Recent Clinical Techniques, Results, and Research in Wounds

Melvin A. Shiffman
Mervin Low *Editors*

Plastic and Thoracic Surgery, Orthopedics and Ophthalmology

Springer

Recent Clinical Techniques, Results, and Research in Wounds

Series Editors

Melvin A. Shiffman
Mervin Low

More information about this series at http://www.springer.com/series/15695

Melvin A. Shiffman • Mervin Low
Editors

Plastic and Thoracic Surgery, Orthopedics and Ophthalmology

Springer

Editors
Melvin A. Shiffman
Tustin, CA
USA

Mervin Low
Newport Beach, CA
USA

ISSN 2524-4590 ISSN 2524-4604 (electronic)
Recent Clinical Techniques, Results, and Research in Wounds
ISBN 978-3-030-10709-3 ISBN 978-3-030-10710-9 (eBook)
https://doi.org/10.1007/978-3-030-10710-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword[1]

It is a great honour for me to be invited to provide a foreword for the series of six books edited by Dr. Shiffman and Dr. Low, which cover a broad expanse of subjects relevant to and important in the care of patients with wounds.

Wounds have existed since the beginning of time and, until recent years, have received scant attention unless major conflicts developed which necessitated innovation in the treatment of patients with wounds. However, in recent years there has been an increasing interest in this subject as evidenced by the explosion of journals, meetings, societies and associations and initiatives that have been developed in this field.

The need for an academic underpinning of the subject of wound healing is without question. Research papers published in recent years have undoubtedly enhanced the scientific basis for wound healing. This, coupled with demographic changes in many countries around the world, has led to increasing numbers of patients developing wounds or wound healing problems. It is recognised that in the vast majority of geographies globally the number of patients with wounds is increasing in everything other than major burns where better health and safety initiatives have been an effective preventive strategy.

This series of books not only attempts to deal with subjects that are normally seen in wound healing text but also provides a huge amount of space to the management of wounds seen in surgical practice, both general and specialist surgery. The sections on infection are an attempt to deal with a very common but poorly managed clinical problem and one that requires urgent attention in view of the global challenge of antimicrobial stewardship. The tradition chronic wounds are also included and provide a medical as well as a nursing and paramedical focus on these subjects.

It is particularly pleasing to see books and chapters focused on specialised surgical practice as these are areas that are rarely covered in other educational products in this area. The opportunity for new therapies, measuring the range of effective and appropriate outcomes and the use of new technologies are all included.

For those of us who work in the area of wound healing, these books will unquestionably be an important reference source. For those readers who want to get an insight into this common, expensive and complex problem they will without doubt find the content of these books an important source of informed opinion and refer to the rapidly expanding evidence base that is developing in this subject area.

I would urge you to immerse yourself in these books. Read, reflect and consider how information that you have had access to can and will change your clinical practice.

Keith Harding
Clinical Innovation Cardiff (ClIC),
College of Biomedical and Life Sciences,
Cardiff University School of Medicine,
Heath Park, Cardiff,
UK

[1]P. S.

We, Melvin A. Shiffman and Mervin Low, are greatly enthralled by Keith Harding's willingness to write the Foreword for the books on wounds. Keith Harding is the Director of TIME Institute (Translation, Innovation, Methodology and Engagement) and Head of the Wound Healing Research Unit in the School of Medicine at Cardiff University. He is Clinical Lead for Wound Healing in the Cardiff and Vale NHS Trust. In September 2013 Harding was appointed Dean of Clinical Innovation at Cardiff University. From 2002 to 2005 he was Head of the Department of Surgery at Cardiff University. He is Editor-in-Chief of the *International Wound Journal*. Harding is a Past President of the European Tissue Repair Society. He was the first President of the European Pressure Ulcer Advisory Panel and first Recorder of the European Wound Management Association. He was Chair of the International Working Group on Wound Healing in Diabetic Foot Disease in 2003. He was Chair of the Expert Working Group that produced a range of International Consensus Documents from 2004 to 2011. Professor Harding was appointed a Commander of the Order of the British Empire in the 2013 New Year Honours for services to medicine and healthcare.

Preface

We are delighted to have the book on wounds extended into six volumes. There is so very much medical literature in journals and books that to cover the whole gamut of wounds would be virtually impossible. We tried to include as many of the experienced practitioners in wound care as possible, but many of them are too busy to spend the time committing to submitting a chapter.

The selection of topics in each of the volumes was decided by the number of authors responded to each of the subjects. As usual in editing a book, many authors who agreed to submit manuscripts finally were not available to complete the chapters. We contacted or tried to contact over 1500 authors and most of them did not respond or the responses were not as good as expected.

The volumes include:

1. Biofilm, Pilonidal Cysts and Sinuses
2. Burns, Infections and Wound Management
3. Pressure Injury, Diabetes and Negative Pressure Wound Therapy
4. Plastic and Thoracic Surgery, Orthopedics and Ophthalmology
5. Vascular Surgery, Neurosurgery, Lower Extremity Ulcers, Antimicrobials, Wound Assessment, Care, Measurement and Repair
6. Chronic Wounds, Wound Dressings and Wound Healing

There are many expert international contributors who have worked in various aspects of wound research as well as clinical practice. We have tried to have chapters that involved humans and in vivo results and avoided as much as possible animals and in vitro results. Chapter conclusions are those of the authors and may not be the same as those of the editors. At times the chapter may appear cumbersome, but the authors try to show some proof of their results. Language difficulties are common when translated into English so that grammar, spelling and sometimes words have to be corrected.

Hopefully, the reader will get information that adds to their care and treatment of patients. Researchers may gain knowledge of other researchers' progress and improve on the results or can continue their work in other directions. Controversy is many times a good thing since looking in other directions to prove or disprove a result can improve knowledge. We have a long way to go to be able to treat all wounds properly and successfully in as short a time as possible.

Tustin, CA, USA — Melvin A. Shiffman
Newport Beach, CA, USA — Mervin Low

Contents

Part III Plastic Surgery

Part IV Thoracic Surgery

Part I

Orthopedics

Management of Complex Distal Lower Extremity Wounds Using a Porcine Urinary Bladder Matrix (UBM-ECM)

Bruce A. Kraemer

1 Introduction

Wounds of the distal third of the leg, ankle, and foot often pose challenging reconstructive problems because of the lack of suitable local available tissues as well as the frequent bone and tendon involvement in a wound bed with compromised arterial inflow or venous outflow. With acute wounds, there is often an associated crushing or shearing trauma to the local tissues, while the more chronic wounds have a marked degree of inflammation and bacterial colonization. Additionally, ambulation can lead to dependent edema as well as added stress and strain on the injured parts which may contribute to repeated wound breakdown.

The recognized ultimate goal of lower extremity limb reconstruction is achieving durable, stable, infection-free, pain-free, minimally scarred wound healing that also facilitates primary bone healing, appears as normal as possible, and allows normal ambulation. Trying to achieve this in an ever-aging population with increased medical comorbidities can be most complicated. Beginning in 2012, we began using UBM-ECM (urinary bladder matrix-extracellular matrix) wound devices (initially marketed as MatriStem® and more recently rebranded as Cytal™, ACell®, Inc., Columbia, MD) as the primary wound management modality to treat lower extremity wounds in patients with significant medical comorbidities that would beat higher complication risk for treatment with a standard regional or free flap [1, 2]. While wound bed excisional debridement is the recommended preparation for Integra™ Bilayer Wound Matrix (Integra™ LifeSciences, Plainsboro, NJ) use [3], we were surprised to find that wounds managed with UBM-ECM responded well with a lesser wound bed debridement, thus allowing for more tissue preservation even in the presence of significant bacterial colonization (Figs. 1, 2, 3, 4, 5, 6, and 7). Unlike the report of Valerio et al. [4] who described UBM-ECM as an adjunct to standard treatments, we have advanced the use of UBM-ECM to a primary reconstructive modality. We found that all wounds, regardless of size, responded to the UBM-ECM wound device. In general, the amount of UBM-ECM wound device needed, the number of device placement procedures performed, and the time needed to heal the wound increased as the wound size increased. Healing times also varied with some patients opting for a split- or full-thickness skin graft once adequate vascularized tissue filled the wound and skin grafting became possible. Despite the longer wound healing times when compared to standard flap therapy for similar wounds, there were no

Disclosure: Dr. Kraemer has been a consultant for ACell®, Inc., (Columbia, MD) since 2014 and has received monies for presenting his clinical experience on the use of the UBM-ECM wound device. He began using the UBM-ECM wound devices in 2010.

B.A. Kraemer, M.D. (✉)
Division of Plastic Surgery, Department of Surgery,
St. Louis University School of Medicine,
St. Louis, MO, USA
e-mail: kraemerb@slu.edu

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_60, © Springer International Publishing AG
Published Online: 04 April 2018

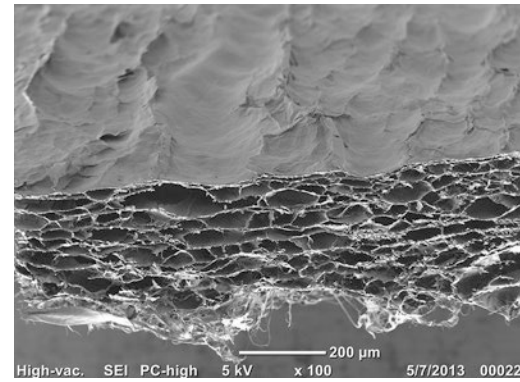


Fig. 1 Scanning electron microscopic image of the UBM-ECM wound device. The intact basement membrane layer is seen as the top layer with the preserved tunica propria ECM lattice structure evident below (Courtesy TW Gilbert, Ph.D., ACell®, Inc., Columbia, MD)

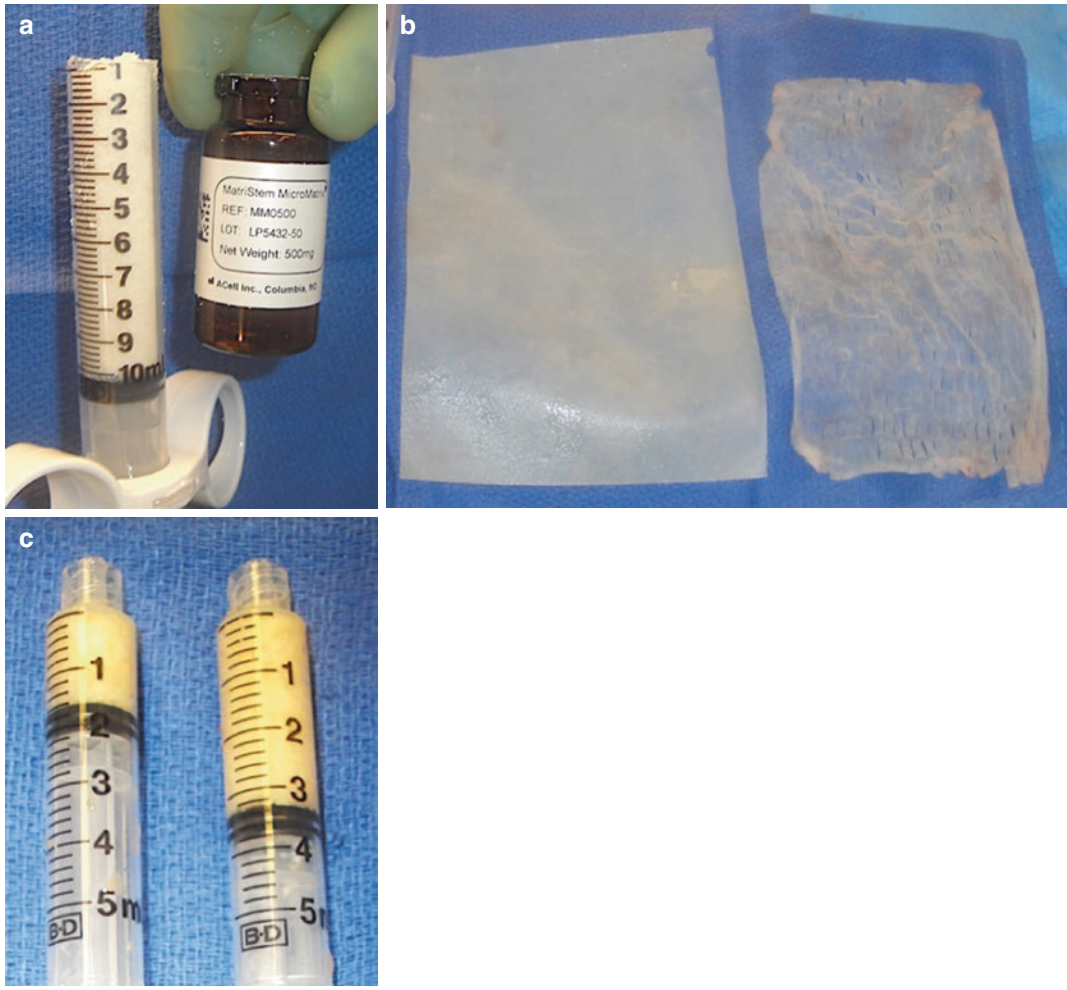


Fig. 2 (**a**) Non-compressed volume of 500 mg of the MicroMatrix powder. After being placed in the wound, the powder does not maintain this volume. (**b**) Appearance of a 10 × 15 cm rehydrated Cytal Burn Matrix (right) and MatriStem Surgical Matrix sheet (left). Note the notch of the Surgical Matrix Sheet in the top right corner indicates the sheet is oriented with the intact basement membrane layer facing up. (**c**) Compressed volume size of a rehydrated Cytal Burn Matrix sheet 7 × 10 cm on the left and 10 × 15 cm sheet on the right

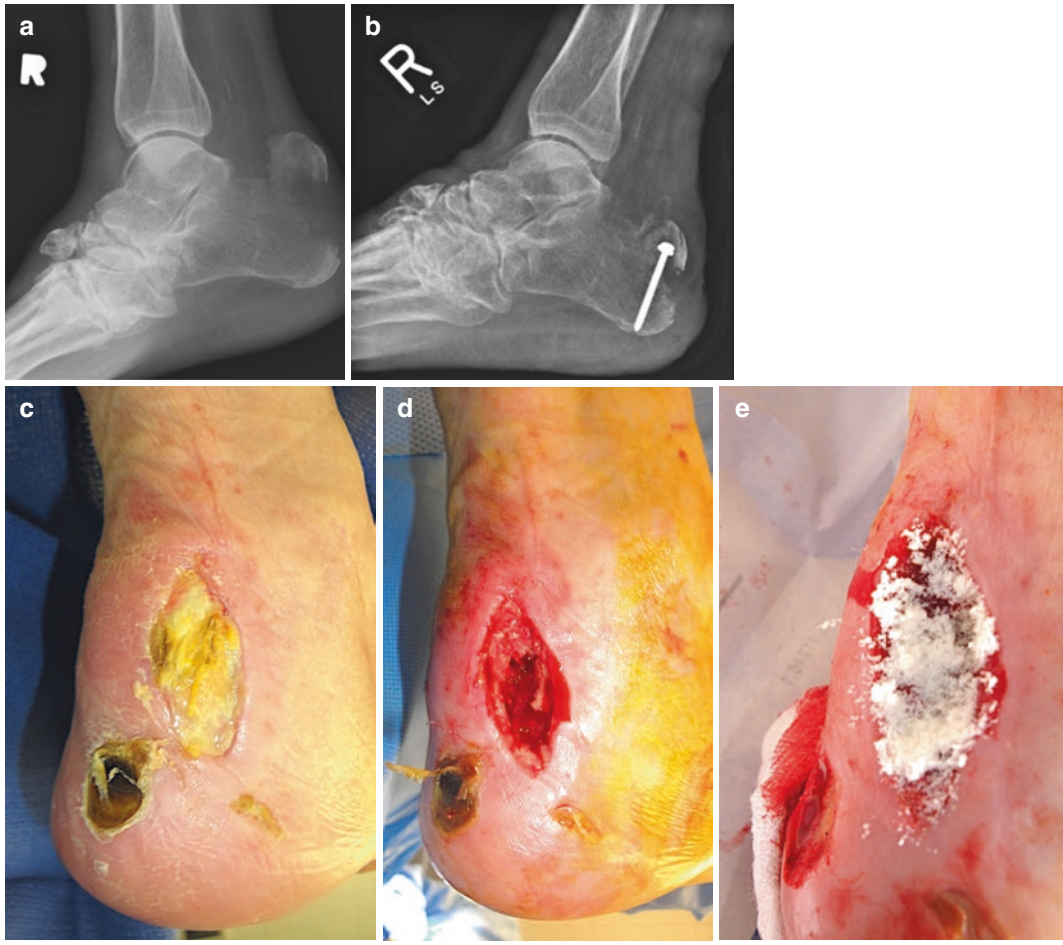


Fig. 3 (**a**, **b**) A 63-year-old legally blind diabetic female S/P pancreas/kidney transplant on immunosuppression sustained a calcaneal tongue-type fracture which failed to hold reduction and (**c**) posterior heel wound which developed. (**d**) Posterior heel wound post-debridement and screw removal due to failure. (**e**) Placement of 100 mg MicroMatrix powder into the wound. (**f**) Placing a cut up 5 × 5 cm Surgical Matrix sheet layered into the wound and covered over with Adaptic and polyurethane sheet dressing. (**g**) Wound appearance 14 days later. (**h**) 3.5 months post-injury she fell and now fractured her ankle mortise. An additional 5 × 5 cm surgical sheet was placed in the remaining cavity. (**i**) An additional 200 mg of MicroMatrix powder was placed into wound by pulling the wound sheet partially out, powdering it, and placing it back into the wound. (**j**) The wound was healed by 9 months post initial injury and follow-up photo shown at 1 year. Reproduced with permission [1]

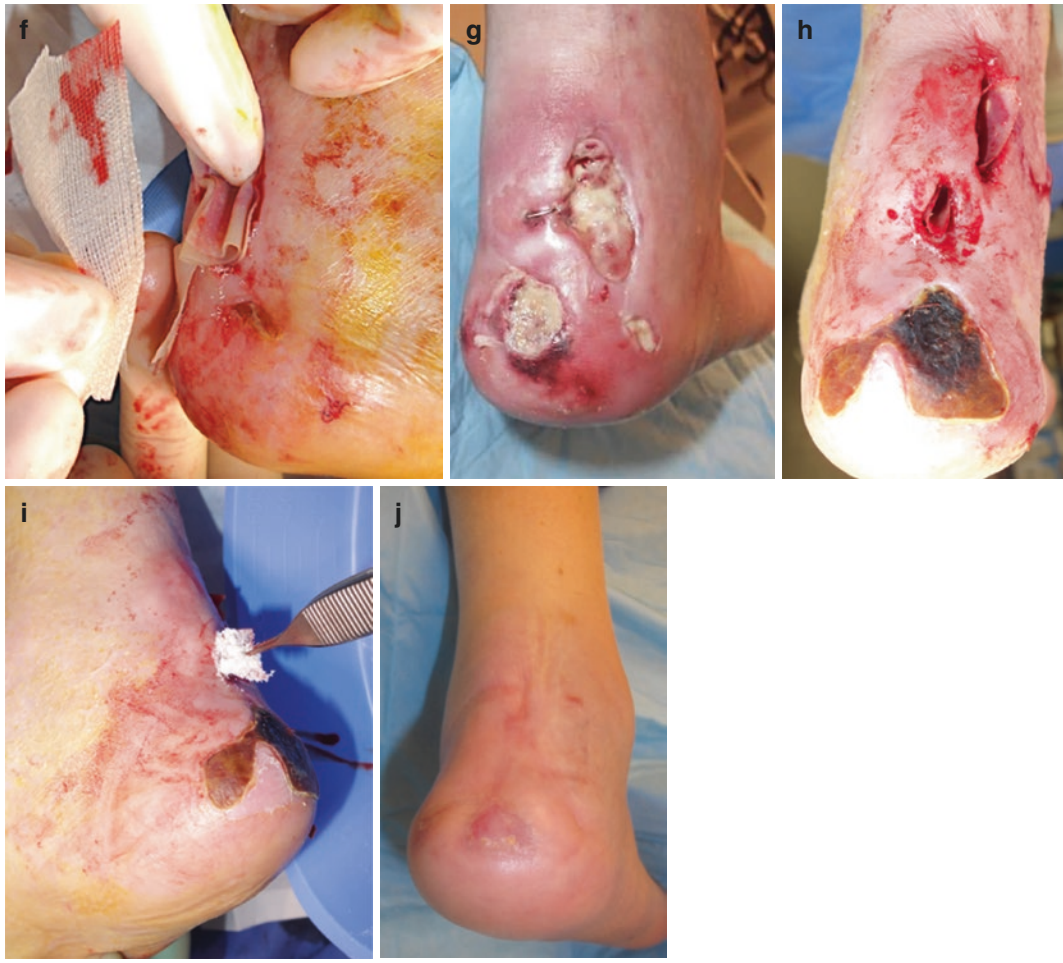


Fig. 3 continued

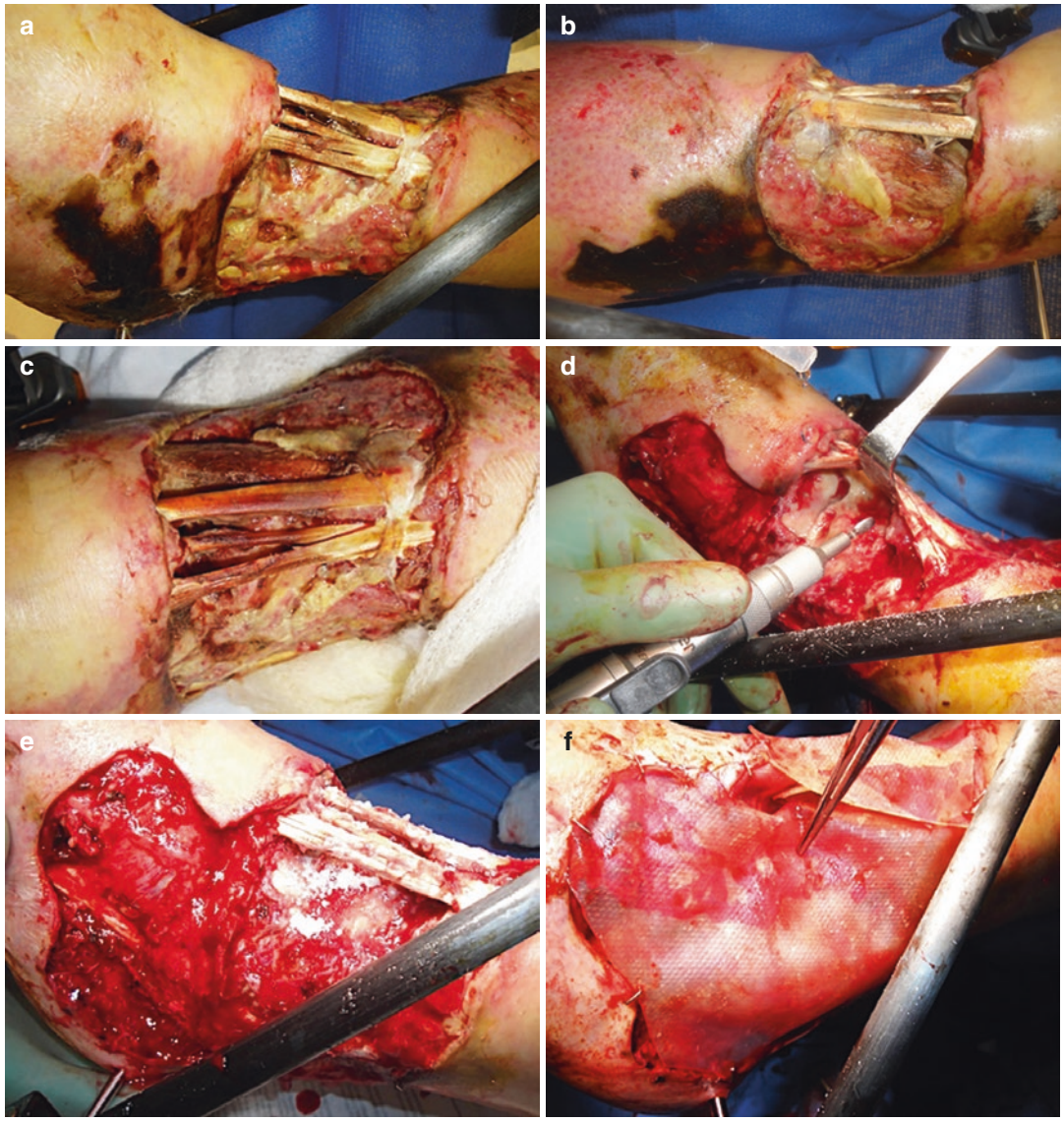


Fig. 4 (**a**–**c**) Lateral, medial, and anterior ankle appearance 2 weeks post-injury of a 57-year-old male whose leg was wrapped around a dump truck axle causing a total talus and ankle dislocation with associated medical problems of facial fractures, a contralateral acetabular fracture, diabetes, and full anticoagulation treating a recent pulmonary embolism. Initial wound management was NPWT, and wounds were culture positive for wound methicillin-sensitive *Staph aureus* and *Pseudomonas*. (**d**) Open ankle joint with distal tibial debridement and exposed talus demonstrated—note rongeurs were used for the final bone debridement. (**e**) Generous coating of MatriStem MicroMatrix powder was applied to the wound bed and tendons. (**f**) Wound bed and tendons were covered with MatriStem Surgical sheet. (**g**) Wound appearance as the UBM-ECM promotes constructive remodeling 2 weeks later. (**h**) Split-thickness skin grafts were applied once sufficient lateral ankle wound healing occurred. (**i**) Further healing of ankle tissues filling up to under the anterior ankle tendons. (**j**) Ankle tissues have grown up around and now envelop the tendons. At this point a full-thickness skin graft is placed over these tendons to complete the closure of the open ankle wound. Wound totally closed at 19 weeks post-injury. (**k**) Early ankle appearance 3 weeks after full-thickness skin graft over anterior ankle tendons. (**l**–**n**) Healing 2 years post-injury. Note the progressive healing and merging of the skin grafts into the normal ankle tissues. (**o**) CT scan demonstrating the damaged talus and the intact anterior ankle tendons of the healed ankle wound. Reproduced with permission [1]

