.

Fibroblast growth factor
Fibroblast growth factor (FGF) is released from fibroblasts and endothelial cells.
• Regulates angiogenesis and keratinocyte migration at wound sites.
• Two main forms – acidic FGF (or FGF-1) and basic FGF (or FGF-2) that binds to the same receptors as aFGF but is 10 times more potent.
• Application of exogenous bFGF to wound sites accelerates re-epithelialisation.
• Eight other isoforms – FGF-7 is keratinocyte growth factor (KGF) 1, which is low in diabetics and steroid immunosuppression. Recombinant KGF has been shown to improve wound re-epithelialisation.

Epidermal growth factor
EGF is released from keratinocytes.
• EGF promotes epithelialisation.
• Promotes collagenase release from fibroblasts (for remodelling).
• Inhibits wound contraction at foetal wound sites.

Vascular endothelial growth factor
VEGF is mainly released from keratinocytes; there is a minor contribution from macrophages and fibroblasts.
• Promotes angiogenesis at wound sites.
• Mediates in the formation of granulation tissue.

Insulin-like growth factor
At wound sites, IGF is released by macrophages, neutrophils and fibroblasts; levels rise to a peak within 24 hours of wounding and persist for several weeks.
• Promotes fibroblast and keratinocyte proliferation, with possible role in angiogenesis.
• Two isoforms – IGF-1 and IGF-2.
• Low IGF levels are observed in diabetic and steroid-suppressed wounds.

COLLAGEN
Collagen forms about one-third of the total protein in the human body. It is a triple helix formed from three α-helical chains; 25 different α-chains have been identified, each encoded by a separate gene. There are at least 16 different types of collagen. Their structural differences determine the ability of their helical and non-helical regions to associate, form fibrils and sheets or cross-link different collagen types; 90% of body collagen is type I. In normal skin, the ratio of types I/III = 3:1. See Table 1.1.

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<th>Number</th>
<th>Distribution</th>
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<tr>
<td>I</td>
<td>Bone, skin, tendon, ligaments, cornea</td>
<td>Deficient in osteogenesis imperfecta</td>
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<tr>
<td>II</td>
<td>Cartilage, vitreous humour of eye</td>
<td>Deficient in chondrodysplasia</td>
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<tr>
<td>III</td>
<td>Skin, blood vessels, intestines, uterus</td>
<td>Excessive: early wound, early Dupuytren’s contracture, hypertrophic scar</td>
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<tr>
<td>IV</td>
<td>Basal laminae, lens</td>
<td>Deficient in vascular Ehlers-Danlos syndrome</td>
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<tr>
<td>V</td>
<td>Associated with type I</td>
<td>Found in active stage Dupuytren’s contracture</td>
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The initial product is the pro-α-chain. Post-translational hydroxylation of proline and lysine residues (requires vitamin C and iron) is important for structural strength and stability by cross-linking the triple helix, as well as being necessary for its export from the cell.

• Procollagen – three polypeptide chains in a triple helix form tropocollagen. All types contain a repeating Gly-Pro-X sequence that allows folding.
• Tropocollagen units form collagen filaments.
• Filaments form fibrils, which form fibres with enormous tensile strength. The typical ‘fibrous’ collagens are I, II, III and V.

Early collagen is thin and randomly orientated parallel to the skin surface; collagen that is laid down during the later stages of wound healing is thicker and lies along stress lines, thus increasing wound strength.

• Initially, type III collagen production is high and then type I replaces type III until a ratio of 3–4:1 is achieved.
• Myofibroblasts cause wound contraction that reduces the wound size (not the same as a contracture that is excessive scar contraction across a mobile surface). There is gradual decrease in vascularity.

See ‘ Syndromes associated with altered healing’.

FACTORS AFFECTING WOUND HEALING

Discussions generally divide factors into patient factors and wound factors.

Wound factors

• Hydration increases the rate of epithelialisation, hence the rationale for occlusive dressings (see ‘Moist wound healing’). The mechanisms proposed for this improved healing include thermal insulation, altering wound oxygen/carbon dioxide/pH, maintaining growth factors as well as acting as a physical barrier.

• Infection – the presence of >10^5 organisms (or lower concentrations of β-haemolytic streptococcus) prolongs the inflammatory phase. Endotoxins reduce tissue oxygenation and stimulate phagocytosis and the release of collagenases and radicals that may damage normal tissue. Taking swabs of open wounds is generally pointless; colonisation does not equate to infection and would not normally inhibit wound healing.

• Foreign bodies (or necrotic tissue) prolong the inflammatory phase, are obstacles to healing and are nidi for bacteria.

• Ischaemia – energy in the form of glucose and oxygen is required for proliferation (cell replication and protein synthesis) as well as fibroblast and neutrophil activity. Reduced oxygen tension causes inefficient keratinocyte migration. Fibroblasts, in particular, are oxygen-sensitive and an oxygen tension of >40 mmHg augments fibroblastic activity and is required for the hydroxylation of proline and lysine in the collagen α-chain. Oxygen also facilitates cell-mediated killing of pathogens in the wound. Ischaemia and reduction of local oxygen tension may be a component of other processes:
  • Oedema – reduces tissue perfusion and leads to capillary closure.
  • Protein extravasation forms a diffusion barrier.
  • Radiation – direct DNA damage, impaired inflammatory response, endarteritis obliterans.
  • Diabetes mellitus (DM).
  • Smoking.

• Tissue expansion – increased rate and strength of healing.

• Low serum protein – prolonged inflammatory phase and impaired fibroplasia.

• Increased ambient temperature (30°C) – accelerates wound healing.

Patient factors

• Age – there is a reduction in the cellular multiplication rate with age. Tensile strength and wound closure rates also decrease with age – the various stages of wound healing are all protracted.

• Nutrition (see ‘Nutrition’) – malnutrition is associated with impairment of fibroblast function and reduced wound tensile strength.
  • Protein malnutrition especially deficiencies of arginine and methionine compromises wound healing.
  • Vitamin C – essential for hydroxylation of collagen.
  • Vitamin E – antioxidant actions neutralise lipid peroxidation (and thus cell damage) caused by ionising radiation, for example.

• Minerals – many are cofactors in collagen production, e.g. zinc influences re-epithelialisation and collagen deposition.

• Systemic illness – such as anaemia or pulmonary disease may impair oxygen delivery and collagen synthesis.

• Smoking (multifactorial) – the nicotine in one single cigarette causes vasoconstriction that lasts 90 minutes, cyanide impairs oxidative enzymes whilst carbon monoxide (CO) impairs the oxygen-carrying capacity of haemoglobin. Stopping smoking will ameliorate the effects of
  • CO after >12 hours.
  • Free radicals (1 week).
  • CDC recommends quitting 4 weeks before surgery, but there is no consensus. The highest risk is in surgeries where tissues may have reduced vascularity, e.g. composite grafts/replants, extensive tissue undermining, e.g. facelifts.
  • There is no evidence that nicotine replacement therapy affects wound healing, but it is probably prudent to avoid in high-risk surgery.

• Diabetes mellitus (see ‘Diabetic ulcers’) – multiple factors are at work in addition to the microvascular disease that reduces oxygenation. These patients are prone to infections that should be treated aggressively. However, with adequate glycaemic control, most surgical wounds should heal satisfactorily.

• Glycosylation of proteins may alter functions, e.g. glycosylated haemoglobin has a higher affinity for oxygen, which impairs oxygen delivery to the tissues.

• Increased blood glucose impairs cellular function. – Sorbitol by-products are toxic.

• Sensory neuropathy decreases protective reflexes and increases vulnerability to ischaemia.

• Autonomic neuropathy leads to anhydrosis (dry skin) and arteriovenous shunting.

• Reduced fibroblast numbers and immune dysfunction.

• Vascular disease and ischaemia.

• Drugs.
• Steroids – anti-inflammatory actions affect wound healing in many ways including impaired macrophage and fibroblast function, reduced angiogenesis and contracture. Vitamin A is usually said to reverse steroid effects and increases collagen synthesis.

• Non-steroidal anti-inflammatory drugs (NSAIDs) – almost halve collagen synthesis in some studies, which is related to the reduction in prostaglandin production.

• Chemotherapy – e.g. cyclophosphamide is anti-inflamatory whilst methotrexate potentiates infections.

• Syndromes associated with altered healing
  • Ehlers–Danlos – a group of patients with defects in collagen metabolism (e.g. lysyl oxidase) commonly affecting type III collagen, though some have deficiencies of types I and V. The skin is really stretchable and recoils without wrinkles. Patients exhibit joint hyper-extensibility with tissue fragility and poor healing with post-operative bleeding, wound infections (defective immune response) and wider atrophic scars. Non-essential surgery is not recommended.
  • Cutis laxa – variable modes of inheritance. There is an elastin defect causing the skin to be thin and stretchable (but does not recoil due to the lack of elastin), with easy bruising; joints are normal. Essential surgery can be performed, though there is an association with cardiorespiratory disease.
  • Homocystinuria – autosomal recessive (AR) inherited deficiency of cystathionine synthase that is needed to metabolise methionine. Accumulated homocysteine initiates the clotting cascade, and causes arterial sclerosis, thrombosis, poor perfusion and platelet malfunction. There is a high risk of developing cardiovascular disease.
  • Osteogenesis imperfecta – patients have a defective collagen I gene, and wounds typically heal with wide scars.
  • Dystrophic epidermolysis bullosa is a hereditary disease of skin and mucosa that causes blistering after trivial trauma and heals by scarring. It is associated with mutations of collagen VII, which form anchoring fibril-specific proteins. Typically, there is cocooning of the digits in an atrophic scar – pseudosyndactyly and flexion contracture; the digits are generally quite mobile despite the deformity, but surgical release is generally not rewarding as recurrence is almost inevitable. Exsanguination during any surgery should be performed by elevation and not bandaging; tourniquets need extra padding. Grafts can be taken with hand knives; both donor and recipients heal fairly well, but haemolytic streptococcal colonisation is not uncommon. Patients generally die young (third decade) from squamous cell carcinoma (SCC).

ADJUNCTS TO HEALING

There are a plethora of modalities and products put forward for enhancement of wound healing. The strength of evidence is variable but overall is fairly low.

• Hyperbaric oxygen therapy (HBOT) increase oxygen delivery to wounds but its use in wound healing in general is controversial. It may be useful in selected wounds, e.g. ischaemic (acute arterial insufficiency, crush injuries), radionecrosis, necrotising fasciitis (NF)/gas gangrene and diabetic ulcers. Medicare covers its use if there are ‘no measurable signs of healing for at least 30 days of standard wound therapy’.

• Negative pressure – the exact mechanism is unclear but reportedly removes interstitial fluid and oedema to improve oxygenation, removes deleterious inflammatory mediators, reduces bacterial counts and speeds up formation of granulation tissue (see ‘Negative pressure wound therapy’).

• Growth factors – some are commercially available and used in some localities, e.g. PDGF, GM-CSF and KGF2. However, the evidence is generally not that convincing, and their use is regarded as mostly experimental. Recombinant PDGF B-chain (becaplermin) is marketed as Regranex®, the only agent shown to be efficacious in double-blind studies. It has FDA approval; however, there is a warning that there is an increased cancer mortality in patients who use three or more tubes. Recombinant human EGF is used in South Korea for wound healing; one product has been used to reduce radiation dermatitis (Kang HC, Radiat Oncol, 2014).

• Electrostimulation (ES) therapy – the premise is that there is an endogenous electric field in wounds and that cells are sensitive to and respond to an applied field. Multiple animal studies seem to have demonstrated some efficacy, but good clinical evidence is lacking; some attribute this to a paucity of uniform protocols/products (e.g. DC or pulsed current at low frequency or high voltage, pulsed EM field, etc.). There were weak recommendations from the pressure sore advisory panels (NPUAP, EPUAP and PPPIA) in 2014.
  • Apligraf® is a bioengineered product, initially marketed as a skin substitute. Although some wounds did heal, it became evident that the material was not actually incorporated – it acted as a wound stimulator – in chronic wounds, there would be outgrowth of previously dormant keratinocytes at the wound edges (see below). Activskin® is a similar product made in China (CRMI).

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• **Lasers** – low-level laser therapy (LLLT), aka ‘biostimulation’, is said to increase cellular activity especially of fibroblasts and keratinocytes. Light is administered at wavelengths of 680–890 nm, over several applications; it does not generate heat and is thus often referred to as ‘cold’ laser.
  - LLLT was introduced in the 1960s by Mester E. Devices have FDA approval (1994) for relief of minor muscle and joint pain and improvement of superficial circulation. The consensus seems to be that it is not more effective for temporary pain relief than heat therapy; most insurance companies do not cover its use.
  - There seems to be some evidence for a role in reducing post-irradiation oral mucositis (Kumar SP, *Indian J Palliat Care*, 2013).
• **Ultrasound** (low frequency, i.e. ~20 kHz, traditionally used to relieve muscular spasms). Cavitation (gas bubbles) and streaming (unidirectional steady mechanical force) seem to alter the characteristics of cell membranes.
  - Use in venous ulcers and pressure sores yields inconsistent results.
  - Systematic reviews in *BMJ Clinical Evidence* (2007) deem it to be of ‘unknown effectiveness’.
  - NICE 2011 stated that there was promise but the low level evidence, and lack of comparisons, meant that its use in the NHS was not supported.
  - Most insurance companies will not cover its use.

See other chapters for healing of bone, tendon and nerves.

**WOUND MANAGEMENT**

Management of wounds involves a comprehensive assessment of the patient as a whole, as well as the wound itself. This includes looking for conditions/factors that can affect healing, and also the nutritional status.

**NUTRITION**

Whilst there has been much research on the subject, as yet, there is no simple, single reliable method of assessing nutritional status. Criteria that have been used for this include the following:

• **Clinical**, e.g. recent weight loss, signs of loss such as muscle wasting/loss of fat, oedema. Unplanned weight loss of more than 10% over 6 months is associated with a poor response to injury.
  - BMI < 18.5 implies nutritional impairment whilst BMI < 15 is associated with significant mortality.
  - Skin fold thickness of triceps, mid-arm circumference.
• **Biochemical markers** – transferrin, retinol binding protein but most commonly prealbumin. Prealbumin has a half-life of 2–3 days and is thus a better measure of protein nutrition than albumin (half-life 20 days, and may be reduced by sepsis/inflammation as well as malnutrition). Closure of surgical wounds is more successful if the albumin is >30.
• **Nutrition Risk Index** = (1.519 × albumin g/L) + 0.417 × (present weight/usual weight × 100). A score below 100 indicates malnutrition.
• Lymphocyte function and body nitrogen are primarily research tools.

NICE recommends nutritional support for patients who have 5 days or more of reduced intake, or those with poor absorption, high losses or increased requirements. Nutrition can be supported by various means:

• **Oral supplements** – over and above a normal hospital diet, is simple and relatively effective.
• **Enteral feeding** for those with inadequate oral intake, is cheaper and safer than parenteral feeding and numerous studies have shown benefit.
• **Parenteral feeding** (peripheral or central) is reserved for those with non-functioning gut, e.g. short bowel, high output fistula. Some trials show that preoperative TPN reduces complications but not mortality in malnourished patients; there is less support for the use of post-operative TPN and it may actually be harmful.

Whilst many micronutrients are important in healing, replacement is only indicated in deficiency states.

• **Vitamin A** is one of the exceptions to this rule. Administration reverses most of the steroids’ effects on inflammation, except for infections and wound contraction. It may be considered in those on chronic steroid therapy.
• **Vitamin E** supplements do not have any beneficial effects on wound healing, and large doses may actually inhibit healing (decreased tensile strength).
• **Taking large doses of vitamin C** does not improve healing.
• The benefit of glutamine is most well studied particularly in burns; arginine seems to have mixed effects.

