Pearls and Pitfalls in Skin Ulcer Management

Michele Maruccia
Giovanni Papa
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Editors

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Foreword 1

To briefly introduce this book is a welcome task for me given the relationships that for many years have bound me to the authors and familiarity with the topics discussed that have fascinated me for a long period of my clinical and research activity.

Advances have been made and innovations introduced in the treatment of ulcers that today make it possible to achieve results that were unthinkable a few years ago; however, the problems to be addressed are increasingly arduous, we are witnessing a greater complexity of infections with much higher rates of antibiotic resistance than in the past, we are called upon to treat increasingly complicated cases in a population of increasing average age, and finally, almost totality of patients urgently demand maximum results and do not hesitate to activate a medicolegal conflict in the face of failure or simple dissatisfaction with the outcomes of treatment.

Based on these premises, it seems obvious to me to emphasize the usefulness of addressing these issues and the need to explore them in an increasingly modern and up-to-date way.

We therefore welcome a discussion that considers the various clinical pictures and suggests solutions while warning against what are the most common errors and complications in the various settings and pathologies.

I think it was not easy to put together so many contributions by coordinating them with each other, albeit with the support of the scientific societies involved, but thanks to the efforts of Michele Maruccia, Giovanni Papa, Elia Ricci, and Giuseppe Giudice, the goal of coordinating and standardize all the chapters in a harmonious way, avoiding pleonastic overlaps and favoring the comparison between orientations that do not always overlap.

I am sure that reading the text will be useful to all those struggling to treat these pathologies in the most appropriate and effective way and will help improve clinical practice by giving some new ideas for refining one's intervention or focusing attention on the appropriate pathway to prevent complications and avoid missteps.

Today it is much easier than in the past to keep up to date by using the Internet and following the scientific literature, we are therefore increasingly confronted with new therapeutic proposals, confirmed over time, often in the absence of an analysis of potential benefits against the face of costs that

are not always sustainable. Lacking in many cases is a fixed point on the state of the art for a review and comparison of different lines of intervention. I think this work is a response to this need, so I hope it is taken into due consideration and has the success that the effort made by the authors undoubtedly deserves.

Nicolò Scuderi
Sapienza University of Rome
Rome, Italy

Foreword 2

I am very pleased to present this monograph on the treatment of ulcers and wound care, the writing of which has benefited from the contributions of eminent scholars on the subject who have approached the subject with a scrupulous and competent scientific approach, to the benefit of its scientific dissemination.

It is a wide-ranging treatment that ranges from etiology to anatomy, from antiseptics to advanced dressings, from therapy with noninvasive preps and the most current and advanced techniques of reconstructive surgery. Ample space is given to vulnology and the diabetic foot, metabolic and nutritional aspects, treatment of infections, and the opening of new horizons that characterize regenerative medicine, not neglecting the basics of prevention and rehabilitation.

The approach to the treatment of the subject is very didactic and competent, especially regarding the most advanced techniques and the interdisciplinary approach, which make the work suitable for its multispecialty dissemination. All topics are approached starting from a rigorous description of the biological processes underlying the occurrence of the various types of ulcers and wound healing, with a detailed analysis under the pathogenetic profile, from which then arises the indication for the most appropriate therapy for each individual pathology.

This monograph has all the prerequisites to provide the reader with the most modern means of evaluating pathological ulcers and scars, highlighting the main clinical aspects, the diagnostic pathways to be followed, as well as the basis for a therapeutic strategy based on knowledge of the pathogenetic mechanisms that led to the onset of the different pathologies.

It is a comprehensive work that stems from the experience and clinical practice of numerous qualified specialists, which gives the researcher and scholar the opportunity to have an up-to-date and comprehensive picture of the subject, from pathophysiology studies to clinical aspects.

The treatment of the various topics distributed in numerous chapters and supported in the exposition by methodological and scientific rigor testifies to the importance of this pathology both under the clinical aspect, supported by the underlying research activity, and for the great economic and social impact it has; therefore, I wish the authors the best wishes for a great publishing success.

Francesco Moschella
Palermo University
Palermo, Italy

Preface

Wound care presents various challenges and complexities, requiring a multidisciplinary approach with input from specialists in different fields. While some wounds heal quickly with minimal intervention, others can become chronic and lead to complications such as infections, delayed healing, and amputations.

To address the needs of healthcare professionals involved in ulcer management, a team of world experts in the field has compiled *Pearls and Pitfalls in Skin Ulcer Management*. This is a comprehensive guidebook, with the participation of experts from two major Italian recognized scientific societies (approved by the Ministry of Health) specializing in chronic ulcers, wound healing, and plastic, aesthetic, regenerative, and reconstructive treatments: AIUC (Italian Association for Cutaneous Ulcers) and SICPRE (Italian Society of Reconstructive, Regenerative Plastic Surgery). The book covers all aspects of wound care and is divided into eight main parts.

Part I provides an introduction to wound care, including cleansing, antiseptics, and local treatment. The second part covers dressing and bandages, discussing the different types, their advantages and disadvantages, and indications for their use. Part III discusses instrumental treatments, including hydrosurgery, negative pressure wound therapy, and photobiomodulation.

Regenerative medicine and tissue bioengineering, including the use of growth factors and stem cells, are covered in Part IV. Measurement and documentation, infection in wound care, the role of plastic surgery, and other aspects of ulcer management are discussed in Parts V through VIII.