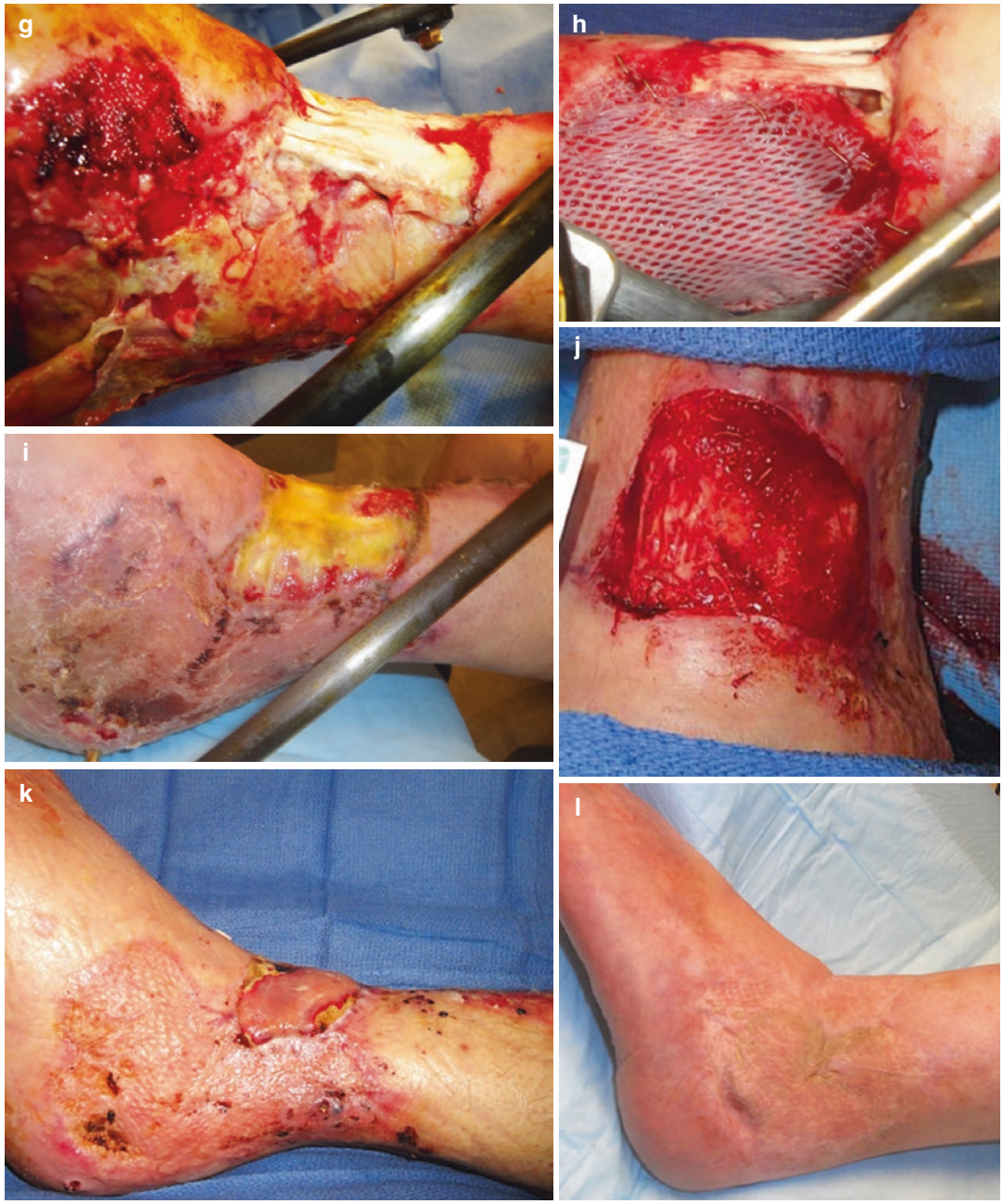


Fig. 4 continued

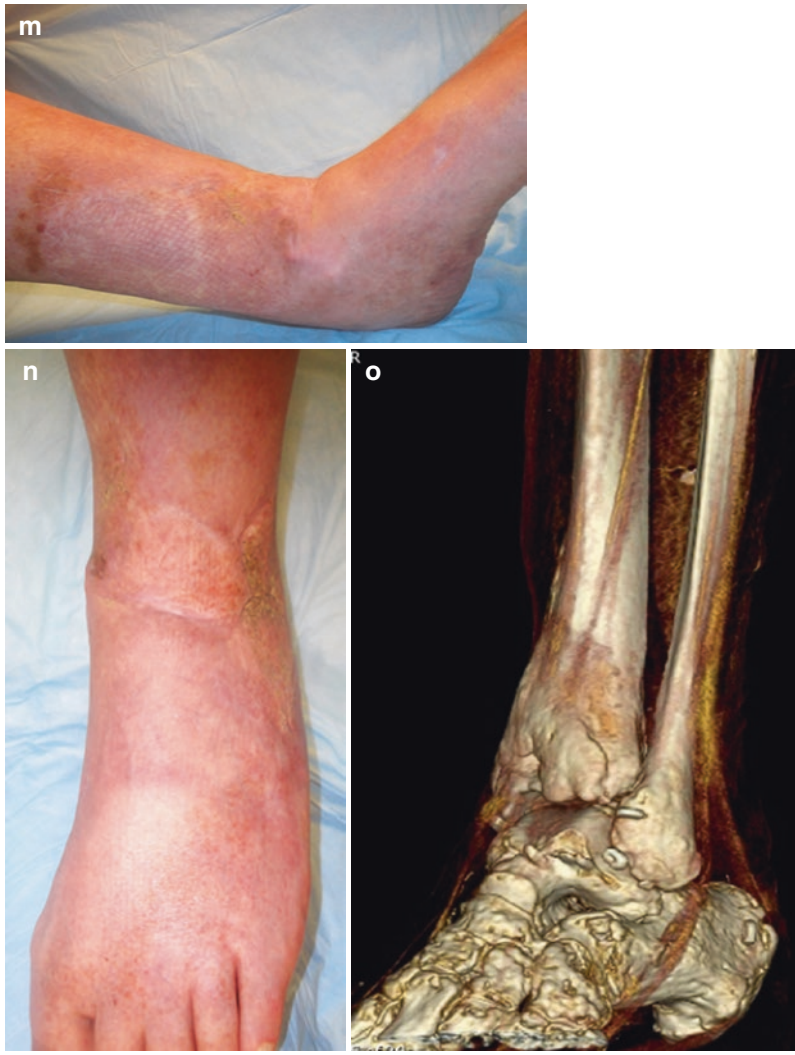


Fig. 4 continued

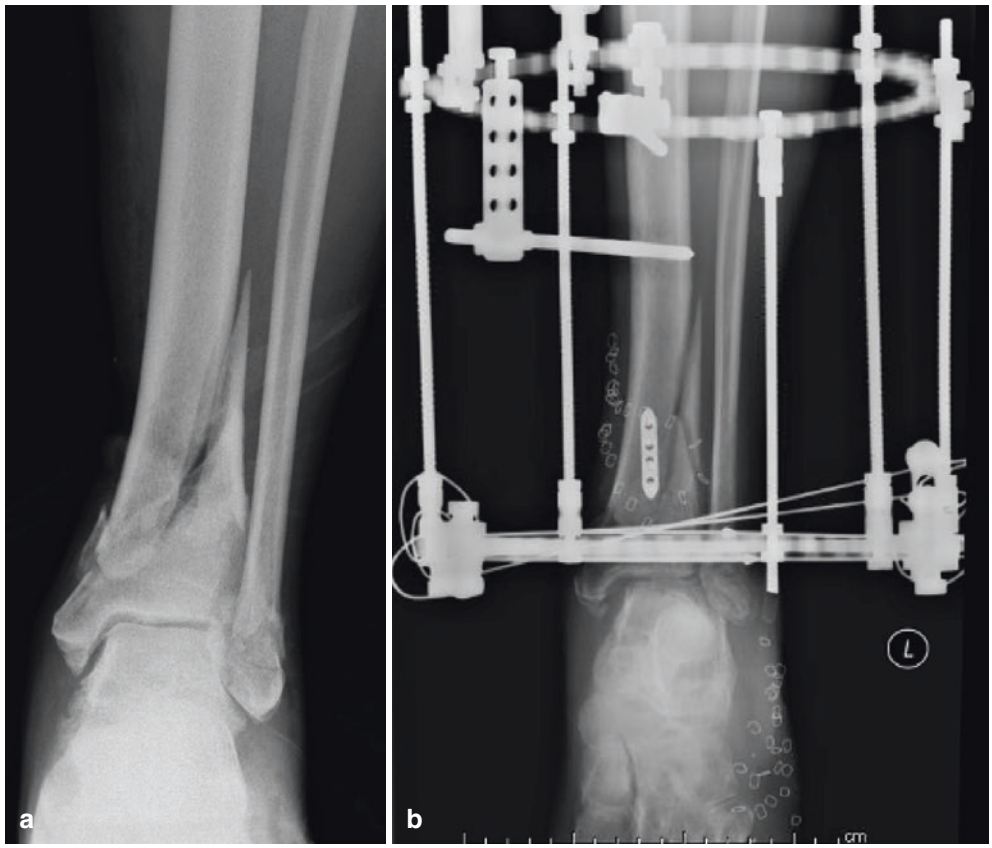


Fig. 5 (**a**) Initial fracture appearance of a 59-year-old hypertensive, polysubstance abusing male smoker who fractured his ankle jumping out of an elevator. Lateral foot wound culture positive for coagulase-negative staphylococci. (**b**) Fracture managed with Ilizarov device and mini-plate placement. (**c**) Lateral foot wound appearance 2 days post-injury. (**d**) Lateral foot degloving wound debrided with Versajet. (**e**) Wound appearance after placement of 500 mg. of MatriStem MicroMatrix powder and two 10 × 15 cm Cytal Burn Matrix sheets into the wound and tucked up under undermined proximal skin. (**f**) Lateral foot wound appearance 2 weeks later. (**g**) Appearance of anterior-medial ankle wound 2 weeks post-injury. (**h**) Appearance of anterior-medial wound after debridement of devitalized tissue with the exposed bone evident adjacent to the fracture in the base of the wound. (**i**) Anterior-medial wound packed with 500 mg. MicroMatrix powder and a 7 × 10 cm Burn Matrix sheet. (**j**) Anterior-medial wound appearance 3 weeks later—tissue remodeling proceeding but needs more hydration. (**k**) Lateral foot wound appearance after 2 weeks of UBM-ECM treatment with Drawtex-polyurethane sheet dressing. (**l**) Lateral foot wound appearance after 3 weeks of UBM-ECM treatment. (**m**) Healing of anterior-medial ankle wound 1 week after split-thickness skin grafting an 4 × 10 cm wound 6 weeks post-injury. (**n**) Lateral foot wound 1 week after split-thickness skin grafting 8 × 12 cm wound, 6 weeks post-injury. Total time from injury to wound closure and healed skin grafts—18 weeks. (**o**) Healed anterior-medial ankle wound appearance close-up 1.5 years after injury—size of healed skin graft—4 × 6.5 cm. (**p**) Healed lateral foot wound appearance close-up 1.5 years after injury—size of healed skin graft—5 × 10 cm. (**q**, **r**) Healed foot and ankle appearance 1.5 years post-injury. (**s**–**u**) Radiographic appearance of healed fracture. Reproduced with permission [2]