**SPECIFIC WOUND MANAGEMENT**

The fundamentals of wound management are usually summarised with the acronym TIME (or DIME).

• **Tissue management** (or Debridement)
• **Infection control**
• **Moisture balance**
• **Edge advancement**

**Debridement**

Debridement of necrotic, non-viable tissue, which also reduces bacterial load, bioburden (and biofilm) is an important part of wound management. The word comes from the French débrider (old French desbrider), meaning to take...
away the bridle, and the procedure is usually attributed to Napoleonic war surgeons (Desault). The aim is to convert a chronic wound into an acute wound.

- **Non-selective**
  - **Mechanical**, which includes
    - Wet-to-dry dressings – characteristically painful
    - Scrubbing
    - Hydrotherapy
  - **Hydrogen peroxide** (usually 3%) – this is a source of reactive oxygen species that when applied to tissues bubbles due to the reaction with tissue catalase releasing water and oxygen. Staphylococci tend to be catalase-positive whilst Streptococci do not have catalase and are thus said to be more susceptible to peroxide. It is commonly used as a wound antiseptic, and whilst it shows broad in vitro activity, the few clinical studies generally show that it is relatively ineffective in reducing bacterial load, though it does appear not to delay wound healing. The AMA (Roderheaver GT, Chronic Wound Care: A Clinical Source Book for Healthcare Professionals, 2nd Edn, 1997) suggested that the effervescence may have some mechanical benefit in loosening debris and necrotic tissue.

- **Antiseptics** such as chlorhexidine (works within 20 seconds but lasts only 6 hours), povidone iodine 10% (equivalent to 1% availability, needs 1 minute to work), alcohol, etc. have a wide spectrum of activity and low risk of resistance, but may damage healthy cells.

- **Topical antimicrobials** include the usual antibiotics mupirocin, fucidic acid and neomycin, but some include silver, honey and cadexomer iodine (Iodosorb, Smith and Nephew). They do not harm healthy tissue, but antibiotics should only be used for 1–2 weeks due to concerns over sensitisation and resistance.

- **Selective debridement**

- **Surgical** (some would put this in the non-selective category). This is the most common method and involves blades/curettes, etc.; some use more complicated systems such as the Versajet®.

- **Enzymatic** – selectively digest dead tissue/slough. Iruxol Mono® is a collagenase, clostridiopeptidase A, but takes several days to work. Others such as Nexobrid® (bromelain, derived from pineapple stems) may work quicker (Rosenberg L, Burns, 2004) but is not widely available.
  - **Autolytic** – the combination of moist dressings, e.g. hydrocolloids and endogenous proteolytic enzymes, can lead to the liquefaction of necrotic tissue that then separates. It can be enhanced with hydrocolloids/hydrogels/occlusive films and products such as medical honey.

- **Biological** – maggots of certain species, e.g. *Lucilia sericata*, can cause benign myiasis, i.e. the larvae only digest dead tissue, extracorporeally through chymotrypsin-like enzymes (note that some species cause malignant myiasis, damaging healthy tissue). There are reports of an antimicrobial action and promotion of healing. There may be pain after 2–3 days, supposedly due to alkaline secretions, whilst other secretions may cause irritation/excoriation of normal skin
  - Maggots have been used in military wounds for a long time. Crile demonstrated that soldiers with maggot-infested wounds actually did better. Following the increasing use of antibiotics, maggot therapy declined, but it has had a resurgence since the 1980s. In the United Kingdom, they can be prescribed and used in the community. They are useful in infected necrotic wounds including diabetic ulcers and pressure sores, particularly those unfit for surgery. One study showed healing of 90% of MRSA-infected wounds after one to two maggot applications over 4–6 days.
  - Maggots take 10–14 days to pupate, requiring a dry place; thus, it is important to keep them in the wound and to dispose of them quickly.

### Infection control

- **Contamination** – there are low numbers of non-replicating bacteria.

- **Colonisation** – bacteria are replicating but are not provoking an inflammatory response. It does not normally inhibit normal wound healing.

- **Infection** – there are a large number of bacteria that are invading wound tissue and are provoking an inflammatory reaction.

Taking wound swabs for bacterial culture is a very common practice but not that useful; swabbing open wounds is particularly pointless. Quantitative analysis of tissue biopsy is the gold standard; >10³ is regarded as significant.

- **Biofilms** are polymeric glue-like structures with collections of bacteria within them. Their significance is that the bacteria are relatively protected from the immune system as well as simple wound care. They often require physical removal, e.g. debridement, as well as topical antiseptics/antimicrobials or systemic antibiotics; Prontosan® (betaine-polyhexanide) uses electrostatic disruption/surfactant action to disrupt a biofilm.

### Moisture balance

There are many wound dressings available; but in simple terms,

- If the wound is dry, add moisture with hydrogels, hydrocolloids or films.
- If the wound is too wet, remove moisture with foams or algicates.
MOIST WOUND HEALING (WINTER G, *NATURE*, 1962)

This concept is a mainstay of modern wound healing and is promoted by occlusive dressings such as hydrocolloids, hydrogels and films.
- Maintains hydration and temperature
- Prevents scab/eschar formation
- Promotes epithelialisation
- Autolysis
- Slightly acidic environment
- Growth factors more active

EDGE ADVANCEMENT

The wound edge may be undermined or rolled due to excessive proliferation. Failure of wound edge migration may be due to persistent/inadequately debrided slough, prolonged wound inflammation or senescent cells.

ULCERS

An ulcer is a breach in the epithelium and there are multiple causes. The ulcer characteristics, particularly the edge and base, provide important information. The surrounding tissues specifically skin condition, circulation and sensation (e.g. glove and stocking neuropathy) also provide clues. Long-standing ulcers should be biopsied to exclude malignancy (*Marjolin’s ulcer*); other problems to consider include vasculitis/autoimmune disease, sickle cell, infection or
- **Hydroxyurea** (an antineoplastic agent used to treat haematological malignancies) can cause painful leg ulcers (usually after prolonged use) that are refractory to local care until the drug is discontinued.
- **Pyoderma gangrenosum** is a necrotising cutaneous vasculitis that may be associated with inflammatory bowel disease or rheumatoid arthritis. Histological findings are non-specific and the diagnosis is clinical. Ulcers in IBD patients may improve when the bowel disease improves. Surgery is contraindicated.

VENOUS ULCERS

This is the commonest cause of leg ulcers in developed countries (70%–90%), affecting 1.7% of the elderly in the United Kingdom and costing 600 million GBP a year in health costs. A minority will also have an arterial component.
- Typically a painless (uninfected) ulcer over medial malleolus (*gaiter area* – a gaiter being a protective item that covers the ankle to the instep area. They also cover the lower trouser, differentiating them from spats). Aching and swelling at the end of the day are improved by elevation.
- The typical skin changes are lipodermatosclerosis (scarring) and pigmentation due to haemosiderin deposition.
- Valvular dysfunction leads to **venous hypertension**; a history of DVT was found only in 28% (Moffat CJ, *QJM*, 2004). This leads to protein extravasation and formation of a perivascular fibrin cuff. Duplex ultrasound studies have shown that superficial venous incompetence is found in most patients with venous ulceration (Magnusson MB, *Eur J Vasc Endovasc Surg*, 2001), sometimes with deep venous reflux, but isolated reflux in deep or perforating veins is uncommon.
- There are many dressings to choose from, and there is little evidence that any one product demonstrates superiority to the others, though hydrocolloids/foams may help reduce pain.
- **Pentoxifylline** (Trental®, normally used for intermittent claudication through increases in microcirculatory blood flow, may be more effective than placebo, with or without compression (Full AB, *Cochrane Database Syst Rev*, 2012). Most of the side effects were gastrointestinal. SIGN (2010) suggests that it may be used; however, it is an unlicensed indication.
- **Compression therapy** (to counteract venous hypertension) by trained nurses is a key treatment. There are some regional preferences but results are similar.
  - Four-layer bandaging (4LB) is popular in the United Kingdom; full healing is achieved in 8 weeks.
  - Short stretch bandaging is preferred in Europe.
  - Unna boots made from zinc oxide and calamine-impregnated bandages, changed once every 1–2 weeks, are common in the United States. They facilitate ambulation.
  - **Superficial vein surgery** (various forms of venaocclusion including high ligation and GSV stripping, sclerotherapy and RFA or endovenous laser) is much more beneficial for ulcer healing/recurrence than deep vein surgery, which has significant complications. The evidence for subfascial perforator ligation in ulcer healing remains unconvincing. Venous surgery/referral to a vascular surgeon does not need to be delayed in patients with healthy granulating ulcers with no evidence of infection. The **ESCHAR trial** (2004) found no difference between compression alone (89% at 3 years) vs. compression with surgery for superficial reflux (93%), but the latter group has a reduced recurrence rate and more ‘ulcer-free time’.
  - Surgery to the ulcer can be considered if conservative treatment fails. Skin grafts work reasonably well, but recurrence is almost inevitable without dealing with the venous insufficiency; flaps are a major undertaking but import vascularity.

DIABETIC ULCERS

Approximately 15% of diabetic patients suffer from ulcers. The aetiology is often mixed: one-third are purely
neuropathic, one-third are neuropathic and ischaemic whilst one-fourth is purely ischaemic. **Neuropathy** is important and has anatomic, ischaemic and metabolic contributing factors:

- Elevated blood sugar levels reduce sodium pump activity and increase intracellular sorbitol, leading to nerve swelling and intraneural compression.
- Alterations in microcirculation lead to focal nerve loss.
- May have ‘double crush’ phenomenon, e.g. concomitant carpal tunnel, cubital tunnel syndrome.
- Sensory neuropathy leads to loss of protective sense.
- Autonomic neuropathy – anhidrosis, dry cracked skin from AV shunting.

Wound care in diabetics is a particular challenge.

- **Off-loading** is very important.
- **Increased infection risk** (usually Staphylococci or Streptococci) due to impaired lymphocyte function and impaired phagocytosis. Antibiotics should be used judiciously; some countries have banned the use of topical antibiotics in diabetic wounds due to resistance problems.
- **HBOT** reduces amputation rates and is covered by Medicare if ulceration has been unresponsive to 30 days of standard treatment.
- **Apligraf** (see later) use is covered in non-responsive diabetic and venous ulcers, though insurers have recently cut back on the reimbursement per treatment.

Microangiopathy does not contribute significantly to the development of ulcers in diabetics; thus, vascular reconstruction can be beneficial. It may be more useful for foot ulcers compared to calf ulcers. Diabetic patients have atherosclerosis similar to non-diabetics but often with different distributions – they tend to have tibioperoneal disease with long segment occlusion and calcification, whilst any femoral disease tends to be diffuse. The peak flow improvement occurs 1 week after a bypass but takes up to 1 month after an endovascular intervention; the latter also has a higher rate of short-term failure.

- **Amputation** – toe fillet, plantar VY, ray/transmetatarsal amputation are choices for gangrenous toes; >½ of all amputations performed are secondary to diabetic disease.
- **Reconstructions** may be ‘simplified’ with the use of negative pressure wound therapy (NPWT) to reduce bacterial counts, improve the formation of granulation tissue especially over non-favourable wounds with exposed tendons, bones and joints and improve the take of skin grafts.
- The current consensus is to aggressively postpone the need for amputation:
  - 1/3 need a more proximal amputation due to poor healing.
  - 1/2 have a contralateral limb amputation within 5 years.
  - The 5-year survival after amputation is 40%.

Diabetic foot reconstruction using free flaps increases 5-year survival rate. (Oh TS, *J Plast Reconstr Aesthet Surg*, 2013)

A retrospective review of 121 reconstructive procedures in diabetic foot wounds. A variety of free perforator flaps (ALT, SCIP, anterior or upper medial thigh flaps) were used with 91.7% success, with overall limb salvage rate at 5 years being 86.6%. Statistical analysis shows improved 5-year survival in patients who had foot reconstruction compared to those who had an above ankle amputation (86.8% vs. 41.4%).

**TISSUE TRANSPLANTATION**

- **Immunology**
- **Skin grafts**
- **Bone grafts**
- **Tendon healing and tendon grafts**
- **Tissue allografts, xenografts and alloplasts**

**IMMUNOLOGY**

Major histocompatibility antigens (MHC, also called human leucocyte antigens – HLA, in humans) are found on the surface of cells.

- Type 1 – all nucleated cells and platelets
- Type 2 – antigen-presenting cells (APCs): Langerhans cells, macrophages and lymphocytes

**RESPONSE TO MHC-ALLOANTIGENS**

- APCs present alloantigen to T-cells and express IL-1.
- IL-1 causes T-helper (CD4+) to produce IL-2.
- IL-2 causes clonal expansion of T-helper cells and B-lymphocytes.
- IL-2 also activates Tc-cells and NK cells (cellular immunity).
- B lymphocytes mediate antibody-mediated cell lysis (humoral immunity).

**ALLOGRAFT REJECTION**

Unmatched tissue grafts from another patient, i.e. allografts, will be rejected; skin is the most allogenic tissue – rejection in hand/face transplants is first manifested as a blotchy rash.

- **Acute rejection** occurs after 7–10 days due to T-cell infiltration (cellular immunity). It may be delayed in immunocompromised patients until the immunodeficient state has passed, e.g. recovery from a severe burn or stopping immunosuppressant drugs.
- **Late rejection** is due to antibody-mediated cell lysis (humoral immunity).
- **Hyperacute rejection** is due to preformed antibodies and the rejection response begins immediately.
• **Graft versus host reaction** occurs when allograft containing lymphoid tissue reacts against an immunocompromised host, and is a particular risk in bone marrow transplant.  

Immunosuppressant drugs are needed to block rejection in allotransplantation:

- Cyclosporin blocks IL-2, which blocks clonal expansion of Tc-cells.
- Azathioprine inhibits T-cell-mediated rejection by preventing cell division.
- Prednisolone blocks the generation and release of T-cells.

**BIOMATERIALS**

These are biological materials used to replace or augment tissues in the human body and can be classified as

- **Autograft** – living tissue from host
- **Isograft** – from a genetically identical twin
- **Allograft** – tissue from same species
- **Xenograft** – tissue from different species
- **Alloplast** – derived from synthetic material.

The biological reactions to a foreign body include

- Immediate inflammation with early rejection
- Delayed rejection
- Fibrous encapsulation
- Incomplete encapsulation with continuing cellular reaction
- Slow resorption
- Incorporation

**TISSUE ALLOGRAFTS, XENOGRAFTS AND ALLOPLASTS**

**Tissue allografts**

These generally do not contain living cells due to processing to reduce antigenicity, though bone allograft may have osteoconductive and osteoinductive properties. They are usually incorporated into host tissues providing a structural framework for the ingrowth of host tissues.

- Their advantages include a plentiful supply; a donor site is not required and operation time is usually reduced.
- Disadvantages include a potential for infection/disease transmission, and they demonstrate a variable amount of resorption.

Examples include

- Lyophilised fascia (dura mater, fascia lata) – risk of Creutzfeldt–Jakob disease (CJD) transmission in the former. Typically there is a 10% resorption rate.
- Homologous cartilage – greater tendency for resorption, replacement with fibrous tissue, ossification and more infection compared with autologous tissue. A tissue is said to be homologous if it performs the same basic function in the recipient as the donor.
- Homologous bone – acts generally as scaffold for formation of new bone; slower to become incorporated and revascularised.
- AlloDerm® (LifeCell Corp) – cadaveric dermis that has been processed to remove cellular elements, allowing incorporation into the host.
- Glyaderm® (Euro Skin bank) is a glycerolised acellular human dermis, which can be used as a dermal substitute, which is then covered by a thin autograft.