Each chapter includes practical tips, case studies, and real-world examples to help readers apply the information to their own practice. The book's goal is to be a practical and accessible resource for healthcare professionals at all levels of experience. It is a valuable "survival manual" for the management of complex wounds and ulcers and may inspire collaboration among different specialties to improve patient outcomes.

The authors extend their sincere gratitude to the contributors who made this book possible, including the multidisciplinary team of experts and the publisher. They hope that healthcare professionals will find this book to be a valuable addition to their library and an indispensable resource in their clinical practice.

Bari, Italy — Michele Maruccia
Trieste, Italy — Giovanni Papa
Pecetto Torinese, Torino, Italy — Elia Ricci
Bari, Italy — Giuseppe Giudice

The original version of this book was revised. Forewords by Prof. Nicolò Scuderi and Prof. Francesco Moschella, respectively, are included in the book.

Contents

Part I

Introduction to Wound Care, Cleasing, Antiseptic and Local Treatment

1 Vulnology (Also Known as Wound Care): History and Myths of Chronic Wounds

Elia Ricci and Monica Pittarello

The name "vulnology" was conceived in memory of Arcagatus, a protophysician of Greek origin who worked in Rome [1]. Born in the third century BC in Sparta in the Peloponnese, son of Lisania, he migrated to Rome in 219 BC. As an important figure, he is described by Pliny, in the seventies of the first century. Pliny, the elder, speaks in a polemical tone about the penetration of Hellenic medicine in Rome, attributing it to the Hippocratic physician Arcagatus of Lisania, who arrived in the city under the consulate of Lucius Aemilius Paulus and Marcus Livius Salinator (219 BC). Arcagatus would have obtained Roman citizenship and the possibility of exercising in an iatreion ("medical workshop"), purchased with public funds in the Acilio task, in what will remain the area of medical practice in Rome until the time of Galen, in the second century [2]. He himself reports that Arcagato was a master in treating wounds, and for this reason, he was called Vulnerarius, but making too casual use of surgical instruments, especially the scalpel and cautery, and an excessive recourse to amputations; he was nicknamed Carnifex, "the executioner."

Ancient Roman medicine, based on body hygiene and magic, tolerated little Hellenic or Hippocratic medicine. Another thing of which the hellenic doctors were accused was to demand payment for this type of service, this would justify the purchase of the medical taberna with public funds. Cato the censor, his contemporary, railed against Hellenic medicine and spoke of exile. But studies conducted by Buck [3]. then taken up by Bonadeo [4] cast doubt on this hypothesis. With in conjunction with his disappearance from the scene the birth of an important Roman family, the Gens Acilia precisely. The importance of Arcagato is undoubted as demonstrated by an intact Greek papyrus [5] where a certain Chairas writes to the doctor Dionisyos to obtain clarification on ointments, the letter of which the translation is reported in Fig. 1.1, dated April 26, 59 AD, shows how over 250 years later the "plaster of Arcagato" was still in use. Of the ointment or patch of Arcagato we came to the recipe, composed of minium (lead oxide 1 and 4), burnt copper, cerussa (white dye), turpentine (oily vegetable resin) and litharge (lead oxide) obviously all these components had an antibacterial function [6].

The name vulnology [7, 8] is derived from the terms vulnus (wound) and logos (study but also word) in honor of Arcagatus the Vulnerarius. The term was born to give dignity and a name to an art as old as the human race. The name is currently evolving in the Anglo-Saxon culture where we

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Charias greets his dearest Dionysios very much and wishes him health forever. When I received your letter I was so extraordinarily happy, as if I had really been with you, in fact except this (letter), there is nothing else. I omit writing great thanks to you: in fact it is necessary to thank with words those who are not friends. I am persuaded to force myself with a certain tranquility, and if not the equivalent, I will give you at least a part of the affection you feel for me. You sent me two versions of recipes, one for Arcagato ointment, the other for healing ointment. The one from Arcagato is composed correctly, while the one from the healing agent lacks the resin dosage. Please let me know about an energetic healing agent that is able to heal the soles of the feet without risk, since I need it urgently. As for the hard one, you wrote to me that there are 2 types; send me the written recipe for the dispersant; in fact even the tetradrug is of the hard type. This letter is sealed. I salute you and remember what I said.
(year) 5th of Nero the Lord, (day) 1st (of the month of) Germanicus.
A. Dionysius Medicus

Fig. 1.1 Translation of the papyrus P. Merton I

Fig. 1.2 Fresco from Herculaneum with Achilles and the centaur Chiron, preserved at the Archeological Museum Naples, Italy (Inventory MANN). Figure under public domain, Photo credits: Giorgio Albano

