

HISTORY OF VENOUS LEG ULCERS

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To retrieve the history of venous ulcers and of skin lesions in general, we must go back to the appearance of human beings on earth. It is interesting to note that cutaneous injuries evolved parallel to human society. An essential first step in the pathogenesis of ulcers was represented by the transition of the quadruped man to Homo Erectus. This condition was characterized by a greater gravitational pressure on the lower limbs, with consequences on the peripheral venous system. Furthermore, human evolution was characterized by an increased risk of traumatic injuries, secondary to his natural need to create fire and hunt (e.g. stones, iron, fire, animal fighting). Humans then began to fight one another until they came to real wars, with increased frequency of wounds and infectious complications. The situation degraded with the introduction of horse riding, introduced by the Scites, who first tamed animals in the 7th century BC. This condition exhibited iliac veins at compression phenomena, favouring the venous stasis. With time, man continued to evolve until the modern age, which is characterized by increased risk factors for venous wounds such as poor physical activity and dietary errors (1, 2).

Venous ulcers and medicine

From remote time man, knowing the importance of venous ulcers as insidious and chronic wounds which lead to complications (e.g. infections), has tried to treat them.

In ancient times, the treatment of the wounds was based on the use of available natural products (e.g. herbs and minerals) and on the direct evidence of their effectiveness, excluding medication that proved to be harmful or lacking in results (2). The aetiology of leg ulcers varied during times. In the 18th century, for instance, scurvy contributed significantly to leg ulcers (3).

Ancient Mesopotamians

The earliest known document of wound treatment was found on tablets of Mesopotamian origin, dated about 2500 BC. For the ancient Mesopotamians, a disease was related to a demon's wrath and its cure was based on magic rituals of wound healing and exorcism. *Gula* (also known as *Ninkarrak* or *Ninisinna*) was the goddess of healing and health and Mesopotamian doctors were the agents through which she worked in order to maintain health. There were two types of doctors: the *Asu*, a medical doctor who worked empirically and the *Asipu*, a magic healer. The scholar Biggs notes that “*the therapeutic*

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medical texts frequently combine the two types of treatment, the medical (*Asu*) and the magical (*Asipu*)” (4). Both knew the properties of water, herbs and plants well and the importance of working in a clean environment. The historical scholar Emily K. Teall writes: “*In the treatment of all wounds, there are three critical steps: washing, applying a plaster, and binding the wound*” (5). Doctors used to carry a portable bed and instruments with them and washed their hands before treating patients. Even if Mesopotamians did not know the existence of microorganisms (e.g. germs, bacteria etc.), they recognized that washing a wound with water or with a mixture of beer and hot water, prevented infection and accelerated healing. After having cleaned the wounds, doctors would apply a plaster of different natural substances (e.g. mud, plants and herbs), to protect the lesion and to absorb exudates. A prescription for an injury to the face says: “*If a man is sick with a blow on the cheek, pound together fir-turpentine, pine-turpentine, tamarisk, daisy, flour of Inninnu; mix in milk and beer in a small copper pan; spread on skin, bind on him, and he shall recover*”. Interestingly, Mesopotamians used to incorporate oil in their plaster, probably for its antibiotic properties

and to prevent the sticking of the bandage to wounds. In addition to these poultices, Mesopotamian doctors also practiced first surgeon operations, such as drainage of abscess and phlebotomies, with a mixture of alcohol, honey, and myrrh (6, 7).

Ancient Egyptians

At the same time of the ancient Mesopotamian medicine, the Egyptian medicine was also starting to develop. Like Mesopotamians, Egyptians believed illness to be the work of evil spirits or their poisons and their medicine was based on rituals and prayers to the gods, such as *Sekhmet*, also known as the goddess of healing. Egyptian physicians (*wab sxmt*, *zwn.w* and *za.w*) had many important functions, such as to treat and prevent human illness, to inspect sacrificial animals and to treat animals. Even if Egyptian medicine had a religious basis, it evolved empirically as the result of clinical experimentations and observations, as written in *Ebers Papyrus* (1550 BC): “*Magic is effective together with medicine. Medicine is effective together with magic*”.