**SKIN ‘ALLOGRAFTS’**

Cadaveric skin was first used as temporary cover in burns by Brown in 1953. It has not been satisfactorily used as a skin transplant (i.e. a true allograft) in major burns (Mahdavi-Mazdeh M, Int J Organ Transplant Med, 2013).

- The skin must be retrieved within 24 hours of death from a refrigerated cadaver under aseptic conditions (screening serology for hepatitis B and C viruses, human immunodeficiency virus and skin samples for culture of bacteria, yeast and fungi). It is stored in nutrient media at 4°C for up to 1 week (‘fresh’) or sterilised (e.g. irradiation) and cryopreserved (controlled freezing at 0.5–5°C/min to –196°C with liquid nitrogen and a cryoprotectant solution). When needed, it is rapidly rewarmed to 10–37°C (~3–4 min). Alternatively it can be processed with 85% glycerol (Euro Skin), which is a slow-acting but effective bactericide.
- Donor exclusion criteria – high-risk categories for HIV, i.e. male homosexuals, drug abusers, those with tattoos, prostitutes and haemophiliacs, those with infection/sepsis, neoplasia and autoimmune disease. Only two cases of viral transmission in 3 million tissue transplants (including skin) have been described.
- Coverage of areas of full thickness skin loss, e.g. after burn debridement, in the face of inadequate donor skin. The cadaveric dermis will adhere tightly to the (fibrin of the) wound bed and keep it clean and reduce losses, whilst the donor sites heal and become available for a second harvest.
- It can also be laid over widely meshed autograft to reduce wound desiccation (Alexander/sandwich technique).
- Some use cadaveric skin or porcine skin as ‘test grafts’ to see if a wound bed is ready to support autografts, e.g. in debrided chemical burns.
CULTURED EPITHELIAL AUTOGRAGFT

Epithelial culture (Rheinwald JG, Cell, 1975) begins with a full thickness skin biopsy of several square centimetres taken from the patient. After culturing for 2–3 weeks, there will be enough cells to cover a 1.8 m² sheet five cells thick. The cells take by adhesion more than revascularisation; overall take is 80% under favourable conditions, though late loss can occur.

- Cultured epidermal cells express fewer MHCII/HLA-DR antigens and thus allogenic keratinocytes could potentially be used. Animal studies have shown temporary take contributing to wound closure, but the cells do not persist for more than a week – they may accelerate wound healing by interaction with host cells, and through cytokines and growth factors. The results so far have been too costly and time-consuming to be clinically useful.

TISSUE XENOGRAFTS

Animal-derived wound dressings have been used as early as 1500 BC. The dressing dries and falls off as the burn heals; they are ‘ejected’ rather than rejected, and thus the term ‘xenograft’ should be avoided for these materials. Similarly, whilst other animal-derived products are used for permanent incorporation, they are acellular after significant processing, and probably do not qualify as true xenografts.

- Surgisis® (Cook) – derived from pig small intestine submucosa (SIS); an updated product Biodesign was released in 2008. It is often used for fascia replacement; the acellular matrix allows tissue ingrowth; it received FDA clearance in 1988 as a hernia repair material.
- Similar products include – Cellis®, Strattice® (Lifecell) and Permacol® (Covidien). There are no good clinical data for its effectiveness over other biological meshes or standard mesh. Some of these are being promoted for use in (covering) breast implants; however, it is much less elastic than human ADMs and is associated with higher seroma rates.

TISSUE ALLOPLASTS

Alloplasts have abundant supply without donor site morbidity, but tend to be expensive and elicit a host reaction of some sort as they are foreign materials. Silicone and Medpor® are the commonest types of implant materials used in the face.

- Silicone is a silicon polymer and its physical state depends on the amount of cross-linking. It is generally inert, which means it tends to be encapsulated rather than incorporated.
- Medpor® (high-density porous polyethylene) – allows vascular ingrowth and reduced tissue reaction, but it is expensive and can be difficult to remove.

- Hydroxyapatite – a calcium phosphate salt available in dense (high-pressure compaction) or porous hydroxyapatite. A natural source of hydroxyapatite comes from coral. It allows a degree of vascular ingrowth but is brittle and can be difficult to shape. It is also available for use as a tissue filler (Radiesse®).
- Nanocrystalline hydroxyapatite (NanoBone®) – new bone formation is seen after 5 weeks. There is a size limit; clinical studies suggest that (cranial) defects larger than 4–5 cm will be incompletely ossified. Such materials are unable to tolerate load bearing. Note that autologous bone is prone to resorption in the absence of load bearing, and thus would offer a few advantages over biomaterials under these circumstances.
- Calcium carbonate also derived from coral (but without additional conversion to phosphate) is resorbed and totally replaced. However, it is not very strong.
- Gore-Tex® – expanded polytetrafluoroethylene (ePTFE) – is available in many different forms. It provokes a weaker foreign body reaction and reduced ingrowth in comparison to polypropylene mesh, and thus is said to have weaker interface with tissues (almost no capsule formation) with potentially more herniation but fewer adhesions and fistulae. However, major differences are not evident in studies.
- Metals, e.g. stainless steel, vitallium alloy, titanium alloys (10 times stronger than bone and well tolerated but has low fatigue tolerance).
- Polylactide compounds, e.g. Lactosorb® plating system used in craniofacial surgery, poly-L-lactic acid (PLLA) tissue fillers (Sculptra®). These are completely resorbed and thus have fewer long-term risks.
- Polygllactin – is available as a suture (Vicryl), film or mesh.

BONE AND BONE HEALING

Bone is composed of 35% organic material (mostly type I collagen), 60% mineral (mainly hydroxyapatite) and 5% trace elements.

TYPES OF BONE

Developmental classification

- Endochondral bone – laid down as cartilage first, usually at an epiphysis, followed by ossification. This occurs in long bones.
- Membranous bone (skull, facial, clavicle) – osteoid is laid down directly by osteoblasts without a cartilaginous stage. Also occurs in primary bone healing.
- Membranous bones are said to undergo less absorption than endochondral when used as onlay grafts on facial bones (Zins JE, Plast Reconsr Surg, 1983).
**Structural classification**

- **Cortical** – concentric lamellae around a Haversian canal.
- **Cancellous** – made up of lamellar bone but in loosely woven spicules/trabeculae. It is not the same as immature/woven bone.

**Fracture healing**

Normal bony union/healing occurs at 4–8 weeks in adults. A good blood supply and stability of the bony ends is essential for healing. The blood supply to bone comes from:

- Nutrient artery, which enters the medulla and usually supplies the inner two-thirds of the cortex
- Periosteal artery, which supplies the outer third of the cortex
- Metaphyseal, apophyseal (at tendon/ligament attachments) and epiphyseal supplies.

**Bony union**

- **Primary union** – healing without an intermediate cartilage phase. The bone forms directly at the opposed Haversian canals at the fracture surfaces by osteoclastic action and osteocyte osteoid formation with little or no external callus reaction. This type of healing requires tight apposition and compression of bone ends, e.g. if a fracture is anatomically reduced and immobilised by rigid compressive fixation, e.g. AO system of facial fracture fixation.
  - It takes about 6 weeks, i.e. typically longer than secondary bone healing; also known as membranous union and is less common.
- **Secondary union** has an endochondral phase with hyaline cartilage deposition. This type of healing occurs in fractures that are not rigidly fixed or have a small gap. There are four phases similar to wound (skin) healing described above:
  - **Haemorrhage, inflammation and proliferation** (1–7 days) – activation of clotting cascade to form a fibrin coagulum (fracture haematoma) between the bone ends, which is invaded by neutrophils, then by macrophages and fibroblasts to form granulation tissue/collagen, whilst osteoclasts resorb necrotic bone.
    - Acid tide
    - Alkaline tide ~day 10 with increased alkaline phosphatase coinciding with the production of woven bone
  - **Soft callus stage** (3–4 days) – capillaries from the periosteum invade the fibrin clot. Periosteal activity peaks at 24–36 hours; undifferentiated periosteal mesenchymal cells differentiate to become chondrocytes that form a cartilaginous external or bridging callus, with further differentiation of chondrocytes into osteoblasts with endochondral ossification of the callus to form woven bone. The hard callus stage occurs about 3 weeks after injury.
  - **Remodelling** (years) of woven bone to mature lamellar bone, orientated along lines of stress.

**Abnormal union**

- **Non-union** – permanent absence of histological osteogenic material between fracture ends
  - Fibrous/fibrocartilage
  - Pseudoarthrosis with fibrocartilage cap
  - Persistence of fracture ends with no cartilage (which implies excessive mobility)
  - Delayed union – slow but will eventually heal to acceptable union. It differs from non-union by the potential for consolidation after proper immobilisation and reduction.
  - Malunion – non-anatomic union exists, which can either be normal or fibrous.

**CAUSES OF POOR UNION:**

- **Local**
  - Inadequate fixation/immobilisation is the most common cause of poor bony union. There is ‘eburnation’ (rounded osseous ends) and medullary blood vessels fail to bridge the gap leading to an avascular zone and potentially osteogenic material turns into a fibrous scar.
  - Inadequate blood supply, which also predisposes to infection.
  - Infection – non-union may be the only sign of infection.
  - Recurrent trauma.
- **Systemic**
  - Age (children can heal in 3 weeks or less, but the elderly may take 8 weeks or more).
  - Medication, e.g. steroids.
  - There is mixed evidence that NSAIDs have adverse effects on fracture healing.
  - Malnutrition and general metabolic disorders (renal failure, deficiency of vitamins ACD).
  - Bone disease (Paget’s, osteogenesis imperfecta).

**HEALING OF BONE GRAFTS**

Bone that is transferred without its blood supply from one region to another will ‘heal’ in various ways. The relative contributions of osteoconduction, osteoinduction and osteogenesis depends on the composition of bone.

- **Osteoinduction** – pluripotential cells in the recipient site (pericytes) are ‘induced’ to become bone cells; this is controlled by growth factors called bone morphogenic proteins (BMPs). Some products include recombinant human BMPs for ‘highly osteoinductive bone grafts’.
- **Osteoconduction** – bone graft acts as a scaffold for the ingrowth of cells and capillaries. Old bone is
reabsorbed and new bone deposited, i.e. ‘creeping substitution’. Most bone fillers fall into this category, e.g. cancellous auto/allografts, demineralised bone matrix, hydroxyapatite, etc.

- **Osteogenesis** – new bone is produced by cells that survive within well-vascularised parts of the bone graft. Cancellous autograft (and bone marrow) will have enough osteoprogenitor cells to be considered osteogenic.
- **Osteointegration** is often mentioned in this discussion. It is the capacity of bone to bind directly to the surface of an implant (usually titanium alloy) without a fibrous layer, making it very rigid.
- Titanium is useful being very strong yet bendable, and well tolerated; however, as there is no bone growth, extrusion is always a risk.

The most basic requirement for a bone graft to work is for it to be osteoconductive, whilst osteoinduction and osteogenesis will theoretically promote faster integration of the graft. All bone grafts undergo some degree of absorption; it is dependent on the microarchitecture (more than embryological origin). Stability is another major determinant. See Table 1.2.

- **Cortical bone** tends to form a non-viable scaffold matrix. The osteocytes within lacunae die leaving an intact Haversian canal system and graft take occurs by osteoconduction, i.e. the bone graft is a surface to ‘conduct’ cells at the recipient bone ends, which migrate into it, proliferate and carry out their functions. Osteoclastic resorption and osteoblastic deposition lead to eventual replacement of the graft. Characteristically, there is initially high strength that decreases with bone resorption and is regained after remodelling is complete.
- **Cancellous bone** graft generally consists of morcellised pieces of bone that are readily vascularised by surrounding tissues, whilst the presence of viable osteoblasts in the graft allows osteogenesis and contributes to new bone growth. Osteoinduction can occur by factors such as BMPs that cause undifferentiated mesenchymal cells to differentiate along osteoblastic pathways. Cancellous bone offers more reliable take due to the larger surface area of contact and can be used to stimulate healing, provide bulk or bridge small gaps, but offers little structural support initially; but this increases as more bone is incorporated.

**Vascularised bone grafts** (VBGs), i.e. bone flaps, are superior to bone grafts in terms of incorporation time, mechanical strength and retention of mass, and thus are recommended for defects larger than 5–6 cm. Most cells in the lacunae are actually non-viable, dying before neovascularisation. VBGs are more resistant to irradiation and infection. In contrast to simple fractures, they can still take over a year for stable union.

- Distraction osteogenesis can be used for selective bony defects.

Bone graft materials are generally classified as autograft, allograft, alloplast and xenograft. They can be fresh (with greater risk of disease transmission), fresh frozen or freeze-dried. **Autografts are the gold standard.**

- Blood (soaked sponge) is the best wrapping for a bone graft, wrapped again in a saline gauze. Antibiotic solutions are harmful; even crystalloid solutions have harmful effects after long exposures. High temperatures and exposure to air kill osteocytes.

Allografts function as a scaffold and are generally slower to incorporate/vascularise than equivalent autograft; they are widely available in a number of forms.

- Exogenous BMPs can lead to new bone growth through conversion of osteoprogenitors into osteoblasts.
- Rh-BMP2 and rh-BMP7 are FDA-approved for spine surgery, fractures and alveolar clefts.
- BMP9 is most potent.

**FACTORS AFFECTING HEALING OF BONE GRAFTS**

In general, take can be improved by ensuring good contact, rigid fixation, increasing the cancellous/cortical ratio and retaining periosteum.

- Patient factors, e.g. age, nutrition, immunosuppression, diabetes, obesity, drugs, etc. (see ‘Wound healing’)
- Bone graft factors
  - Intrinsic properties – there is usually less resorption if the periosteum is intact and possibly in membranous bone. Processing of allografts such as freeze-drying reduces immunogenicity and the risk of disease transfer, compared to fresh bone.
  - Recipient site – irradiation, infected or scarred.
  - Fixation – rigidity of, (see ‘Bone and bone healing’)
  - Mechanical stress – physiological loading speeds up union and creeping substitution.

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<tr>
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<th>Vascularised bone</th>
<th>Cortical graft</th>
<th>Cancellous bone</th>
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Table 1.2 Characteristics of types of bone grafts related to their healing and strength over time
BONE GRAFTS VS. CARTILAGE GRAFTS

- **Bone autografts**
  - Can be incorporated without host reaction and is relatively resistant to infection.
  - Donor site morbidity is a problem, as is the variable resorption rate in the graft – cortical grafts maintain their volume better than cancellous (see above).
- **Cartilage autografts**
  - Relatively easy harvest and less donor site morbidity; infection and resorption are rare but grafts may calcify.
  - Have a tendency to warp and memory is very difficult to overcome.
  - Quantities are quite limited (septum, rib, conchal).

TENDON HEALING IN THE HAND

Tendons consist of a dense network of spiral collagen fibres that are predominantly type I; there is some type III collagen, some ground substance and a small amount of elastin.

- Ground substance (~60% water) provides support and spacing to the collagen.
- Elastin facilitates recoil and recovery.
- Smooth gliding is facilitated by lubricin (proteoglycan 4).
- They are relatively acellular – mostly (~95%) specific tendon cells (tenoblasts and tenocytes); the remainder include fibroblasts and synoviocytes. The low metabolic/anaerobic activity of mature cells is suited for the tensile stresses, but makes repair slow. Tendon stem/progenitor cells (TSPC) were found (Bi Y, Nat Med, 2007), but their role is uncertain.

The **endotenon** envelops tendon fascicles and binds them together. It also supports the sparse vessels and nerves; it is continuous with perimysium and periosteum. The **epitenon** is a vascular, cellular outer layer of a tendon, which runs through a synovial sheath (zones 1 and 2 in the hand), whilst in zones 3 and beyond, where there is no tendon sheath, the outer vascular layer is called ‘paratenon’.