begin to talk about woundology [9]. We could talk about vulnology in all fields of human history, from mythology, to religion, to art in general, in history, but it would be a separate book, and we will give here a few hints in the various sectors. The history of vulnology begins in ancient times, and it has roots in mythology and history. The father of medicine in Hellenic culture was the centaur Chiron (Fig. 1.2), son of the titan Cronus, and the oceanine Filiria who had a relationship in the form of horses, the curse of Hera on the illegitimate son, gave rise to the centaur [10]. Abandoned, he was adopted by Apollo and Athena, and he grew up in a cave in Thessaly [11]. He was master to many demigods and heroes such as Achilles, Heracles (or Hercules), Asclepius, Actaeon, Peleus, Jason, Palamedes, Aeneas, Aristeus and Actaeon, Cephalus, Dioscuri, Nestor, Macaon, Castor and Pollux, Theseus, Amphiaraus, Meleager, Telamon, Hippolytus, Icifle, and Ulysses. Chiron in fact was famous for the treatment of wounds in general, what we now call ulcers were then called "Chironian" in his honor. From him originates the name of the gentian who was then called Chironia, precisely because it was used by the centaur in wound care, a plant already known for its anti-inflammatory properties. Then, Chiron is famous for its culture, which he transmitted to humans. The death of Chiron is interesting: Ovid in the Glories tells that *"… while the old man was handling the horrible arrows, for the poison, one fell and struck his left foot. Chiron shouted and pulled the iron out of his limb; Alcide and the child Emonius (Achilles) groaned. The centaur, meanwhile, stirred (in a container) herbs picked on the Pegasei mountains; then with those medicines he tried to soothe the wound; but the poison was stronger than the medicament, and the evil spread deep into the bones and throughout the body; the blood of the hydra Learnea, mixed with that of the centaur, left no time for any help."* According to *Antisthenes,* the wound would be due to an accidental shot of Heracles that hit him in the knee, but as a demigod he was immortal, and he could not die and the pain became unbearable, so he asked Zeus for the gift of death, not being able to leave the position vacant, Prometheus, his pupil, offered himself as a vol-

unteer, and Chiron was transformed into the constellation of Sagittarius to eternal memory.

The story of Chiron in vulnology continues with his students; first of all, the titan Prometheus, his heir who, for having brought fire to men, which today symbolizes knowledge, would be punished by the gods with an eternal torture, chained to a rock by Vulcan, to be torn apart by Aithon during the day, a monstrous eagle, which would eat his liver, being him immortal, during the night the liver would grow back and the cycle would start again the following day. Prometheus will be freed by Heracles, putting an end to his torture freeing him. What a wonderful evolution, from the father of vulnology, the myth of tissue regeneration and chronicity cured with gentian, the control of inflammation. Of his students, the most famous in medicine will be Asclepius who, for his ability as a doctor, will be disliked by Hades as he is capable of recalling the dead. Put to death by Zeus, who will later repent his choice and turn him into the god of medicine. According to Pindar [12], Asclepius had no surgical skills, and he only treated wounds and ulcers of external origin, in most cases, wounds from spears and arrows, and only on these, he used to apply his remedies; for others, he frequently resorted to spells, magic formulas, hymns, and invocations to the gods. The inventor of the Panacea had, according to some, five daughters; according to others, his descendant would be Macaone, who had an important part in Troy. Many of the Argonauts were students of Chiron, the journey in the white ship, whose meaning reminds us of the Grail and as such a search with a final test. The Golden Fleece had the ability to heal wounds if wrapped in it. The Golden Fleece was, according to Greek mythology, the golden mantle of Chrysomar, a winged ram capable of flight, which Hermes gave to Nepheles, mother of Jason. The Argonauts will make the journey and obtain the fleece thanks to Medea. The trial, having Jason betrayed his lover Medea, would not be passed, and the hero would be punished. In the myth, there is also the story of Philoctetes, who was the bearer of Heracles' weapons and had sworn never to reveal the location of the tomb but betrayed the oath and was punished. Most of the original works are lost, and we have two versions of the punishment [13]. In one, the wound occurs through one of the Heracles' arrows (soaked in the hydra poison Learnea ed), and in the second, the wound occurs bitten by the viper in custody of the tomb. It resulted in a wound so foul-smelling that for 10 years he was confined to the island of Lemnos. Resumed for the Trojan War, it would be cured by Macaone, a pupil or son of Aesculapius with Pramna wine, honey, onion, and flour. It will be Philoctetes who, by killing Paris, will determine the beginning of the fall of Troy. Still here a wound as punishment of the divine.

In religion, vulnology is very well represented, just think that in the Bible it is the most cited pathology, found in 129 verses [14]. Here, we find the concept of plague as divine punishment well rooted (*Psa. 38: 5* My wounds are fetid and purulent for my folly), standards of care (*Isaiah 38:21* Isaiah had said, "Take a poultice of dried figs, apply it to the ulcer, and the king will heal."), hygiene rules (*Leviticus 13: 27* On the seventh day, the priest will examine it, and if the stain has spread on the skin, the priest will declare it impure: It is a plague of leprosy), and finally as proof of faith, think of job. The martyrs attained holiness through the wounds that Christian iconography depicts precisely as blissful images. Perhaps the most famous wounds are those of the crucified Christ, and through this the representation of the Stigmata, the first of which is attributed to St. Francis of Assisi, and to date about 800 saints have been made. St. Camillus, suffering in the past from an ulcer, after conversion, will devote himself to assisting the sick, especially the wounded, and is the protector of nurses. We include Saint Isabella of Portugal for the care of ulcer bearers and Saint Roch as a bearer of ulcers as atonement. Finally, the Miracle of Saints Cosmas and Damian performed the first transplant in history by replacing a gangrenous limb.