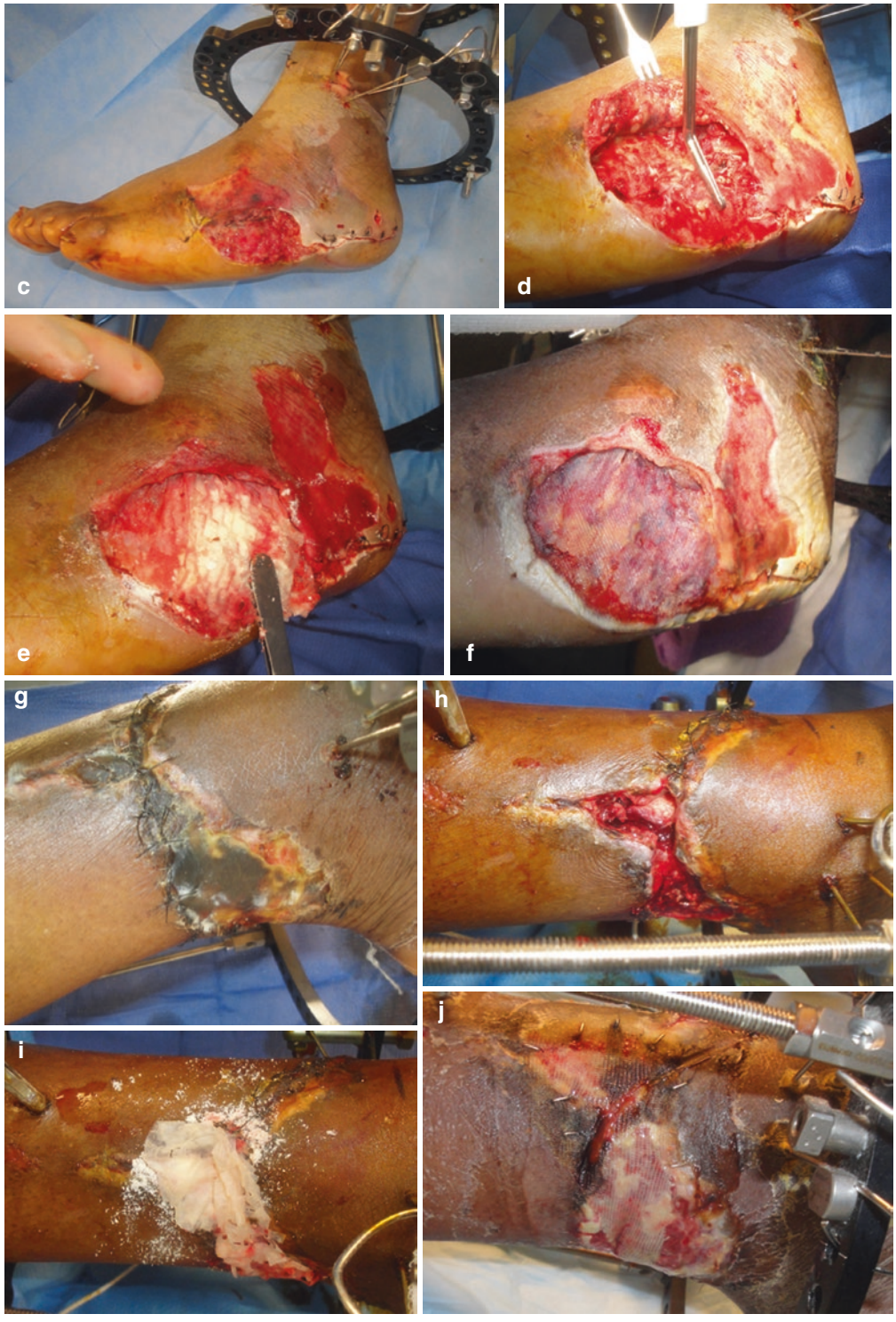


Fig. 5 continued

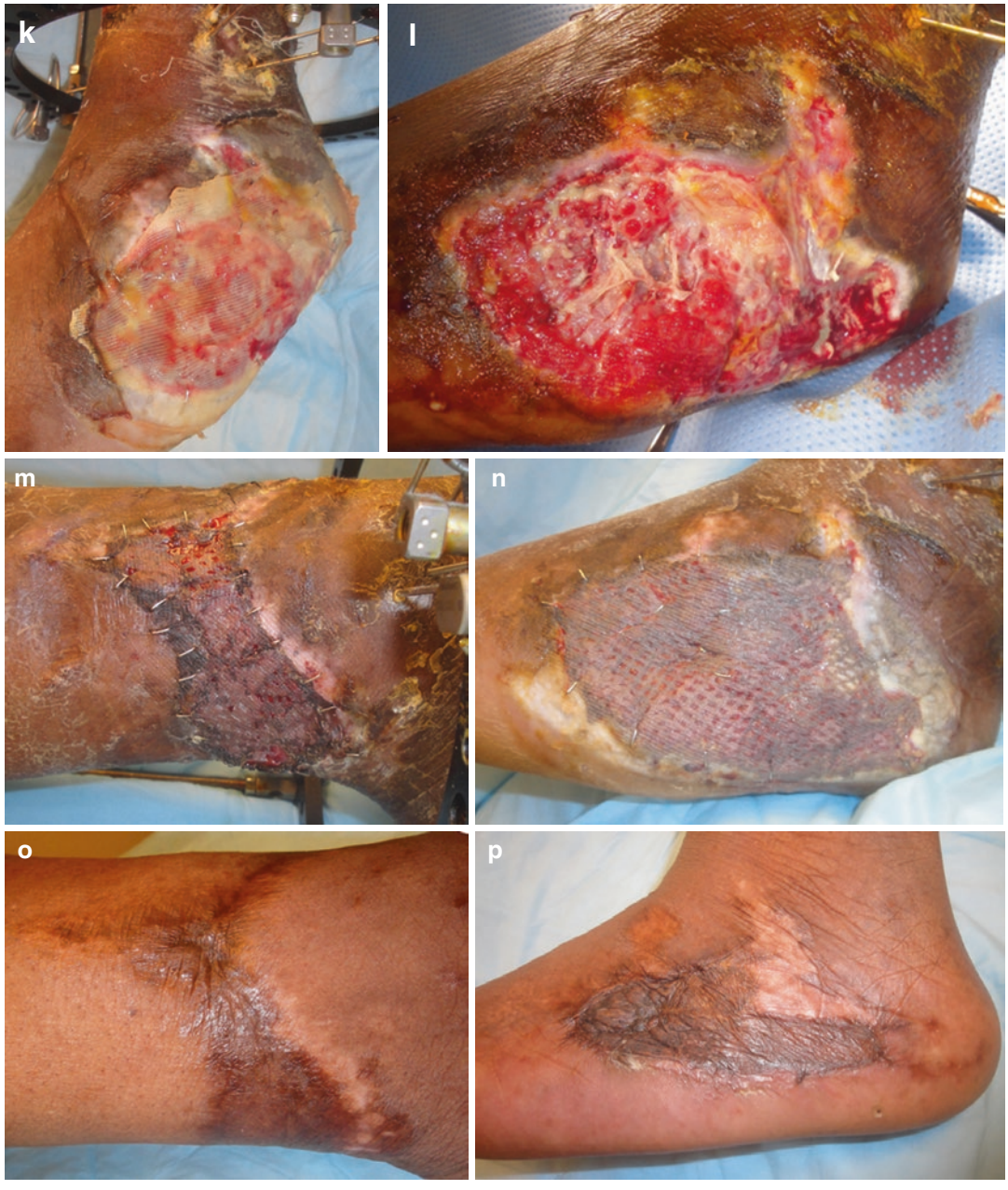


Fig. 5 continued

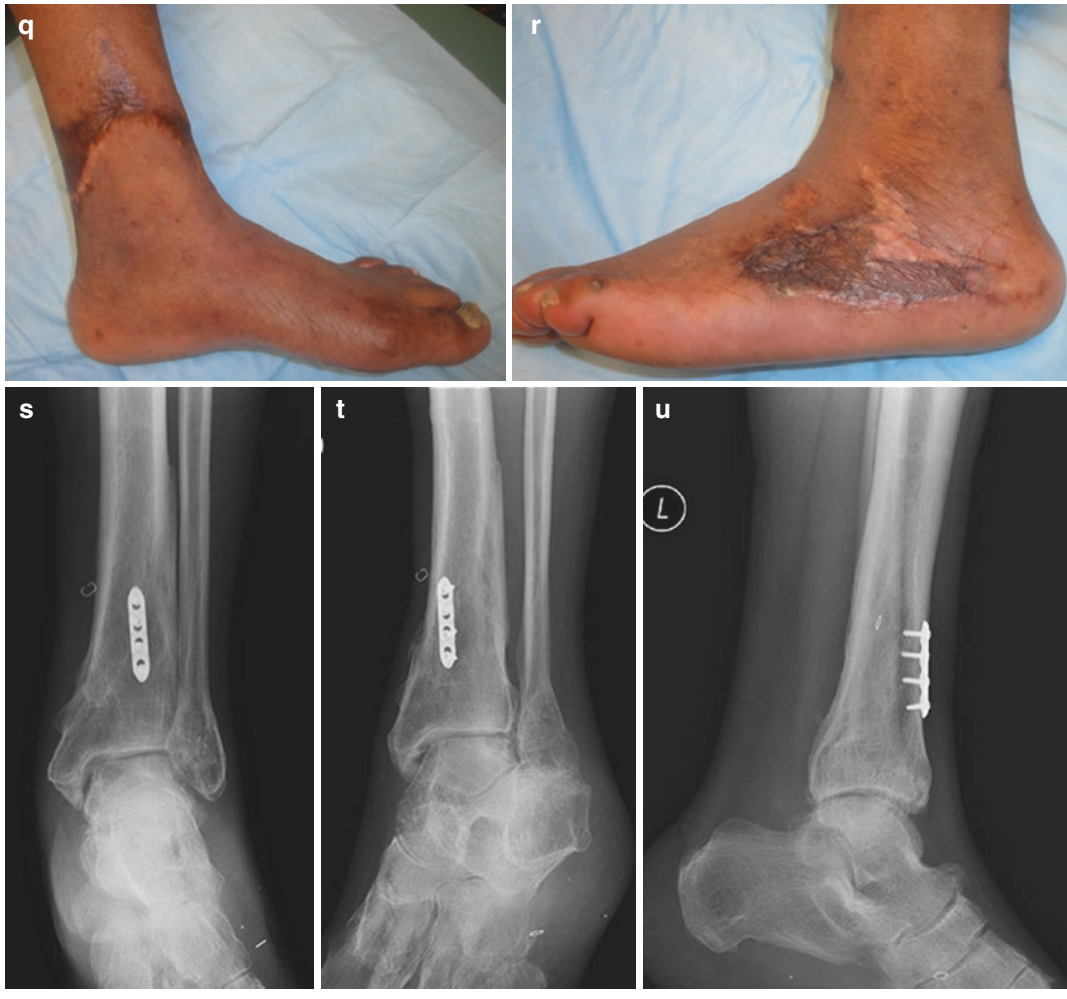
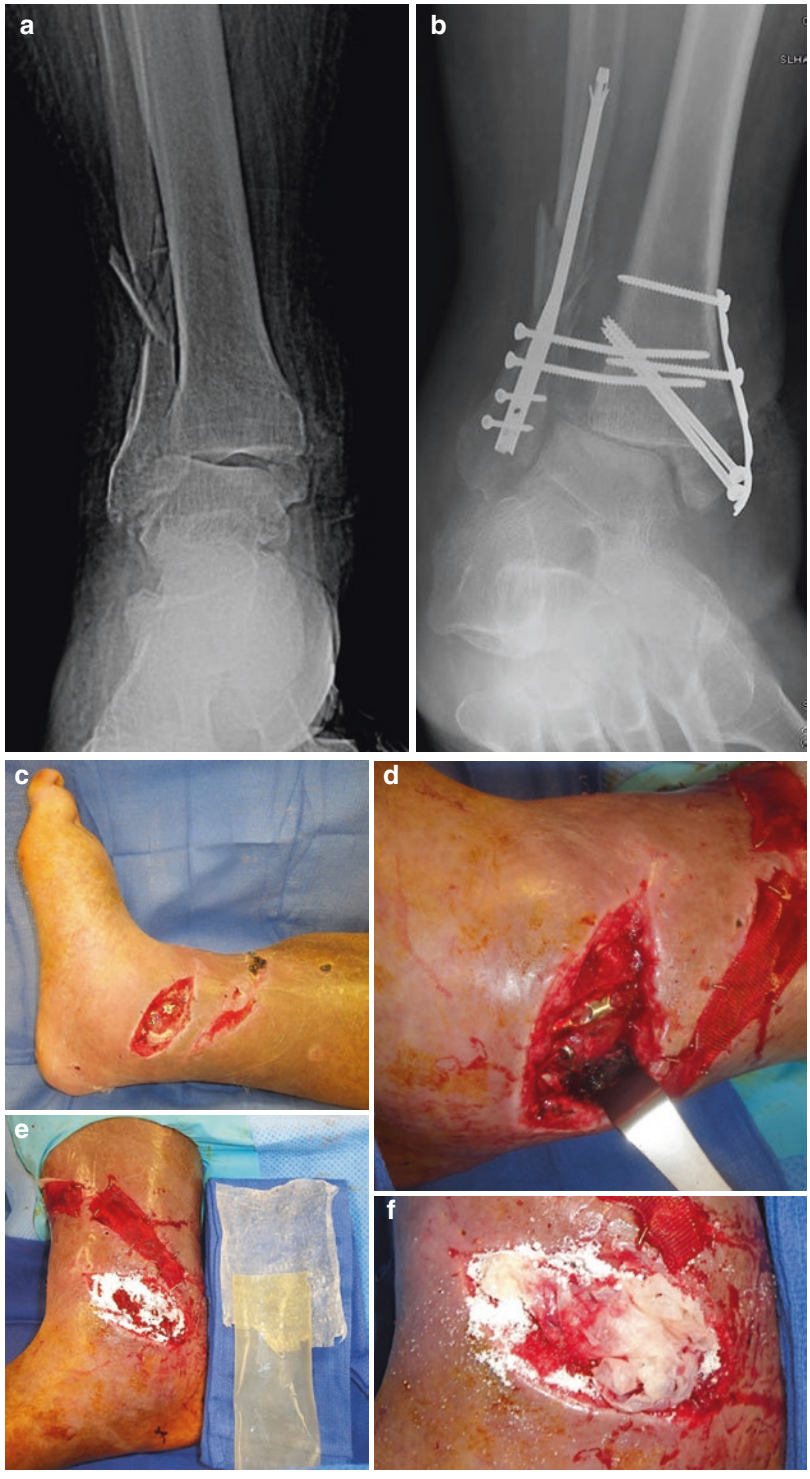


Fig. 5 continued


a
b
c
d
e
f

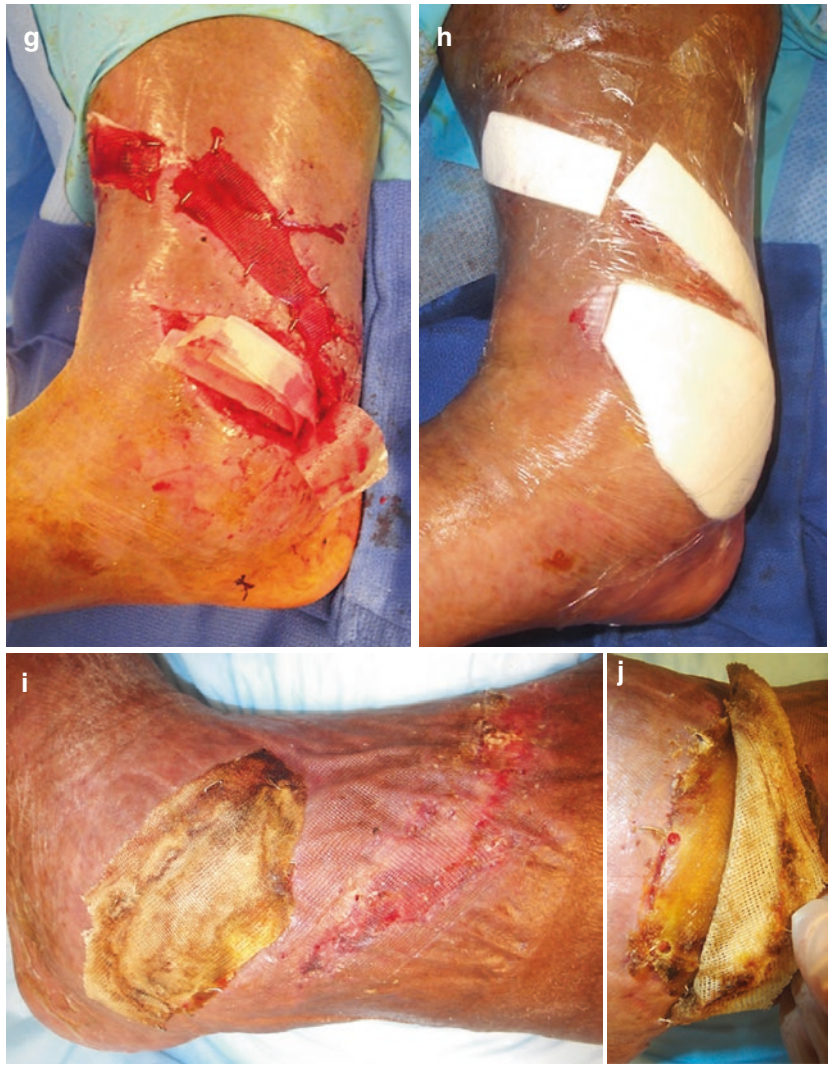


Fig. 6 continued

Fig. 6 (**a**) Initial ankle fracture X-ray of an 80-year-old obese diabetic male (BMI = 64) with asthma, COPD, and venous stasis disease who fell in his shower at home and had to be cut out of his shower for treatment. The open ankle wounds were managed for 31 days by NPWT and at time of wound consult were culture positive for *Enterobacter cloacae*, *Bacteroides fragilis*, and diphtheroid bacilli. (**b**) Orthopedic plating of ankle fracture. (**c**) Wound appearance at time of consult. (**d**) Degloving component of ankle wound. (**e**, **h**) Open wound management with the UBM-ECM. (**e**) Wound after placement of 500 mg MatriStem MicroMatrix powder and showing the 10 × 15 cm Cytal Burn Matrix and 6 × 15 cm MatriStem Surgical Matrix sheets that will be used. (**f**) Cytal Burn Matrix sheet placed filling the wound cavity. (**g**) MatriStem Surgical Matrix sheets cut into pieces and layered on wound to fill the wound cavity. (**h**) Adaptic, Drawtex, and polyurethane sheet dressing applied. (**i**) Leg appearance at 59 days—the upper wounds have healed. (**j**) Closer view of the larger wound shows the surgical sheet is adherent but too dry and needs more moisture applied for optimal activity. (**k**) Wound appearance at 30 days later—note the moist salmon pink color of the granulation tissue which is indicative of ECM-stimulated healing. (**l**) Wounds totally healed 50 days later—total time to heal from injury to closure—20 weeks. Estimated total wound care physician time for providing all of this wound care—1.5 h including three brief postoperative office visits

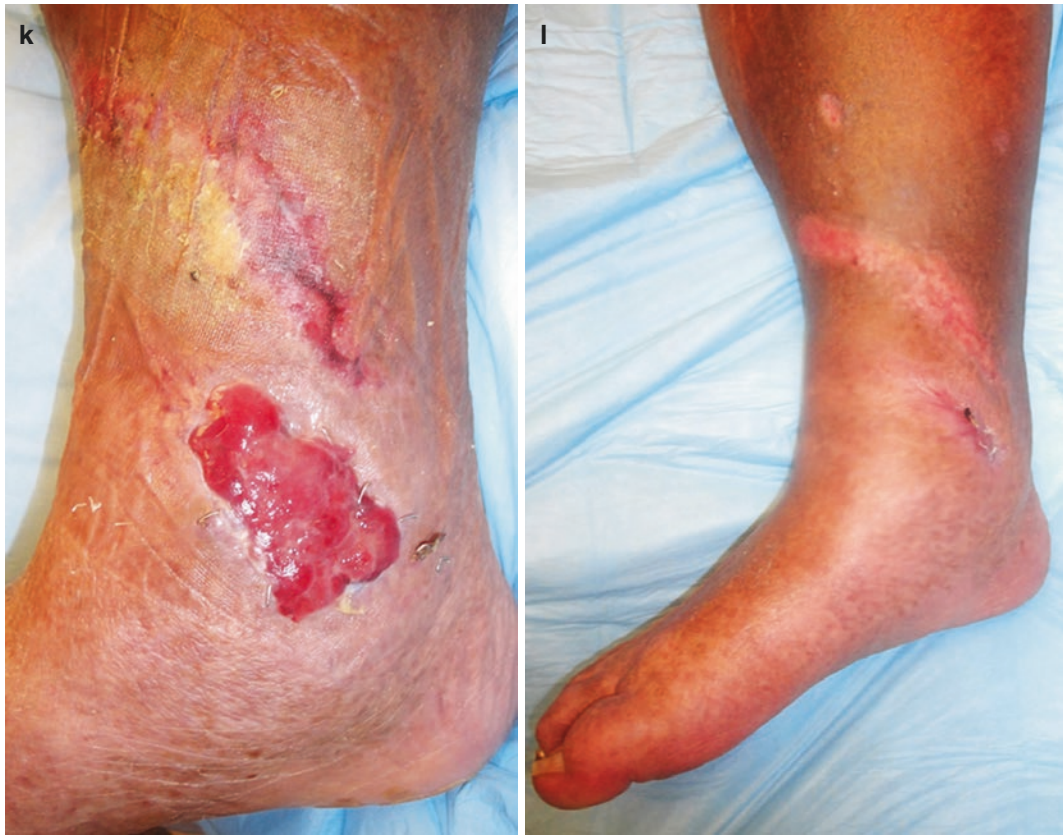
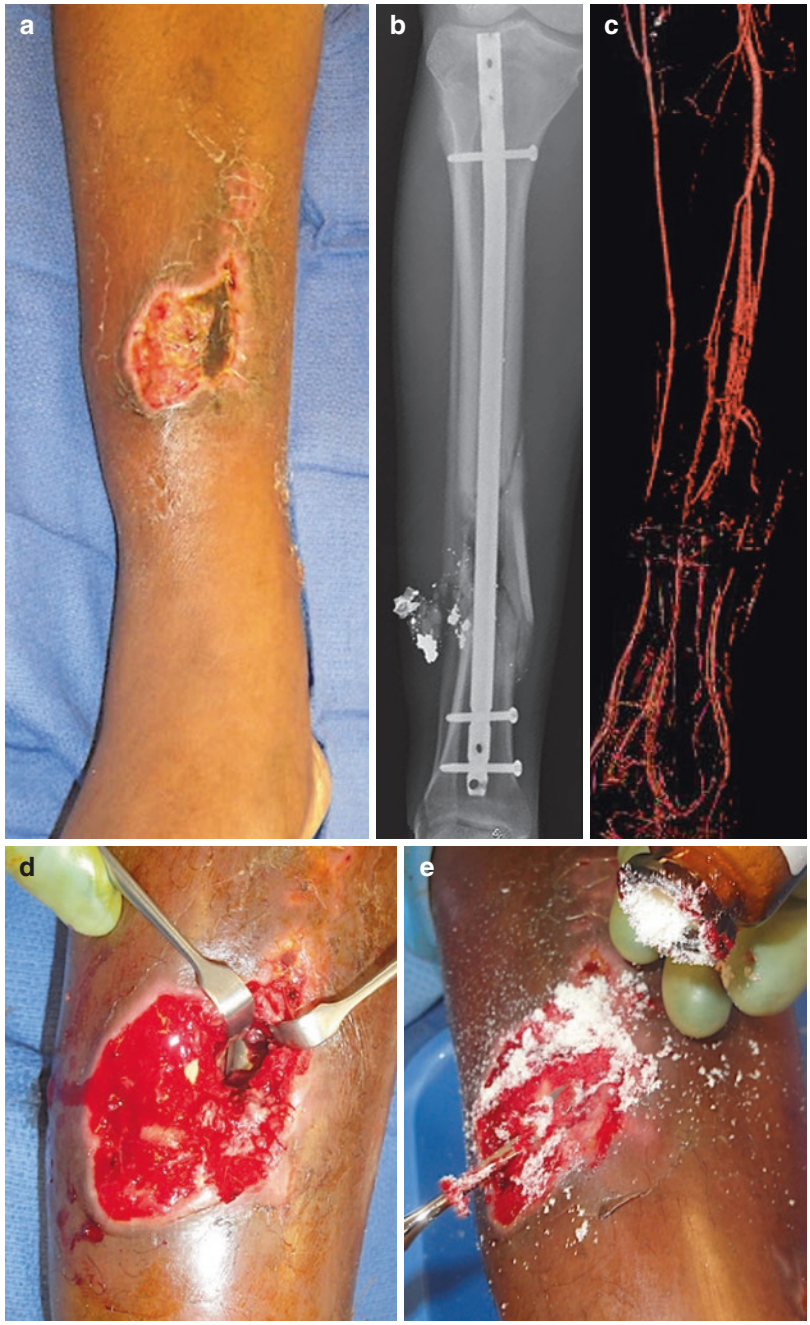


Fig. 6 continued

Fig. 7 (**a**) Wound appearance at the time of consult 20 days post-injury of a 29-year-old male with a gunshot injury to his right leg treated with an IM locking nail. The open tibial wound managed for 20 days with NPWT and the wound was culture positive for methicillin-sensitive *Staph aureus*, Group B strep, and pan-sensitive *Pseudomonas*. (**b**) Treated tibial fracture X-ray. (**c**) CT angiogram (already into venous phase) showing single posterior tibial vessel leg, arterial spasm, and distal arterial reconstitution. (**d**) Operative wound debridement showing the exposed intramedullary nail. (**e**–**h**) Operative treatment utilizing the UBM-ECM wound device: (**e**) 1000 mg MatriStem MicroMatrix powder placed liberally and packed around the intramedullary nail. (**f**) Rehydrated Cytal 10 × 15 cm Burn Matrix sheet laid on the wound and then folded into the wound with the majority placed over the tibial defect. (**g**) Rehydrated MatriStem Surgical Matrix 5 × 5 cm sheet stapled over top of the tibial wound region to secure it and the fold Burn Matrix sheet in place with a folded Adaptic sheet ready to secure all of this. (**h**) Drawtex secondary dressing covered with a large polyurethane sheet dressing. (**i**) Healthy UBM-ECM granulation tissue formation 10 days later. (**j**) Healed wound appearance at 80 days post device placement—note the good healing over the tibial nail site and the pinker site where there were retained bullet fragments remote from the open fracture. (**k**) X-ray of final healed tibial fracture. Time to healing from injury—13 weeks; time to healing from wound device placement, 10 weeks. Estimated total wound care physician time for providing all of this wound care—1 h including two brief postoperative office visits


a
b
c
d
e

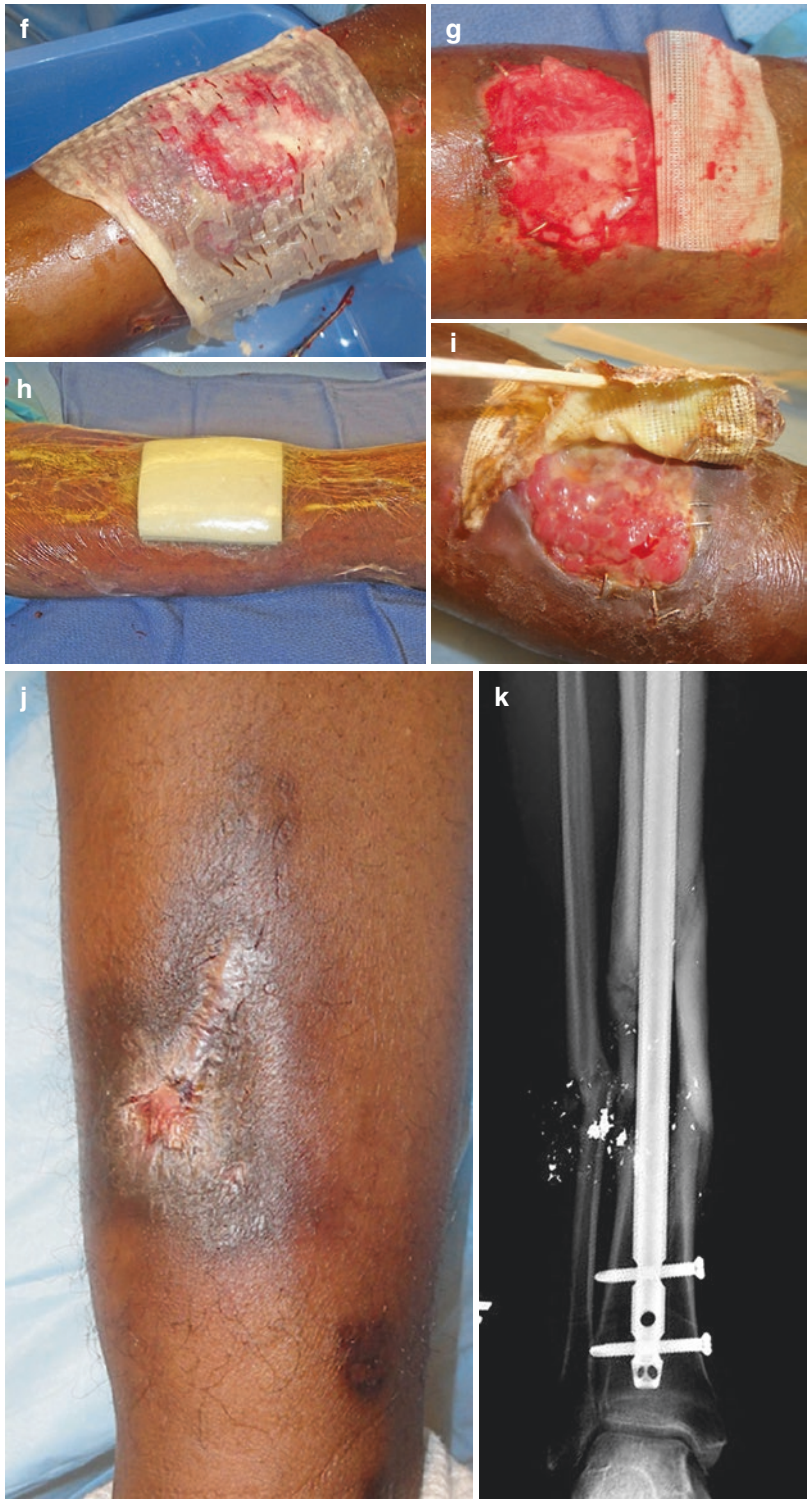


Fig. 7 continued

infected non-unions, the wounds closed over all of the exposed tendons, and the exposed hardware was retained or easily removed after the fracture healed. More importantly, once the wounds healed, the wounds remained healed. Compared to standard flap therapy [5–21], the distal limbs had a much more normal appearance and did not require subsequent revisions after healing, and the patient suffered no donor site scars other than a full- or split-thickness skin graft donor site.

This chapter first reviews the evolution of topical wound care which has lead up to this advance followed by the evolution of orthopedic fracture management that has also made this treatment advance possible. Following a summary of our reported case series, we present several clinical cases included in the reported series (Figs. 3, 4, and 5) and then more recent cases (Figs. 6 and 7) which were not part of the reported clinical series to demonstrate our evolution and present thinking regarding UBM-ECM wound device use in lower extremity trauma. We believe that the UBM-ECM wound devices have great utility whether they are used as the primary reconstructive modality or as an adjunct to standard reconstructive techniques.

2 Topical Wound Healing

Great advances have been made regarding the topical management of open wounds. Beginning with the work in the 1960s by George Winter showing that open wounds covered with a polyurethane sheet dressing had improved healing [22], the era of moist wound healing was ushered in [23]. It became appreciated that there was improved healing both in terms of the rate and quality of healing by achieving the "proper" moisture level at the wound surface. A wide variety of topical dressings with variable moisture and absorptive capacities including hydrogels, hydrocolloids, hydrofibers, alginates, foams, collagen, polyacrylates, copolymer starch, manuka honey, and oxidized regenerated cellulose alone and in various combinations have proliferated [23, 24]. Topical dressings incorporating silver and iodine have also been developed. The use of the growth factors, such as PDGF, EGF, and FGF, to promote topical wound healing showed improvements in diabetic and pressure ulcer management [25, 26] but failed to gain widespread use because of rapid enzymatic degradation and the requirement for repeated factor administration of high, nonphysiological concentrations [27].