BLOOD SUPPLY AND HEALING

The blood supply in zones 1 and 2 of the hand comes via mesenteries (‘mesotenons’) called the **vinculae** – long and short, that enter the dorsal surface of the tendons from the transverse digital arteries at the level of the cruciate pulleys. Synovial fluid also contributes to nutrition via imbibition and is an important source in the hand; in the forearm, tendon nutrition is mainly derived from vessels in the paratenon.

Tendon healing occurs by processes analogous (to skin healing) of inflammation (with cellular response), proliferation (fibroplasia) and remodelling. The early vascular response in particular seems to be important and ensures the survival of the new fibrous material.

- **Extrinsic healing** by cells recruited from synovial sheaths and surrounding tissues forming adhesions.
- **Intrinsic healing** by cells within the tendon itself.
- The two occur together and in cooperation.
  - Early collagen production is predominantly type III and ‘random’.
  - Remodelling begins 6–8 weeks after injury (consolidation phase) and lasts up to 2 years (maturation phase).
  - In most, the tendon does not regain full ‘strength’ – it usually thickens and stiffens to partly compensate.
- Studies have demonstrated that the strength and rate of healing are maximal in a tendon that is moving and stressed. A repaired tendon is weakest during the period of collagen lysis at about days 10–14.
- Strategies to improve tendon healing include
  - Growth factors – animal experiments seem to indicate a role for VEGF, TFGβ, PDGF and bFGF.
  - **Platelet-rich plasma** (PRP) as a source of autologous growth factors was popular for awhile. Systematic reviews did not show any improvement in the healing of tendinopathy (de Vos RF, JAMA, 2010).
  - Mesenchymal stem cells (MSCs) including marrow and adipose derived (ADSCs).
- **Biomaterials** to avoid autologous tendon transfer/graft.
  - Xenografts, e.g. Permacol™, and allografts, e.g. GraftJacket™, have been used in rotator cuff and Achilles tendon repairs (Lee DK, J Foot Ankle Surg, 2008).
  - Collagen gels, often with bone marrow MSCs, have been used in animal studies only.
  - Scaffolds composed of cell-loaded collagen I nanofibres/composites (Kishore V, Biomaterials, 2012); these have been used in animal studies but have been difficult to scale up to humans.


Despite the vogue for PRP, this RCT provides level 2 evidence that FRP is not useful for the treatment of Achilles tendon ruptures.

The risk of fluoroquinolone-induced tendinopathy and tendon rupture. (Del Rosso JQ, J Clin Aesthet Dermatol, 2010)

Levofoxacin, ciprofloxin and ofloxacin are antibiotics of the fluoroquinolone (FQ) class. After the first report of Achilles tendinopathy in 1983, many other cases followed. In 2008, the FDA mandated a black box warning of increased adverse events including tendon rupture – based on epidemiological studies, there is a 3.8× risk compared to other antibiotics. FQs have a high affinity for connective tissue and inhibit tenocyte metabolism including proliferation and collagen synthesis. Age >60 and concurrent steroids
seem to increase the risk; half of cases occur within 1 week of administration.

The Achilles tendon is affected in 95% of FQ-related cases in a literature review (Lewis T, J Athl Train, 2014); rupture of finger and thumb tendons, shoulder, hip and knee tendons have been reported less frequently.

II. NECROTISING FASCIITIS

NF was first described by Wilson in 1952. It is a potentially life-threatening infection (up to 53% mortality) that progresses along fascial planes and subcutaneous tissues.

CLASSIFICATION

• Type I. Mixed/polymicrobial (80%) – anaerobes (Escherichia coli, bacteroides) and aerobes (Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis). In most cases, streptococci and/or staphylococci are the initiating agents; anaerobic bacteria proliferate in areas of local hypoxia such as traumatic/surgical wounds or medical compromise. Type I NF is more common in the elderly or those with illness such as diabetes, alcoholism and malignancy.
  • Vibrio vulnificus (Latin vulnus, a wound and facere, to make) is often seen in those with chronic liver disease and may follow raw seafood ingestion as well as injuries in fishmarkets. This type of disease sometimes called saltwater NF classically demonstrates subcutaneous bleeding.

• Type II. Monomicrobial. Although more recently methicillin-resistant Staphylococcus aureus (MRSA) has been implicated, the causative agent is usually group A β-haemolytic streptococci (e.g. Streptococcus pyogenes) carried in the nose/throat of 15% of the population. This is the classic ‘flesh-eating bacteria; it can also contribute to type I infections. Type II NF can affect all age groups and the healthy (up to a half); there is an association with varicella zoster and NSAIDs. The (lower) extremity is affected most often. There are a number of virulence factors:
  • Exotoxin, e.g. streptococcal pyrogenic exotoxin A (SpeA); this superantigen (antigens that cause non-specific activation of T-cells resulting in polyclonal T-cell activation and massive cytokine release) causes systemic upset.
  • Streptokinase that activates plasminogen and fibrinolysis.
  • Hyaluronidase.
  • Haemolysins.
  • M proteins that inhibit opsonisation by an alternative complement pathway.

• Type III. Clostridial ‘gas gangrene’ with myonecrosis, is due to Clostridium perfringens (Gram-positive rods) in 80%, although it can be caused by other species, e.g. novyi and septicum. It often follows trauma/surgery; local tissue hypoxia leads to activation of spores with α (exo)toxin, i.e. lecithinase production that breaks down cell membranes.
  • Classically there is characteristic surgical emphysema (crepitus, also found in some forms of non-clostridial gangrene) and ‘dishwater’ exudate. Myonecrosis may give rise to deeper pain.
  • Cases with bloody blisters contain Clostridium welchii if aspirated.
  • High mortality – aggressive surgical approach needed with some evidence to support role of HBOT.

Meleneey’s synergistic gangrene is rare but rapidly progressive due to synergism between aerobic haemolytic staphylococci (aureus) and microaerophilic non-haemolytic streptococci. It was described in 1924 by Frank L. Meleneey, a US surgeon working mostly at Columbia University in New York, but saw the cases in China; he was also one of the first to use bacitracin.

Jean-Alfred Fournier described five cases of perineal gangrene of (then) unknown cause in 1883; Baurienne had described idiopathic gangrene of the male genitalia over 100 years earlier. It has since been recognised as a polymicrobial NF, i.e. type I, originating possibly from local abscesses or urogenital tract infections. Diabetes and other causes of immune impairment are risk factors. Infection spreads along the potential spaces bounded by the fascial layers; thrombosis of the external pudendal arteries compromises the circulation of the scrotum. There is early skin necrosis due to thin subcutaneous tissue; the corpora, testes and cord structures are usually spared.

RISK FACTORS

• Surgery and even intravenous infusions or intramuscular injections have been associated with NF.
• Insulin-dependent DM (IDDM).
• Cirrhotic liver disease (Hung TH, Singapore Med J, 2014).
• NSAIDs, e.g. ibuprofen.
• Varicella zoster virus infections.

CLINICAL FEATURES

A high index of suspicion is required to act quickly on the early signs (disproportionate sepsis and pain).

• Local swelling and redness, intense pain out of proportion to the appearance. There is very rapid spread subcutaneously; the dissemination of infection through tissue planes causes thrombosis of blood vessels and violaceous skin changes with dusky/grey hues and haemorrhagic bullae, with crepitus (in less than 10%) and anaesthetic zones due to nerve necrosis. The underlying fascial necrosis is more extensive than overlying skin changes, which are secondary.

• Systemic toxicity – apathy, confusion and septic shock, that is classically out of proportion to the skin disease. The elderly may be unable to mount a pyrexial response.
MANAGEMENT

The early stages of the condition may be difficult to recognise, but diligence is required as it can develop rapidly; early treatment is vital – those who present in shock have the worst prognosis. NF remains a largely clinical diagnosis; imaging may help in delineating the extent or excluding other processes. Early debridement is the key and should not be delayed for radiology or other studies.

- **Tissue biopsy** – rapid Gram stain of deeper tissue – surface biopsies may detect other bacteria that do not actually contribute to the disease.
- There are rapid streptococcal diagnostic tests and PCR for Spe.
- The so-called ‘finger test’ via a 2 cm incision is said to demonstrate the loosened tissue planes, cloudy or ‘dishwater’ exudate and lack of bleeding but is very much dependent on the experience of the physician.
- Hans Christian Gram (1853–1938) was a Danish bacteriologist who developed the staining technique.
- **Radiology** – subcutaneous gas may be seen on plain X-rays but is usually of little value.
- The use of Doppler ultrasound has also been described. Sharif (Am J Roentgenol, 1990) found CT and MRI to be more useful than ultrasound or plain X-rays.
- Computed tomography (CT) with contrast may help (see below) but can be normal in early stages.
- **Magnetic resonance imaging (MRI)** can demonstrate fascial necrosis by T2 hyperintensity in the deep fascia, and a variable pattern of gadolinium enhancement on T1 – in general, the sensitivity of MRI exceeds its specificity. Studies have not demonstrated significant superiority over contrast CT – the latter is a much more efficient way to screen cases, but (contrast) CT may be contraindicated due to acute renal failure.
- Imaging should be used cautiously; non-diagnostic tests may hinder/delay diagnosis and treatment.

TREATMENT

- Resuscitation including ICU supportive therapy – ventilation/oxygenation, inotropic support and dialysis where necessary.
- **Intravenous antibiotics**, e.g. clindamycin (stops the production of toxins and M proteins), gentamicin (covers Gram negatives), third-generation cephalosporins (covers Gram negatives) and imipenem. Immunoglobulins may be given to those with streptococcal toxic shock syndrome.
- Many propose **gentamicin with clindamycin** as standard coverage, adding ampicillin if Gram stain shows enterococci.
- Anaerobes suggested by ‘foul-smelling’ lesions are covered by clindamycin or metronidazole.
- Radical surgical debridement to healthy tissues, with a ‘second look’ at 24 hours. Several debridements are often needed. McHenry (1995) found that survivors had surgery after a mean of 25 hours after admission, whilst in non-survivors, this interval was 90 hours.
- HBOT has been proposed for clostridial NF.


The finding of gas tracking along fascial planes in an ill patient is almost pathognomonic, but imaging is often not needed and can delay treatment. The diagnosis is still primarily clinical.

- CT may show dermal thickening, soft tissue attenuation and inflammatory fat stranding, but the hallmark is soft tissue air with deep fascial fluid collections.
- MRI will show dermal and soft tissue thickening with increased signal on fluid-sensitive sequences. Late stages will demonstrate gas collections in the fascial layers seen as hypointense foci. IV gadolinium increases sensitivity but is not essential. MRI is the modality of choice for soft tissue infection, but acquisition is time-consuming and its availability is often more limited than CT.

III. CLOTTING AND HAEMOSTASIS

There are four components to clotting and haemostasis.

- **Vasoconstriction** – contraction of vascular smooth muscle both as a local reflex and in response to thromboxane release from platelets.
- **Activation of platelets** – with disruption of the endothelium, platelets adhere to the underlying tissue and the intrinsic pathway is activated. Aggregated platelets promote local thrombin and fibrin generation.
- **Coagulation** – intrinsic (involves normal blood components) and extrinsic (requires tissue thromboplastin from damaged cells) pathways both activate factor X. Most coagulation factors are made in the liver except for VIII and thromboplastin.
- **Fibrinolysis** – i.e. fibrin removal, which is the result of the action of plasmin (plasminogen activators from endothelial cells promote conversion of plasminogen to plasmin).

DISORDERS OF COAGULATION

- **Congenital**
  - Haemophilia A – factor VIII deficiency that is X-linked.
  - von Willebrand’s disease – autosomal dominant (AD) deficiency of von Willebrand factor (vWF) that will also reduce factor VIII somewhat (as it normally protects VIII from breakdown).
Wound care

It is the commonest inherited abnormality of coagulation and is actually a collection of conditions with vWF deficiency rather than a single disease entity.

- **Acquired**
  - Vitamin K deficiency inhibits the synthesis of II, VII, IX and X; warfarin also inhibits the production of these (as well as protein C and S).
  - Liver disease – reduced synthesis of clotting factors and reduced/abnormal fibrinogen.
  - Disseminated intravascular coagulation (DIC) – simultaneous coagulation and fibrinolysis, causes reduction of platelets and fibrinogen, but increase in FDPs.

**DISORDERS OF HAEMOSTASIS**

- Thrombocytopaenia – due to reduced production, increased destruction or abnormal function of platelets, e.g. aspirin (blocks platelet cyclo-oxygenase) and clopidogrel (reduces platelet aggregation by inhibiting adenosine diphosphate [ADP] binding).
- Blood vessel abnormalities, e.g. due to Cushing’s syndrome/steroids, Henoch–Schönlein purpura (HSP).

**HYPERCOAGULABILITY STATES**

Between 5% and 15% of venous thromboses are caused by inherited deficiencies. Some causes include

- Activated protein C resistance (APC) (factor V Leiden mutation) – APC normally inactivates factors V and VIII. This is one of the most common inherited causes.
- Antiphospholipid antibody.
- Homocysteinaemia.
- Elevated factors VIII and XI.

**HAEMOSTASIS IN PLASTIC SURGERY**

See also ‘Burns’.

**ADRENALINE**

Adrenaline causes vasoconstriction by binding to post-synaptic α-2 adrenoreceptors on vascular smooth muscle. It is often used to reduce bleeding in plastic surgery (see also ‘Liposuction’) and thus improves surgical visibility. It also prolongs the effect of lidocaine.

- Many textbooks state that adrenaline is contra-indicated for local infiltration/nerve blocks of the extremities due to the ‘end’ arteries. A literature review (Denkler, *Plast Reconstr Surg*, 2001) found 48 cases of necrosis after digital blocks reported in 1880–2000; most cases occurred prior to the 1950s and none involved lidocaine. They were probably related to the use of acidic procaine–epinephrine.

- Similarly, there have been no reports of finger necrosis in accidents with EpiPens® – there may be some minor local necrosis, but the main side effect has been ‘reperfusion’ pain. Adrenaline has a plasma half-life of 2–3 minutes (compare that to the warm ischaemia time for a digit), though the end effects on vascular smooth muscle will last for longer. There are no evidence-based remedies, but the use of phentolamine seems logical; some report that it reduces the incidence of pain afterwards.

There have been several literature reviews supporting the safety of adrenaline use in the digits, including a Cochrane review in 2015, and a big case series (Lalonde D, *J Hand Surg Am*, 2005) with 3110 consecutive cases of surgery on the digits using lidocaine with adrenaline.

The general advice is to use the lowest possible effective concentration of adrenaline – whilst adrenaline will still have a vasoconstrictive effect at dilutions up to 1 in 1,000,000, it will take longer to work. It is important to wait 4–5 minutes before making the incision; there can be increased blood flow in the first minute or so presumably due to the vasodilatory effects of lidocaine. Maximal vasoconstriction occurs after ~20–25 minutes.

- Use of 1 in 100,000–200,000 adrenaline seems to be safe for digital blocks.
- Other recommendations include the following:
  - Do not inject >20 mL of 1 in 200,000 solutions within 10 minutes.
  - Caution in patients with severe hypertension, phaeochromocytoma, etc.

**Adrenaline with lidocaine for digital nerve blocks. (Prabhakar H, Cochrane Database of Syst Rev, 2015)**

They found four eligible studies on ring blocks for digits. There were no reports of adverse events such as ischaemia, but also no cost analysis or benefits – one study had weak evidence to suggest that adrenaline prolonged the duration of anaesthesia. Two studies suggested a reduced incidence of bleeding with the use of adrenaline. The authors concluded that there was limited evidence to recommend use or avoidance of adrenaline in nerve blocks.