Wounds and cures have been depicted in art since ancient times, from the wounded man represented in the caves of Lascaux in the Upper

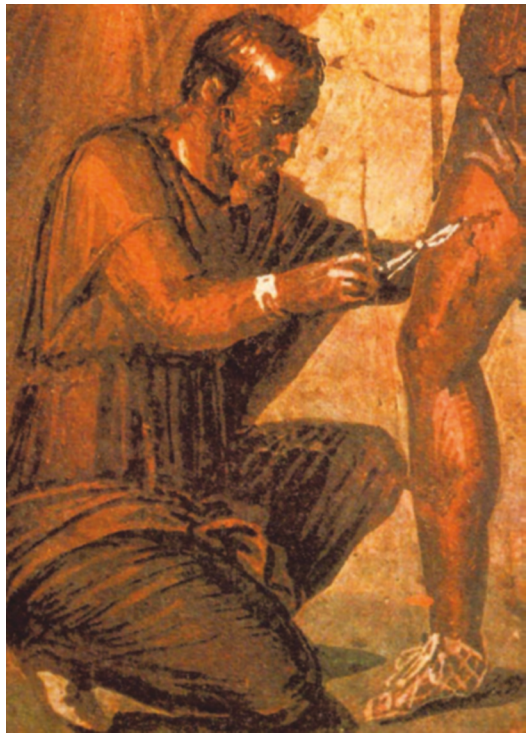

Fig. 1.3 Mural in Pompeii, Lapige cleanses the wounds of Aeneas 45–79 A.D. Archeological Museum Naples, Italy (Inventory MANN). Figure under public domain

Fig. 1.4 Wounded Philoctetes at Lemnos, Attic Vase circa 420 B.C. (Collection of the Metropolitan Museum New York, figure under public domain)

Paleolithic, to the famous fresco of Pompeii where Lapige cleanses the wounds of Aeneas (Fig. 1.3), or the representations of Philoctetes on the Attic vases of Magna Graecia (Fig. 1.4). Over the centuries, art depicted religious subjects or the powerful and then religious ones prevailed, of which the main representation was that of the Martyrs.

In these depictions, the wound often emits light, or the expression of the martyrs suggests a relationship with the divine, as depicted in Fig. 1.5. This is also true in sculpture where, in my opinion, above all is the sculpture of Santa Cecilia by Stefano Maderno, in which the girl appears as sleeping and the horrendous wound by beheading looks almost like a jewel (Fig. 1.6), beautiful the combination with the painting of Riminaldi (1620) of Palazzo Pitti where an angel oversees everything on martyrdom. In the twenty-seventh century, with the new pictorial currents we begin to represent everyday life, and here also

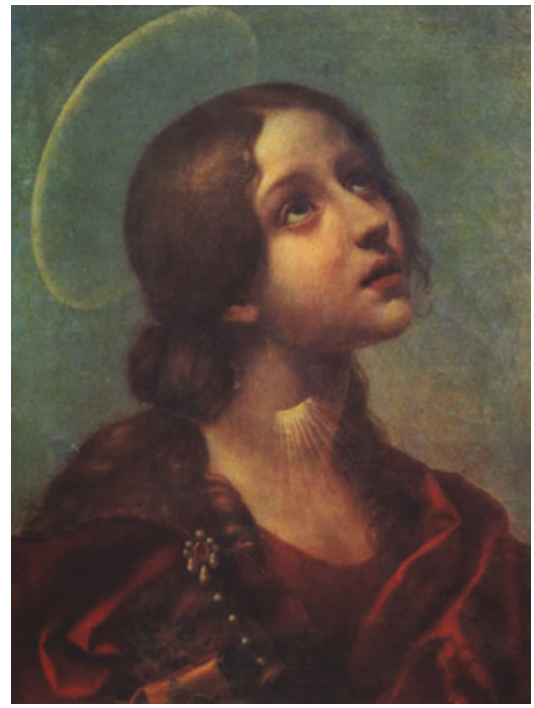

Fig. 1.5 Saint Lucia: Carlo Dolci 1687, Palatine Gallery, the Uffizi, Florence, Italy (figure under public domain)

Fig. 1.6 Saint Cecilia Martyr, sculpted by Stefano Maderno, 1600, preserved in the Basilica of Santa Cecilia, Trastevere, Rome, Italy (figure under public domain)

appear the wounds, from Teniers who in the seventeenth century depicts a dressing in a house, to Ryckaert who in 1638 depicts the surgeon until that day, thousands perhaps millions of paintings represent wounds and ulcers, and I would like to conclude, however, with the work "The broken column" by Frida Khalo (Fig. 1.7), the result of a personal experience that however expresses well what is the life of the carriers of skin ulcers. We could write books, but I would like to move on to the last part, history.

On the history of vulnology, much has been written; in Italy, we owe it mainly to Bonadeo and Guarnera, and I will limit myself to a quick outlook on ancient periods and civilizations (Table 1.1).