Historical documents underline how Ancient Egyptians were familiar with cutaneous wounds as well as infected or inflamed lesions and were able

Table I. Main compound used topically by Ancient Egyptian for wound healing.

Compounds	Properties
Honey	Antibiotic
Grease (animal fat)	Barrier to bacteria
Lint	Wound drainage
Tree resins	Fragrance controls wound odour
Meat	Haemostasis
Mouldy bread	Antibiotic
Paints containing copper (e.g. green colour)	Antibiotic

to treat them with early, rudimentary but still valid therapeutic approaches. For example, in *Edwin Smith Papyrus* (1650 BC), which is a copy of an older document, more than 48 types of wounds and their medical approaches are described (8). Egyptians thought that wounds could be a possible entry for devils and covered them with repellent, plasters and bandages. Among the repellents, it is interesting to remember the use of donkey's faeces, which seems to contain antibiotic substances and other proteins (e.g. trypsin) able to aid the healing process (9). Less repugnant and most commonly used to treat skin ulcers were the plasters. Ancient Egyptians had the merit of discovering the properties of important animal-derived and natural compounds, both herbal and mineral (Table I), which are largely described in *Ebers Papyrus*. Lint, honey and animal fat (grease) were the most commonly used ingredients: lint aided the wound drainage, honey had antibacterial properties and grease provided a physical protection from infections. In some cases, Egyptians also used to cover wounds with fresh meat, for its haemostatic properties, mouldy bread as an antibiotic and paints containing oxidated copper (i.e. green colour), for their toxicity to bacteria (10). Other types of herbal and mineral plasters were used in case of infection or inflammation.

Nevertheless, Egyptians are considered the masters in using bandages: they were able to apply and arrange adhesive tape (linen strips soaked in gum) and gauze bandages in different ways, also introducing innovative techniques (e.g. patches in an X-pattern), which are still considered valid (11).

Apart from spiritual and natural medicine, ancient Egyptians practiced different types of body massage. In *Kahun Papyrus* (1825 BC), for example, they cite: "Examination of a woman aching in her legs and her calves after walking. You should say of it 'it is discharges of the womb'. You should treat it with a massage of her legs and calves with mud until she is well". Rarely was surgery performed.

Indian Traditional Medicine

Ancient Indians knew cutaneous ulcers and the importance to treat them well. In the *Sushruta Samhita* (सुश्रुतसंहिता, which means "Compendium"),

an ancient Sanskrit book which is considered one of the fundamental text of Indian traditional medicine (*Ayurvedic medicine*), there are two different chapters about wound healing. The text describes different pharmacological treatments (either of animal, plant or mineral origin) to obtain a clean wound, its healing and its cicatrizing process (Table II) (12). The use of larvae for the wounds debridement and of herbal medicines and bandages with Chinese tissues for their healing, are well described. Moreover, a big chapter is dedicated to the surgical procedures for wound cleaning (*Ashtavidha Shastrakarma*), and the suturing process (13).

Chinese medicine

Traditional Chinese Medicine (TCM) had a holistic approach to healing, based on the *Yin and Yang* concept of the Taoist philosophy (, which means "teaching of Tao"). Chinese thought that every natural and human manifestation is the result of two opposite and complementary driving forces: the Yin, that represents the negative and obscure appearance of any phenomenon (black, dark, night, female principle), and the Yang, that is the positive one (white, light, sun, male principle). For a healthy organism, Yin and Yang must be balanced. According to the Taoist philosophy, it is possible to reconcile Yin and Yang acting on the *Five Tangible Elements* of the Cosmos: Metal, Water, Wood, Fire, and Earth. Each element corresponds to a precise anatomical part, whose function is closely related to that of other organs (8, 14).