**HAEMOSTATIC AGENTS**

There is a range of tools to stop/reduce intra-operative bleeding, such as radiofrequency, argon beam coagulators, lasers, harmonic scalpels as well as the usual cautery, clips and sutures. Other products can be classified as follows:

- **Passive agents** – these rely on clotting factors of the patient. They need blood/bleeding in order to work – they absorb blood, activate platelets and induce coagulation. There are a variety of products:
  - Cellulose (oxidised), e.g. Surgicel®. Note that it has a rim-enhancing appearance on CT that may mimic an abscess.
B. Pressure sores

I. AETIOLOGY AND RISK ASSESSMENT

‘Pure’ pressure sores begin with tissue necrosis near a bony prominence leading to a cone-shaped area of tissue breakdown with its apex at the skin surface. Affecting this is the additional impact on the soft tissue from moisture, infection and shear forces, etc. (see below). Acute sores are often ‘iatrogenic’ in the sense that there is an episode of prolonged unrelieved pressure, whilst chronic sores tend to be seen in those with spinal cord injury or chronic debilitation. The latter tend to have multiple recurrences; thus, flaps should be planned in a way to allow re-elevation or not to interfere with other flaps.

- ~10% of patients in acute care facilities develop pressure sores (mainly sacral); up to 24% in chronic hospitalised patients.

- 66% of elderly patients with neck of the femur (NOF) fractures and 60% of quadriplegic patients develop pressure sores.

- Supine patients develop sacral, heel and occipital sores (~40–60 mmHg of pressure); whilst the wheelchair/chair bound develop ischial sores (~100 mmHg when sitting).

- Lying on one side causes trochanteric sores.

RISK ASSESSMENT

Many different systems that stratify the risk of developing a pressure sore have been described. In the end, whilst it is the standard of care that will have the greatest contribution, it is not fair to blame all pressure sores on ‘poor’ care, as not all can be prevented in the susceptible.

- Norton Scale for elderly patients.

- Waterlow score – pressure sore risk assessment chart (at risk/high risk/very high risk depending on scores) – the higher the score, the higher the risk.
  - Body mass index (BMI)
  - Continence
  - Mobility
  - Nutrition
  - Skin changes/type
  - Sex/age
  - Adverse wound healing factors/tissue malnutrition
  - Neurological deficit
  - Major surgical intervention(s)/trauma
  - Drugs (steroids, cytotoxics, anti-inflammatory)

- Braden Scale. This is one of the most commonly used scoring systems, and like all systems should be used together with clinical judgement. The scale stratifies the risk according to six parameters: sensory perception, skin moisture, activity, mobility, friction, shear and nutritional status. The lower the score, the higher the risk. Starting from a maximum value of 23 (no risk), the risk of developing a sore comes at a threshold value of 18 (originally 16), whilst those with a minimum score of 6 have the highest risk. Inter-rater reliability is fairly high at 0.83–0.99. Identification of risk should lead to action.

NECESSARY ACTIONS (THE 3 R’S)

- Redistribute surfaces (pressure relieving surfaces)
- Remobilise
- Reposition

- Avoid higher pressure positions such as lying on the side, semi-recumbent; instead choose 30° lateral or elevating the head of the bed (up to 30°, as a compromise between sacral pressure and respiratory function/protection)

- Change up to Q2H, supplementing with small shifts

PATHOGENESIS

In simple terms, prolonged unrelieved pressure will lead to ischaemic necrosis if the tissue pressure is greater than
perfusion pressure; the damage is proportional to the pressure and its duration. Many believe that lower pressure for longer periods does more damage than high pressure for shorter periods.

- **Muscle is more susceptible** than skin to pressure necrosis. Animal studies (pigs) demonstrated that 500 mmHg for 2 hours or 100 mmHg for 10 hours caused muscle necrosis, but it took 11 hours of 600 mmHg to cause skin ulceration.

- Kosiak found that continuous pressures of 70 mmHg (in dogs) produces irreversible necrosis after 2 hours, but this could be prevented by relieving the pressure every 5 minutes.

In reality, there are many other factors that contribute to the pathogenesis:

- Altered sensory perception, as well as
  - **Incontinence** and exposure to moisture (skin maceration and breakdown).
  - **Friction and shear force** – traction on perforator vessels to the skin causing vessel angulation may occlude flow, subcutaneous degloving.
  - **Infection** – apart from causing tissue damage by itself, infection increases susceptibility to pressure, whilst pressure also increases susceptibility to infection.
  - Intrinsic factors may also contribute to
    - Ischaemia, sepsis and peripheral vascular disease (PVD), DM, smokers, etc. reducing perfusion
    - Loss of protective sensation
    - Malnutrition and reduced wound healing

**GRADING OF PRESSURE SORES**

Grading was originally described by Shea in 1975 and has been modified/updated into various sets of guidelines. There were separate European and American systems, the European Pressure Ulcer Advisory Panel (EPUAP) grading system and the National Pressure Ulcer Advisory Panel (NPUAP) system, respectively. The many similarities led eventually to a combined International NPUAP/EPUAP classification system (2009, then 2014).

- **Stage I** – Intact skin with non-blanchable redness of a localised area, usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area.
  - The area may be painful, firm, soft, warmer or cooler as compared with the adjacent tissue.
  - Generally, this would be expected after an hour of sustained pressure.

- **Stage II** – Partial thickness loss of dermis presenting as a shallow open ulcer with a red-pink wound bed, without slough. It may also present as an intact or ruptured serum-filled blister.
  - This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.
  - **Bruising** indicates suspected deep tissue injury.

- **Stage III** – Full thickness tissue loss. Subcutaneous fat may be visible, but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. There may be undermining and tunnelling.
  - The depth of a stage III ulcer varies by anatomical location. The occiput and malleolus do not have much subcutaneous tissue, and stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III pressure sores.
  - Generally follows >6 hours of pressure.

- **Stage IV** – Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed; there is often some undermining and tunnelling.
  - They can extend into muscle and/or supporting structures (e.g. fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

However, it is important to appreciate that the surface appearance does not reliably reflect the underlying extent of the sore.

- **Suspected deep tissue injury (depth unknown)** – purple/maroon localised areas of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure/and or shear. This may be preceded by stage I type changes.
  - Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed, or this may further evolve and become covered by thin eschar.
  - **Evolution may be rapid** exposing additional layers of tissue even with optimal treatment.

- **Unstageable (depth unknown)** – Full thickness tissue loss in which the base of the ulcer is obscured by slough and/or eschar.
  - Until the obscuring layer has been removed (at least partly) to expose the base, the true depth, and therefore stage, cannot be determined.
  - **Stable eschar** (dry, adherent, intact without erythema or fluctuance) on the heels serves as ‘the body’s natural (biological) cover’ and should not be removed.

**Unavoidable pressure injury: State of the science and consensus outcomes.** *(Edsberg LE, J Wound Ostomy Continence Nurs, 2014)*

The formation of a pressure ulcer is a multifactorial process that at times cannot be prevented even with excellent prevention and management. A consensus conference in 2014 came to the conclusion that main risk factors were impaired cardiopulmonary status/tissue oxygenation, hypovolaemia and sepsis, oedema and PVD. Manoeuvres such as elevation of the head of the bed >30° significantly increase risks.
II. MANAGEMENT

PRESSURE ULCER MANAGEMENT

National Clinical Guideline Centre. Clinical guideline 179 April 2014

• Pressure relief – Use high-specification foam mattresses, or consider a dynamic support surface.
• Ulcer measurement – Record and document wound dimensions including undermining using validated measurement techniques where possible.
• Wound measurement is notoriously difficult and ‘standard’ methods such as using tape measures or grids are prone to error. Photography needs to be standardised in terms of lighting and angle; the latter can cause apparent increases or decreases in size.
• Debridement – promote autolysis by dressing choice, unless it would take too long – in which case, choose sharp debridement (or larval therapy).
• Nutrition – supplements should not be routinely offered for patients without identified deficiencies.
• Dressings – many choices of dressings that promote warm moist healing in stage II–IV sores.
• Antimicrobials – not indicated without clinical signs of infection.

TREATMENT

A multidisciplinary team environment is desirable and should include nursing staff, physiotherapists, occupational therapists, diéticians and community nurses.

GENERAL

• Assess and optimise nutrition including correction of anaemia, optimise blood glucose; patients should stop smoking. Patients are often chronically malnourished, though the direct association has not been demonstrated. Whilst nutritional support of those with adequate intake has not been shown to prevent the development of sores (NICE 2014), there is low-quality evidence that protein-rich nutritional support may improve healing.
• In the absence of a deficiency, there is limited evidence for additional supplementation of micronutrients. The role of zinc supplementation is unproven, whilst vitamin C has no effect beyond 10–20 mg/day according to RCTs, i.e. no role for 1 g dosage.
• Treatment of infection (commonly Staphylococcus aureus, Proteus, Pseudomonas, Bacteroides) with oral antibiotics.
• Colonisation is common (swabs represent surface contamination only; do not treat positive wound cultures alone) – proof of actual tissue infection requires a deep biopsy. A pressure sore may cause sepsis, but it is most commonly due to a UTI.
• According to NICE, systemic antibiotics are not indicated unless there is clinical evidence of sepsis, spreading cellulitis or underlying osteomyelitis. There is also no evidence for the routine use of topical antimicrobials/antiseptics.
• Osteomyelitis must be actively sought for (see below); bone biopsy is most sensitive.
• Adjuncts to healing.
• The role of HBOT is largely unproven, whilst LLLT or ultrasound has been shown to be not useful.
• Direct contact capacitative electrical stimulation (strength A-3 EPUAP NPUAP. Treatment of pressure ulcer: Quick reference guide 2009). NICE does not recommend electrotherapy, but some suggest that it can be considered for recalcitrant stage III–IV sores.
• The role of growth factors has not been fully elucidated, though some studies have shown improved healing with bFGF and PDGF.
• Catheterise if incontinent.
• Relieve spasm (common in spinal cord injury); otherwise, sores will inevitably recur – baclofen, diazepam or dantrolene may be useful but some may require botulinum toxin, surgical release, amputation or neurosurgery, e.g. cordotomy/rhizotomy.

RELIEVE PRESSURE

The effect of relieving pressure by regular turning and using a suitable bed has been confirmed by three RCTs; it is also important to take care during transfer and pad pressure points prophylactically.

• Effective pressure relief for 5 minutes every 2 hours (seated patients should lift themselves every 10 minutes). Reducing head elevation, i.e. 30° or less, will reduce sacral shear forces/pressure.
• Repositioning every 4 hours on an appropriate support surface is as good as every 2 hours (strength A-1 EPUAP-NPUAP 2009).

NICE 2014 recommends high-specification foam mattresses as a cost-effective treatment in patients with pressure sores as well as in prevention, and if inadequate, an electronic mattress should be considered.

• Electronic mattresses
  • Pegasus – alternating pressure system for periodic offloading.
  • Nimbus – dynamic flotation system. Seems to be more comfortable for patients.
• Cochrane Review (McInnes, Cochrane Database Syst Rev, 2015): the relative merits of constant low pressure vs. alternating pressure are unclear. Medical-grade sheepskins reduce the risk of ulcer development.
Wound care

• Beds
  • **Clinitron** – ceramic beads fluidised by warm air, i.e. air fluidised bed – aims for pressures <20 mmHg. The forced warm air reduces skin moisture, but this, in turn, may cause excessive fluid and electrolyte losses from those with large wounds. These beds lose their effectiveness if the patient sits up 45° or more. In addition, they are rather bulky; turning of patients may be difficult and pulmonary toilet may be impaired in those with breathing problems.
  • **Mediscus** low air loss beds, made of groups of cells that inflate and deflate independently; unlike the Clinitron, there is little/no drying effect, but there is a tilting mechanism to allow the patient position to be altered. The contact surface area is maximised; it aims to exert <25 mmHg at any one point.
  • Those in wheelchairs are suggested to have 8 cm thick cushions and to relieve the pressure for 10 seconds after every 10 minutes.

DRESSINGS

Many dressings for pressure sores have been described; generally there are few substantial differences as long as they promote moist wound healing. Negative pressure (NPWT) dressings can be used in larger defects, particularly those with excessive exudate, or after debridement until the patient is ready for definitive surgery – the wound can be improved or reduced in size, but only a minority of cases will avoid surgery in this way. Patient acceptance of a dressing regime is affected by

- Leakage and odours that affect social interaction
- Length of time between changes for convenience
- Pain especially during dressing changes

INVESTIGATIONS

• Blood – albumin, FBC, ESR, LFT, RFT, glucose.
• Wound swabs (see above), tissue biopsy.
• **Osteomyelitis** is associated with a higher risk of wound breakdown and the development of sinuses and deep abscesses. It needs to be actively excluded using a combination of investigations including ESR, white cell count and X-rays (to identify sequestra); bone scans and CT are not particularly sensitive. **Bone biopsy** is the single most useful test with a specificity of 96% but a low sensitivity of 73%. MRI may be better than CT (97% sensitive, 89% specific, Huang AB, *J Comput Assist Tomogr*, 1998) but not quite as good as bone biopsy; PET is prone to false positives.
• Some suggest a two-stage plan to wait for the results of bone biopsies taken at debridement before embarking on formal reconstruction, whilst others, in general, aim empirically for ‘healthy’ bleeding bone with further therapy dependent on results.

III. SURGERY

PRINCIPLES

Surgery is best suited to the well-motivated patient (able to adhere to post-operative measures) with a stable condition (or liable to improve). Proper patient selection is particularly important – the wound must have the capacity to heal. Heel sores are generally best healed by secondary intention. Faecal diversion may be helpful in selected patients.

• ‘Oncological’ debridement of the sore, i.e. ‘pseudotumour technique’ – some use methylene blue or a betadine pack inserted into the cavity to guide the completeness of excision. All devitalised tissue should be removed, along with osteomyelitis and the pseudobursa.
• Excision of bony prominences (caution with ischial tuberosities).
• The choice of flap/closure depends on the site of the sore (see below) and may be modified by the patient’s ambulatory status.
  • A range of local flaps have been described; it is important to maintain future flap options as the pressure sore is likely to recur. Flaps should be designed to be as large as possible. Muscle flaps are good for filling in dead space, but muscle is vulnerable to ischaemia and tends to atrophy; furthermore, sacrifice may affect ambulation; fasciocutaneous (FC) flaps are durable but generally offer less tissue bulk.
  • Wounds should be closed at maximum stretch; tension should be judged in various positions; closures that depend on positional changes are doomed to failure.
  • Free flaps, e.g. latissimus dorsi to the superior gluteal artery, are usually a last resort for large defects or where local options have been exhausted.
  • Avoid having suture lines in the areas of pressure. Sutures should be left for 3 weeks.

POST-OPERATIVE CARE

There is a high rate of recurrence (40%–60%) that may be reduced to 25% by optimising post-operative rehabilitation, which is a long process.

• Skin care optimised (start pre-operatively with general management measures mentioned above).
• Take care with transfers as surgery is often performed with the patient prone, and patients need to be flipped over for extubation and transfer. **Avoid pressure on the reconstructed area for at least 2 weeks** post-operatively with the patient position prone/decubitus for weeks with low-pressure mattress/bed, followed by limited sitting protocols, e.g. three 4-hour periods of sitting per day with pressure-relieving manoeuvres every 15 minutes.
• Use of drains and antibiotics (quantitative cultures recommended by some). Timing of drain removal is variable; some wait until there is only scant drainage, whilst others wait at least 2 weeks.
• Patient education. Patients should be discharged only after home assessment and necessary facilities, e.g. low-pressure mattress, are in place.
• Outpatient support – to maintain patient motivation, to reinforce need to modify risk factors (both clinical and social), to maintain wound closure.