Negative-pressure wound therapy (NPWT) was another great stride forward in topical wound management, and it has become one of the most widely used treatments for deeper open wound management [28–34]. It has been used successfully to treat open wounds previously thought to be too big or complex for topical wound management alone. It has been successfully used to treat open exposed bone and tendons alone and in conjunction with the use of Integra [21, 35–42]. The traditional NPWT dressing is changed every third day and provides a time saving by precluding daily wound care.

The reports by Burke and Yannas on their creation of an artificial bilayer skin substitute to treat major burn patient skin loss in the 1980s helped usher in the era of extracellular matrix (ECM) use [43–46]. Now, commercially available as Integra, it has had wide applications outside the field of burn surgery [47]. Janis et al. [48] even suggested the widely accepted plastic surgery reconstructive ladder be modified to incorporate this novel advance in wound management. Following the artificial Integra Bilayer Wound Matrix devices, other devices were developed from a variety of tissues (dermis, placenta, liver) including porcine small intestine submucosal (SIS) and porcine bladder (UBM-ECM) [49–62]. Bioengineered skin has also been reported (Apligraf®, Organogenesis, Inc., Canton MA) [63, 64] along with fetal fibroblast therapy (Dermagraft®, Organogenesis, Inc., Canton MA) [65]. Reimbursement limitations for wound device use coupled with the need for more reports of clinical outcomes so these wound devices are not considered "experimental" are the present impediments to more patients receiving these newer wound therapies.

Research has shown that there are a number of variables that affect a patient's biologic response to ECM wound therapy. The actual tissue source, the age of the ECM tissue source, and the preservation of the biologic integrity and three-

dimensional lattice structures during the decellularization process (used to rid the device of foreign antigens) are all critical factors regarding the biologic wound healing response elicited [66–68]. Depending on the tissue source density, thickness, and complexity, the duration and intensity of the decellularization process varies. While decellularization of an acellular dermal matrix may involve up to a week of processing with a variety of chemicals including harsh detergents, the UBM-ECM tissue only requires agitation in mild acids, salt solutions, and water and can be processed in as little as 1 day. Each additional chemical used in the decellularization process has an effect on the ultimate ECM biologic activity, and this can ultimately impact the host response to the device [69, 70].

The UBM-ECM, derived from the porcine tunica propria layer of the urinary bladder of an approximately 6-month-old pig, has an intact basement membrane layer along with a diverse biochemical composition, which is preserved during the decellularization process [62, 71]. The UBM-ECM is one of most completely characterized ECM wound devices [72] and is commercially available in multiple formations ranging from a micronized powder to a bilayer lyophilized sheet and a three- to eight-layer vacuum-pressed sheet of varying sizes (Figs. 2, 3, 4, 5, 6, and 7). Experimental histology evaluation of the observed remodeled scaffold has shown that there is an increased M-2 macrophage presence relative to the M-1 macrophages, which is associated with the deposition of site-appropriate tissue in a number of body locations [57, 59]. The robust remodeling response along with the multiple available UBM-ECM formulations led us to consider its use as the primary reconstructive modality to treat patients with multiple medical comorbidities and challenging lower extremity wounds.

3 Evolution of Orthopedic Management of Lower Extremity Injuries

Over this same period, orthopedic fracture management evolved leading to improved fracture healing as well as less treatment-related injury to the bone, its blood supply, and wound bed. Beginning in the 1950s, the study group, Arbeitsgemeinschaft für Osteosynthesefragen (AO), proposed fracture management principles which grew to dominate the orthopedic management of long bone fractures [72]. The dynamic compression plate (DCP) with its oval holes provided stability and compression at the fracture line, minimized callus formation, facilitated immediate neighboring joint mobilization, and became the implant of choice for the next two decades [73, 74]. Clinical and laboratory observations, however, revealed that stress protection under the plate led to cortical bone loss and possible refracture following its removal. Plate removal after as long as 20 months after healing still led to significant refracture with failure occurring where bone bridging was absent. It was felt the contact of the plate with the outer cortical bone decreased its perfusion and led to outer cortical bone necrosis. Limited contact dynamic compression plates (LC-DCP) were introduced in the early 1990s which limited the bone-plate contact by over 50% and shifted the emphasis from mechanical fixation to biological fixation. Nevertheless, subsequent studies showed little improvement in the biomechanics or cortical blood flow [75]. The introduction of locking compression plates (LCP) and point contact devices in 2000 further reduced contact between the plate and the bone and is useful in treating fractures with significant osteoporosis and comminution. The evolution of pre-shaped LCP plates has shown great utility in treating fractures adjacent to joints. The less invasive stabilization system (LISS) is being used to achieve minimally invasive percutaneous osteosynthesis (MIPO) by having the screws lock into the plate tightly and not cause the bone-plate friction caused by the compression screws (Fig. 6). Closed intramedullary fixation with or without locking screws has been extensively used with an aim to protect fracture hematoma and preserve periosteal blood supply (Fig. 7) [76, 77]. In addition, the use of Ilizarov-type devices along with selective miniplate(s) to control the major fracture segments has led to less operative injury to the already injured wound bed (Fig. 5). This emphasis on the blood supply to the bone and the surrounding soft

tissue envelope with a greater respect of the biologic tissue support of the fractures has meant that the wound bed potentially has a greater chance of healing. With regard to our reported series, I fully recognize that much of our success in treating these complex wounds is in attributable to working with very skilled orthopedists who respect the biology of the bone and wound bed [78] and use the latest orthopedic devices.

4 Wound Bed Preparation

Proper wound bed preparation, the cornerstone of modern wound healing, encompasses removing obviously necrotic tissue, putting the wound in bacteriological balance, and ensuring a wound surface with vascularized tissue, all of which support topical wound healing [79]. In our practice, prior to UBM-ECM placement, if the initial orthopedic post-debridement wound culture is positive for organisms, the patient's initial IV antibiotic prophylaxis is appropriately adjusted, the wound is managed with NPWT, and the patient undergoes serial alternate day wound debridements and irrigation until the cultures become negative [78]. Our UBM-ECM wound bed treatment protocol involves initial judicious excisional debridement of the wound bed tissues including bone and tendon with scalpel, scissors, or hydrosurgical debridement (Versajet II, Smith & Nephew, Hull, UK). All intra-tendinous sutures are removed, and exposed orthopedic hardware that is providing solid bony fixation is left intact. While high-speed burrs may be initially employed in removing devitalized bone, the terminal debridement of exposed bony surfaces is performed with low energy techniques such as curettes or rongeurs. Wounds with exposed bone must demonstrate some degree of bone bleeding from the exposed bone, while wounds associated with mobile tendons or tendons lacking surrounding tissues are immobilized and supported until tissue reforms around the tendons. The decision to retain exposed hardware depends on the wound bed tissue interaction with the hardware and the bone, the stability of the fixation, and the type of plates and screws used.

5 UBM-ECM Wound Treatment

The foundation of UBM-ECM wound management is the use of a generous amount of the MicroMatrix® powder coating the entire margin of the wound with extra amounts placed in regions of anticipated slower or problematic healing. This should be pressed into the wound bed so that it remains where it is placed as additional layers of the bilayer Cytal Burn Matrix and/or the six-layer Cytal Wound Matrix sheet dressings are added. We then fill the wound cavity with the rehydrated sheet dressings using the multilayer Wound Matrix sheet sutured into the wound as the outermost layer to help retain the other formations within the wound bed (Figs. 3, 5, 6, and 7). Next, we secure the UBM-ECM in the wound with either Adaptic or Mepitel stapled or sutured over the wound as added protection to ensure the device is retained in the wound. Finally, we try to close as much of the wound margin skin as possible over the MatriStem devices so as to maximize the interaction of as much of the wound bed with the wound device and promote maximal constructive remodeling.

6 Secondary Dressings

Adaptic® (Johnson & Johnson, New Brunswick, NJ) or another suitable dressing such as Mepitel® (Mölnlycke Health Care AB, Göteborg, Sweden) is utilized to keep the wound device retained in the wound and opposed to the wound bed. These dressings help retain the body's local moisture and the ingress or egress of additional fluids. Additional secondary dressing bulk may be needed for deeper wounds in which case we have used sheets of Telfa, Allevyn (Smith & Nephew Medical Limited, Hull, UK), or Drawtex® (SteadMed®, Fort Worth, TX) under a polyurethane sheet dressing. With significant bacterial colonization or infection concerns, we have employed Acticoat 7 (Smith & Nephew Medical Limited, Hull, UK), Silverlon Burn Dressing (Argentum Medical, LLC, Geneva, IL), or V.A.C. GranuFoam Silver® (Acelity, San Antonio, TX) directly over the retaining Adaptic or Mepitel dressing. With wounds draining 30 mL or more

per day, we have used NPWT until the daily drainage amount is lessened. These dressing are then changed every 2–3 weeks in the office when additional UBM-ECM may also be added if further volume is desired and prior material has been remodeled into the wound bed. It is important not to debride existing product from the wound surface, as this can slow the healing process. Excess fluid leakage that may occur from under the polyurethane sheets is easily managed with an outer absorptive dressing changed periodically at home as needed. Occlusive wound management concerns of periwound maceration and significant bacterial overgrowth has not been observed in our patients.

7 Clinical Series Report

We have previously reported on our clinical experience with 13 patients with foot or lower third extremity wounds involving their tendons and 9 lower third or foot fracture patients with 11 open wounds [1, 2]. The medical comorbidities of the patients were as follows: culture-positive wounds 82%, smoking 41%, diabetes mellitus 36%, leg edema/venous stasis 27%, significant peripheral vascular disease 14%, and BMI >35–9%. Two patients had end-stage renal disease on hemodialysis and one patient each had congestive heart failure, advanced cirrhosis, coronary artery disease with prior myocardial infarction, and active atrial fibrillation on anticoagulation and one patient was anticoagulated with a pulmonary embolism. One Achilles wound patient was on immunosuppression for a prior pancreas and kidney transplant. The time of initial UBM-ECM treatment relative to the date of injury varied depending upon when the patient was referred and when the patient agreed to comply with the treatment regimen of no cigarette smoking, leg elevation, and limited tendon motion. Appropriate oral or IV antibiotics were administered based on clinical cultures and continued until wound healing progressed to closure over exposed tendon, bone, or hardware.

Wound debridement was done as described above, and all wounds received a topical application of MicroMatrix powder to the wound bed and tendons, around the hardware, and into the remaining interstices. Earlier patients then had two-, three-, or six-layer vacuum-pressed MatriStem Surgical Matrix sheets (now marketed under the name Cytal Wound Matrix) applied (Figs. 3 and 4), while later patients had the two-layer lyophilized Cytal Burn Matrix sheet applied in place of or along with the vacuum-pressed sheets (once the Burn Matrix formulation became clinically available) (Fig. 5). Experience led to placement of more UBM-ECM into the wound at the time of the initial surgery in the later patients (Figs. 6 and 7). The UBM-ECM devices were placed such that the wound was filled to skin level, and in some cases, the skin was closed over the UBM-ECM. Examples of the volume of the MicroMatrix powder, rehydrated Burn Matrix, and surgical sheet are seen in Fig. 2. When used in combination, the MicroMatrix powder was used to coat the wound bed; the rehydrated Burn Matrix was then applied over the MicroMatrix, followed by the rehydrated six-layer vacuum-pressed sheet which was oriented with the basement layer facing outward as the outermost layer. The wound device was retained in the wound with sutures or staples and an occlusive type dressing placed over the wound to keep it moist. The subsequent care involved NPWT for the moister wounds or hydrofiber or hydrogels for the drier wounds. Earlier patients were observed in the clinic more frequently due to concerns about potential complications, but as our experience increased, patients were observed less frequently. Tendon wound patients had the tendon movement limited until the tendon was covered with tissue. Specifically, the open Achilles tendon wound patients had their active tendon excursion limited by external pin fixation systems, ankle immobilizers, or healing ankle-foot orthosis (AFO) boots. Patients were offered a split- or full-thickness skin graft to close the wound once the wound had a sufficiently vascularized tissue base and the remaining open wound size would require several weeks for final re-epithelialization or thicker skin coverage was desired.

The number of applications of UBM-ECM in the tendon group was as follows: Achilles tendon

wounds, 1–3 (average 1.83, median 2); tibialis anterior tendon wounds, 1–2 (average 1.2, median 1); and peroneus longus and brevis tendon wound, 1 treatment. The time from initial UBM-ECM wound device application to wound closure varied from 6 to 78 weeks with the larger wounds requiring longer healing times. All of the wounds achieved closure despite a variety of positive cultures at time of initial UBM-ECM application. In the exposed Achilles wound group, healing times ranged from 7 to 78 weeks (average 33 weeks, median 28 weeks). In the exposed tibialis anterior tendon group, healing was achieved by 6–18 weeks (average 11 weeks, median 9 weeks). The peroneus tendons patient's wound closed in 14 weeks. Time to skin graft application after initial UBM-ECM device placement ranged from 3.5 to 16 weeks overall (average 10 weeks, median 11 weeks). Two of six Achilles wounds were ultimately grafted at 5 and 16 weeks after UBM-ECM placement. Three of five exposed tibialis anterior tendon wounds were grafted 3.5–15 weeks after initial UBM-ECM device placement (average 8 weeks, median 5 weeks).

A majority of fracture wound patient (70%) had multiple UBM-ECM treatments with a range of 1–4 (average 1.7, median 2) treatments. Multiple UBM-ECM device applications were more common in larger wounds and with earlier treated patients while gaining experience with the use of the device. Complete wound healing occurred in these patients over a range of 16–42 weeks (average of 26.5 weeks, median 25 weeks) after initial UBM-ECM device placement. Half of these wounds heal without subsequent skin grafting, while the time to skeletal healing from the last orthopedic fixation ranged from 12 to 40 weeks (average 26.1 weeks, median 30 weeks). All patients achieved normal leg contours, and no patient required later wound revision except the one patient who opted for a BKA (vide infra). Four fracture patients required long-term compressive stockings for edema control.

The following complications were observed in four patients:

One heavy smoking patient with a severely comminuted open distal tibia fracture required readmission for 2 days of intravenous antibiotics to treat a superficial cellulitis 3 weeks prior to his wound completely closing, and he had a successful secondary bone grafting procedure for fracture stabilization.

One severe ankle fracture patient who was not treated with UBM-ECM until post-injury day 112 had uncontrolled chronic ankle pain with ambulation, so she opted for a below-the-knee amputation at post-op month 24 for pain relief.

One fracture patient expired from her overall poor post-traumatic cardiopulmonary status.

One Achilles wound patient with bilateral venous stasis disease redeveloped a small wound during a venous stasis ulcer flaring episode shortly after initial healing that subsequently healed with leg compression and standard topical wound care.

8 Discussion

Advances in the treatment of distal open orthopedic leg fractures and injuries coupled with a deeper understanding of the biology of wound healing has allowed us to rethink our standard soft tissue reconstructive techniques of the complex distal leg patients. The present retrospective studies show that UBM-ECM wound devices facilitate wound healing in open, traumatic, lower extremity wounds involving exposed fractures, hardware, tendons, and positive bacterial cultures [1, 2]. We also have found the UBM-ECM wound devices, when employed early, seem to limit the zone of injury and overall regional wound swelling which favorably allows for local tissue salvage. We showed that exposed orthopedic hardware can be managed with UBM-ECM and either heal the wound or provide more simplified wound management until the fracture heals allowing plate removal in the case larger ankle plates. Exposed tendons in these lower extremity wounds with their frequent associated desiccation, marked epitenon inflammation, and drainage can now be more reliably salvaged with UBM-ECM wound device use (Fig. 4). We showed the UBM-ECM performs well in wounds that are culture positive but not grossly infected

(Figs. 3, 4, 5, 6, and 7) [1, 2]. The history of orthopedic fracture fixation highlighting the biology of the bone-plate healing was included in this review because if faced with older orthopedic plate exposure, we would base our decision of hardware removal upon the type plate, the quality of the solid fixation achieved, and the host response of the surrounding tissues to both the plate and bone.

We now feel that regional or free flaps are no longer the sole, primary modality for treating all major distal lower extremity wounds but rather a more exigent technique that should be used when more rapid closure is needed or a flap can be easily done. All tendon patient's wounds remained healed once solid healing occurred, and all but the one fracture patient that expired from poor health had fracture healing without bony infection despite the more prolonged time of open wound management. We found the assumed need for rapid early wound closure less imperative with the use of ECM devices that promote a constructive remodeling healing response. Also, our present series suggests that the earlier one uses the device the faster the wound heals.

The UBM-ECM wound devices are available in several formulations, and there is great utility in placing a combination of the formulations in the wound at the time of the initial operative debridement (Figs. 2, 3, 4, 5, 6, and 7). UBM-ECM wound devices are tissue-derived scaffolds that are minimally processed to preserve the complex biochemical, which is thought to facilitate the constructive remodeling response by the patient [68]. The MicroMatrix powder appears to facilitate the most robust healing response but only for a period of days, likely due to the increased surface area of the device. The Cytal Multilayer Burn Matrix facilitates more sustained healing in the wound bed and can persist for several weeks depending upon the volume used. This lyophilized UBM-ECM sheets used to make Cytal Burn Matrix are the same sheets that are ground to product the MicroMatrix powder (Fig. 2). The Cytal Wound Matrix vacuum-pressed sheets have a longer multi-week period of persistence as the wound fills in and incorporates the device into the wound bed. UBM-ECM has shown efficacy in both acute and chronic wound healing by facilitating the body's ability to produce site-specific, constructively remodeled tissue [56, 60, 70–82]. The amount of the wound device we place is based on size or volume of the wound and the author's experience as to the expected time it will take for the wound to heal (Figs. 2, 6, and 7). While earlier patients had more serial device placements, our more recent patients have been managed with sufficient device placement at the initial procedure to see the wound through to total healing (Figs. 6 and 7).

ECM wound device healing occurs as the wound device is broken down and replaced with the host's native tissues in a process referred to as constructive remodeling, a term used to connote that the formed tissue is not identical to but a close facsimile of the missing tissue. As host cells degrade the ECM, the newly generated peptide fragments referred to as matricryptic peptides, matricryptins, or matrikines exert potent bioactivity with their newly exposed adhesions sites [83, 84]. The principle of matricryptic peptides forming from a parent protein molecule is well established and has led to the study of anti-angiogenic peptides from collagen for the treatment of cancer and study of antimicrobial behavior in peptides from alginate from shellfish. In general, these shorter fragments have biologic responses that are distinct from, and often more potent, than those of the parent molecule. Further, the peptides regulate a wide variety of injury and healing processes including angiogenesis, antiangiogenesis, migration, differentiation, adhesion, as well as the associated antimicrobial activity. It is this antibacterial property specifically identified in the degradation products of UBM-ECM [80, 85] which we believe allowed for the observed successful wound healing we report in our infected patient's wounds.

It has also been noted that many of the fundamental processes that occur during the ECM-mediated tissue repair process are similar or identical to those which occur during prenatal tissue development and growth but would otherwise be absent or at least inhibited during the normal

repair processes which occur following tissue injury in postnatal mammals [82]. We believe that it is this improved healing, induced by the UBM-ECM wound device, that is the source of the ongoing improvements we have observed in many of our UBM-ECM healed wounds post wound (Figs. 4 and 5).

UBM-ECM device use requires an appreciation of the differences in the appearance of the treated wound bed. As the ECM is constructively remodeled in the wound, UBM-ECM becomes incorporated into the healing wound surface and may have the appearance of wound slough or adherent exudate (Figs. 3, 4, 5, 6, and 7). Classical wound management experience would suggest this apparent wound slough or adherent exudate should be removed from the wound surface as it will limit wound bed granulation formation and promote bacterial colonization. Our UBM-ECM experience shows that the adherent ECM matrix is desired and promotes the formation of a salmon pink, moist, cobblestone appearing, granulation tissue (Figs. 6 and 7) which is subtly different from the granulation tissue produced with standard topical moist wound healing treatments. It is important that ancillary care providers appreciate that these wounds do not need debridement but instead need to be kept moist and undisturbed. With later healing stages, any exuberant granulation tissue that extends beyond the skin margin of the wound can be easily managed with topical silver nitrate application.

The overall management of wounds with UBM-ECM has proven to be less complex and time consuming than traditional topical wound care or long-term NPWT regimens. We presently recommend UBM-ECM wound device placement as soon after injury as possible. In the early wound management period when there is more copious drainage, NPWT is often employed. After 1–3 weeks, less complex management regimens can typically be designed that allow for simple daily home care by placing an absorptive layer around the outermost wound dressing to handle the smaller amount of excess fluid draining under a polyurethane sheet dressing. Also, after the wound bed is treated with the layered UBM-ECM wound devices, the patient experiences much less wound care pain as the actual wound bed can be left untouched for several weeks at a time (Figs. 5, 6, and 7). The periodic addition of moisture to the wound via hydrogel or tubing placed into the dressing is easily performed and well tolerated. When concerns about infection arise, silver-releasing dressings such as described above have been added to the topical dressing layer with success. An ongoing remodeling and softening of the wound is noted with progressive skin mobility after final closure. When healed, the normal appearance and contour of the leg allows for more optimal edema control.

The time to achieve a healed wound in these patients was more prolonged than traditional pedicle or free flap procedures and more similar to that achievable with NPWT alone. However, the use of UBM-ECM device is less manpower intense, was applicable to all patients, avoided frequent dressing changes, and in many cases avoided skin graft donor site(s) (Figs. 6 and 7). The observed favorable healing in our UBM-ECM series is due to M-2 macrophage phenotype predominance experimentally shown after ECM application [57, 58]. None of these patients required wound revisions, which is not infrequent with flap-based wound management. The patients' limb contour was excellent and in most cases exceeded that possible with flap management. Distal limb edema was easily control with standard compression hosiery, and with little wound manipulation, patients reported minimal wound discomfort during ECM wound treatment. There is also significant wound remodeling that occurs following the initial wound closure (Figs. 4 and 5). The ability of the UBM-ECM devices to manage large complex wounds now makes the management of these wounds possible in most medical facilities that can perform a wound debridement and skin grafts. In addition, there can be a great reduction in the time requirement needed to provide wound care to medically complex patients (Figs. 6 and 7) treated after the reported series case collection.

Our clinical experience with UBM-ECM has taught us the following lessons:

1. Wounds respond very well to the MicroMatrix powder; the more the better.
2. The wound surface should be coated with powder with a thicker layer applied over exposed bone, hardware, and tendons.
3. UBM-ECM performs best in a moister environment than is traditionally achieved with topical moist wound healing regimens. Wounds draining in excess of 30 mL/day are best managed with a NPWT device, while lesser amounts are managed with dressings which transfer fluids away from the wound such as an Allevyn, Drawtex, or some other dressings mentioned above.
4. Tendons must be immobilized in the wound bed until they are incorporated into the wound bed.
5. UBM-ECM wound devices should be mechanically retained in the wound with staples or sutures and then further retained in the wound with a petroleum-impregnated dressing or silicone-meshed sheet dressing.
6. Management of deeper wounds often requires placement of multiple formulations of the UBM-ECM wound devices which we now place at the initial operative procedure in sufficient quantity to promote either complete closure of the wound or healing up to the skin surface level for skin graft closure.