Huangdi Neijing, the Emperor's Inner Medicine canon, is an ancient treatise of TCM (4th century BC) that widely discusses Taoist theory and its application in the treatment of different human illnesses. Yin and Yang must be in harmony also for wound healing. Acupuncture, herbal medicines (e.g. green tea, liquorice, mushrooms), bronze instruments, breathing exercises, body massages and living in harmony with Nature (*Feng Shui*), help wounds to heal.

Ancient Greeks

Ancient Greeks knew wounds and have the merit in knowing how to differentiate between acute

injuries, chronic and non-healing wounds. Greeks knew the difficulty in treating cutaneous ulcers, underlying the importance of cleaning the wounds with hot water, vinegar and wine (15). Homer also wrote about the treatment of Troy's battle wounds in his epic *Iliad*.

Nevertheless, the first scientific reference to ulcers dates back to Hippocrates (460-377 BC) (also known as the father of medicine), in his book *Perihelkoon* (16). Hippocrates first discovered the correlation between leg ulcers and varicose veins and wrote about useful practices in preventing ulcer formation (e.g. to avoid standing up for a long period to limit leg trauma) and medical approaches in wound healing (Table III).

He advocated the use of wine or vinegar to irrigate open wounds, and the topical application of honey and other herbs or metals (e.g. copper) for

their healing and antibiotic properties. The use of wool, boiled in hot water or wine, or of fig leaves was considered good bandages. Moreover, Hippocrates proposed the use of suction cups as anti-inflammatories and advocated the use of hot iron to stop bleeding (*cauterization* by the greek word *καυτηριάζειν*, *kauteriazein*).

Some years later, Rufus of Ephesus (2nd century CE) was to be the first to prescribe an oral therapy, based on absinthe, aristolochia, rhamnus and shrimp, for ulcer treatment (2).

Wound healing in the Bible

Even in the Bible, there are documentations on ulcers as chronic and disabling wounds and their possible treatments (2). In the book of Exodus, skin ulcer was one of the ten Egyptian sores (Exodus 9:8,12): "*Et dixit Dominus ad Mosen et Aaron tollite*

Table II. *Ayurvedic medicinal plants.*

Ficus bengalensis	Pterocarpus santalinus	Curcuma longa
Cynodon dactylon	Ficus racemosa	Centella asiatica
Symplocos racemosa	Glycyrrhiza glabra	Euphorbia nerifolia
Rubia cordifolia	Berberis aristata	Aloe vera

Table III. *Hippocrates' guidelines for wound healing.*

To wash wound with wine and vinegar
To apply cold to stop bleeding
To relieve pressure for avoiding leg ulcers
To drainage pus with piece of tin pipe
To inject liquids with a syringe in wound for washing it and sucking out pus
To use different type of herbal and mineral salves to prevent infections and to heal the ulcer
To wrap dressings around wounds to prevent further injury
To ensure a dry condition for a best wound healing

plenas manus cineris de camino et spargat illud Moses in caelum coram Pharaeo sitque pulvis super omnem terram Aegypti erunt enim in hominibus et in iumentis vulnera et vesicae turgentes in universa terra Aegypti tuleruntque cinerem de camino et steterunt contra Pharaeo et sparsit illud Moses in caelum factaque sunt vulnera vesicarum turgentium in hominibus et in iumentis nec poterant malefici stare coram Mosen propter vulnera quae in illis erant et in omni terra Aegypti induravitque Dominus cor Pharaonis et non audivit eos sicut locutus est Dominus ad Mosen”.