Common complications include haematoma, infection, dehiscence and recurrence. The published literature shows a wide range of success rates. Overall short-term surgical results are good, but sores may recur (scarred tissue has only about half of the original strength) especially in young paraplegics and the compromised elderly (70%–80%), compared to single figures in the non-paraplegics. In the largest published series, the best results are 20% recurrence after 4 years. There was no association found with the number of previous surgeries; second sores were found in other sites in >½ of cases. Studies have shown that patients with pressure sores are more likely to die, but this seems to be related to the generalised state rather than the ulcer itself, i.e. it is an indirect marker for malnutrition, coexisting illness, etc.

SPECIFIC PRESSURE SORES

**Ischial pressure sores (28%)**

These are the commonest sores in paraplegics who sit in wheelchairs. They are usually quite large, and thus are the most difficult type of sore to treat. Ischial sores have a slightly higher recurrence rate than sacral sores – using flaps that can advance can again be advantageous. Some surgeons prefer to use the flaps from the leg rather than the gluteal region, and vice versa (Kua EH, *J Plast Reconstr Aesthet Surg*, 2011). Patients are not allowed to sit for 3–6 weeks after surgery; thereafter, sitting is allowed for short periods with a wound check each time for dehiscence or erythema (should not last for more than 30 minutes).

• **Muscle (hamstring) VY flaps** have decent bulk. Whilst a single muscle flap (e.g. long head of biceps) may be sufficient in the ambulatory, a larger posterior thigh flap (VY hamstring, Hurteau JE, *Plast Reconstr Surg*, 1981) with biceps, semimembranous and semitendinous can be used in paraplegics. The muscles, supplied by branches of the profunda femoris, have their origins and insertions divided. These flaps can be readvanced if the sore recurs; these flaps do not seem to heal as well as gluteal flaps.

• **Posterior thigh FC flaps** (medially or laterally based) can be used as rotational or transposition flaps with SSG to the donor site. This is similar to the (inferior) gluteal thigh flap described by Hurwitz (*Plast Reconstr Surg*, 1981) based on the inferior gluteal artery (IGA) branch that runs close to the posterior femoral cutaneous nerve and thus could be sensate. The thigh flap should be broadly based; although it is usually an axial pattern flap, the occasional absence of the artery means that it may be largely random.

• **Tensor fascia lata** (TFL) is a type 1 flap based on the ascending or transverse branch of the lateral circumflex femoral artery (LCFA). The muscle arises from the anterior superior iliac spine (ASIS) and greater trochanter of the femur and inserts as fascia lata/iliotibial tract to the lateral tibial condyle, and thus helps to maintain lateral knee stability.

• The axis is from ASIS to lateral patella with the pedicle entering about 6–10 cm from the ASIS. A myocutaneous flap can be harvested with a skin paddle reaching up to 8 cm above the lateral femoral condyle. However, the distal (and the important) part is unreliable and may not reliably cover ischial defects. Some have suggested delaying the distal end (Zufferey J, *Eur J Plast Surg*, 1988) 3 weeks before. The flap can be made sensate by including the lateral femoral cutaneous nerve. It is also a suitable option for reconstruction of perineal and lower abdominal/groin defects; dividing the proximal attachments can increase the arc of rotation. The inferior part of the donor site often needs to be grafted.

• **Gracilis** – a relatively flimsy flap that may be used in smaller defects, with relatively little donor morbidity.

• **Gluteal** FC/musculocutaneous (MC) flap especially based on the IGA (see below), as large rotation/transposition flaps (see below).

• A more elegant option, particularly for small defects, is to use local propeller flaps based on nearby perforators (‘freestyle’). Some describe the existence of enlarged perforators by the edge of a chronic wound (Wound Edge Based Perforator Flaps, WEBP flaps) (Kelahmetoglu O, *Plast Reconstr Surg*, 2015).

• **Anterolateral thigh** (ALT) is a versatile flap with a long pedicle and significant mass particularly when a portion of the vastus lateralis is included. It is a bit of a reach to the ischial region; the flap can travel medially (Yu P, *Plast Reconstr Surg*, 2002) or laterally (Kua EH, *J Plast Reconstr Aesthet Surg*, 2011), usually subcutaneously, though a route through the muscles has been described (Lee JT, *J Plast Reconstr Aesthet Surg*, 2007).


The inferior gluteus maximus (GM) island flap was the most commonly used flap for reconstruction in this series, with the highest success rate, which was attributed to less tension with hip flexion. The use of this flap was first reported in 1979 (Mathes SJ, *Clinical Atlas of Muscle and

Mean time to healing was 38 days with complications in 37% including wound infection, edge dehiscence and partial flap necrosis. Necrosis was most common in TFL flaps (nearly half) and least in V-Y hamstring flaps.

- Predictors of poor outcome included large sore size, previous surgery and adverse wound healing factors.

Trochanteric sores (19%)
Patients with trochanteric sores often have hip/leg contractures – making closure more difficult and less reliable. There may be significant undermining due to the tissue mobility over bone.

- TFL – probably the most commonly used. The flap is usually moved as a transposition flap but can be VY, hatchet, bipedicled, etc. The flap can be potentially sensate in those with intact L3.
- Vastus lateralis (type 1) based on descending branch of the LCFA (10 cm from ASIS) can cover greater trochanter, pubis and lower abdomen.
- Lateral thigh fasciocutaneous flap (first lateral perforator of the profunda femoris artery) can be posteriorly or anteriorly based.
- Rectus femoris flap.

Sacral sores (17%)
Sacral sores tend to be quite painful. If the sore is small and due to a reversible short illness, direct closure/grafting/conservative management can be considered – particularly in those who will be ambulatory and are sensate. These methods may have a recurrence rate up to 70%.

- Gluteal rotation flap(s) (FC or MC) are most commonly used. They are straightforward and reliable to use; they can be raised again and advanced further if the sore recurs. Bilateral flaps can be used. The trend is to use perforator-based flaps, reserving myocutaneous flaps for larger cavities, particularly with osteomyelitis.
  - V-Y GM myocutaneous flaps ‘burn bridges’ as they cannot be (easily) elevated again.
  - Lumbar perforator flaps can be based on any of the four perforators, but the second is largest (Kato), whilst others suggest using two perforators.
  - Smaller defects can be filled with ‘freestyle’ islanded perforator flaps/WEBP flaps.

GLUTEAL FLAPS
The GM muscle is parallelogram-shaped and can provide a 24 × 24 cm, type II muscle flap that is supplied largely by the superior and gluteal arteries (SGA and IGA), with extensive anastomosis with the lumbar perforators. The gluteal region can be used in many ways, e.g. MC, muscle or FC flaps (see below). The muscle can be quite atrophic in quadriplegic patients.

GLUTEAL MUSCLE/MYOCUTANEOUS FLAP
The GM MC flap has high shear resistance and can cover a large area. The muscle origin is divided off the gluteal surface of the ilium and the edge of the sacrum to allow rotation into the defect; the arc of rotation may be limited by the superior gluteal vessels, but these can be divided and the flap will survive on the inferior gluteal vessels alone. The muscle insertion on the femur can be detached to allow the muscle to be reflected as a turn-over flap into the sacral defect (and can also close lower lumbar defects). Harvesting the entire muscle may lead to some loss of hip stabilisation; the muscle can be split and the upper part can usually be used in ambulatory patients with relatively few problems.

GLUTEAL FASCIOCUTANEOUS/PERFORATOR FLAPS
The skin of gluteal flaps is supplied by 20–25 perforators (1–2 mm in diameter) from the gluteal arteries, but will survive on one or two decent-sized perforators; 50% of perforators are superior to the piriformis, 30% inferior and the remainder in the middle. SGA perforator (SGAP) flaps are type C (Mathes and Nahai) FC flaps; Koshima (1993) described their use in sacral sores. Morbidity is reduced as muscle is not sacrificed; hip stability is maintained and thus can be used in ambulatory patients.

- The surface marking of the SGA is a point 5 cm inferior to PSIS and 5 cm lateral to midline (or at the junction of proximal and middle one-thirds of a line from PSIS and the apex of greater trochanter), with the IGA 3 cm below that. During surgery, the buttocks are strapped apart and the exit point of SGA on skin is marked and a handheld Doppler used to find the main perforators, which are usually inferolateral to this point and above piriformis.
- Piriformis is the key muscle that runs between the gluteal arteries and lies along the middle third of a line that runs from the middle of a line joining the posterior superior iliac spine to the coccyx, to the greater trochanter.
- Harvest a flap that is as large as possible even for apparently small defects. The first incision is made along the superior border to the subfascial level to search for a suitable perforator from medial to lateral; if a substantial vessel is not found, then it can be converted into a random rotation flap. Laterally placed flaps tend to have a longer intramuscular course that needs to be dissected out, but the extra pedicle length will allow greater flap movement. Flaps should be rotated less than 180°; torsion is the main cause of problems, i.e. venous congestion. Using a single large perforator is preferable to several smaller ones.
Long-term outcome of pressure sores treated with flap coverage. (Yamamoto Y, Plast Reconstr Surg, 1997)
The generally accepted view is that ischial sores typically have large dead spaces and are more likely to need muscle flaps, whilst sacral sores have smaller dead spaces and can be closed with FC flaps. However, in this series, sores reconstructed with FC flaps seem to exhibit less recurrence than with MC/muscle flaps:

- Muscle flaps provide good early cover, but the muscle becomes atrophic.
- Muscle is more susceptible to ischaemia (all pressure points in the body are naturally covered by skin fascia, not muscle).

Their conclusion was that muscle flaps are actually inadequate for the surgical management of sores in the long term.

Management of pressure sores by constant tension approximation. (Schessel ES, Br J Plast Surg, 2001)
The authors describe their management of chronic pressure sores:

- By wound excision with partial suturing and continued dressings to residual wounds.
- The remainder of the wound is closed by using a constant low-grade tension with a Proxiderm® device that acts on subcutaneous tissues, based on the principle of ‘internal tissue expansion’.

Time to healing in a mixture of wounds was 5–42 days with a success rate of about 70%–80%. The advantages put forward include the avoidance of major surgery in debilitated patients. Contraindications include an inflamed wound, wounds with excessive discharge or contamination (faeces) or a deep cavity.

A refinement is to use NPWT in combination with the tension devices/sutures. Some call this arrangement vacuum-assisted dermal recruitment (VADER, van der Velde, Ann Plast Surg, 2005). There seems to be some synergy – the negative pressure reduces oedema, removes inflammatory exudate and relieves some of the localised tension forces that can develop around tension sutures/devices.

Perforator-sparing buttock rotation flap for coverage of pressure sores. (Wong CH, Plast Reconstr Surg, 2007)
The authors describe their experience with buttock FC rotation flaps based on visualisation and preservation of the perforators from superior or inferior gluteal arteries. The flaps were used for sacral, ischial and trochanteric sores.

- Other papers have suggested similar approaches to pressure sore coverage, perforator based or at least perforator-aware flaps may represent a shift in the way pressure sores are managed.

- Seyhan T, Ann Plast Surg, 2008. This team from Ankara describes their experience with gluteal perforator flaps, though they used them as islanded perforator flaps (like Kim YS, J Plast Reconstr Aesthet Surg, 2009 and Jakubietz RG, Microsurgery, 2009 who modified it further by taking a plug of muscle [where needed] along with the distal perforator, which they thought would hopefully be supplied in a retrograde fashion).

- Lin PY, Microsurgery, 2012. They describe the use of superiorly based gluteal FC rotation flaps for ischial sores – the main pedicles are perforators from the SGA, but other perforators from the IGA are preserved, with intramuscular dissection to facilitate flap movement. Conversely, an inferiorly based rotation flap in a similar manner is used to cover sacral sores. These flaps were successfully elevated again when sores recurred. They offered a simple algorithm for flap choice:
  - Sacral – large gluteal rotation flap; they stress the need for a large flap even for small defects.
  - Trochanteric – TFL.
  - Ischial – posterior thigh flap or gluteal rotation flap without muscle.

IV. NEGATIVE PRESSURE WOUND THERAPY
NPWT is used on a variety of wounds particularly pressure sores (stages III and IV). The principle is that negative pressure (strictly it is a pressure lower than atmospheric rather than actually being ‘negative’) can improve the state of a sore (stages III and IV). The principle is that negative pressure (strictly it is a pressure lower than atmospheric rather than actually being ‘negative’) can improve the state of a wound, converting it into one that may be healed by a lesser surgical procedure.

Suggested mechanisms of action include the following:

- Wound fluid that inhibits fibroblast and keratinocyte activity and contains MMP responsible for collagen breakdown is removed. Reduction of oedematous fluid in the tissues also facilitates oxygen delivery.
- Encourages wound contraction – analogous to tissue expansion relying upon creep; exerts mechanical deformational forces upon the ECM and upon cells, which promotes growth factors, modifies apoptosis and stimulates mitosis.
- Some call this microstrain, distinguishing it from macrostrain, which is the contracting foam causing the wound edges to come closer together.
- Encourages formation of granulation tissue.
- Increases local blood flow.
- Decreases bacterial colonisation. In one study, it reduced bacterial count to below 10^5 quicker (5 days instead of 11) than with dressings alone, but others have shown little effect. One study showed that whilst Gram negative bacilli counts decreased, Staphylococcus aureus increased; sepsis and TSS have been reported with NPWT probably due to inadequate debridement. Overall, the effects on wound microbiology per se are probably minor.
• Some research done recently suggests that the polyurethane (PU) foam itself increases angiogenesis possibly related to a foreign body effect, inducing a better quality granulation tissue and reducing the bacterial count.
• NPWT is not a substitute for debridement.

The basic setup consists of

• Evacuation tube placed within PU foam dressing that has been tailored to fit the wound that is relatively clean
• Airtight seal created by covering the wound and sponge with an occlusive dressing
• Vacuum pump connected via a canister/trap for collection of wound ‘effluent’
• 75–125 mmHg subatmospheric pressure is commonly used (more ‘negative’ pressures supposedly cause collapse of vessels and decreased blood flow). Intermittent therapy (5 minutes on/2 minutes off) is supposedly more effective at promoting granulation tissue, but tends to cause more discomfort.
  – Some systems use a cyclical mode (Curavac®), which is meant to incorporate the advantages whilst reducing the pain involved with intermittent vacuum.
• Dressings are changed every 48–72 hours depending on the clinical situation. This, in addition to the enclosed nature of the dressing, offers major advantages over conventional dressing in complex wounds. NPWT can be used in the community with portable/home machines.

The list of indications for the use of NPWT is increasing and includes the following:

• Secure skin grafts particularly in awkward areas, e.g. perineal or in complex wounds; lower pressures are used, i.e. continuous 50–75 mmHg for 4–5 days.
• NPWT can also be used to secure dermal scaffolds such as Nevelia® and Integra®.
• Sternotomy wounds – NPWT has been a useful option in treating this difficult problem. Apart from improving the wound condition, they also stabilise the chest, improving the mechanics of ventilation (Harlan JW, Plast Reconstr Surg, 2002).
• ‘Burst abdomen’ from acute loss of abdominal wall tissue or wound dehiscence, swollen viscera – the dressing should not be placed directly on abdominal viscera: an intervening layer should be used; there are dedicated dressings, e.g. Vivano® abdominal kit (Hartmann), whilst a cheap alternative is a split IV fluid bag (Bogota bag).
• Wounds with small areas of bare bone (DeFranzo AJ, Plast Reconstr Surg, 2001)/tendon/cartilage, or exposed orthopaedic metalwork, mesh (de Vooght A, Plast Reconstr Surg, 2003) or other prosthetics; NPWT allows granulation tissue to cover the defects whilst keeping the wound clean and moist.
• Venous ulcers generally need lower pressures ~50 mmHg in continuous mode with or without adjuvant therapy such as cultured keratinocytes or SSG.
• Vulnerable suture lines – may be supported/protected with lower-pressure NPWT, e.g. Prevena®, Pico®, with reduced surgical site events compared to conventional dressings. Sometimes called incisional or preventive NPWT (Pellino G, Int J Surg, 2014).
• Sponges
  • Black PU sponge (400–600 µm) supposedly encourages formation of granulation tissue.
  • White polyvinyl sponge denser with smaller pores, said to be gentler and can be used over fragile structures.
  • Silver impregnation.
• It is important to remember that NPWT sponges are not designed to have an intervening layer of tulle/non-adherent dressing, which alters the mechanics of the setup, the exceptions being use with skin grafts or overexposed bowel.