Conclusions

We report a positive experience with UBM-ECM device use in managing open lower leg wound exposed tendons and fractures with or without exposed hardware in non-ideal flap patients. No wound was too large for ECM treatment, and there is no concern treating single-vessel leg wounds or patients with severe cardiopulmonary compromise or other medical comorbidities. The patients were spared flap-associated anticoagulation, arteriograms, dangling protocols, ICU care, frequent monitoring, and need for emergent OR "take backs" that are associated with flap treatment. With experience, we have found this management to be a less time-intense, resource-requiring treatment for managing patients with these complex wounds.

This method of wound management is reliable with the best results occurring with earlier wound device use. Clinical benefits include operative cases that are short and easy to perform, a high degree of patient acceptance and comfort, and durable wound healing. While flap closure of major distal lower extremity and foot wounds is the present accepted standard of care, the present case series showed that UBM-ECM wound treatment may provide a reasonable alternative to these more complex operative procedures. We believe that UBM-ECM wound devices have a demonstrated utility whether they are used as the primary reconstructive modality or as an adjunct to standard reconstructive techniques.

References

1. Geiger SE, Deigni OA, Watson JT, Kraemer BA (2016) Management of open distal lower extremity wounds with exposed tendons using porcine urinary bladder matrix. Wounds 28(9):308–316
2. Kraemer BA, Geiger SE, Deigni OA, Watson JT (2016) Management of open distal lower extremity wounds with concomitant fracture using porcine urinary bladder matrix. Wounds 28(11):387–394
3. Integra™ Bilayer Wound Matrix Treatment Guidelines-Collagen Soft Tissue Technology. (2010) Integra Life Sciences Corp, Plainsboro, NJ
4. Valerio IL, Campbell P, Sabino J, Dearth CL, Fleming M (2015) The use of urinary bladder matrix in the treatment of trauma and combat casualty wound care. Regen Med 10:611–622
5. Ger R (1970) The management of open fractures of the tibia with skin loss. J Trauma 10:112–121
6. Byrd HS, Spicer TE, Cierney G (1985) Management of open tibial fractures. Plast Reconstr Surg 76:719–730
7. Godina M (1986) Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg 78:285–292
8. Yaremchuk MJ, Brumback RJ, Manson PN, Burgess AR, Poka A, Weiland AJ (1987) Acute and definitive management of traumatic osteocutaneous defects of the lower extremity. Plast Reconstr Surg 80:1–14
9. Arnez ZM (1991) Immediate reconstruction of the lower extremity—an update. Clin Plast Surg 18:449–457
10. Francel TJ, Vander Kolk CA, Hoopes JE, Manson PN, Yaremchuk MJ (1992) Microvascular soft tissue transplantation for reconstruction for reconstruction of acute open tibial fractures: timing of coverage and long-term functional result. Plast Reconstr Surg 89:478–487

11. Pollak AN, McCarthy ML, Burgess AR (2000) Short-term wound complications after application of flaps for coverage of traumatic soft tissue defects about the tibia. The lower extremity assessment project (LEAP) study group. J Bone Joint Surg 82-A:1681–1691
12. Weitz-Marshall AD, Bosse MJ (2002) Timing of closure of open fractures. J Am Acad Orthop Surg 10:379–384
13. Ong YS, Levin LS (2010) Lower limb salvage in trauma. Plast Reconstr Surg 125:582–588
14. Hohmann E, Tetsworth K, Radziejowski MJ, Wieniewski TF (2007) Comparison of delayed and primary wound closure in the treatment of open tibial fractures. Arch Orthop Trauma Surg 127:131–136
15. Pollack AN, McCarthy ML, Burgess AR (2000) Short-term wound complications after application of flaps for coverage of traumatic soft tissue defects about the tibia. The lower extremity assessment project (LEAP) study group. J Bone Joint Surg 82-A:1681–1691
16. Kumta SM, Maffulli N (2003) Local flap coverage for soft tissue defects following open repair of Achilles tendon rupture. Acta Orthop Belg 69:59–66
17. Wei ZR, Sun GF, Wang DL, Tung XJ (2014) Reconstruction of the Achilles tendon and overlying skin defect. Ann Plast Surg 73:325–329
18. Iorio ML, Han KD, Evans KK, Attinger CE (2015) Combined Achilles tendon and soft tissue defects. Ann Plast Surg 74:121–125
19. Nazerali RS, Hakimi M, Giza E, Sahar DE (2013) Single-stage reconstruction of Achilles tendon rupture with flexor hallucis longus tendon transfer and simultaneous free radical fasciocutaneous forearm flap. Ann Plast Surg 70:416–418
20. Osman S, Chou S, Rosing J, Sahar DE (2013) Total posterior leg open wound management with free anterolateral thigh flap: case and literature review. Eplasty 13:425–442
21. Attinger CE, Ducic I, Hess CL, Basil A, Abbruzzesse M, Cooper P (2006) Outcome of skin graft versus flap surgery in the salvage of the exposed Achilles tendon in diabetics versus nondiabetics. Plast Reconstr Surg 117(7):2460
22. Winter GD (1962) Formation of a scab and the rate of epithelialization of superficial wounds in the skin of the young domestic pig. Nature 193:293–294
23. Field CK, Kerstein MD (1994) Overview of wound healing in a moist environment. Am J Surg 167:2S–6S
24. Sood A, Granick MS, Tomaselli NL (2014) Wound dressings and comparative effectiveness data. Adv Wound Care (New Rochelle) 3:511–529
25. Cross KJ, Mustoe TA (2003) Growth factors in wound healing. Surg Clin N Am 83:531–545
26. Leahy PJ, Lawrence WT (2007) Biologic enhancement of wound healing. Clin Plast Surg 34:659–671
27. Borena BM, Martens A, Broeckx SY, Meyer E, Chiers K, Duchateau L, Spaas JH (2015) Regenerative skin wound healing in mammals: state-of-the-art on growth factor and stem cell based treatments. Cell Physiol Biochem 36:1–23
28. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 38:553–562
29. Argenta LC, Morykwas MJ (1997) Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg 38:563–576
30. Sibbald RG, Mahoney J (2003) Use of vacuum-assisted closure in chronic difficult-to-heal wounds. Ostomy Wound Manage 49(11):52–66
31. Lee HJ, Kim JW, CW O, Min WK, Shon OJ, JK O, Park BC, Ihn JC (2009) Negative pressure wound therapy for soft tissue injuries around the foot and ankle. J Orthop Surg Res 4:14
32. Jeschke MG, Rose C, Angele P, Fuchtmeier B, Nerlich MN, Bolder U (2004) Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. Plast Reconstr Surg 113:525–530
33. Repta R, Hoberman L, Rechner B (2005) The use of negative-pressure therapy and skin grafting in the treatment of soft-tissue defects over the achilles tendon. Ann Plast Surg 55:367–370
34. Orgill DP, Bayer LR (2011) Update on negative-pressure wound therapy. Plast Reconstr Surg 127(Suppl):105S–115S
35. Kang GCW, Por YC, Tan BK (2010) In vivo tissue engineering over wounds with exposed bone and tendon. Autologous dermal grafting and vacuum-assisted closure. Ann Plast Surg 65:70–73
36. Molnar JA, DeFranzo AJ, Hadaegh A, Morykwas MJ, Shen P, Argenta LC (2004) Acceleration of Integra incorporation in complex tissue defects with subatmospheric pressure. Plast Reconstr Surg 113:1339–1346
37. Violas P, Abid A, Darodes P, Galinier P, de Gauzy JS, Cahuzac J-P (2005) Integra artificial skin in the management of severe tissue defects, including bone exposure, in injured children. J Pediatr Orthop 14:318–384
38. Muangman P, Engrav LH, Heimbach DM, Harunari N, Honari S, Gibran NS, Klien MB (2006) Complex wound management utilizing an artificial dermal matrix. Ann Plast Surg 57:199–202
39. Iorio ML, Shuck J, Attinger CE (2012) Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. Plast Reconstr Surg 130:232S–241S
40. Shores JT, Hiersche M, Gabriel A, Gupta S (2012) Tendon coverage using an artificial skin substitute. J Plast Reconstr Aesthet Surg 65:1544–1550
41. Yeong EK, Yu YC, Chan ZH, Roan TL (2013) Is artificial; dermis an effective tool in the treatment of tendon-exposed wounds? J Burn Care Res 34:161–167
42. Graham GP, Helmer SD, Hann JM (2013) Khandelwal. The use of Integra® dermal regeneration template in the reconstruction of traumatic degloving injuries. J Burn Care Res 34:261–266

43. Yannas IV, Burke JF (1980) Design of an; artificial skin: I. Basic design principles. J Biomed Mater Res 14:65–81
44. Yannas IV, Burke JF, Gordon PL, Haung C, Rubenstein RH (1980) Design of an artificial skin: II. Control of chemical composition. J Biomed Mater Res 14:107–132
45. Burke JF, Yannas IV, Quinby WC, Bondoc CC, Jung WK (1981) Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg 194:413–427
46. Heimbach D, Luterman A, Burke J, Cram A, Herndon D, Hunt J, Jordan M, McManus W, Solem L, Warden G, Zawacki B (1988) Artificial dermis for major burns. Ann Surg 208:313–319
47. Dantzer E, Braye FM (2001) Reconstructive surgery using an artificial dermis (Integra): results with 39 grafts. Brit J Plast Surg 54:659–664
48. Janis JE, Kwon RK, Attinger CE (2011) The new reconstructive ladder: modifications to the traditional model. Plast Reconstr Surg 127(Suppl 1):205S–212S
49. Schultz GS, Wysocki A (2009) Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen 17:153–162
50. Plotner AN, Mostow EN (2010) A review of bioactive materials and chronic wounds. Cutis 85:259–266
51. Lazic T, Falanga V (2011) Bioengineered skin constructs and their use in wound healing. Plast Reconstr Surg 127(Suppl 1):75S–90S
52. Polanco TO, Xylas J, Lantis JC (2016) Extracellular matrices (ECM) for tissue repair. Surg Technol Int 28:43–57
53. Brown BN, Badylak SF (2016) Extracellular matrix as an inductive scaffold for functional tissue reconstruction. In: Lawrence J, Baptista P, Atala A, Beusekom MV (eds) Translating regenerative medicine to the clinic. Elsevier, Amsterdam, pp 11–29
54. Badylak SF (2004) Xenogeneic extracellular matrix as a scaffold for tissue reconstruction. Transpl Immunol 12:367–377
55. Badylak SF (2007) The extracellular matrix as a biologic scaffold material. Biomaterials 28:3587–3593
56. Gilbert TW, Stewart-Akers AM, Simmons-Byrd A, Badylak SF (2007) Degradation and remodeling of small intestinal submucosa in canine Achilles tendon repair. J Bone Joint Surg Am 89(3):621–630
57. Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF (2009) Macrophage phenotype and remodeling outcomes in response to biologic scaffolds with and without a cellular component. Biomaterials 30(8):1482–1491
58. Badylak SF, Valentin JE, Ravindra AK, McCabe GP, Stewart-Akers AM (2008) Macrophage phenotype as a determinant of biologic scaffold remodeling. Tissue Eng Part A 14(11):1835–1842
59. Brown BN, Londono R, Tottey S, Zhang L, Kukla KA, Wolf MT, Daly KA, Reing JE, Badylak SF (2012) Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials. Acta Biomater 8(3):978–987
60. Reing JE, Zhang L, Myers-Irvin J, Cordero KE, Freytes DO, Heber-Katz E, Bedelbaeva K, McIntosh D, Dewilde A, Braunhut SJ, Badylak SF (2009) Degradation products of extracellular matrix affecting cell migration and proliferation. Tissue Eng 15:605–614
61. Brennan EP, Reing J, Chew D, Meyers-Irvin JM, Young EJ, Badylak SF (2006) Antibacterial activity within degradation products of biological scaffolds composed of extracellular matrix. Tissue Eng 12:2949–2955
62. Brown B, Lindberg K, Reing J, Stolz DB, Badylak SF (2006) The basement membrane component of biologic scaffolds derived from extracellular matrix. Tissue Eng 12:519–526
63. Kirsner RS, Falanga V, Eaglstein WH (1998) The development of bioengineered skin. Trends Biotechnol 16:246–249
64. Englstein WH, Falanga V (1998) Tissue engineering and the development of Apligraf, a human skin equivalent. Cutis 62(1 Suppl):1–8
65. Gentzkpow GD, Iwasaki SD, Hershon KS, Mengel M, Prendergast JJ, Ricotta JJ, Steed DP, Lipkin S (1996) Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes Care 19(4):350
66. Badylak SF, Gilbert TW (2008) Immune response to biologic scaffold materials. Semin Immunol 20:109–116
67. Tottey S, Johnson SA, Crapo PM, Reing JE, Zhang L, Jiang H, Medberry CJ, Badylak SF (2011) The effect of source animal age upon extracellular matrix scaffold properties. Biomaterials 32(1):128–136
68. Sicari BM, Johnson SA, Siu BF, Crapo PM, Daly KA, Jiang H, Medberry CJ, Tottey NJ, Badylak SF (2012) The effect of source animal age upon the in vivo remodeling characteristics of an extracellular matrix scaffold. Biomaterials 33:5525–5533
69. Gilbert TW (2012) Strategies for tissue and organ decellularization. J Cell Biochem 113(7):2217–2222
70. Soto-Gutierrez A, Wertheim JA, Ott HC, Gilbert TW (2012) Perspectives on whole organ assembly: moving towards transplantation on demand. J Clin Invest 122(11):3817–3823
71. Sadtler K, Sommerfeld SD, Wolf MT, Wang X, Majumdar A, Chung L, Kelkar DS, Pandey A, Elisseeff JH (2017) Proteomic composition and immunomodulatory properties of urinary bladder matrix scaffolds in homeostasis and injury. Semin Immunol 29:14–23
72. Müller ME, Allgöwer M, Willenegger H (1963) Technik der operativen frakturen behandlung. Springer, Berlin, Germany, pp 223–231
73. Müller ME, Allgöwer M, Willenegger H (1970) Manual of internal fixation; technique recommended by the AO-Group. Schatzker J, (translator). Springer, New York, NY
74. Muller ME, Allgower M, Schneider R, Willenegger H (1995) Manual of internal fixation. Techniques recommended by AO ASIF group, 3rd edn. Springer, New York, NY

75. Perren SM (1991) The concept of biological plating using limited contact dynamic compression plate (LCDCP). Scientific Background, Design and Application Injury 22(Suppl):1–41
76. Helfet DL, Haas NP, Schatzker J, Matter P, Moser R, Hanson B (2003) AO philosophy and principles of fracture management-its evolution and evaluation. J Bone Joint Surg Am 85(6):1156–1160
77. Matter P, Bruch HB (1990) Clinical experience with titanium implants, especially with limited contact dynamic compression plate system. Arch Orthop Trauma Surg 109:311–313
78. Lenarz CJ, Watson JT, Moed BR, Israel H, Mullen JD, Macdonald JB (2010) Timing of wound closure in open fractures based on cultures obtained after debridement. J Bone Joint Surg Am 92(10):1921–1926
79. Schultz GS, Barillo DJ, Mozingo DW, Chin GA (2004) The wound advisory board members. Wound bed preparation and a brief history of TIME. Int Wound J 1:19–32
80. Brennan EP, Reing J, Chew D, Myers-Irvin JM, Young EJ, Badylak SF (2006) Antibacterial activity within degradation products of biological scaffolds composed of extracellular matrix. Tissue Eng 10:2949–2955
81. Beattie AJ, Gilbert TW, Guyot JP, Yates AJ, Badylak SF (2009) Chemoattraction of progenitor cells by remodeling extracellular matrix scaffolds. Tissue Eng 15:1119–1125
82. Swinehart IT, Badylak SF (2016) Extracellular matrix bioscaffolds in tissue remodeling and morphogenesis. Dev Dyn 245:351–360
83. Davis GE (2010) Matricryptic sites control tissue injury responses in the cardiovascular system: relationships to pattern recognition receptor regulated events. J Mol Cell Cardiol 48:454–460
84. Davis GE, Bayless KJ, Davis MJ, Meininger GA (2000) Regulation of tissue injury responses by the exposure of matricryptic sites within extracellular matrix molecules. Am J Pathol 156:1489–1498
85. Medberry CJ, Tottey S, Jiang H, Johnson SA, Badylak SF (2012) Resistance to infection of five different materials in a rat body wall model. J Surg Res 173(1):38–44

Uses of Negative-Pressure Wound Therapy in Orthopedic Trauma

Arianna L. Gianakos, Richard S. Yoon, and Frank A. Liporace

1 Introduction

Negative-pressure wound therapy (NPWT) in the field of orthopedic surgery has gained increased attention and popularity for its use in a variety of clinical applications. Randomized controlled trials and larger studies have been published demonstrating the potential clinical benefits of NPWT in the setting of high-energy trauma, open fractures, traumatic soft tissue wounds, and infections (Fig. 1). NPWT functions by reducing edema, facilitating wound drainage, and increasing perfusion. NPWT stimulates granulation tissue formation and enhances the wound bed environment, improving the likelihood for closure or coverage. Although the success of NPWT has been demonstrated in the setting of orthopedic trauma, further research is required to determine the evolving clinical indications and benefits, as well as establish appropriate protocols and guidelines in a variety of clinical scenarios. This chapter attempts to review the application, mechanism of action, clinical indications, complications, and recommendations of NPWT in the field of orthopedic surgery.

A.L. Gianakos · R.S. Yoon, M.D. (✉)
F.A. Liporace
Department of Orthopaedic Surgery,
Jersey City Medical Center, RWJ Barnabas Health,
Jersey City, NJ, USA
e-mail: yoonrich@gmail.com

2 Components

NPWT typically consists of the following main components to create a subatmospheric pressure environment: an open pore reticulated foam, occlusive semipermeable dressing, a suction device, and a connector that allows for communication. The open porous dressing allows negative pressure to be transferred across a sponge-wound interface from a suction source which is connected to the surface of the sponge. The first clinical report utilized a premoistened and presterilized polyvinyl alcohol (PVA) foam with pore sizes between 60 and 270 μm (KCI, San Antonio, TX, USA) [1]. Although the hydrophilic nature and smaller pore sizes in PVA foam reduces the amount of tissue ingrowth thereby limiting the amount of bleeding and pain during dressing changes, PVA foam offers a less adherent application with significantly less granulation and perfusion [2]. Therefore, the dressing of choice in orthopedic trauma has become a dry, black, hydrophobic reticulated polyurethane ether foam with a 400–600 μm pore size (KCI, San Antonio, TX, USA) which has been demonstrated to maximize fibrovascular tissue ingrowth [3]. Occlusive dressings such as adhesive drapes have been utilized to produce an effective vacuum suction while avoiding protein loss and wound desiccation. Iodophor-impregnated drapes have also been used to help control bacterial colonization of the skin. Lastly, the goal of NPWT is to create a localized negative-pressure environment. Previous animal

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_61, © Springer International Publishing AG
Published Online: 04 April 2018

Fig. 1 NPWT can be extremely instrumental and vital in the orthopedic trauma setting, especially in the setting of severe soft tissue injury that requires temporizing measures until definitive coverage can be obtained. (**a**) A 37-year-old patient following a small plane crash landing that required multiple debridements; definitive fixation and NPWT offered a temporizing bridge to flap coverage. (**b**) A 45-year-old male approximately 6 weeks out from sustaining an acute, grade 1 open tibia fracture that later became infected and required debridement; again, NPWT can bridge the debridements until definitive soft tissue coverage. (**c**) A 35-year-old male following fixation for a pilon fracture required excision of soft tissue that left the wound unclosable. Here again, NPWT was vital in bridging the gap until free flap placement

models have demonstrated that a standard pressure of 125 mmHg given in intermittent cycles results in a fourfold increase in blood flow when compared to conventional dressings [4]. Studies have shown that negative pressures greater than 400 mmHg decrease blood flow from baseline [4]. In addition, negative pressures between 50 and 200 mmHg increase the risk of skin breakdown and infection [5]. Streubel et al. [1] demonstrated a reactive increase in blood flow for at least 2 min during "off times." Morykwas et al. [4] reported that intermittent pressure resulted in a 103% increase in granulation tissue compared to a 63% increase with continuous pressure.

3 Mechanism of Action

The primary goal of NPWT is to provide improved wound management and healing. A systematic review by Orgill et al. described the four primary effects of NPWT: (1) wound contraction, (2) decreased edema, (3) stabilization of wound environment, and (4) microdeformation [6]. Macrodeformation of the wound occurs when NPWT contracts wound edges together after prolonged gapping after traumatic skin disruption. This reduces the space required to be healed. An inflammatory response following an insult or injury results in an increase in interstitial edema. This increased pressure results in diminished nutrient inflow and congested outflow of cellular waste, ultimately leading to cell death and necrosis [3]. NPWT utilizes continuous draining of excess fluids which maintains both osmotic and oncotic gradients between wound bed and soft tissue [1]. Removal of excess fluid reduces edema, inflammatory mediators, and bacteria whose prolonged effect can hinder microcirculation [3, 7]. This improved tissue perfusion, and cell proliferation creates an environment conducive to healing. NPWT provides a warm and moist environment, which enhances granulation formation and decreases the risk of infection typically seen with repetitive wet-to-dry dressing changes. The negative-pressure environment places mechanical strain on the tissue, resulting in microdeformation and stretch at the cellular level. This mechanical loading stimulates cellular chemotaxis, angiogenesis, and tissue growth and repair through recruitment of growth factors [8]. Labler et al. noted higher levels of IL-8 and VEGF in wound fluid from NPWT dressings when compared to fluid from a standard dressing [9]. Chen et al. [10] reported significantly higher levels of C-MYC, C-JUN, and BCL-2 in negative-pressure environments which correspond to cells required for granulation tissue formation. These findings demonstrate the clinical effects of NPWT at the cellular level [3, 10].

4 Application of the VAC Device

Proper application of the VAC device is critical in the success of the negative-pressure system. The polyurethane ether sponge is available in several sizes but should be cut to properly fit over the wound until a stable skin base is achieved. When using NPWT over surgical incisions, a nonadherent dressing can be placed over the length of the incision, and a 1-inch-wide strip of sponge can be placed over the dressing with care to avoid direct contact with the skin. If wound coverage requires several sponges, staples can be utilized to hold the sponges in place. The wound or incision can be lined with an adjunctive liquid adhesive in order to reduce the likelihood of dressing migration once placed. Before applying the adhesive dressing, the skin must be kept dry to ensure an adequate seal; liquid sealant can be placed on the skin to allow for a better seal. The adhesive dressings should be placed over the sponges but should not be applied in a circumferential manner in order to prevent a tourniquet effect [1]. A 2 × 2 cm hole is then cut in the center of the sponge where the suction track can be applied and attached. This connection is then attached to the VAC device, which will dry and decompress the sponges over the wound. At this time, the VAC device will assess for any residual leakage, which can then be addressed by applying additional adhesive dressings before final sealing. The size and severity of the wound or incision will dictate the duration and pressure of the therapy. NPWT is typically set on either intermittent or continuous suction and is changed or discontinued every 2–5 days [1].

5 Clinical Indications

NPWT in the field of orthopedic surgery has been utilized in the treatment of high-energy traumas, open fractures, soft tissue defects, and combat-related wounds. It has also been indicated for surgical incisions at risk of skin breakdown or infection, skin grafts, and infected wounds.

NPWT for soft tissue traumatic wounds has been indicated to provide temporary wound coverage following thorough debridement when definitive closure is not possible (Fig. 2) [3]. Reported success has been seen in its use when treating critically ill patients and patients with either significant wound contamination or significant edema [3]. NPWT has been used in combination with surgical debridement and irrigation to reduce bacterial load and remove devitalized tissue, especially for wounds that are not closable [1].