In Job’s book, his faith was tested by the development of suppurative sores (Job 2:1,10: “*Factum est autem cum quadam die venissent filii Dei et starent coram Domino venisset quoque Satan inter eos et staret in conspectu eius ut diceret Dominus ad Satan unde venis qui respondens ait circuivi terram et perambulavi eam et dixit Dominus ad Satan numquid considerasti servum meum Iob quod non sit ei similis in terra vir simplex et rectus timens Deum ac recedens a malo et adhuc retinens innocentiam tu autem commovisti me adversus eum ut adfligerem illum frustra cui respondens Satan ait pellem pro pelle et cuncta quae habet homo dabit pro anima sua alioquin mitte manum tuam et tange os eius et carnem et tunc videbis quod in facie benedicat tibi dixit ergo Dominus ad Satan ecce in manu tua est verumtamen animam illius serva egressus igitur Satan a facie Domini percussit Iob ulcere pessimo a planta pedis usque ad verticem eius qui testa saniem deradebat sedens in sterquilinio dixit autem illi uxor sua adhuc tu permanes in simplicitate tua benedic Deo et morere qui ait ad illam quasi una de stultis locuta es si bona suscepimus de manu Domini quare mala non suscipiamus in omnibus his non peccavit Iob labiis suis”.* Still interesting is the lecture (Isaiah 38:21) in which Isaiah, directed by God, healed king Ezechia’s wounds with figs, suggesting that the boric acid and the fruit proteins had an important detergent and antiseptic action: “*Et iussit Isaias ut tollerent massam de ficis et cataplasmarent super vulnus et sanaretur”.* Years later in his Gospel, Saint Luke wrote how the good Samaritan treated the wounds of Jericho’s traveller with oil and wine (Luke 10:34): “*Et adproprians alligavit vulnera eius infundens oleum et*

vinum; et inponens illum in iumentum suum duxit in stabulum et curam eius egit”.

Ancient Roman

Even Roman doctors dedicated much of their practice to wound healing, building special hospitals near the sites of battles.

In Ancient Rome, the first physician who dedicated his practice to the wound treatment was the Greek Arcagato (219 BC), also known as *vulnerarius* surgeon. In fact, due to his cruel methods and frequent recourse to amputation, Arcagato was soon redefined *carnifex* (butcher) and forced to leave the city (2).

Some years later, Aurelius Celsus had the merit of being able to distinguish cutaneous trauma from chronic ulcers and to describe the four cardinal signs of inflammation (*rubor, tumor, calor, dolor*). Moreover, in his book “*De Medicina*”, Celsus described a list of planters and ointments, and the importance of lint bandage for wound healing.

Galen (129-199 CE), a Greek physician who tended to gladiators and to the Emperor Marcus Aurelius, improved the knowledge on wound healing, especially on surgical treatments. He was the first to use silk to tie off bleeding vessels and to experiment different haemostatic procedures. In his work “*De Ulceribus*”, Galen wrote about the importance in applying styptics with antibiotic properties and of keeping the wound moist (e.g. use of sea sponges soaked in wine), for better healing (17).

Middle Ages

Unfortunately, after the fall of the Roman Empire, the medical knowledge in regards to wounds and their care was lost. The Middle Ages was characterized by a regression in wound treatment with use of potions and magic spells. In this period, only a few Arab physicians continued their medical studies. Medieval Islamic medicine emerged from different sources such as Bedouin, Greek, Indian, and Chinese, to mention some important ones. In the *Complex Book of the Medical Arts*, A-Majusi, included wounds as disorders of specific body parts.

Among these, there was Ibn Sīnā (980-1037), better known as Avicenna, a Persian philosopher and

Table IV. *Some physicians of the Renaissance and their anatomic discoveries.*

Physician	Nationality	Period	Discovery	Note
Andreas Vesalius	Flemish	1514-1564	Anatomy of circulatory system	
Girolamo Fabrici d'Acquapendente	Italian	1533 – 1619	Venous valves	He was a great supporter of elastic bandages. He introduced the use of bandage of calfskin.
William Harvey	English	1578-1657	Anatomy and physiology of circulatory system. He discovered the linkage between venous insufficiency and wound formation	
Richard Wiseman	English	1622-1676	He discovered how ulcers formation were due to a valve failure secondary to a varicose vein	He dedicated large studies on wound healing, especially on amputations.

physician. In his work “*The Canon of Medicine*” (“*Al-Qanun fi’t-Tibb*”), Avicenna first introduced the concept of malignant tumors and their need to emerge through the open wounds.