The first commercial system was the VAC® (vacuum-assisted closure) from KCI (Kinetic Concepts, Inc.). The patents, based on the work of Dr Argenta and Mr Morykwas at Wake Forest University who published two papers in the same issue of Annals of Plastic Surgery in 1997, have been fiercely protected. Other manufacturers eventually produced alternative systems citing earlier examples of the use of subatmospheric pressure in wounds, particularly from Russia. There were many rounds of litigation particularly from 2005 onwards. Presently, KCI has ended its litigation with both Smith and Nephew as well as Wake Forest University – having stopped paying royalties in 2011 after an unfavourable judgement in the United States.

In 2009, the Agency for Healthcare and Research Quality reviewed the literature concerning devices from 11 manufacturers with no evidence of significant differences. Some systems include modifications, such as using cyclical pressure modes, e.g. Curavac®, or silver impregnated sponges or an instillation system (VAC Veraflo®) that allows for wound irrigation with saline, Prontosan or 0.5% silver nitrate or antibiotic/antiseptic solutions.

PRECAUTIONS

NPWT is not an alternative to adequate debridement; non-viable material should be debrided away before NPWT. Where NPWT is used before closing a larger complex cavity, e.g. sternal/abdominal dehiscence, the CRP count can be used to monitor progress and suitability for definitive surgical closure. CRP levels rise and peak at 72 hours, presumably due to surgical trauma, and fall again afterwards. A persistently high or increasing CRP level suggests wound infection.
• Residual tumour in the wound is the main contraindication to therapy as increased blood flow may cause accelerated growth.
• **Exposed vessels** – patients have died after NPWT was used on groin wounds after femoral endartectomy. Caution is required with the bleeding risk in patients on anticoagulation, particularly after dressing change/removal. Overgranulation is a risk associated with leaving dressings in situ for too long.

• **Fistulae** used to be a contraindication, but studies have shown that NPWT can be used in selected cases to treat explored fistulae with a piece of foam fitted to the fistula opening; a lower pressure, e.g. 75 mmHg, is usually used. Remember to take a note of the number of sponge pieces inserted.

**COMPLICATIONS**

FDA issued a preliminary public health notification in 2009 regarding serious complications with NPWT – there were six deaths reported in 2 years (associated with bleeding) and 77 injuries including infection and dressing retention. It was updated in 2011 with six further deaths. Less serious complications include

- Pressure necrosis of adjacent skin if the patient lies on the tubes.
- Maceration of surrounding intact skin if the sponge inadvertently overlaps it.
- Pain (mainly in venous ulcers).
- Overgranulation with ingrowth into sponge – this leads to traumatic dressing changes with bleeding. This can be related to leaving dressings in situ for too long; some suggest using a non-adherent layer such as paraffin gauze or silicone dressings, e.g. Mepitel®, but generally the systems are not designed for use with an additional layer.
- Large volumes of exudate may be lost from larger acute wounds – monitor fluids and electrolyte balance as necessary.
- Air leaks encourage wound dehydration and may cause the wound condition to deteriorate. If a leak cannot be sealed with Tegaderm, etc., either do it again from scratch or change to conventional dressings; a leaking system should not be allowed to remain in situ.

Despite the common usage of NPWT, well-designed trials are lacking. Cochrane reviews have failed to find strong supporting evidence for

- Healing of **chronic wounds** compared to hydrocolloids, hydrogels and alginates (2001 and 2008).
- Healing of selected acute surgical wounds such as sternal wounds or incisions on obese patients; there were reports of ‘blistering’. Rates of graft loss were lower, but ‘homemade’ systems performed similarly (2014).
- Partial thickness burns (2014).
- Pressure sores, when compared to ‘moist wound healing’ (2015).

- Leg ulcers (2015), except perhaps in combination with a skin graft.

There is some preliminary evidence that suggests NPWT used in diabetic wounds (Dumville JC, *Cochrane Database Syst Rev*, 2013) may show improved healing compared to other treatments.

**Negative-pressure wound therapy with instillation: International consensus guidelines.** (*Kim PJ, Plast Reconstr Surg, 2013*)

NPWT with instillation (NPWTi) is the introduction of solutions such as Prontosan®, Lavasept® in a volume sufficient to saturate the sponge and held for 10–20 minutes before resuming NPWT, i.e. **not irrigation**. The consensus committee reviewed available evidence and suggested that it can be used in infected/contaminated wounds, including those with exposed bone/osteomyelitis or exposed prostheses, and diabetic and pressure ulcers. However, it cannot replace debridement.

*Kim* (*Plast Reconstr Surg, 2015*) suggested that normal saline is as effective as antiseptics in NPWTi.

**Meta-analysis of negative-pressure wound therapy for closed surgical wounds.** (*Hyldig N, Brit J Surg, 2016*)

The authors reviewed 10 studies and concluded that there was a significant reduction in wound infection (relative risk 0.54) compared with standard care. There was no significant reduction in wound dehiscence.

**C. SCAR MANAGEMENT**

**I. SCAR FORMATION**

**REGENERATION VS. REPAIR**

Cells can be classified according to their proliferative potential:

- **Labile cells** divide and proliferate throughout life (M to G1 of the cell cycle), e.g. epithelia, bone marrow haematopoietic cells.
- **Stable cells** are normally quiescent but can be stimulated to replicate (G0 to G1), e.g. hepatocytes, endothelium, mesenchymal cells, e.g. osteoblasts.
- **Permanent cells** have left the cell cycle and cannot undergo mitosis (postnatally) and thus are never regained after loss, e.g. neurones, cardiac muscle.

**Repair** can be regarded as equivalent to healing. **Regeneration** is the formation of lost tissue without scarring. In tissues with labile or stable cells, true regeneration requires an intact supporting network. Thus, adult tissues tend to heal with some degree of scarring (healing by fibrous tissue, or gliosis in brain), except perhaps following parenchymal cell death in the liver (e.g. after exposure to hepatotoxic chemicals) or very superficial skin/mucosal wounds (above the basement membrane).
Fetal wound healing. (Rowlatt U, Virchows Archiv, 1979)
This was the first report of scar-free healing in humans.
The term ‘foetal wound healing’ is used to describe the regenerative process that occurs with minimal or no scar formation; it only occurs in the skin and bone of the foetus, but not nerve or muscle, i.e. it is organ specific. There is a wound size limit for scarless healing, which decreases with gestational age.
The ability to repair is also age-dependent. In humans, scarring of cutaneous wounds will begin from about 24 weeks gestation, depending in part on the size of the wound. The exact reasons for this are unclear, though some have postulated on the significance of various findings including the following:

- Environment – sterile intrauterine environment, amniotic fluid rich in HA and growth factors. However, early studies have shown that the intrauterine environment is neither necessary nor sufficient for scarless repair, i.e. it is a property intrinsic to foetal skin.
- Lorenz (Development, 1992) showed that foetal skin transplanted into adult athymic mice healed scarlessly.
- Wounds are conspicuous by an absence of inflammation and angiogenesis; healing is largely controlled by fibroblasts rather than macrophages.

It is not true regeneration per se, but it is well-organised healing.
- Rapid increase in HA and receptors on fibroblasts.
- Type III collagen deposition is more organised.
- Reduced levels of TGF-β, PDGF, bFGF.
- More fibromodulin (inhibits TGF-β), less decorin.
- More adhesion proteins, e.g. fibronectin and tenascin (modulator of cell growth and migration in foetal wounds).

NORMAL SCAR FORMATION
Dermal injury triggers a cascade that results in the deposition of a vascular collagen matrix that, as it accumulates, becomes a red, raised scar – fibrous connective tissue formed when healing by repair. As the matrix matures and remodels, the scar will become flatter, less vascular and paler after ~9 months (takes longer in children and in those with more darkly pigmented skin).

CLASSIFICATION OF SCARS (MUSTOE TA, PLAST RECONSTR SURG, 2002)
- Immature – red and lumpy, itchy or painful, eventually matures to become paler and flatter (occasionally hyper- or hypopigmented).
- Linear hypertrophic – arises within weeks of surgery and grows over 3–6 months to a rope-like appearance with maturation within 2 years. They are possibly due to excessive tension or delayed wound healing; external taping is proposed by some surgeons as a preventative measure, but the efficacy is unknown/doubtful.
- Widespread hypertrophic – widespread raised, red itchy scar; typically a burns scar that remains within the borders of the injury.
- Minor keloid – focally raised, red, itchy scar that extends beyond the borders of the original injury. It may take up to a year to develop and fails to resolve; excision is typically complicated by recurrence. There may be genetic and anatomical influences.
- Major keloid – as for minor keloid but may continue to extend over years. These typically occur over the anterior chest wall.

FACTORS PROMOTING A FINE SCAR
Surgical Factors
- Atraumatic technique. This may sound obvious, but it is important to respect the tissues and blood supply.
- Eversion of wound edges. Wound inversion leads to a difficult to correct scar deformity.
- Placement of the scar – adjacent to or within contour lines (e.g. nasolabial fold), within or adjacent to hair-bearing areas (e.g. facelift, Gillies lift) and parallel to relaxed skin tension lines (RSTL, Borges 1962 ‘facial wrinkles’ that were made obvious by squeezing the skin), that usually lie perpendicular to the axis of the underlying muscles.
- Langers (cleavability) lines. Karl Langer (1861). Dots of ink pushed into the skin surface with a 2 mm awl were seen to form lines (spalbarkeit) – does not always correspond to generally accepted best lines particularly in scalp, forehead, periorbital areas, etc.
- Kraissl’s ‘wrinkle lines’ – similar to Borges but described for the whole body.
- Shape of the scar – ‘U’-shaped scars tend to become pin-cushioned/trapdoor, e.g. bilobed flap. Trapdoor scars can be difficult to correct; W-plasty/multiple Z-plasty is usually recommended. Flap thinning rarely helps.
- Ellipse (strictly fusiform) length should ideally be 4× its width to avoid dog-ears.

CHOICE OF SUTURE
- Cutting versus non-cutting needle.
- Monofilament vs. braided. Skin sutures are usually monofilaments; braided sutures are more ‘traumatic’ and may increase infection risk. There are antibiotic-coated sutures on the market, e.g Vicryl plus® with Triclosan.
- Absorbable vs. non-absorbable: absorption by proteolytic enzymes; non-absorbable sutures tend to cause less tissue inflammation.
- Vicryl is polyglactic acid – tensile strength gone by 30 days, absorbed by 90 days. It is braided.
  - Vicryl rapide® (irradiated) is absorbed more rapidly (7–10 days of support) and is useful for skin closure in children.
  - Catgut (actually sheep intestine) is a good temporary suture but is not available in all localities due in part to BSE concerns (Japan, Europe). The sutures were withdrawn in the United Kingdom and Hong Kong.
C. Scar management

• PDS is a polydioxanone monofilament – loses tensile strength at 60 days, absorbed by 180 days, i.e. both double that for vicryl.
• Staples are often used for speed, particularly on the scalp or for securing skin grafts. Animal studies have shown mechanical equivalence with sutures (Roth JH, Can J Surg, 1988). Cochrane review (Anderson ER, Cochrane Database Syst Rev, 2004) and a meta-analysis (Clay FS, Am J Obstet Gynecol, 2011) showed no demonstrable difference between staples and sutures for closure of caesarean section wounds.

PATIENT FACTORS
• Age – infants (1–3 months) and the elderly tend to have good scars, whilst children are prone to have hypertrophic scars (HTS).
• Region of the body. The presternal and deltoid regions seem prone to develop problem scarring.
• Skin type – glabrous skin seems to be more prone to scar hypertrophy.
• Individual’s scar-forming properties – some patients seem to be more prone to form hypertrophic/keloid scars; ‘keloid families’ have been described.

FACTORS THAT CONTRIBUTE TO SUTURE MARKS
It is important to note that the suture itself is not the most important variable. Suture marks are partly due to epithelialisation of the suture track; in some cases, it may be related to local pressure necrosis or infection including ‘stitch abscesses’.
• Length of time the suture is left in place – sutures removed within 5–7 days usually do not leave stitch marks whilst sutures removed at 14 days will.
• Tension on the wound edges/skin sutures tied too tightly. Skin wound tension can be relieved by placing deeper stitches to bring the skin edges together in apposition, obviating the need for tight skin sutures.
• Region of the body – the hands are rarely affected by stitch marks, whilst trunk, upper extremities more likely to be affected.
• Infection – braided sutures are more likely to harbour bacteria (Staphylococcus); some have antimicrobial activity. In general, minimise the number and weight of sutures used to close a wound.
• Degradation by proteolysis (e.g. catgut) is likely to cause more tissue reaction than degradation by hydrolysis (e.g. Vicryl®).

II. HYPERTROPHIC AND KEOID SCARS

The history is an important key to differentiating between HTS and keloids. Both types of scarring can coexist within one scar, e.g. a largely hypertrophic midline laparotomy scar may have some keloidal parts.

HYPERTROPHIC SCARS
See also ‘Burn scars’, Chapter 2, Section D.I.
• HTS are raised scars limited to the initial boundary of the injury, including burns.
• More contractile component – there are myofibroblasts, with actin expression.
• They may be related to wound factors such as tension and delayed wound healing.
• Meyer (Br J Plast Surg, 1991) demonstrated areas of high tension in the presternal area.
  – Pull in one direction causes a stretched scar.
  – Pull in multiple directions causes a hypertrophic scar.
• They tend to occur soon after injury and show spontaneous regression over months/years.

KELOID SCARS
Alibert (1817) coined the term cheloides from the Greek word for crab claws.
• These extend beyond the boundary of the original injury. Histologically, there are large collagen bundles with less cross-linking and more disorganisation than HTS.
• They tend to appear after a longer time interval following the injury (months/years).
• These first two criteria are the most useful clinically.
• They do not show any significant regression without treatment.
• They seem to be more closely correlated with dark skin colour (15x more common in dark-skinned people).
• Patients with keloid scars tend to be of a younger age, and there are instances of a familial tendency.
• A survey of 32 patients with ear keloids after piercing demonstrated that the risk of developing a keloid was higher (80%) if they were pierced at or after the age of 11, compared to 23.5% if they were pierced before that age (Lane JE, Pediatrics, 2005). Some speculate that this may be related to hormonal factors; there may be accelerated growth of keloids during pregnancy, and some may resolve after menopause.
• There seem to be sites of predilection including anterior chest, shoulders and deltoid. Some suggest that this is related to skin stretching tension, which is greatest at the outer edges (Akaishi S, Ann Plast Surg, 2008), but keloids can also develop in places that do not seem to be under tension – e.g. earlobes. It is apparent that not all keloids behave in the same way; for example, ear keloids are more amenable to surgery than sternal keloids, further complicating any discussion that lumps all scars altogether.
Some believe ear keloids to be caused by an immune response to sebum and thus may be secondary to damage of pilosebaceous structures. High piercings are more likely to get infected, and also develop keloids.