Then, the story began, starting with the wound of Henry VIII Tudor (1491–1547), described in the annals of the time, and habits began to change with the arrival of Ambroise Parè (1510–1580). Surgeon Henry II of France reintroduced the ligation of the vessels in amputations and abandoned the use of cauterium replacing it with dog oil. (Take a liter of rose oil. Put four newborn dogs and earthworms. Bring to a boil until the flesh detaches from the bones. Excellent revulsant and to promote the suppuration of wounds). In 1551, he wrote the famous text "La manière

Fig. 1.7 Frida Kahlo, 1944, La Columna Rota (the broken column), original painting at the Museo Dolores Olmedo, Xochimilco, Mexico City, Mexico (figure under public domain)

de traiter les plajes," with numerous illustrations for prostheses. Followed by Cesare Magati (1579–1647) who with the De rara medicatione vulnerum in two volumes published in 1616 began a new era. Starting from 1800, with Lister we enter the modern medicine that has evolved to the present day and that will be the task of the subsequent chapters to analyze, with the transition to the wet microenvironment and advanced dressings with winter, to the wound bed preparation of Falanga and Sibbald of the eighties up to the time currently applied with the developments that are currently in use.

Table 1.1 Vulnology in the history of medicine

Civilization	Source period	Data
Mesopotamia	4000 and—331 BC	Knowledge of herbs and poultices "Pulverize pears and manna, mix with beer bottom and apply on the sick part" "Shred the roots of plants and snake skin, pour into boiling water and wash the diseased part"
	Codex Hammurabi, seventeenth century BC	If a doctor treats a free man for an ulcer and the patient dies, the doctor will have his hands cut off
Egypt	3000 BC	Prosthesis of a big toe found on female mummy, articulated, and with signs of wear
	Smith Papyrus 1600 BC	48 cases of traumatic injuries
	Ebers Papyrus 1550 BC	Various cases including skin diseases
	Hearst papyrus circa 2000 BC	260 recipes including abscesses and paterecci
Israel	2000 BC–135 AC	Medicine is reserved for priests, the Levites Here, the concept of health or illness joins the divine with the concept of reward and punishment (parable of job)
	Leviticus Bible	Inspection of sores and removal of lepers The wounded cannot offer to the god
	Isaiah Bible	**38:21** Isaiah said, "take a poultice of dried figs, apply it to the ulcer, and the king will heal"
Magna Graecia	Alcmeon of Crotone VI century BC	The theorization begins that man is the microcosm, and the body is formed by the four fundamental elements, in order air, fire, earth, and water
	Ippocrate 460 and—331 BC	School of Kos, where clinical observation and semeiotics take shape, the focus will shift definitively to Greece Diseases originated from an imbalance of the four humors of the human body: Blood, phlegm, white bile, and black bile, which combined in different ways lead to health or disease (humor theory) The technique of bandages was very detailed; these were carefully sterilized, washed with soap and hot water, and dried in the sun It proposes a first rudimentary method of compression through the usage of sponges for the treatment of venous ulcers *"In the presence of an ulcer it is not advisable to stand, especially if it is located on the leg We must avoid wetting any ulcer except with wine unless it is in close proximity to a joint, since the dry is closer to the healthy and the wet to the unhealthy"* (varicose vein–ulcer ratio) He taught how to cauterize wounds He taught how to reduce and immobilize fractures He taught to incise abscesses
Magna Graecia (continued)	Aristoteles 384 BC–322 BC	On his advice, Alexander the great sent an entire army to conquer the island of Socotra, near the horn of Africa. This was to obtain the aloe crops used for the healing of wounds of men and horses In his "history of animals," he mentions propolis, considered a useful remedy in skin diseases, ulcers, and suppurations He proposes poultices, remedies based on bran, water, and mustard, which gave relief to joint inflammation and cured infections

Table 1.1 (continued)

Civilization	Source period	Data
Ancient Rome		From ancient times when the pater familias was responsible for health, with Caesar begins a path that, following the Greek tradition, will first come to identify doctors and care facilities in the military, and then later extend to civilians with medical tabernae
	282 BC	The first temple to Asclepius is founded on the Tiber Island, functioning as a protohospital
	Arcagato II sec BC	In 219, he arrived in Rome, and the term vulnology is dedicated to him
	Celsus 25 BC–About 45 AC	Writes the "De Medicina" first great medical text Write down the signs of inflammation: Rubor, tumor, Calor, dolor. Talks about ulcers in book IV In book V, he describes medicaments including hemostatic, suppurative, excoriate (healing), those designed to drop the crust, to smooth the sourness, and to make meat. "It stops any suppuration, a mixture of galbanum, crushed broad beans, myrrh, incense, bark of the root of the caper. It is also valid to dissolve the abscesses, the oyster lime, burned and pulverized, and then diluted in vinegar." in the second part, it deals with wounds, defined as external, and it differentiates them according to the severity in easy, difficult, and incurable, considering the depth and vastness of the wound and the part of the body where it occurred. Describes the pus. Next, it shows how to stop bleeding with the help of gauze and how to heal the wound by suturing, buckles, or bandages. Defines amputation for gangrene In book VII, he provides plastic rudiments for amputations and ligation of varicose veins
	Scribonio largo first half first century AC	He used torpedoes for various therapies including ulcers that did not heal (hence torpid ulcers)
	Galen 129–201	Strong proponent of humoral theory, anatomist He studied the wounds of gladiators and noted that the nerve injury caused numbness He did not use bandages, supporter of enemas, and purgants
Arab	Avicenna 980–1037	His medical canon survived for over 700 years He hypothesized the presence of microorganisms in infections Occlusive treatments with silver and gold foils were initiated The concept of antisepsis began
Norse	From V century AC	Based on the philosophy of the Celtic area, therefore of druidic shamanic competence, they based the concept of wound as a loss of soul parts, therefore, to be sought through the journeys of the curators Extensive use of fire, not only to cauterize and stop bleeding, but also as a moment of transformation as one of the four founding elements of matter

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2 Aetiology, Classification and Advocating for a Holistic, Multidisciplinary Approach

Alessandra Michelucci, Giammarco Granieri, Valentina Dini, and Marco Romanelli

2.1 Epidemiology

Chronic wounds are characterised by an inability to heal within an expected period of time, although there are no prospective studies establishing the time frame to define an ulcer as chronic.