The Damascene physician Ibn al-Quff (passed away in 1286) wrote the first Arabic treatise dealing solely with surgery for wounds and tumors (18).

By the end of the 14th century, something in Europe was changing: new studies were conducted on wound healing. In 1320, Henry de Mondville advocated the importance of elastic bandage in reducing oedema; in 1363, Guy de Chauliac wrote

about the use of aluminium patches in wound care, like the ancient Egyptian practice.

Renaissance

With the renaissance, a new era of major advances in wound healing emerged, due especially to discoveries in the anatomy and physiology of the cardiovascular system (Table IV). Important innovations had also been introduced in wound care.

In the 14th century, physicians thought that surgical cleaning around and within the wound was essential for healing along with dietary advice

and analgesic herbal therapy. Franciscus Petrarca (1304-1374) wrote a medical and moral treatise – *De remediis utriusque fortunae* - that included some chapters on wounds (19).

A 15th century anonymous English manuscript about cutaneous ulcers, underlines the importance of a sequential treatment of wounds: after lesion cleansing, it is fundamental to control the infection and finally, to promote the granulation tissue. Moreover, a large section in the treaty is dedicated to the use of topical therapies (e.g. natural oils and ointments, honey and wine), oral analgesics and adequate nutrition.

In the same period, other physicians, such as the Italian Michele Savonarola (1385-1468), advocated the importance of the use of bandages in a distal-proximal direction.

However, one of the most important renaissance wound healers was Ambroise Paré (1510-1593), a French barber surgeon with a great battlefield experience, considered one of the fathers of modern surgery. In his book “*Journeys in Diverse Places*”, Paré referred to a new cauterization technique, less painful than the traditional use of boiled oil. The treatment was based on the application of a mixture of egg yolk, oil of roses and turpentine, which is resin-derived with antiseptic properties. In his “*Treatise on Surgery*”, Paré detailed a new method of arterial

ligature (“*Bec de Corbeau*” or “*crow’s beak*”), useful to control bleeding during amputation.

Interesting is the report in 1677, of the first sclerotherapy operated by Elchott, a physician of Brandenburg, through injection of an herbal product in the crural vein (20).

18th and 19th centuries

The 18th Century was a particularly florid period for the study of ulcers and their treatments. Many physicians (Table V) continued to study the importance of venous insufficiency in wound pathogenesis, also identifying some risk factors such as weight and pregnancy, to name a few. Denis Diderot (1713-1784), dedicated a large chapter on wound healing in his *Encyclopédie*. The writer described the use of wool bandages wet with wine or vinegar, protective leather knee-socks, striped bandages, and different patches (e.g. wax-, pitch- and therebinthina-patches). An English physician, Michael Underwood (1736–1820), in his “*A treatise upon ulcers of the legs*”, also advocated the use of lead patches and elastic wool bandage, stressing the importance of physical activity. In the same period, Thomas Baynton (1761-1820), another English surgeon, published a book on leg ulcers (“*A descriptive account of a new method of treating old ulcers of legs*”), in which he described the causes of the disease as well as its treatment.

Table V. Physicians of 18th century and their discoveries.

Physician	Nationality	Period	Discoveries
Samuel Sharp	English	1709-1778	Gravitational effect on peripheral circulation
Everard Home	British	1756-1832	Ulcers origin from varicose veins
John Hunter	Scottish	1728-1793	Inflammatory process and angiogenesis phenomenon

Nevertheless, the 18th Century was also an important period for surgery, which began to be considered a distinct and respected branch of medicine.