NPWT has been successful when applied over incisional wounds at fracture sites as well as in the treatment of fasciotomy incisions (Fig. 3) [11, 12]. This therapy results in delayed closure of the wound which reduces edema and compartment pressures. Stannard et al. [5] performed a prospective randomized study on patients with high-risk wounds such as lower extremity and pelvic fractures and reported reduced draining time and rate of wound infection in patients undergoing NPWT compared with standard dry dressing changes [5]. Stannard et al. [11] also performed a prospective randomized study evaluating NPWT in calcaneus, pilon, and tibial plateau fractures and found a significant reduction in infection in the NPWT group compared with the group receiving standard postoperative dry wound dressings.

NPWT has also been in the preservation and incorporation of skin grafts. A number of studies

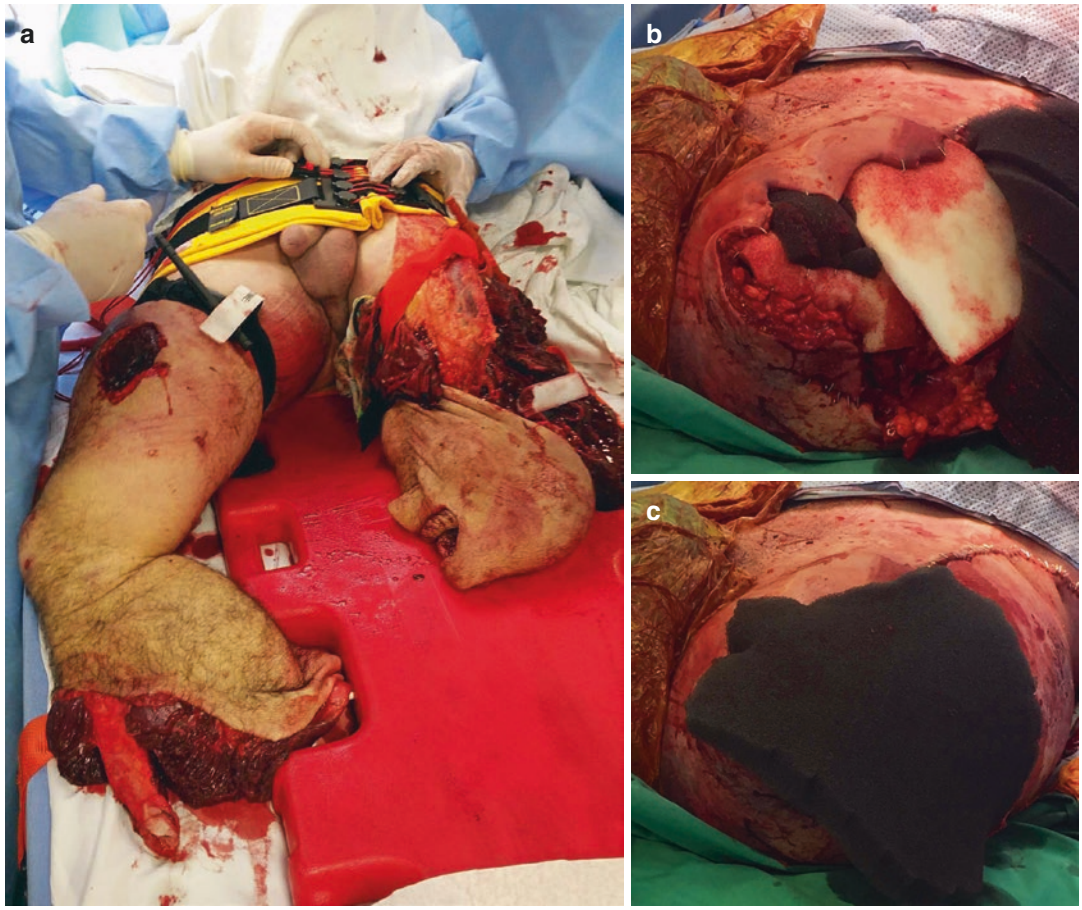


Fig. 2 (**a**) A 22-year-old male in the trauma bay following high-speed motorcycle crash, sustaining massive, bilateral lower extremity injuries causing traumatic amputation. (**b**) Several debridements were required after the first night, and here layering of a white sponge on more vital tissue covered by (**c**) black sponge completed NPWT treatment and bridged the gap until (**d**) final debridement and (**e**, **f**) latissimus dorsi free flap placement

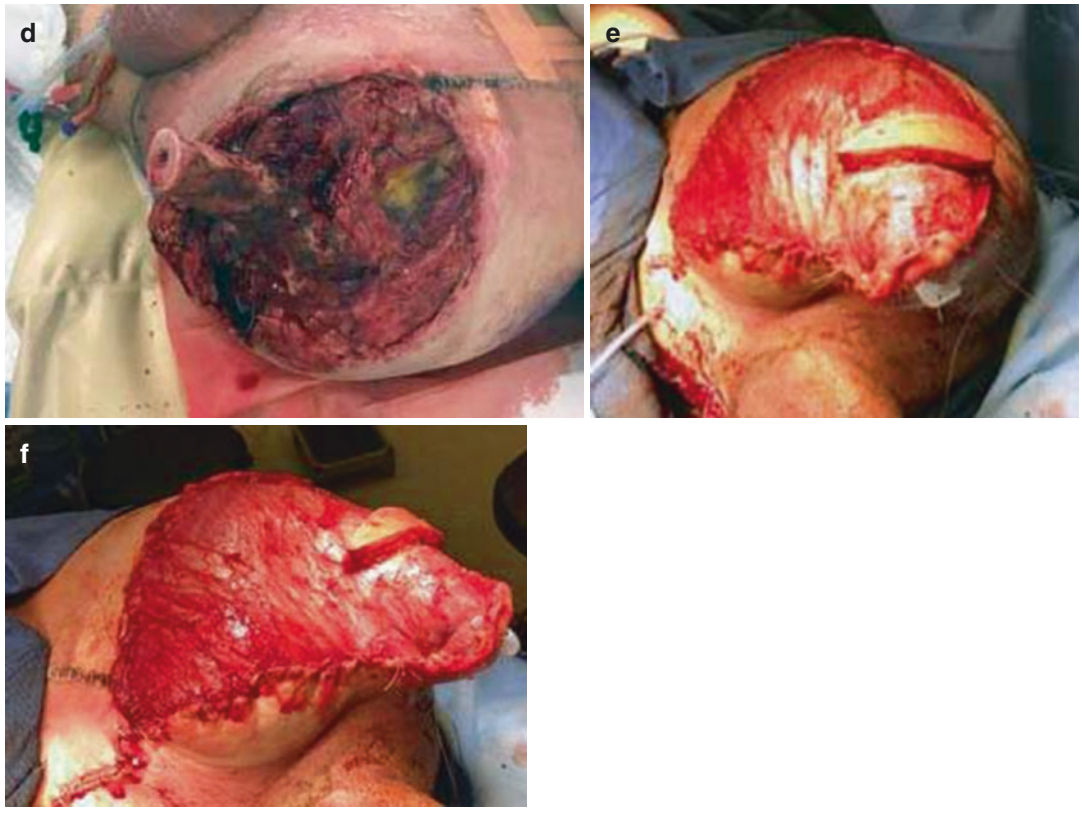


Fig. 2 continued

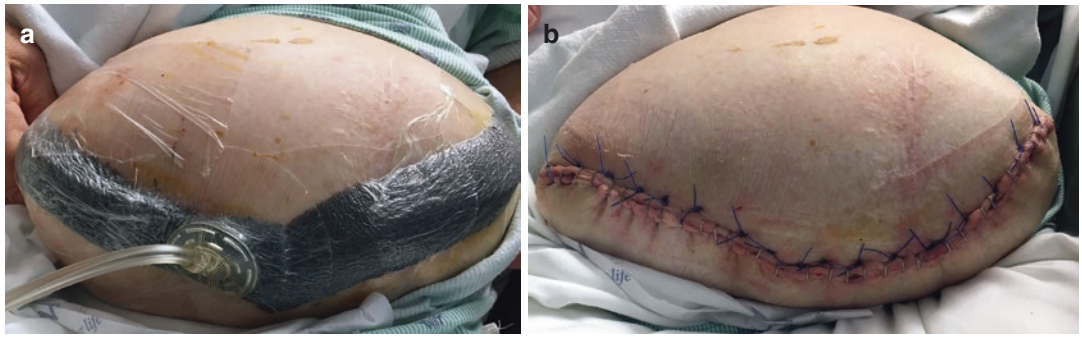


Fig. 3 Incisional VAC placement can offer a sterile, enclosed environment that allows for improved wound healing, especially in the compromised patient. Here, following an above-knee amputation, due to a history of chronic renal disease with previous infection, an (**a**) incisional wound VAC was placed and removed on postoperative day 3 (**b**) exhibiting a dry, clean wound

have demonstrated improvement with graft incorporation when using pressure ranges between −50 mmHg and −80 mmHg [13, 14]. A randomized trial by Llanos et al. [15] reported a significant reduction in the rate of skin graft loss and hospital stay when utilizing NPWT over a newly applied skin graft. Moisidis et al. [16] conducted a randomized controlled clinical trial comparing wounds receiving a standard bolster dressing versus a topical negative-pressure dressing and demonstrated that NPWT improved the qualitative appearance of split-thickness skin grafts postoperatively.

The use of NPWT has gained increased popularity in the treatment of closed surgical incisions at risk of wound complications, specifically wounds with increased drainage or hematoma. Stannard et al. [5] conducted a randomized controlled trial in the management of persistent wound drainage and reported that the period of drainage was significantly shorter in patients receiving NPWT when compared to the standard pressure dressing group. In addition, they found that the rate of infection was reduced in the NPWT group at 8% compared to 16% in the pressure group.

NPWT has also been successful in reducing the complexity of wounds by promoting granulation tissue growth. Parrett et al. reported a reduction in the number of free flaps needed when NPWT was employed in reconstruction of soft tissue with no additional risk of complications [17]. NPWT also affords the ability of staged closure when definitive closure may not be feasible.

Although there is debate as to whether NPWT reduces bacterial load, recent literature has demonstrated that patients undergoing NPWT may be less likely to develop infection. Lalliss et al. [18] evaluated contaminated open fractures in the animal model and reported a decrease in *Pseudomonas aeruginosa* after 6 h with 48 hourly debridements, although reported no reduction in *Staphylococcus aureus* when compared to wet-to-dry dressings. There has been concern whether NPWT reduces effectiveness of antibiotic-loaded bone cement when used postoperatively. Stinner et al. [19] demonstrated an overall reduction in effectiveness of both vancomycin-impregnated cement beads with NPWT as wounds not subjected to NPWT had a sixfold reduction in bacteria after 2 days of treatment. Therefore, although these dressings may be beneficial for the coverage of the wound, formal irrigation, debridement, and systemic antibiotics should still be the standard approach when addressing infection [3].

6 Complications and Recommendations

Although the use of NPWT is widely indicated to promote wound healing, reports have demonstrated that it has been associated with complications, although infrequent. These include bleeding, infection, pain during dressing changes, wound breakdown, and complications secondary to interrupted therapy [3]. However, close monitoring can help avoid and reduce some of these complications.

The most frequent serious adverse effect associated with NPWT is bleeding. Patients with significant adhesions between wound bed and dressing have an increased risk of bleeding when dressing are either changed or removed. Streubel et al. [1] addressed both patient and wound factors that should be considered when using NPWT including but not limited to the following: patients with coagulopathies, patients on anticoagulants, presence of osteomyelitis or spinal cord injury, wounds located near large vessels, exposed tendons or ligaments, infected wounds, and sharp edges in the wound from bone fragments or hardware. It is recommended to place a non-adherent dressing or using a PVA sponge in the base of the wound to prevent excess bleeding.

Failure of NPWT to maintain adequate suction and loss of seal of the occlusive dressing may pose a risk of wound infection. Interrupted therapy due to either a loss of power, poor seal, or blocked tubing leads to a moist, closed environment conducive for bacterial growth and skin maceration and breakdown [3]. Collinge et al. [20] demonstrated a significantly increased rate of wound complications in patients who had interrupted NPWT when compared to patients

who did not have interruptions. NPWT should be used only in infected wounds that are adequately debrided and should be discontinued if purulent exudate occurs in order to avoid worsening infection or sepsis. Close monitoring of outputs and proper device functioning can help address any interruptions in a timely fashion.

Although dressing changes with NPWT are less painful and less frequent than the standard wet-to-dry dressing changes, risk of wound bed disruption and fragments of foam in the wound still remain a cause of discomfort during dressing changes. It has been documented that pressure dressing changes may lead to an increase in patient anxiety when compared to the typical gauze dressing which may be attributed to pain, restrictions of activities, and unfamiliarity with the type of foam [21]. To limit pain, dressings should be changed every 2–4 days. Moistening the interface between the sponge and soft tissue can also prevent unnecessary pain during dressing removal. Christensen et al. [22] performed a randomized controlled trial evaluating pain levels, narcotic requirements, and wound characteristics in patients who had dressing changes after 1% lidocaine was injected into the VAC sponge compared with sponges injected with topical normal saline. Patients undergoing extremity wound VAC dressing removal pretreated with topical lidocaine demonstrated a significant decrease in both pain levels and narcotic requirements.

The US Food and Drug Administration (FDA) released guidelines for healthcare providers using NPWT devices with NPWT contraindicated in the presence of the following: necrotic tissue with eschar present, untreated osteomyelitis, non-enteric and unexplored fistulas, malignancy in the wound, exposed vasculature, exposed nerves, exposed anastomotic site, or exposed bone or tendons [23, 24]. In addition, the FDA recommends appropriate training protocols for patients and their caregivers who will be using the VAC device at home. Patients should be provided with a copy instructions and be able to respond to alarms, perform dressing changes, recognize signs and symptoms of complications, and contact appropriate healthcare providers in emergency situations [23, 24].

7 Authors' Preferred Treatment/Use

7.1 Cost

To date, there is limited data addressing the cost-effectiveness of NPWT in the current literature. The cost for reusable NPWT is based on contracts between insurance providers and treatment facilities. Costs include rent of the machine, dressing supplies, replacement canisters, and additional special dressings. Purchased NPWT systems typically cost between $500 and $600 [1]. Future research should be directed at evaluating the cost-effectiveness of NPWT in terms of total costs, wound-related costs, and hospital readmission rates.

Conclusions

The benefits of NPWT in the field of orthopedic surgery have been demonstrated in the literature, with NPWT indicated for a variety of clinical scenarios including high-energy trauma, open fractures, traumatic soft tissue wounds, and infections. Although NPWT has been associated with complications including bleeding, infection, pain, and wound breakdown, strategies to reduce these complications offer promising results. Outputs should be monitored to avoid bleeding, and the use of non-adherent barriers between the sponge and soft tissue can help reduce pain. Further research is required to establish appropriate protocols and guidelines, as well as, to determine the effectiveness of its use with adjunctive therapies.

References

1. Streubel PN, Stinner DJ, Obremskey WT (2012) Use of negative-pressure wound therapy in orthopaedic trauma. J Am Acad Orthop Surg 20(9):564–574
2. Timmers MS, Le Cessie S, Banwell P, Jukema GN (2005) The effects of varying degrees of pressure delivered by negative-pressure wound therapy on skin perfusion. Ann Plast Surg 55(6):665–671
3. Gage MJ, Yoon RS, Egol KA, Liporace FA (2015) Uses of negative pressure wound therapy in orthopedic trauma. Orthop Clin North Am 46(2):227–234

4. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg J 38(6):553–562
5. Stannard JP, Robinson JT, Anderson ER, McGwin G Jr, Volgas DA, Alonso JE (2006) Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. J Trauma 60(6):1301–1306
6. Orgill DP, Bayer LR (2011) Update on negative-pressure wound therapy. Plast Reconstr Surg 127(Suppl 1):105S–115S
7. Tarkin IS (2008) The versatility of negative pressure wound therapy with reticulated open cell foam for soft tissue management after severe musculoskeletal trauma. J Orthop Trauma 22(10 Suppl):S146–S151
8. McNulty AK, Schmidt M, Feeley T, Kieswetter K (2007) Effects of negative pressure wound therapy on fibroblast viability, chemotactic signaling, and proliferation in a provisional wound (fibrin) matrix. Wound Repair Regen 15(6):838–846
9. Labler L, Rancan M, Mica L, Harter L, Mihic-Probst D, Keel M (2009) Vacuum-assisted closure therapy increases local interleukin-8 and vascular endothelial growth factor levels in traumatic wounds. J Trauma 66(3):749–757
10. Chen SZ, Cao DY, Li JQ, Tang SY (2005) Effect of vacuum-assisted closure on the expression of proto-oncogenes and its significance during wound healing. Zhonghua Zheng Xing Wai Ke Za Zhi 21(3):197–200
11. Stannard JP, Volgas DA, McGwin G 3rd et al (2012) Incisional negative pressure wound therapy after high-risk lower extremity fractures. J Orthop Trauma 26(1):37–42
12. Zannis J, Angobaldo J, Marks M et al (2009) Comparison of fasciotomy wound closures using traditional dressing changes and the vacuum-assisted closure device. Ann Plast Surg 62(4):407–409
13. Argenta LC, Morykwas MJ (1997) Vacuum-assisted closure: a new method for wound control and treatment: a clinical experience. Ann Plast Surg 38:563–576
14. Webb LX (2002) New techniques in wound management: vacuum-assisted wound closure. J Am Acad Orthop Surg 10(5):303–311
15. Llanos S, Danilla S, Barraza C et al (2006) Effectiveness of negative pressure closure in the integration of split thickness skin grafts: a randomized, double-masked, controlled trial. Ann Surg 244(5):700–705
16. Moisidis E, Heath T, Boorer C, Ho K, Deva AK (2004) A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. Plast Reconstr Surg 114(4):917–922
17. Parrett BM, Matros E, Pribaz JJ, Orgill DP (2006) Lower extremity trauma: trends in the management of soft-tissue reconstruction of open tibia-fibula fractures. Plast Reconstr Surg 117(4):1315–1322
18. Lalliss SJ, Stinner DJ, Waterman SM, Branstetter JG, Masini BD, Wenke JC (2010) Negative pressure wound therapy reduces pseudomonas wound contamination more than Staphylococcus Aureus. J Orthop Trauma 24(9):598–602
19. Stinner JD, Waterman SM, Masini BD, Wenke JC (2011) Silver dressings augment the ability of negative pressure wound therapy to reduce bacteria in contaminated open fracture model. J Trauma 71(1 suppl):S147–S150
20. Collinge C, Reddix R (2011) The incidence of wound complications related to negative pressure wound therapy power outage and interruption of treatment in orthopaedic trauma patients. J Orthop Trauma 25(2):96–100
21. Upton D, Andrews A (2013) Negative pressure wound therapy: improving the patient experience part 2 of 3. J Wound Care 22(11):582; 584–591
22. Christensen TJ, Thorum T, Kubiak EN (2013) Lidocaine analgesia for removal of wound vacuum-assisted closure dressings: a randomized double-blinded placebo-controlled trial. J Orthop Trauma 27(2):107–112
23. US Food and Drug Administration (2017) Class II special controls guidance document: non-powered suction apparatus device intended for negative pressure wound therapy (NPWT). http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/GuidanceDocuments/UCM233279.pdf. Accessed 23 July 2017
24. Putnis S, Khan WS, Wong JM (2014) Negative pressure wound therapy-a review of its uses in orthopaedic trauma. Open Orthop J 27(8):142–147

Prevention of Prosthetic Joint Infections

Ricardo Sousa and Ana Nogueira

1 Prophylaxis

Infection is one of the most frequent and dreadful complications after all kinds of total joint arthroplasty (TJA) [1–5]. Treatment is cumbersome and causes significant negative impact on the patient's quality of life and even increased mortality [6].

Prevention is naturally the best way to avoid its dire consequences. Due to the presence of an implant, a very small number of bacteria reaching the wound are enough to cause relevant infection making prevention of prosthetic joint infections (PJI) extremely demanding. Most traditional prophylactic strategies (e.g. skin decontamination, operating room asepsis, etc.) aim to reduce the number of bacteria reaching the wound via the surrounding environment, the so-called exogenous contamination. Notwithstanding its remarkable importance, a second route for bacterial seeding into the joint has been recently recognized. The host itself harbours a huge number of bacteria that, in the right circumstances, may become pathogenic. This so- called endogenous contamination and its real weight are yet to be fully understood.

As such, effective prophylaxis depends on several different aspects, and ultimately, it is not possible for the orthopaedic surgeon alone to manage all of them. Patients should be properly advised, and a multidisciplinary team should seek to optimize conditions before elective joint replacement surgery. It has been proven that such a team is able to implement multimodal strategies that effectively reduce PJI rates [7].

2 Preoperative Considerations

The first step towards effective prevention of PJI is preoperative risk stratification. Knowing each patient's specific risk of infection would be ideal in terms of preoperative decision- making and counselling. Several epidemiological and intrinsic patient factors closely relate to the risk of infection. Males, for instance, have been shown to be at greater risk [8]. Revision surgery or simply previous joint surgery (e.g. posttraumatic situations), previous history of joint infection and prior steroid injection into the joint or history of bone cancer are also known risk factors that are simply not influenced [9–13]. While it is not possible to sway such factors, they are helpful in establishing a specific risk of infection for each patient that ultimately allows for better preoperative decision-

R. Sousa, M.D., Ph.D. (✉)
Orthopedics Department, Centro Hospitalar do Porto, Instituto de CiênciasBiomédicas de Abel Salazar School of Medicine, Oporto University, Porto, Portugal
e-mail: ricardojgsousa@gmail.com

A. Nogueira
Dermatologist, Dermatovenereology of Department, Centro Hospitalar São João, Porto, Portugal
e-mail: ananogueiradermatologia@gmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_62, © Springer International Publishing AG
Published Online: 24 April 2018

making and resource allocation and enable more effective patient counselling [14, 15].

Prevention efforts should focus on those known yet modifiable patient risk factors. Some are straightforward such as treating active or potential septic focus (e.g. pneumonia, infected leg ulcers) before surgery, but others require considerable commitment such as nutritional optimization and management of medical comorbidities. Screening for potential sources for endogenous contamination such as *Staphylococcus aureus* colonization or unrecognized bacteriuria has also been advocated.

2.1 Medical Risk Factors

Countless patient-related factors have been implicated in the increased risk of PJI. Associated chronic comorbidities such as heart failure, pulmonary disease, renal or liver disease, coagulopathies, rheumatologic arthropathy, etc. cannot be eliminated preoperatively but can and should be optimized in order to mitigate the risk of postoperative complications [9, 16–18]. There is strong evidence that overall health status and greater illness severity are independent risk factors for infection [8, 17, 19].

2.1.1 Diabetes

It is well established that diabetic patients often present delayed wound healing and a disordered inflammatory/immune response. It is therefore not surprising that they are at increased risk for infection after TJA [10, 16, 17]. It has been shown that the current status of glycaemic control is more predictive than simply having a diabetes diagnosis. Marchant et al. [20] found not only a twofold greater risk of infection in patients with uncontrolled diabetes compared with nondiabetics but more interestingly an identical risk of infection between patients with controlled diabetes compared to the nondiabetic population.