Chronic ulcers represent a disease with a worldwide emotional and socio-economic impact [1–3]. Approximately 1–2% of the world's population will develop a chronic ulcer during their lifetime. It is estimated that 6.5 million people in the United States alone are affected by chronic wounds [4, 5]. The incidence of chronic wounds varies with age, gender and geographical location. Limitations of epidemiological studies lie in the differences in the terminology used, as well as the difference in prevalence with age and geographic location and the high rate of recurrence after healing [6, 7].

Venous leg ulcers (VLUs), representing the most common form of ulceration of the lower extremities (80–90% of leg ulcers), have an average prevalence of 2.2 cases per 1000 persons. They are more common in the elderly population and in females. The prevalence and incidence double in patients >65 years of age [8–11].

The prevalence of pressure ulcers (PUs) from cross-sectional studies presented in the literature ranges from 3% to 31%. They predominantly affect a population with low mobility, and the prevalence is influenced by the age and status of the patient (assessable by the Norton scale and the Braden scale) and the structure of residence (hospital, community and nursing homes) [12–16].

The risk of a patient with diabetes to develop diabetic foot ulcers (DFUs) during their lifetime is on average of 19–34% [17–19]. Worldwide DFU prevalence is 6.3%, and it is influenced by structure of residence, age, sex, diabetes type, region and other diabetes-related comorbidities [6, 20, 21]. Subjects with a DFU are >10 times more likely to have a lower extremity amputation (LEA) and a higher risk of death compared to healthy people [22, 23].

2.2 Aetiopathogenesis

The physiological healing process consists of several sequential and overlapping phases, namely haemostatic, inflammatory, proliferative and remodelling phases [24]. In chronic ulcers, this linear succession of phases is lost and the different phases follow each other without a specific time frame [25, 26]. The role of the inflammatory phase in the tissue healing process is widely recognised. The inflammatory phase is generally

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followed by the proliferative phase, in which the immune response moves towards an anti-inflammatory and proliferative stage, which is essential for the tissue repair process. Chronic wounds, on the other hand, present a dysregulation of the inflammatory response that prevents progression to the next healing phase. In addition, distinct areas of the chronic ulcer may be at different healing stages, thus complicating the therapeutic approach. Wound debridement aimed at synchronising the various areas of the wound at the same healing phase. The pathophysiology is complex and multifactorial, involving genetic predisposition, environmental factors, hormones, endothelial dysfunction, dysregulation of the immune response, and both innate and specific alterations of vascular endothelium, as well as imbalances of cytokines and matrix metalloproteinases (MMPs).

2.3 Classification

Chronic ulcers are classified according to their heterogeneous aetiology into vascular ulcers including those due to venous insufficiency, arterial insufficiency, vascular mixed aetiology, diabetic ulcers, pressure ulcers and atypical ulcers.

2.3.1 Venous Ulcers

Chronic venous disease (CVD), afflicting 2% of the population in Western countries, constitutes a significant socio-economic burden on the healthcare system due to the strong psychophysical impact on the affected individual [27].

The internationally accepted classification system for approaching the complexity of chronic venous disease is identified by the acronym Clinical-Etiology-Anatomy-Pathophysiology (CEAP).

Developed in 1993, updated in 1996 and reviewed in 2004, CEAP is a classification system based on our current knowledge of clinical manifestations, aetiology, anatomy and underlying venous pathology [28, 29]. Each parameter is subclassified into several groups, which allows the clinician to evaluate the complexity of the patient's condition.

Based on the clinical manifestations of chronic venous disease, six distinct stages can be identified: telangiectasias (C1), varicose veins (C2), oedema (C3), dystrophic lesions (C4), the presence of outcomes (C5) or an ongoing ulcer (C6) [30].

The pathophysiology leading to venous hypertension is complex and multifactorial, involving genetic predisposition, environmental factors, hormones, endothelial dysfunction, inflammatory cells and molecules, as well as imbalances of cytokines and matrix metalloproteinases [31].

For a proper management of such a debilitating disease, the therapeutic approach, largely based on elasto-compression, must be initiated in the early stages of the disease and must be followed by an adequate territorial and home management of the patient.

The characteristics of VLUs reflect their patho-physiological features, with the involvement of perforant vein between the deep and superficial circulation and the occurrence of venous hypertension [32, 33]. VLUs are typically superficial and affect the medial supramalleolar region. The wound bed is usually red or yellow, due to the presence of fibrin, and presents a large amount of exudate. The wound edges have irregular shape, and perilesional skin presents signs of chronic venous disease (oedema, varicose veins or lipodermatosclerosis). Pain is not generally too intense and decreases by lifting the limb [34–37].