Among the most important surgeons, we must remember the French Jean Louis Petit (1674-1750), who developed a tourniquet to stop bleeding during amputations. Another important French surgeon was Pierre-Joseph Desault (1738-1795), who advocated the importance of wound debridement and coined

the term. With a trimming blade, Desault removed dead skin in order to help wound closing and prevent infection. A mention is also due to Dominique Jean Larrey (1766-1842), a French surgeon in Napoleon's Grand Army, who first introduced triage and the "*ambulance volantes*", a rapid transport of wounded. He is also known for the use of maggots to treat wounds (21).

Even if the 18th Century was characterized

Table VI. *Milestones in surgery for venous wounds.*

Type of operation	Physicians	Age
Saphen stripping	Keller	1905
Saphenectomy	Mayo	1906
Saphen stripping	Tavel and Jacobson	1912
Overfascial binding of communicating veins	Linton	1938
Valve reconstruction	Bauer	1948
Intravascular stripping	Myers	1954
Femoral bypass with saphena vein	Warren and Taheri	1954
Subfascial binding of communicating veins	Felder	1955
Femoral bypass with saphena vein	Palma	1958
Mini invasive flebectomy	Muller	1966
Subfascial intravascular binding of communicating veins	Hauer	1985
External Valvuloplasty	Hetenul	1985
Valve transplantation	O'Donnel	1985
Saphen and femoral valvuloplasty	Belcaro	1988

by a wide use of antiseptics (e.g. mineral acid, turpentine, alcohol, benzoin, aloe), it was only in the 19th Century that antiseptic techniques had a major breakthrough. Important contributions in this period we given by Ignaz Philipp Semmelweis (1818-1895), a Hungarian physician, who is still considered the father of “washing hands”.

The discovery of germs and bacterial contamination by the French Louis Pasteur (1822-1895) marked the origin of a new era, characterized by antiseptic surgery (22). Joseph Lister (1827-1912), a British surgeon, applied Pasteur’s ideas to surgery and promoted the use of carbolic acid to sterilize surgical instruments and to clean open wounds (23). In the same period Joseph Sampson Gamgee (1828-1886) also considered a pioneer in aseptic surgery and a colleague of Lister, developed an innovative surgical dressing, made of wool and gauze (“*Gamgee tissue*”) (24). Carl Reyher (1846-1890), a Russian military surgeon, focused on wound cleansing and stressed the importance of debridement (25).

The use of topical plasters and bandages remained the elective therapy of ulcers regardless of the great developments in surgery in the 19th century. The most common and popular plasters were made from a wide mesh curtain net cut into squares and impregnated with olive oil, Balsam of Peru and soft paraffin. Interestingly, in 1846, the physician Brodie first described the risk of sensitization reactions to

the topical use of plaster and bandages. In 1870, Dr Martin of Boston introduced an innovative bandage of pure Indian rubber, containing a small amount of sulphur. Finally, a mention is due to the German Paul Gerson Unna (1850-1929), one of the fathers of dermatopathology. Unna has the merit of introducing zinc oxide paste in the treatment of stasis dermatitis, and the “*Unna Boot*”, a special bandage associated to the topical application of zinc oxide in the therapy of leg wounds (26).

By the end of the century, new studies improved the knowledge of the patho-physiology of wounds. The German Rudolf Ludwig Carl Virchow (1821-1902), for example, elucidated the pulmonary thrombo-embolism condition and described the main factors (hypercoagulability, hemodynamic changes and endothelial injury/dysfunction) involved in venous thrombosis (“*Virchow’s triad*”) (27). Another important physician was the Bohemian baron Carl von Rokitansky (1804-1878), who described *phlebitis*. An important contribution to wound knowledge had also been made in 1867, by John Gay, who first described perforating veins and noted that ulcers could occur without varicose veins.

20th century

The Twentieth century was characterized by more extensive studies on the pathophysiology of venous ulcers (e.g. J. Homans described the post-

Table VII. Current debridement options.