Ideally one should strive to reach a good consistent glycaemic control as measured by a haemoglobin A1C below 7–8%. Several papers have confirmed the increased risk of infection above that threshold [20–25]. Nevertheless, in clinical practice, some patients are simply unable to reach such a good control [21], and a risk-benefit decision should be made on an individual basis. Proper close postoperative glucose control may be just as important and should not be disregarded especially in diabetic patients. Perioperative hyperglycaemia is also associated with increased risk for infection even in patients without diabetes [23, 24].

2.1.2 Obesity

Although it is not easily influenced, obesity is very common in total joint arthroplasty candidates, and some considerations are mandatory. Not only has it been repeatedly found to be an independent risk factor for infection [10, 11, 16–19, 26], but it is also associated with increased risk of other comorbid conditions such as diabetes and cardiovascular disease. A somewhat linear relation seems to exist between increased body mass index (BMI) and the risk of infection. A few papers have shown that more elevated BMI categories seem to have increasingly higher risk of PJI [8, 10, 17, 27]. Lubbeke et al. [28] clearly illustrate this trend. In their study including over 9000 primary hip and knee arthroplasties, infection rates were similar in the first three BMI categories (<35), but they were twice as high with BMI 35–39.9 and four times higher with BMI ≥ 40 [28].

It therefore seems logical that patients should be strongly advised to lose weight before TJA. There are some reports showing more favourable outcomes if bariatric surgery is performed before TJA, especially if more than 2 years have passed [29–31]. Notwithstanding, there is no clear evidence to support or refute if the use of bariatric surgery prior to arthroplasty has a positive effect on postoperative complications such as PJI or even on the long-term clinical outcome, and quality of life is yet to be proven [32]. Naturally it is important that both the patient and the surgeon discuss infection as a possible outcome when weight loss is not feasible.

2.1.3 Malnutrition

From a nutritional perspective, it is desirable that patients presenting for total joint arthroplasty

have a lymphocyte count of >1500 cells/mL, an albumin level of >3.5 g/dL and a transferrin level of >200 mg/dL. The negative influence of preoperative malnutrition below these thresholds has long been recognized [33, 34]. There is enough evidence to show that multiple nutrient-enhanced formulas can be used to prevent surgical site infections in adult patients undergoing major surgery [35]. However, the use of enhanced nutrition support is expensive and requires additional expertise from nutritionist and/or pharmacists. Except for elderly patients with femoral neck fractures, such debilitated patients are extremely rare in the total joint arthroplasty setting.

Preoperative anaemia is also often associated with poor nutritional status, and it has also been shown to be an independent risk factor for infection [16, 18]. Prior studies have also shown that these patients are more likely to require blood transfusions postoperatively [36, 37] which are associated with an increased risk of infection. Although prospective studies are still missing to confirm the real benefit of improving haemoglobin before surgery, we believe it is a reasonable recommendation.

2.1.4 Tobacco Use

Cigarette smoking increases the risk for perioperative complications, soft tissue and wound healing complications and ultimately musculoskeletal infection [38]. Singh et al. [39] analysed data from over 33,000 patients who underwent elective primary lower limb joint replacement. They found that current smokers at the time of elective surgery were more likely to have postoperative complications, especially surgical site infections and pneumonia, and suggested preoperative smoking cessation programmes should be considered. Although cessation is easier said than done, the effects of smoking on the skeleton may be (at least partially) reversible and that should encourage patients. Immune function appears to recover after 2–6 weeks of abstinence and wound healing after 3–4 weeks [38, 40, 41]. The benefits of preoperative smoking cessation interventions in reducing postoperative complications have been well established with each week of cessation prior to surgery increasing the magnitude of effect [42–44]. Moller et al. [45] conducted a randomized trial specifically before hip and knee replacement. They found a decrease in overall complication rate, especially wound-related complications, that has been documented after a 6–8 weeks' smoking intervention [45].

2.1.5 Alcohol Abuse

Patients who consume alcohol on a frequent basis may have a significantly increased risk for postoperative complications after arthroplasty [46]. Although the benefit of alcohol cessation programmes before surgery is not well established in the literature, it is reasonable to expect patients to reduce alcohol consumption prior to surgery and to delay elective arthroplasty in alcoholic patients until the issue has been addressed [47].

2.1.6 Immunosuppression

Immunosuppressive therapy is becoming increasingly common among TJA candidates. End- stage inflammatory arthritis (rheumatoid arthritis being the most frequent) is a common indication for joint replacement. These patients are fundamentally different from osteoarthritis in terms of pathogenesis, and it is therefore natural to expect these patients would have increased infection rates. In fact, many have found rheumatologic disease to be an independent risk factor for PJI [8, 16, 18, 48, 49]. Organ transplant recipients are also becoming more common candidates to TJA due to degenerative osteoarthritis or osteoporotic-related disease (e.g. hip fractures) as survival rates after transplant surgery are improving. Naturally these patients have increased risk of infection and other perioperative complications due to inherent medical comorbidities and immunosuppressive medication [13, 15, 50].

Immunosuppressive medical therapy with corticosteroids, disease-modifying antirheumatic drugs (DMARDS) and other drug(s) is often blamed for this risk. Still, evidence regarding the benefits of therapy discontinuation before surgery is conflicting [51, 52], and recommendations are also contradictory. Considering the scarce evidence to support discontinuation of treatment and even potential harm it may cause such as the risk of flare-up of the underlying con-

dition, recently issued World Health Organization guidelines on preoperative measures for surgical site infection prevention state immunosuppressive medication should not be discontinued routinely [35]. On the other hand, the International Consensus Meeting on PJI advocates disease-modifying agents should be stopped prior to elective joint replacement [47]. Decision to discontinue immunosuppressive medication should be made on an individual basis and involve the prescribing physician.

Human immunodeficiency virus (HIV) carriers constitute another group of patients with compromised immune system that, given their increasing long-term survival and high rates of osteonecrosis, are increasingly being considered for TJA as symptom relief and functional outcome seem to overlap those found in general population [53]. As HIV medical management, together with educational strategies, continues to improve, the risk of PJI seems to be much lower than earlier studies stated. More recent studies suggest that HIV-positive patients without medical comorbidities or other risk factors (e.g. intravenous drug users or haemophiliacs) may have postoperative complication rates similar or only slightly higher than uninfected patients [53–56]. Appropriate candidates must have CD4 counts greater than 400 cells/mL and undetectable viral load [47].

2.1.7 Oral Hygiene

Although it is well established that seeding from a remote source of infection can lead to PJI, there is still much debate regarding the use of active preoperative screening and treatment of dental pathology to ensure adequate oral hygiene as an effective measure to prevent postoperative bacteraemia and PJI in all patients undergoing TJA. Barrington et al. [57] showed 23% of TJA candidates had dental issues requiring treatment preoperatively. However, there is no evidence to support routine screening and treating all patients for every dental abnormality. Still, signs and symptoms of active dental infection should be sought and treated before elective joint replacements [47].

2.1.8 *Staphylococcus aureus* Screening

Staphylococcus aureus is a major pathogen implicated in PJI all over the world. In our own experience, it is involved in around half the cases [58]. About 20–30% of the general orthopaedic population is *S. aureus* carrier, and the anterior nasal cavity is the main site of colonization (Fig. 1) [59, 60]. It has been extensively shown that patients who carry it in their nasal flora are at increased risk for infection in a multitude of clinical scenarios including orthopaedic surgery [59, 61–65]. There is also evidence that, among carriers who develop *S. aureus* surgical site infection, there is great individual concordance between nose and surgical site isolates suggesting the importance of the endogenous contamination pathway [65]. This apparently modifiable risk factor has driven a recent trend on preoperatively screening and treating carriers to potentially reduce infection rates also in total joint arthroplasty surgery. Although there is convincing data

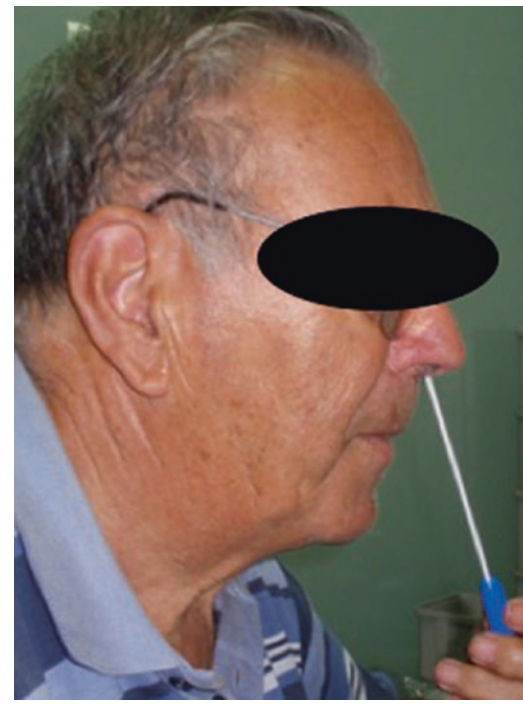


Fig. 1 Patient being screened for *S. aureus* colonization in the outpatient setting. Swabs were taken from both nares

favouring this approach in overall surgical site infection (SSI), data on arthroplasty surgery specifically is not so convincing [66].

In a paramount prospective randomized controlled study by Bode et al. [67], the number of *S. aureus* deep SSI was significantly lower in the treatment than in the placebo group. Still, further analysis of Bode's paper shows only 172 out of 808 surgical patients were orthopaedics and no information is given regarding how many of those were total joint replacements. In this specific subgroup of patients, there was no significant difference regarding *S. aureus* infections between treated and untreated carriers. In 2010, Kim et al. [68] enrolled over 7000 patients before elective orthopaedic surgery including arthroplasty but also spine and sports medicine cases. Noncarriers showed the lowest infection rate, and MRSA carriers showed a significantly higher infection rate. MSSA carriers showed a not significant difference compared to noncarriers. Unfortunately, also in this paper, no information regarding specifically total joint replacement patients was given. A year later, Rao et al. [69] reported their results on a cohort study of 3724 total joint arthroplasty patients. Infection rate in the carriers group was reported to be 0.0%, and the authors conclude preoperative screening/selective decolonization was associated with fewer SSI after elective TJA. However, more detailed scrutiny shows there were 17 cases of PJI among the 1440 patients of the intervention group and 19 infections in the concurrent control group of 2284 patients operated by non-participating surgeons [69]. Only when assuming that all infections of the control group occurred in the subgroup of expected to be *S. aureus* nasal carriers could the authors find a significant reduction of infection between treated and untreated carriers. This raises methodological issues that hamper this paper's conclusions as it is incorrect to assume that noncarriers in the control group would have zero infections.

A major multicentre study performed in American hospitals involving over 30,000 hip or knee arthroplasties was recently published [70]. Patients were screened in the outpatient setting, and carriers were treated using mupirocin intranasally twice daily and bathed with chlorhexidine gluconate once daily for up to 5 days immediately before their operations. A modest but statistically significant decrease in *S. aureus* infections among hip or knee arthroplasties was found (difference per 10,000 operations, −17 [95% CI, −39 to 0]; RR, 0.48 [95% CI, 0.29 to 0.80]) [70]. However, patients during the intervention period were younger, had lower Charlson Comorbidity Index scores and were less likely to have a history of MRSA carriage (all of which are known risk factors for infection) than those during the pre-intervention period. Furthermore, and perhaps the major limitation of this finding is that patients were followed up for no more than 90 days after their operations which is admittedly a short period for determining PJI rates. Although the endogenous route of contamination in nasal carriers is clearly supported by the evidence, the exogenous *S. aureus* contamination pathway may still be preponderant in some settings. A French multicentre study including almost 4000 joint replacements found that most cases of *S. aureus* surgical site infections, either an endogenous origin could not be demonstrated or preoperative nasal colonization retrieved a strain that was different from the infecting pathogen [64]. Of the 22 documented *S. aureus* infections, 13 occurred in patients classified as nasal noncarriers and 9 in nasal carriers. Among nine carriers that developed infection, six were due to similar strains, and three were different.

This controversy has led us to perform research on this topic. We found a significant proportion of methicillin-sensitive *S. aureus* carriers (22%), but MRSA colonization was under 1% among our total joint replacement candidates [71]. There was a higher infection rate among carriers, but no clear benefit of the preoperative treatment protocol could be demonstrated [71]. We also showed that patients carrying *S. aureus* are significantly different from noncarriers regarding other variables that admittedly influence infection rates such as the presence of inflammatory arthritis [71]. Maoz et al. [11], analysing data from 3672 primary and 406 revision hip arthroplasties, also found *S. aureus* colonization to be associated with higher infection rate,

but it was not proven to be an independent risk factor as it was not significant in multivariate analysis.

Although treating known nasal carriers with intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash is currently recommended to prevent surgical site infection by the World Health Organization [35], the International Consensus Meeting (ICM) on PJI did not recommend universal screening of all patients undergoing joint arthroplasty [47]. Implementing a screening and targeted decolonization strategy in daily practice is complicated. A universal decolonization protocol would have the advantage of easy and less resource-consuming implementation, no carrier would be left untreated due to screening sensitivity issues or timely identification and treatment problems, and it would probably be less expensive as costs with screening outweigh treatment. The chief concern with universal decolonization is that unnecessary treatment may promote mupirocin resistance spread. Although it has been suggested that universal decolonization seems to be associated with an equally low risk of mupirocin resistance in *S. aureus*, a better option would be to find adequate alternatives for mupirocin nasal ointment [72]. Povidone-iodine-based skin and nasal antiseptic has already been shown to be just as effective as mupirocin with the added advantage of fast acting. Significant reductions in the levels of *S. aureus* CFU were found after just 1 h of treatment and extending up to 12 h [73]. There is some evidence that universal treatment with such products may be equally effective with significant cost savings and ease of implementation [74] but further studies are necessary.

2.1.9 Urine Screening

Concern with the genitourinary tract as a possible source of haematogenous seeding has been present as far back as the 1970s when a few case reports [75–77] and a retrospective study [78] found a relation between patients with deep joint infection and perioperative urinary tract infection (UTI). Although there seems to be enough evidence supporting a relation between postoperative symptomatic UTI and PJI [9, 19, 78–80], literature studying the correlation between asymptomatic bacteriuria (ASB) and surgical site infection after joint arthroplasty is scarce [80–84]. Nevertheless, urine screening before total joint replacement has found its way into clinical practice among the orthopaedic community. A recent survey in the United Kingdom revealed that two-thirds of surgeons would treat ASB prior to knee arthroplasty, although 70% would not have any evidence to cite evidence in favour of this practice [85].

This controversy has led us to perform research on this topic. The hypothesis was that a preoperative screening and treatment programme of asymptomatic bacteriuria (ASB) would potentially have an impact on prosthetic joint infection rates. To the best of our knowledge, with almost 2500 patients enrolled, it remains up to now the largest prospective survey of its kind [86]. We found the prevalence of asymptomatic bacteriuria among total joint replacement candidates to be around 12% (16% in women and 5% in men) which is comparable to previous descriptions of the prevalence of asymptomatic bacteriuria in similar age groups of the general population and other total joint replacement cohorts ranging from 4% to 19% [81, 83, 84, 87, 88].

Adjusting for known risk factors in a multivariate model, our data clearly show ASB independently raised the risk of PJI > threefold [86]. It is of great significance that microorganisms found in PJI had no direct correspondence with the species found in urine cultures [86]. These findings are also found in two previous classic papers, often cited to illustrate the lack of association between ASB and PJI despite the fact that PJI rate was found to be higher in ASB patients [81, 83]. Ritter and Fechtman [81] studied 364 total joint replacements and found the infection rate in ASB group was 2.8% and 0.6% in the non-ASB group. Glynn and Sheehan [83] reported data on 299 patients who underwent total joint replacement and found the infection rate in patients with bacteriuria was 3.5% and 0% in non-bacteriuria group. Notwithstanding, our cohort is much larger, which made it possible not only to show an increased risk for PJI but also a significant higher rate of

Gram- negative microorganisms [86]. However, we observed no difference in the infection rate comparing patients who underwent total joint arthroplasty after an appropriate course of preoperative antibiotics and those who did not [86]. This lack of benefit of preoperative bacteriuria treatment was also registered in a previous smaller study by Cordero-Ampuero et al. [84].

It is extremely difficult to be sure of the exact pathogenesis of infection. If ASB is an independent risk factor for PJI but no causal relation seems to exist, does ASB itself constitute a real threat or is it just a surrogate marker of vulnerability? If so, are the same mechanisms that facilitate urinary tract colonization involved in facilitating joint infection? Remarkably, a significantly higher proportion of Gram- negative bacteria PJI is found in ASB patients suggesting there is maybe some kind of specific susceptibility. Another possible explanation could be that skin flora of patients with ASB is different from patients without ASB. The study of Ollivere et al. [89] on a cohort of 558 elective for orthopaedic surgery patients supports the fact that ASB patients are at increased risk for wound contamination. Over 36% of the 39 patients with preoperative positive urine culture showed some form of postoperative delayed wound healing or confirmed superficial infection versus 16% in the other subgroup.

Currently available data advises against routine preoperative ASB screening and treatment due to its associated costs, possible side effects of unnecessary antibiotic therapy (i.e. adverse drug reactions, altering native flora, contributing to antimicrobial resistance) and, most of all, no apparent efficacy [90]. However, further trials are needed to clarify persistent questions. Until such trials can be completed, preoperative screening for ASB should be avoided, apart from careful research protocols. This statement should be interpreted cautiously, and it should not be extrapolated for those showing signs and symptoms of active urinary tract infection. It is reasonable to treat symptomatic UTI before surgery [47].

3 Perioperative Considerations

Before surgery, every patient should be educated about the importance of skin problems, and a thorough examination should be performed at admission. If any skin irregularity over the surgical site or the lower leg is present, a thorough assessment should be made regarding potential wound healing complications. Such skin problems may include

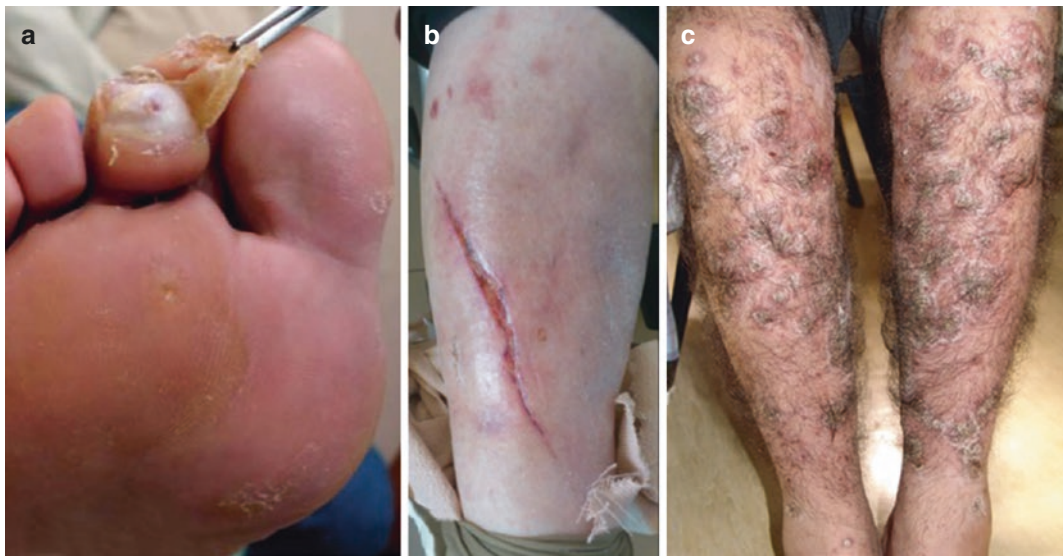


Fig. 2 Patients presenting for total joint arthroplasty with skin problems that had surgery postponed. (**a**) Second toe diabetic foot ulcer hidden beneath a callus (**b**) Cat scratch in the lower leg. (**c**) Plaque psoriasis in both lower legs

simple conditions such as abrasions, scratches from pets, contact dermatitis, eczema, psoriasis, skin ulcers or even cellulitis, and postponing surgery may be indicated [47] (Fig. 2).

3.1 Patient Preparation

Preoperative bathing is recommended in order to wash gross contamination and reduce bacterial load. Chlorhexidine is commonly used although there is no evidence to show a clear benefit for preoperative showering or bathing with chlorhexidine over other wash products [35, 91]. Chlorhexidine gluconate-impregnated cloths have also been advocated as a possible improvement over simple bathing. They are used by the patient at home during the morning of or the evening prior to surgery. There are scarce yet favourable results including a small prospective randomized trial, suggesting they are effective in decreasing the rate of infection in lower extremity TJA and surgeons may wish to consider using them [92–94].

Hair removal is also a classic concern. Although theoretically the patient's hair may be a source of contamination, it has been shown that there is no difference in infection rate among patients who have had hair removed prior to surgery and those who have not [35, 95]. Therefore, removing hair is not necessary unless the hair at or around the incision site will interfere with the operation, dressings or wound care. When hair removal is performed, concern over shaving has been raised because abrasions formed from the shaving process can become sites of bacterial growth. In fact, clipping as opposed to shaving is the preferred method for hair removal as it has been shown to lead to inferior infection rates [35, 95]. It is also consensual that hair removal should be performed as close to the time of the surgical procedure as possible [35, 47].

3.2 Skin Disinfection

The human skin is home to a large number of resident bacteria Although a small proportion are restricted to deeper layers and hair follicles and are not accessible to standard antiseptic formulations, most bacteria are located in superficial layers [96]. The aim of skin disinfection is to reduce the microbial load as much as possible before surgery both within the patient's own skin and the medical staff hands.

3.3 Surgical Site Skin Preparation

To date, no clear difference between various skin preparation agents has been established regarding the prevention of deep infection in total joint arthroplasty. Directly comparing chlorhexidine to povidone-iodine regarding skin antisepsis and rate of surgical site infection offers conflicting evidence. Darouiche et al. [97] showed that chlorhexidine-alcohol was significantly more protective than povidone-iodine against both superficial and deep infections after clean-contaminated surgery. However, iodine preparation used in this study was aqueous and not alcohol- based. This is a major issue as evidence suggests that combining alcohol with antiseptics may be critical. Two recent meta-analyses showed that alcohol-based antiseptic solutions are more effective than aqueous solutions in reducing the risk of surgical site infection [35, 98]. Swenson et al. [99] found that when alcohol was used (either as a solvent or a scrub following iodine paint), iodophor-based compounds may be superior to chlorhexidine. Other studies were unable to show a clear advantage of one agent over the other [100, 101]. Theoretically chlorhexidine would be more advantageous in a long-lasting surgery such as total joint arthroplasty, since its bactericidal effect is sustained over a longer period of time than iodophor-based compounds [102, 103]. In fact, current recommendations are to use alcohol-based chlorhexidine gluconate antiseptic solutions as pooled results seem to suggest it is more effective than povidone-iodine [35, 98].

Staff should be trained and informed about the potential harms of alcohol-based solutions. They should not come into contact with mucosa, and caution should be exercised to allow time for adequate drying as operating room fire is a real possibility.

As a final part of the surgical skin preparation, plastic adhesive drapes have been advocated as a way to protect the wound from organisms that may be present on the skin surrounding the incision. A recent Cochrane review [104] showed a significantly higher proportion of patients in the adhesive drape group developed a surgical site infection when compared with no drapes. Even the newer iodine-impregnated adhesive drapes had no effect on the surgical site infection rate [104]. As such their use is not recommended [35].