2.3.2 Arterial Ulcers

Arterial ulcers typically involve the lateral surface of the lower limb and the distal extremity (back of the foot and toes). On objective examination, it is possible to identify a reduction of the peripheral pulses (dorsal pedidium or posterior tibial), which can be confirmed by colour Doppler examination. Clinically, they appear as smaller size ulcers but with greater extension in depth compared to venous ulcers, sometimes involving tendon and bone. Symptomatology is intense and

increases as the limb is lifted. The wound bed often has necrotic adhered tissue. The wound edges are regular (punched-out appearance). The perilesional skin shows signs of atrophy with a pale appearance and loss of hair follicles [38].

2.3.3 Diabetic Foot Ulcers

DFUs, depending on the main pathogenetic mechanism, may be neuropathic, ischaemic or neuroischaemic [38]. Neuropathic diabetic ulcers are located in areas of increased pressure, at the plantar surface of the foot and above the metatarsal regions. The presence of the callus in pressure areas increases the risk of pressure at the level of the foot. Charcot's foot is typically found in neuropathic diabetic ulcers as a consequence of bony deformation, resulting from the inflammatory process [39, 40].

Neuropathic diabetic ulcers, on the other hand, present similar characteristics to those originating from arterial insufficiency. The basic pathogenetic mechanism is in fact the ischaemic process. The wound bed is frequently necrotic, and the perilesional skin reveals signs of atrophy. When these ulcers increase in size, they may involve a large portion of the foot with increased risk of over-infection and amputation [39].

Diabetic neuroischaemic ulcers combine the characteristics of the two previous types.

2.3.4 Pressure Ulcers

PUs are nowadays more properly called pressure injuries, mainly involving skin regions located above bony prominences, i.e. the heel, hips, occiput and sacral region. They result from the combination of pressure and traction forces at the affected site, in patients generally with reduced mobility or immobility [41]. According to the latest National Pressure Ulcer Advisory Panel (NPUAP) classification, different stages of pressure injuries can be identified. The first stage is characterised by non-blanchable erythema. The second stage involves the dermis, while the third stage reaches the subcutaneous tissue. When tendons and bones are involved, the fourth stage is defined. Recently, two other stages are described: an unstageable full-thickness pressure injury, in which the real extent of tissue loss cannot be confirmed because it is obscured by slough or eschar, and deep tissue pressure injury with a persistent and non-blanchable deep red, brown or purple discoloration [42]. The growing interest in these kinds of wounds is related not only to the high incidence in hospitalised patients or residents of RSAs but also to the possibility of prevention by means of appropriate anti-decubitus devices [43].

2.3.5 Atypical Ulcers

Atypical ulcers include on average 20% of all chronic wounds and are characterised by atypical parameters regarding location, clinical features and aetiology [44]. They are usually caused by immunological dysregulations (such as pyoderma gangrenosum), micro-occlusion of blood vessels in the lower limbs (mainly due to intravascular thrombi, embolization or coagulopathies), vasculitides of small and medium vessels, ischaemic arteriolosclerosis (Martorell's hypertensive ischaemic leg ulcer (HYTILU) and calciphylaxis), primary skin tumours or metastases to the skin, infection and artefactal ulcers. In less developed countries, aetiologies also include nutritional deficiencies, chronic parasitic and fungal infestations and leprosy. If a wound has an abnormal presentation or location, causes severe pain compared to size and fails to heal within 12 weeks of standard treatment, an atypical wound can be suspected and must be confirmed through a skin biopsy [45, 46].

2.4 Diagnosis

Chronic ulcers present a wide heterogeneity according to their aetiology, pathogenesis, appropriate management approach and prevention. The objective examination of the patient focuses on the assessment of the site and the clinical features of the lesion, i.e. the wound bed, the edges and the perilesional skin. A clinical evaluation of the

patient's general clinical condition and past medical and pharmacological history must be carried out. Finally, physical examination, including the evaluation of peripheral arterial pulses and the identification of other clinical signs suggestive of underlying pathology, must be performed. The ankle-brachial pressure index (ABI) is measured by dividing the systolic ankle pressure by the systolic brachial pressure. Normal values are considered 1.0 and 1.1, while values <0.8 are abnormal and indicate poor extremity perfusion. Colour Doppler examination is useful in objectively assessing the state of arteriovenous insufficiency [47–49].

For confirmatory diagnosis, especially in the case of an ulcer that does not heal despite an adequate therapy, laboratory tests, imaging examinations and biopsy examination may be necessary. Histological examination is necessary to rule out the diagnosis of malignancy or other atypical wounds. Punch biopsy must be performed at the edge of the lesion and must include a portion of perilesional skin [50].

The search for a specific biomarker to predict wound healing status is still an open challenge in the field of non-healing wounds.

Among the biomarkers, considered for the evaluation of chronic ulcers, we have to mention the tumour necrosis factor-alpha (TNF-alpha), which, if elevated, suggests the use of monoclonal antibodies (mAb) directed against TNF-alpha, to reduce the inflammation state and promote healing [51].

Increased expression by the smooth muscle cells of the blood vessels of osteopontin, on the other hand, suggests a diagnosis of calciphylaxis [52]. Another promising biomarker in the evaluation of non-healing wounds is the level of MMPs in wound exudate [53, 54].