Type of debridement	Methods
Mechanic	Water, gauzes
Chemical	Enzymatic (e.g. collagenases) Autolytic (medication such as hydrocolloids) Osmotic (sugar, activated carbon, saline solution)
Surgical	Scalpel, curette, laser
Others	US, <i>Lucilia Sericata</i>

Table VIII. *Some of the pioneers in the use of modern wound dressings.*

Type of medication	Age	Physician
Non-adherent dressing	First World War (1914-1918)	Lumiere
Semi-permeable films	1920	Dickson
Semi-permeable films	1945	Bloom
Calcium alginate	1947	Blaine
Spray-on dressings	1953	Olow and Hogeman
Odour-absorbent dressings	1976	Butcher
Hydrocolloid dressings	1970s	

Table IX. *Characteristics of an ideal wound dressing.*

Scales, 1954	Nowadays
1. It should have a high porosity to water vapour.	1. It must keep a moist environment of the lesion.
2. It should not adhere either to blood clot or to granulating surfaces.	2. It should avoid maceration due to excessive moisture.
3. It must absorb free blood or exudate and give "protection" to the wound.	3. It should be waterproof.
4. It should be a barrier to the passage of microorganisms.	4. It should allow the exchange of oxygen, carbon dioxide and water vapour with external environment.
5. It should be capable of following the contours around a joint during movement.	5. It should ensure thermal insulation of the lesion.
6. It should be unaffected by domestic or industrial fluids.	6. It should not produce a tissue reaction.
7. It should not produce a tissue reaction when applied to normal skin or granulating surface, nor a state of allergy or hypersensitivity.	7. It should have a high absorbent power of the exudates.
8. It should be non-inflammable.	8. It must not release any residue on the wound bed.
9. It should be capable of being sealed to the skin.	9. It should be a barrier to the passage of microorganisms.
10. It should be capable of being sterilized.	10. It does not have to stick to the ulcer.
	11. It must provide a mechanical barrier to the lesion.
	12. It must ensure patient's compliance.
	13. It must conform to the various anatomical sites.
	14. It should be simple to use and safe.
	15. It should allow the monitoring of healing progression.

Table X. *The wound bed preparation is defined as 'the management of a wound in order to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures'. To help in this purpose, a group of experts has developed the TIME acronym, as a practical guide in wound management.*

T	Tissue management
I	Inflammation and infection control
M	Moisture balance
E	Epithelial edge

Table XI. *Actual major types of advanced medication.*

Wound dressing	Material	Advantages	Disadvantages
GAUZE	Cotton fibres	Cheap, accessible, physical debridement, impregnable	Sheds fibres, traumatic removal, lateral bacterial migration
SEMI-PERMEABLE FILMS	Non-porous, plasticised polyvinyl polymer	Transparent, sterilizable, maintains moist environment, prevent bacterial migration	Possible maceration, adheres to fragile periwound skin
CALCIUM ALGINATES	Polymer extracted from seaweed	Haemostatic, non-adherent, few dressing changes, absorbs excess moisture, prevents maceration	Require secondary dressings, foul-smelling gel, requires moisture to ensure not traumatic removal
FOAMS	Polyurethane	Conforms to body, absorbs excess exudate, impregnable	Opaque, require secondary dressing, may adhere to wound
SPRAY-ON	Acrylic resin dissolved in acetic esters.	First aid, reduces infection in some surgeries	Possibly haemolysing
HYDROFIBERS	Sheets which contain polymer carboxyl-methyl-cellulose	Soft, interacts with exudate to form gel	Opaque, may require second dressings, difficult to remove
HYDROCOLLOIDS	Gelatine, pectin, sodium carboxyl-methyl-cellulose and poly-iso-butylene	Fibrinolytic, enhance angiogenesis, barrier to bacterial and physical agents	Opaque, foul smelling, highly adherent.