On macroscopic examination, both keloids and HTS are raised disordered accumulation of collagen, particularly type III. Some describe heavily hyalinsed collagen nodules called ‘keloidal collagen’ and less blood vessel density in keloids. However, even histological examination may be inconclusive. It was once thought that α-smooth muscle actin (SMA) expression was found in HTS but not keloids (Ehrlich HP, Am J Pathol, 1994), but this has been disputed – keloid myofibroblasts do express α-SMA but less often than HTS (Lee JY, Am J Dermatopathol, 2004;26:379).

When interpreting the literature, it is important to note their shortcomings: many studies do not properly distinguish between HTS and keloids, do not distinguish between excision and debulking/intralesional surgery or have follow-up times that are too short to study recurrence rates in keloids (see imiquimod studies). Finally, there is a failure to refer to their shortcomings: many studies do not properly distinguish expression was found in HTS but not keloids (Ehrlich HP, Am J Pathol, 1994), but this has been disputed – keloid myofibroblasts do express α-SMA but less often than HTS (Lee JY, Am J Dermatopathol, 2004;26:379).

When interpreting the literature, it is important to note their shortcomings: many studies do not properly distinguish between HTS and keloids, do not distinguish between excision and debulking/intralesional surgery or have follow-up times that are too short to study recurrence rates in keloids (see imiquimod studies). Finally, there is a failure to refer to original articles – many articles are fond of stating that the recurrence rate after surgery alone for keloids is 45%–100% whilst listing the following references:

- This Indian study included 108 cases treated with surgery with 80% recurrence, with no mention of adjunctive treatments, histological evidence or follow-up period.
- This study of 18 keloid surgeries only had 4 that did not also have post-operative radiotherapy, with one recurrence in the average follow-up period of 1 3/4 years, i.e. 25%.
- This retrospective review had 340 cases of keloid over 1932–1958 with an overall recurrence rate of 38.5%, whilst the 25 cases that were excised with no post-operative radiation had a 54% recurrence rate.
- This study investigated the adjunctive effect of dexamethasone. The recurrence rate with surgery alone was 45%.

Thus, articles quoting a recurrence rate with surgery alone with these references must be referring to a study of Indian patients in 1974 (n = 58, 80%) or American patients in 1972 (n = 4, 25%), in 1961 (n = 25, 54%) and in 1960 (45%). Several other commonly quoted papers do not actually include patients treated with surgery alone (Darzi MA, Br J Plast Surg, 1992; Lawrence WT, Ann Plast Surg, 1991).

The link between hypertension and pathological scarring. (Huang C, Wound Repair Regen, 2014)
The authors discuss the potential association between hypertension and the development of pathological scarring. Previous articles by the senior author have shown that Japanese patients with multiple or large keloids were more likely to have hypertension than those with small keloids, and that hypertensive patients were more prone to bad scars after surgery. There are some speculative ways keloids could be connected with hypertension including fibroblast function and ECM remodelling. The connection may explain why ACE inhibitors (Ardekani GS, Plast Reconstr Surg, 2009) and calcium channel blockers (D’Andrea F, Dermatol, 2002) have been reported to be useful in keloid treatment.

Asians have three times risk for hypertrophic scarring compared to Caucasians; even ‘normal’ scars tend to have prolonged erythema and pigmentation. Asian skin is thicker, particularly the dermal layer, which has greater collagen density, and a more vigorous fibroblastic response. Asian skin also has increased melanin content and sebaceous gland numbers.

According to this and other literature reviews, the following therapies could be considered for (routine) therapy. Again, it is stressed that properly controlled studies are lacking.

HYPERTROPHIC SCARS

These scars have a tendency to regress with time.

Silicone therapy – Silicone gel with or without pressure therapy is often the first-line treatment for HTS. If used for close to 24 hours a day for 3 months (an arbitrary ‘course’), the response rate is approximately 65%–88%. There is little evidence for its use in the prevention of problem scarring.

- There are various formulations of silicone gel. Clear gel sheeting (Cica Care®) may be more effective than liquid gel (Dermatix Ultra®) for reducing scar height, itch and erythema; however, compliance is much improved when using the latter, making the overall effect similar.
- The mechanism of action is uncertain. One theory is that in a scar even with a grossly intact epidermis, the barrier to water loss is disrupted and this increases transepidermal water loss (TEWL), resulting in keratinocyte dehydration that alters their behaviour with upregulation of pro-fibrotic cytokines fibroblasts, e.g. IL-1β and down-regulation
of anti-fibrotic (TNF-α), that leads to increased TFG-β and fibroblastic activity (Mustoe T, Aesthet Plast Surg, 2008). Cytokines may act via the IL-8 effect on MMP-9 (Xu W, J Invest Dermatol, 2014). The theory is that silicone would work by reducing TEWL by occlusion and improving hydration, rather than by any effect intrinsic of silicone.

- Other forms of occlusion, e.g. polyurethane films, also work.
- Some patients will report ‘allergy’ to silicone. True allergic is extremely rare; what is more likely is an intolerance to the occlusion.

**Pressure therapy** – pressure garments can be fitted as soon as the wounds have healed and should be used continuously, i.e. >23 hours/day, until wound maturation, i.e. 6–12 months. Obviously compliance may be an issue (~41%).

- Pressure may work through local tissue hypoxia/ischaemia causing decreased collagen synthesis and increased collagenase activity. Optimal pressures have not been scientifically established, though it is commonly believed that compression pressure should be higher than capillary pressure (25 mmHg); but the literature can be contradictory. Some suggest 15–24 mmHg can still be effective, whilst higher pressures are faster-acting; but others say that high pressures are harmful and uncomfortable (particularly if 30–40 mmHg).
- The fit should be reassessed regularly (oedema settles and children grow) and garments replaced as necessary. Pockets can be made to accommodate additional padding, but it can still be difficult to apply pressure to concave and flexor areas.
- Some suggest they should be used prophylactically in wounds that take more than 2 weeks to heal, but prospective data suggest that the use of pressure garments has no effect on the speed of maturation of burn scars (Chang P, J Burn Care Rehabil, 1995).
- It is much less effective in older scars.

**Laser** – there seems to be a role for laser therapy, but it is not well defined.

- Alster (Plast Reconstr Surg, 1998) demonstrated that 585 nm pulsed dye lasers (PDL) may improve scar pliability, erythema and texture (though not everyone has had similar results); multiple treatments with lower fluences may reduce dyspigmentation, particularly in patients with Asian skin. It is more useful for early scars (Dierickx C, Plast Reconstr Surg, 1995).
- Intense pulsed light (IPL) with a 590 nm filter can also be used to treat vascular/mature scars, with improved mVSS (Sarkar A, Indian J Plast Surg, 2014). It has deeper penetration and is more painful than PDL. There is less purpura.
- Fractional ablative lasers, i.e. carbon dioxide, e.g. Ultrapulse DeepFx/SCAAR Fx®, can be used for mature burn scars (Shumaker PR, Trauma Acute Care Surg, 2012). The thin pillars of ablation heal quickly with collagen remodelling in the surrounding zone. This can be combined with topical medications, e.g. triamcinolone or 5-FU, to increase bioavailability, i.e. laser-assisted drug delivery (LAD).
- Nd:YAG may be helpful in acne scarring.

- Quercetin is a derivative of A. cepa and has anti-histamine effects.

**KELOID SCARS**

**Steroid injection**, e.g. triamcinolone, is first-line treatment for keloids (Al-Attar A, Plast Reconstr Surg, 2006). The exact mechanism of action is unclear, but it may act to decrease collagen synthesis, stimulate collagenase production and reduce inflammation. Triamcinolone has been shown to reduce levels of α-1 antitrypsin and α-2 macroglobulin that are high in keloids. Side effects include dermal atrophy, telangiectasia and depigmentation; systemic side effects are rare. The current use of intralesional steroid (concentration, dosages and timing) is mostly based on the empirical findings of Ketchum (1974). There are very little data to support variations in practice such as

- 10 mg/mL vs. 40 mg/mL
- Mixing with lignocaine to reduce pain

**Cryotherapy** – scar cryotherapy was first proposed by Shepherd in 1982 with delivery by spray or surface contact. The proposed mechanism was vascular damage (thrombosis) whilst leaving the collagen matrix intact, supposedly reducing scarring. The area around the contact point consists of the lethal zone (temp < –22°C) with cryonecrosis and the recovery zone (~22°C to 0°C) with cells that tend to survive. With surface cryotherapy, the dermis lies in the recovery zone (thus perhaps less efficacious), whilst with intralesional therapy, the epidermis (with its melanocytes) is in the recovery zone and explaining the supposed reduced rate of hypopigmentation.

- Early reports suggested an average 51.4% scar volume reduction after one session with reduction of symptoms (Har-Shai Y, Plast Reconstr Surg, 2003). Early equipment consisted of lumbar puncture machines (Intralyze®) that offer quicker and more precise freezing.

**Surgery.** Surgery alone may be contemplated for localised lesions in certain locations, e.g. ear keloids that tend to respond better; however, in most cases, recurrence risk should be reduced by combining surgery with other treatments such as post-operative radiotherapy (25% recurrence
surgery plus radiotherapy, surgery alone >50% recurrence), steroids or 5-FU.

- **Fillet flap** (Kim DY, *Plast Reconstr Surg*, 2004) – this skin-preserving debulking concept has been described to reduce recurrence rates for ear keloids with ‘5 As and 1B’: asepsis, atraumatic, absent raw surface, avoid tension, accurate approximation and bloodless surgery, i.e. ‘good surgical technique’.
- There are proponents for either total excision vs. intralesional excision/debulking. Supporters of the former suggest that it is easier to prevent than treat keloids.
- Scar revision can be contemplated in HTS with a definite history of problems with wound healing or in scars that have crossed skin tension lines.

**Radiotherapy** – the exact mechanism is unclear, but it seems to be related to damage of keloid fibroblasts; in vitro studies showed an increase in apoptosis (Ogawa R, *Ann Plast Surg*, 2007). In 2015, the Royal College of Radiologists said that although there is no robust type 1 evidence, it seemed that administering RT after keloid excision is associated with a reasonably low recurrence rate (grade C) and should be used within 24–72 hours after excision (grade D). It can be considered in situations with high risk of recurrence, e.g. in Asians, in areas such as the sternum. Radiotherapy alone (i.e. without surgery) is not recommended. The use of post-operative radiotherapy is much higher in Japan than the United Kingdom.
- Different RT regimes exist depending on local practices. It seems that the higher the dose, the greater the risk of problems such as dyspigmentation and malignant disease. The risk of carcinogenesis is low when surrounding tissues, e.g. thyroid and breasts, are adequately protected (Ogawa R, *Plast Reconstr Surg*, 2009).
- Kovalic (*Int J Radiat Oncol Biol Phys*, 1989) gave 12G in three fractions over 3 days, which halved the recurrence rate in 113 keloids compared to surgery alone (73% control rate). There was a greater risk of recurrence if the keloid was >2 cm, had previous treatment or occurred in men. The authors said that delivery within 24 hours made no difference.
- Van Leeuwen (*Plast Reconstr Surg Glob Open*, 2015) conducted a systematic review with 33 studies, with the 6 best graded level II evidence.
  - High-dose-rate brachytherapy is better than low-dose-rate brachytherapy or external irradiation. Single dose regimes are effective.
  - Short time interval (<24 hours) more effective.
  - Recurrences occurred at a mean of 15 months.


A total of 147 keloids were excised followed by 15 Gy electron beam post-operatively. The overall recurrence rate at 24 months was 32.7%, being higher in ‘high stretch tension’ areas such as chest wall, scapula and suprapubic regions compared to neck, earlobes and lower limbs. Side effects included hyperpigmentation (45.6%) and hypopigmentation (2%), and were mostly mild and temporary.

**OTHER TREATMENTS**

More recently, there has been a plethora of intralesional treatments suggested for keloids (and HTS) that are largely case reports/small case series, i.e. low evidence level. Some have combined fractional ablative CO2 laser with topical steroids, 5-FU, etc. (Laser-Assisted Delivery LAD).

- **5-fluourouracil (5-FU)** – this is an antimetabolite (pyrimidine analogue) that is antiproliferative with widespread actions on cell growth. It is cytotoxic, but the doses used in keloids (intralesional injection of up to 50 mg of 50 mg/mL per session) are supposedly subtoxic; some propose a lower dose regime (<10 mg/mL) particularly in combination therapy, e.g. with steroids. Overall, the evidence is equivocal, but there may be a role in lesions refractory to steroid injections.
  - Uppal (*Plast Reconstr Surg*, 2001) – 11 Afro-Caribbean patients had 5-FU applied after lesions were removed; control scars (patients were self-controls) were soaked with saline. Biopsies showed reduced markers (ki-67, vascular cell adhesion molecule VCAM1, TGF-β1), but not CD68; fibroblasts in 3/5 treated patients had reduced contractile capacity.
  - A literature review in 2016 by Shah VV suggested that 5-FU monotherapy achieves good scar improvement in 45%–78% of patients, whilst combination with triamcinolone (average 1–4 mg steroid vs. 45 mg 5-FU) increases the response rate to 96% of patients. Systemic side effects were not seen; some studies reported local erythema, ulceration and dyspigmentation.
  - **Imiquimod** 5% cream has been used to prevent recurrence after surgery (see below). It is an immune response–modifying agent; chemically, it is an imidazoquinolone compound that stimulates the production of interferon α, TNF and IL-2 by binding to surface receptors (e.g. Toll 7) on macrophages and other inflammatory cells including T-cells.
  - When applied once daily for 8 weeks following excision of keloid scars in 12 patients, no recurrence was observed at 24 weeks (Berman B, *J Am Acad Dermatol*, 2002). The study was supported by an educational grant from 3M Pharmaceuticals, manufacturers of Aldara®.
  - Side effects included pain, irritation and mild hyperpigmentation. Others found that keloids recurred after the cream was stopped (Malhotra AK, *Dermatology*, 2007), usually by the 12th week after surgery (Cacao FM, *Dermatol Surg*, 2009).
• Antimetabolites/cytotoxics:
  • Interferons, 5-FU, Bleomycin, mitomycin, retinoic acid. Wang (Ann Plast Surg, 2009) and Shridarani (Ann Plast Surg, 2010) found substances of ‘promise/potential’. However, the studies, in general, suffer from problems with methodology (small numbers, short follow-up) with most patients having had other therapies in addition to the one of interest.
  • Others include doxorubicin, verapamil, tacrolimus, tamoxifen, TGF-β, interleukins and vitamin E. Topical vitamin E is popular, but without supporting evidence; it can cause allergic dermatitis.
• Botulinum toxin (BTX) – The theory is that tension vectors acting on the edge of wounds affect the synthesis of immature collagen fibres and lead to widened/abnormal scars. BTX would reduce scar formation by reducing wound tension.
  • One of the first reports used BTX A in eyelid surgery (Choi JC, Ophthal Plast Reconstr Surg, 1997) to reduce wound complications such as dehiscence. Some papers suggested an improvement in scarring.
  • Ziade (J Plast Reconstr Surg, 2013) – a prospective trial where facial wounds were randomised to BTX A (mean 20U) or no injection within 72 hours. Although assessment of photographs after 1 year suggested an improvement in the scar, there were no differences in PSAS, OSAS and VSS.
  • A meta-analysis of nine RCTs by Zhang (PLoS One, 2016) showed differences in scar width, patient satisfaction and VAS.
References

Jull AB . Cochrane Database Syst Rev. 2012;CD005083. note spelling