2.5 Multidisciplinary Approach

The management of chronic wounds has experienced a great development in the last two to three decades, and it is based on a complex combined systemic and local approach. Treatment of the condition underlying the chronic wound must be associated with local management of the wound bed [55]. Nowadays, the largest part of the knowledge regarding the treatment of chronic wounds is based on clinical guidelines and expert opinion. However, the development of standardised guidelines on the local management of chronic ulcers, based on the principles of wound bed preparation (WBP), is necessary [56–58]. The improvement in the field of wound dressings has occurred, especially in the last two decades. Regarding local wound management, the choice of the appropriate dressing is based on the characteristics of the wound: the features of the wound bed and perilesional skin, the amount of exudate and the presence of proliferative growth bacteria [59]. Microorganisms frequently colonise the wound surface and making a simple swab often provokes the unnecessary use of systemic antibiotics. Instead, the biofilm formation plays an important role in impaired healing [60].

The scoring system used for wound bed assessment is based on the evaluation of black eschar, eczema/dermatitis, fibrosis or tissue callus, wound bed colour, oedema, resurfacing epithelium and amount of exudate. This scoring system, called wound bed score (WBS), analysing the main clinical components of WBP, is useful for bedside assessment and treatment choice.

Due to increasing levels of antibiotic-resistant bacteria, the application of topical antibiotics is not recommended and the use of antimicrobial dressings is preferred [61–64].

Occlusive dressings, also known as moisture-retentive dressings, are used to maintain a level of hydration in the wound bed, favourable to the healing process [32, 59, 65].

Wound dressings are used in wounds with a lower level of exudate, while foams are employed for very exuding wounds.

Hydrocolloids promote wound bed debridement, while alginates increase the moisture level in very dry wounds [59, 65]. More recently, composites of these dressings, in order to continuously release antiseptic and antimicrobial substances, have been introduced [66].

The use of negative pressure wound therapy (NPWT) can stimulate granulation tissue and maintain an adequate moisture balance. It has

been shown that an excess of exudate may delay the healing process, so proper fluid balance is necessary to promote faster healing [67–70].

VLUs are treated with compression bandages or layered compression bandages. Systemic drugs used to promote healing of VLUs include pentoxifylline [71, 72]. Chronic wounds due to arterial insufficiency are managed by stenting and revascularisation, which can restore the normal flow to the ischaemic region.

UPs require continuous repositioning of the patient and avoidance of pressure on bony prominences. Nutritional support may be necessary to restore an adequate level of blood albumin.

DFUs' management needs the offloading for the insensate foot, the use of padding and protection and the callus removal with surgical debridement. Diabetes monitoring and weight control must be performed. The acronym Metabolic-Assessment-Debridement-Antibiotics-Dressing--Offloading-Referral-Education (MADAMORE) was introduced by Lazzarini, Fernando and Netten in 2019 to identify the main principles to assist the clinicians in diabetic foot ulcer management [73].

When a surgical approach is needed, vascular reconstruction or the use of grafting and limb salvage may be considered. The debridement of the necrotic tissue must be followed by a maintenance debridement to keep the healing process active [74].

Biological therapy in chronic ulcers has only recently been developed [24, 75]. Platelet-derived growth factor (PDGF) was the first topical recombinant growth factor approved by the Food and Drug Administration (FDA) for the treatment of neuropathic DFUs [24, 76–79]. The use of topical growth factors, however, reveals several limits. Their effectiveness is impaired by the difficult penetration of a topical agent within the wound bed. Moreover, the risk of protein breakdown prevents the combination with other synergistic growth factors [24]. However, other studies suggest that growth factors may be effective [80, 81].

More recently, the research of scientific community has been focused on the use of tissue engineering in the treatment of chronic wounds. In particular, epidermal and dermal cells cultured were considered a viable therapeutic option to promote tissue healing [82, 83]. The use of bioengineered skin is not a simple cell replacement, like that carried out by grafted skin, but rather a constant stimulation of the healing process [84, 85]. Although the use of tissue engineering is approved for the treatment of VLUs and DFUs, the results in terms of efficacy are not always satisfying and repeated treatments may be required [48, 86–91].

More recently, the focus has been stressed on the use of bone marrow-derived mesenchymal stem cells (BM-MSCs) to promote wound healing. BM-MSCs have been shown in vivo and in vitro studies to stimulate angiogenesis and cell proliferation through the release of cytokines and growth factors. Autologous or allogeneic administration of BM-MSCs does not exhibit a high risk of immune rejection. Other multipotent cells are those derived from adipose tissue [92, 93]. In contrast, the high risk of rejection and the need for only autologous sources have limited the use of tissue-resident stem cells, such as dermal or epidermal stem cells [94–96].

2.6 Conclusions

Wounds represent a worldwide socio-economic problem both in terms of direct and indirect costs, and because of the high psychological and physical burden for the patient. In this context, a proper and early diagnosis allows to identify an appropriate treatment. Treatment currently available for wound management is a combination of local and systemic therapy, based on the clinical and pathogenetic features of the wound. However, there is still no standardised guideline and clinical practice is guided by expert opinion and data presented in literature. Raising awareness about such a debilitating disease among the different health professional figures means providing structured guidance for the prevention and management of chronic wounds.

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