Wound dressing	Material	Advantages	Disadvantages
HYDROGELS	Cross-linked polymers such as starch, cellulose or other plant- or animal-derived polysaccharide	Donate water to dry wound, non-adherent, facilitates autolysis of necrotic tissue, does not support bacterial growth.	May require secondary dressing. Only suitable for dry and low exuding wounds
CHEMICAL-IMPREGNATED DRESSINGS			
1. HONEY DRESSING	Medicinal honey incorporated into a hydrogel or alginate	Antimicrobial, anti-inflammatory, deodorising	Frequent dressings
2. SILVER DRESSING	Different forms of silver incorporated in foams, hydrofibres and hydrocolloids	Antibacterial	Possible systemic toxicity
3. IODINE DRESSING	Iodophors-povidone-iodine and cadexomer-iodine impregnated dressings	Antiseptic	Cytotoxic
NATURAL SCAFFOLDS	Acellular cadaver dermis de-epithelialised	Biocompatible, degradable	Collagen may enable the transmission of infectious agents
SYNTHETIC SCAFFOLDS	Silicone, collagen, glycosaminoglycan	Variety of methods of construction, limit host immune response	Protein damage
SILICONE	Polyamide net coated with soft silicone	Prevents maceration of the surrounding tissue, non-traumatic removal, suitable for wide range of wound types	Necessary secondary absorbent dressing

thrombotic syndrome) and by innovative surgical and medical treatments of wounds, which lead to a better and faster healing by specifically targeting therapy on the condition of the individual patient. This was possible also because of the introduction of diagnostic technologies (e.g. ultrasounds, laser and others).

Among surgical therapies (Table VI), different approaches had been proposed for the treatment of the diseases of both superficial and deep venous system and more recently for valve disorders. However, the progress achieved with surgery is also a result of the discovery and successive introduction of heparin (Jay McLean, 1916) and antibiotic treatments (Sir Alexander Fleming, 1928) (28).

At the same time, sclerotherapy eventually associated to bandage, was becoming a valid therapeutic option in wound care (e.g. Schiassi 1908, Sigg 1930) (20) the two World Wars and the parallel scientific and technological progresses were the basis for continued innovation in the medical care of topical wounds.

Both the approaches of wound debridement and re-epithelialization was deeply revolutionized during the course of the last century. While the principle of a cleansed wound was largely accepted, new methods of wound debridement were developing (e.g. chemical and osmotic debridement), according to the different characteristics of lesions (Table VII).

On the other hand, even the techniques for wound re-epithelialization were being innovated (Table VIII). The findings of Scales was fundamental (1954) (Table IX), outlining the features of an ideal dressing, likewise G.D. Winter (1963), who first noted that keeping the wound moist led to faster healing of improved quality (29). The continuous clinical trials conducted in the 1980s, to review the principles of ideal dressing (Table IX) and the concept of “*Wound Bed Preparation*” for the purpose of adopting appropriate therapeutic approaches, on the basis of the lesional characteristics, has allowed faster and better healing (30) (Table X).

With what was a simple cotton gauze, the 20th century saw the introduction of gauze impregnated with antiseptic or antibiotic substances through to the latest in advanced dressings (Table XI).

Along with these innovations in wound care, in this period there is also an affirmation of hyperbaric therapy and VAC therapy, both of which are considered as a valuable therapeutic option for chronic ulcers, in order to facilitate their healing (31).

The treatment of burn patients has significantly improved by the refinement of surgical wound healing techniques (with grafts and skin flaps) and a constant emergence of modern laser technology. In fact, there has been the introduction of surgical laser for wound debridement and low-level laser therapy (LLLT) to stimulate the re-epithelialization of ulcers (32, 33).

21st century

The 21st century is characterized by continuous development of already existing medications and by the introduction of innovative methods to induce the re-epithelialization of chronic wounds such as silica-based wound-dressings among others (34). In fact, topical therapies have been introduced based on growth factors and new studies on potential use of stem cells including hair follicle-derived stem cells (35).

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