3.4 Surgical Team Handwash

Surgical team hand preparation is of vital importance no minimize surgical field contamination especially in the case of glove puncture that is not uncommon in arthroplasty surgery. However, much as for patient skin preparation, no consensus exists as to the optimum agent or duration of the wash. A 1997 study by Pereira et al. [105] showed chlorhexidine and povidone-iodine aqueous scrubs to be equally effective in reducing skin contamination. The same study offered evidence that alcohol-based antiseptics could be just as effective. A subsequent large, prospective multicentre equivalence cluster, randomized crossover study showed similar finding. Traditional (5 min) scrubbing methods with aqueous agents (4% chlorhexidine or 4% povidone-iodine) were equally effective at reducing the incidence of infection compared to a single handwash for 1 min with non-antiseptic soap at the start of the day followed by alcohol-only rubs [106]. A Cochrane systematic review [107] found that chlorhexidine gluconate scrubs may reduce the number of colony- forming units (CFU) on hands compared with povidone- iodine scrubs. They also found that alcohol rubs with additional antiseptic ingredients may reduce CFU compared with aqueous scrubs [107]. However, just how much clinical relevance this surrogate endpoint is at predicting surgical site infection is unknown, and there is no firm evidence that one type of hand antisepsis is better than another. In their systematic review, Allegranzi et al. [35] found a limited number of studies with surgical site infection as primary outcome, and they were also unable to find a difference between the use of alcohol-based solutions and povidone-iodine or chlorhexidine gluconate antimicrobial soap.

As such, alcohol hand rubs are effective and no more damaging to the skin than more time-consuming, conventional methods using detergent-based antiseptic wash. Although no evidence exists regarding this specific topic, we believe alcohol handwash seems to ensure more adequate compliance. Despite the variability present in the literature, a reasonable recommendation is to perform either a scrub or soap-and-water wash for the first case of the day (or whenever there is gross contamination) followed by surgical hand antisepsis using an alcohol-based product for a minimum of 2 min before each case.

3.5 Prophylactic Antibiotics

Surgical prophylactic antibiotic therapy refers to administering antimicrobial drug(s) to the operative site in effective concentrations to lessen the consequences of bacterial contamination thus reducing the number of clinically relevant infections. Its efficacy is currently indisputable, and it is widely endorsed as one of the most powerful tools used to reduce infection rate after TJA [35, 47, 108, 109].

3.5.1 Systemic Antibiotics

The goal is to reach optimal surgical site tissue concentrations of antibiotic(s) when the procedure begins. Therefore, it is usually recommended that they should be given within 60 min of the incision or the use of a tourniquet [47, 109]. There is evidence proving the administration of antibiotics after incision is associated with a significantly higher incidence of infection compared with administering them before incision [35, 110]. There is also enough evidence to support that administration earlier than 120 min is less effective [35]. In a large multicentre collaborative study, Steinberg et al. [111] found that infection risk increased incrementally as the time

interval between antibiotic infusion and the incision increased. They found a not quite significant trend towards reduced infection rate when antibiotics were infused within 30 min of incision (1.6%) compared to 31–60 min (2.4%). A Dutch multicentre study found a similar non-significant trend to reduced infection rates when prophylaxis was given in the preceding 30 min [110]. However, the authors of a systematic review did not find significant differences in time intervals under 120 min [35]. They do however recommend administration should occur closer to the incision time (<60 min) for antibiotics with a short half-life such as commonly used cephalosporins [35]. When a tourniquet is used, it should be inflated at least 5–10 min after antibiotic infusion in order to allow for adequate tissue concentrations [47, 112]. It has also been suggested that giving prophylactic antibiotics before tourniquet deflation may be just as effective (Table 1) [113].

In some circumstances, there is the need for repeat antibiotic dosing during surgery. The goal is to maintain adequate antibiotic concentrations throughout the procedure, and redosing is indicated if the procedure lasts longer than two half-lives of the chosen drug(s) or when there is increased blood loss and/or fluid resuscitation (>2000 mL) [35, 47, 109]. It is also agreed upon that the duration of antibiotic prophylaxis should not exceed 24 h postoperatively, and there is extensive evidence that a single preoperative dose (and possible additional intraoperative redosing) might not be inferior [47, 109, 114–116]. Longer regimens offer no added benefit and are associated with increased risk of development of resistance, increased risk of toxicity and even higher costs [109]. There is also no evidence to support continuing therapy while urinary catheter or surgical drains are in place [47].

While proof of its worth is overwhelming, specific antibiotic(s) regimen selection remains controversial. Level I evidence studies in this setting are difficult to perform. For example, to demonstrate a reduction in infection rate from 2% to 1% with a power of 90%, at the 95% confidence interval, a study would need over 3000 patients per group. For that reason, it is no surprise that no hard evidence favouring any drug(s) over another exists and therefore many different regimens can be adopted [109, 117]. Prophylactic antibiotics need to be effective against the most common organisms responsible for PJI. Given the varying levels of antibiotic resistance between institutions, it is often imperative to customize prophylaxis based on local trends. They should also have adequate pharmacokinetics and (ideally) reduced toxicity and side effects profile.

Table 1 Common antibiotics used for total joint arthroplasty prophylaxis

Drug	Recommended initial dose	Redosing schedule
Cefazolin	1 g (<80 kg body weight)	2–5 h
	2 g (80–120 kg body weight)	
	3 g (>120 kg body weight)	
Cefuroxime	1.5 g	3–4 h
Clindamycin	600–900 mg	3–6 h
Vancomycin	1 g or 10–15 mg/kg	6–12 h
Teicoplanin	600–800 mg or 10 mg/kg	None[a]

[a]Very long half-life precludes the need for redosing during surgery

Cephalosporins (first or second generation) are still widely recommended as first choice in orthopaedic surgery and TJA specifically [47, 109, 116]. This is due to their safety profile, broad-spectrum and good tissue penetration, low cost and proven effectiveness. Cefazolin tissue distribution reduces with increasing body weight and is lower in morbidly obese patients [118]. Dose adjustments are therefore required, and doses up to 3 g in patients over 120 kg are recommended [119]. In patients with documented or suspected allergy, clindamycin is a good choice. It has good bioavailability and shortly after infusion reaches effective bactericidal bone concentrations [120]. A 900 mg dose is recommended [109].

Vancomycin is another alternative in patients with documented beta-lactam allergy. There is increasing interest in vancomycin and other drugs which are effective against MRSA such as teicoplanin due to its significant prevalence in PJI also in Europe [58, 121]. In this regard, it has been shown that the standard 1 g dose may lead to suboptimal concentrations in a significant proportion of patients, thus recommending adopting a

15 mg/kg weight base dose [122]. A small trial focusing on total joint replacement specifically with little over 100 patients in each group in an institution, where MRSA and methicillin-resistant *S. epidermidis* prevalence exceeds 25% of orthopaedic infections, showed no advantage of vancomycin compared to cefuroxime or fusidic acid [123]. Merrer et al. [124] conducted a prospective observational study comparing the incidence of infection after vancomycin or cefazolin prophylaxis in femoral neck fracture and found no significant difference. Finkelstein et al. [125] in a study with slightly over 800 patients who underwent cardiac surgery requiring sternotomy showed an overall surgical site infection rate similar in both groups. There was a not significant trend towards lower proportion of MRSA in the vancomycin group [125]. In contrast, surgical site infections caused by methicillin-susceptible staphylococci were significantly more common in the vancomycin group [125]. Smith et al. [126] retrospectively analysed data comparing two historical cohorts after switching routine prophylaxis before TJA from cefazolin to vancomycin. Overall infection rate dropped from 1% (23/2221 primary TJA) during the earlier 29-month cefazolin period to 0.5% (14/2815 primary TJA) during the later 31-month vancomycin period [126]. The most significant improvement seen was a decrease in the number of coagulase-negative *Staphylococcus* infections. MRSA infections also decreased but the difference was not statistically significant. There was also a not significant increase in the number of methicillin-sensitive *S. aureus* and *Streptococcus* species infections [126]. Of course, the historical control group introduces a major bias in interpreting these results. In order to try and overcome this apparent limitation, dual- antibiotic regimens have been investigated [127, 128].

Sewick et al. [128] compared dual prophylaxis with cefazolin and vancomycin versus cefazolin alone. In their retrospective analysis of 1828 primary THA/TKA, with 1-year follow-up, the authors found that the rates of infection did not significantly differ (1.1% and 1.4%, respectively). Although the prevalence of MRSA infections was significantly lower in the dual-antibiotic group (0.02% and 0.08%, respectively), these infections were very rare, and therefore, the number needed to treat to prevent one MRSA infection was very high [128]. Courtney et al. [127] on the other hand looked at 500 primary THA/TKA performed with cefazolin prophylaxis and 1328 with cefazolin and vancomycin and found patients receiving dual antibiotics were more likely to develop acute kidney injury. The lack of clear evidence of efficacy and safety along with the concern of promoting bacterial vancomycin resistance advises against routine vancomycin use. In the United States of America, there seems to be an increasing frequency of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* (VISA and VRSA) isolates identified in clinical practice [129], but the problem is already present also in Europe with the first case being recently identified in Portugal [130].

As such, vancomycin prophylaxis is best reserved for cases of documented MRSA colonization or previous infection [47] or other cases with increased risk of methicillin-resistant infections such as institutionalized patients, healthcare workers or revision surgery [47, 131]. In addition, vancomycin administration is more cumbersome than other antibiotics. If administered too rapidly, vancomycin can cause histamine release, resulting in hypotension and a skin reaction called red man syndrome; therefore, infusion of vancomycin should take place over a longer period of time (60 to 120 min) [109]. Teicoplanin is an alternative that offers high and rapid soft tissue and bone penetration and is more easy and practical to administer than vancomycin. There are some favourable reports on the use of teicoplanin in total joint replacement showing that teicoplanin is at least as effective as traditional prophylaxis with the added advantage of addressing MRSA [132–134]. Recently, Tornero et al. [135] compared dual prophylaxis with cefuroxime and teicoplanin versus cefuroxime alone in patients undergoing primary lower limb arthroplasty. A significantly lower PJI rate was found in the dual-antibiotic group than in patients in the cefuroxime group, 1.3% (10/791) and 3.5% (35/995), respectively [135]. There was also a significant reduction of *S. aureus* infections with

no cases of *S. aureus* PJI in the combined prophylaxis group [135].

3.5.2 Antibiotic-Loaded Bone Cement

Routine use of local antibiotic prophylaxis using antibiotic-loaded bone cement (ALBC) is still a matter of open debate. Classical evidence of its efficacy comes from large studies of the Scandinavian hip registries [136, 137]. Malchau et al. [137] reported on 92,675 THA from the Swedish database performed from 1978 to 1990. They found significantly decreased rates of revision for infection with the use of gentamicin-containing cement [137]. Engesaeter et al. [136] presented the results of 22,170 THA procedures out of the Norwegian registry. They showed lower revision rates when antibiotic prophylaxis was given both systemically and in cement versus systemic or cement alone [136]. Information regarding total knee arthroplasty (TKA) is meagre and not as compelling. Earlier studies that suggest its efficacy are clearly underpowered [138, 139]. More recent studies by Namba et al. [140] and Hinarejos et al. [141] involving 2030 and 2948 total knee replacements performed with ALBC, respectively, failed to demonstrate superiority in reducing infection rates. This lack of effectiveness regarding infection as an endpoint is also shown by Bohm et al. [142] in a larger retrospective study including 20,016 TKA with plane cement and 16,665 with ALBC from the Canadian registry. They did find a significantly higher proportion of revision for aseptic loosening in the non- ALBC group [142]. Tayton et al. [12] recently presented the results of 64,566 TKA from the New Zealand joint registry. At the 12-month follow-up, there was no advantage in the infection rate among the 42,038 patients where ALBC was used (0.29%) compared to the 22,528 cases where plane cement as used (0.25%) [12]. Currently no conclusive evidence exists regarding the real efficacy of ALBC in preventing PJI [143–145].

There are also questions regarding mechanical issues. A classical concern is that adding antibiotic(s) to bone cement may have a negative impact on its mechanical strength. However, it has been proven that the doses required for prophylaxis (<2 g antibiotic per 40 g cement) do not compromise fixation which is critical to achieve a functional and painless joint [145]. This statement is further reinforced by the fact that a lower incidence of aseptic loosening is consistently found using ALBC [136, 142]. A more relevant concern is that routine use of ALBC may promote the emergence of antibiotic-resistant microorganisms and evidence seems to suggest this is real. An in vitro study by Thomes et al. [146] showed a lower overall rate of infection in the gentamicin-loaded cement group but also a significantly higher rate of gentamicin-resistant germs in this group. Hope et al. [147] on a study of 91 patients with deep infection of a cemented total hip arthroplasty demonstrated that the use of gentamicin-loaded cement was significantly associated with the emergence of gentamicin-resistant coagulase-negative staphylococci. This concern is further reinforced by recent clinical studies that have found an increasing prevalence of gentamicin-resistant microorganisms, especially coagulase-negative staphylococci [148, 149].

To this date, data on the use of ABLC in primary uncomplicated arthroplasty is mostly retrospective, and it is possible surgeons are using it in patients with higher baseline risk of infection. It is not entirely clear whether a potential advantage of using ABLC outweighs the potential disadvantage of its routine use such as promoting resistant microorganisms. Therefore, a clear recommendation for or against its use in the general population cannot be made. One common recommendation is to use it only in patients with a high risk of infection in primary arthroplasty (e.g. patients with diabetes mellitus, morbid obesity, prior history of PJI) and whenever cemented fixation is used for revision surgery [47, 109].

3.6 Operating Room Conditions

Despite all the recent advances in surgical site infection prophylaxis, respecting the rules of good conduit in the operating room (OR) may never be disregarded. Traffic in and out the OR increases air bacterial counts by two methods, bacterial shedding from the additional personnel

and air exchange between the OR and the hallway. Unwarranted traffic should therefore be avoided, and doors should be kept closed throughout surgery [47, 150, 151]. Optimizing OR conditions should be considered a team work including the surgeon as well as the rest of the surgical team and even hospital administrations whenever necessary.

3.7 Surgical Team Equipment

Over the years, surgical attire has remained relatively unchanged. This uniform has traditionally been thought to play two roles: to protect scrubbed personnel from exposure to body fluids and to maintain the sterile surgical field. Health care personnel is admittedly one of the major sources of bacterial contamination. However, many of our time-honoured practices have limited literature support.

The use of scrubs, masks and some kind of head covering has become universally recommended. Despite the absence of clear evidence-based proofs of efficacy, wearing them should be considered in the best interest of both patients and medical staff pending evidence of advantage to not wearing them. Sterilized surgical gowns are demonstrably relevant, and impervious gowns seem to be superior although no clear advantage of disposable non-woven versus reusable woven gowns has been shown [114, 152]. The use of sterilized gloves is absolutely critical and is introduction resulted in a dramatic reduction of surgical site infections [152]. Many orthopaedic surgeons prefer double gloving, but there is no direct evidence that additional glove protection reduces surgical site infections [152, 153]. Nevertheless, the addition of a second pair of surgical gloves significantly reduces perforations to innermost gloves and blood stains on the skin, indicating a decrease in percutaneous exposure incidents [153]. In addition to perforation, gloves are also at risk for bacterial contamination during the procedure. It is recommended that they are changed whenever they are perforated, before prosthesis implantation and after handling PMMA as it has been shown to affect permeability or at least every 90 min in longer surgeries [47].

In order to minimize bacterial shedding, body exhaust suits were initially described and popularized by Charnley in the 1970s [154]. Despite the initial enthusiasm around these suits in arthroplasty, their use remains controversial. In fact, modern day's data shows that compared with conventional clothing, the use of body exhaust suits could not be proven to provide more protection against microbial contamination [155, 156]. Recent data out of the New Zealand Joint Registry by Hooper et al. [157] also calls into question its efficacy. Their retrospective review included more than 50,000 primary THA and 30,000 primary TKA and showed that the use of space suits was actually associated with a significant increased rate of surgical site infections compared with traditional head coverings regardless of the type of operating room ventilation for both THA and TKA [157]. As such their use in routine joint replacement seems to be unjustified especially considering the added costs they represent.

3.8 Laminar Air Flow and Ultraviolet Lighting

Laminar air flow was also first introduced in THA surgery by Charnley [154]. In his paramount study, the use of laminar air flow and body exhaust suits showed an impressive (9% to 1%) reduction in the rate of infection. However, this study was undertaken before the implementation of routine antibiotic prophylaxis.

More recent studies question the real value of this methodology, especially considering its high cost. The first indication that antibiotic prophylaxis could reduce the impact of laminar air flow is brought by Lidwell et al. [158]. Although the infection rate in rooms with laminar air flow was 0.6% as opposed to 1.5% in rooms without it, they also found a significantly lower rate of infection (0.6%) in patients with preoperative antibiotics regardless of the laminar air flow. More recent data, reflecting modern OR air filtration and routine antibiotic prophylaxis, is not able to show an

advantage in the use of laminar air flow. A study including over 8000 total knee replacements in over 250 hospitals in the United States of America showed no significant advantage in laminar air flow [159]. Another major multicentre German study involving almost 100,000 surgeries and controlling for many patient and hospital-based confounders also found a lack of benefit in OR ventilation with laminar airflow [160]. They found it was even associated with a significantly higher risk for severe infection after hip prosthesis [160]. The same deleterious impact was noted by Tayton et al. [12] in their analysis of 64,566 primary TKA recorded on the New Zealand joint registry between 1999 and 2012. This seemingly paradoxical effect may be explained by several factors that influence air flow such as specific architectonic OR characteristics, equipment positioning, pressure and ventilation conditions or even lack of adequate protective clothing (i.e. body exhaust suits). As such, current recommendations state that laminar air flow should not be used to reduce infection rate in TJA surgery [114].

An alternative to laminar air flow could be the use of ultraviolet (UV) lighting. Ritter et al. [161] found a statistically significant reduction of infection in total joint arthroplasty with and without UV light. In their study with almost 6000 joint replacements, the infection rate with the use of laminar airflow and no UV lighting was 1.8%, and the infection rate with UV lighting only was 0.6%. Although the costs of its use are 100 times lower than laminar air flow, UV lighting throughout surgery is not without dangers that limit its use. It requires appropriate safety precautions and staff protective equipment to minimize the risk of cutaneous and ocular injuries that may still occur.

3.9 Patient Homeostasis

Despite the indisputable importance of enhancing operating room background, optimizing the host environment must not be overlooked. Patient homeostasis in the intraoperative and immediate postoperative period is also critical to reduce the risk of infection, and surgeons must articulate with anaesthesia staff and other operating room personnel.

Supplemental oxygen should be provided both intraoperatively and for 2–6 h in the immediate postoperative period [114]. Tissue oxygenation benefits are maximized when normothermia and normovolaemia are also maintained [114]. Warming devices should be used to avoid hypothermia that commonly occurs in prolonged surgical procedures because of impairment of thermoregulation by anaesthesia combined with body exposure to the cold environment in the operating room [114]. Adequate intravascular volume is an essential part of tissue perfusion and subsequent oxygenation. Intraoperative goal-directed fluid therapy has also been shown to reduce the risk of surgical site infection [114].

3.10 Duration of Surgery

Prolonged surgical time is consistently associated with increased risk of infection, and there seems to be a direct linear association [9, 11, 19, 26, 86, 140]. Naturally some surgeries are notably complex and will require more time. Still, some time-consuming variables are modifiable, and staff education in how to operate efficiently and follow systematically defined and predictable steps might decrease the risk of PJI.

4 Postoperative Considerations

It is thought that most surgical site infections occur as a consequence of intraoperative surgical field contamination. However, some may occur in the immediate or even in the late postoperative period.

4.1 Drains and Blood Management

Surgical wound drains are a widespread tradition after orthopaedic surgery and total joint arthroplasty specifically. The rationale behind its use is

to reduce the formation of haematoma and subsequent need for re-intervention or over infection. However, several studies have demonstrated they can be colonized by bacteria [162]. The risk of bacterial colonization is directly time related and increases dramatically after the first 24 h [163, 164]. It has also been suggested that the use of a surgical drain for more than 1 day may be associated with MRSA infection [165]. As such when choosing to use a drain in uncomplicated primary TJA, the authors believe it should be discontinued in the first 24 h. The main controversy is whether to use drains at all. Two recent meta-analyses on orthopaedic surgery [166] and total joint replacement specifically [167] both reached the same conclusion. No significant difference between the wounds treated with a drain and those treated without a drain was found with respect to the occurrence of wound infection, wound hematoma or reoperations for wound complications. On the other hand, a drained wound was significantly associated with a greater need for blood transfusion [166, 167].

Moreover there is increasing evidence that allogeneic blood transfusions, though required in some circumstances after joint replacement surgery, are not innocuous [168]. A retrospective 1999 study [169] found transfusion of allogeneic blood after total joint replacement was significantly associated with infection, fluid overload and increased duration of hospitalization. These findings have consistently been confirmed in more recent studies [19, 170–172]. Although the clear aetiology is not fully understood, it seems that some kind of adverse immunomodulation occurs. On the one hand, autologous blood transfusion does not seem to increase the risk so clearly [47]. Friedman et al. [170] looked at data from more than 12,000 patients after primary total hip or knee arthroplasty. Most of them received no transfusion (n = 6313), and among those requiring it, most received allogeneic blood (n = 3962), and some received autologous blood only (n = 1902). Infection rates in patients receiving no transfusion or autologous blood transfusion were similar. All kinds of infections, including wound infection, were significantly higher in patients receiving allogeneic blood transfusion [170]. On the other hand, allogeneic blood seems to be associated with a lower infection rate when it is depleted of leukocytes prior to transfusion although the real value of such practice in the total joint arthroplasty setting has not been established [173].

As such, orthopaedic surgeons should make an effort to reduce the need for perioperative allogeneic blood transfusions during total knee and total hip joint arthroplasty. A more restrictive haemoglobin threshold strategy is currently advisable with no evidence that it impacts mortality or morbidity after elective surgery [174]. Decision should be based on clinical and not just laboratory criteria. A discussion regarding preoperative haemoglobin optimization, cell salvage technology, the use of tranexamic acid or other strategies is beyond the scope of this chapter, but medical teams should be aware of this predicament when deciding whether or not to implement them or even use a drain.

4.2 Wound Care

Careful haemostasis and meticulous closure of the joint capsule and subcutaneous tissue at the end of the procedure to avoid dead space are crucial in obtaining good wound healing. Persistent wound drainage or wound dehiscence has been shown to be a significant risk factor for PJI [17, 175, 176]. Antimicrobial specifically triclosan-coated sutures seem to be effectively protective against infection [114].

The goal of wound dressings applied after closure is to provide physical support, protection and absorb exudate. The traditional approach to wound care after TJA consists of gauze bandages that are usually removed after 1 or 2 days with the idea that the wound re-epithelializes during that time and can then be left with a simple dressing. There is nonetheless no evidence that early removal of dressings (<48 h) has detrimental effect on outcomes [177]. In a further effort to prevent surgical site infection, commercial dressings have been developed to optimize wound healing, seal wound drainage and have antimicrobial properties. Occlusive dressings with

hydrofibre have shown favourable results after total joint arthroplasty, and its use was recommended in the latest International Consensus on PJI [47]. Ravenscroft et al. [178] in prospective randomized trial compared it against an absorbent perforated dressing and found that new hydrofibre occlusive dressing was 5.8 times more likely to result in a wound with no complications. A similar advantage regarding skin blisters, wound leakage and number of dressing changes has been repeatedly noted since [179, 180]. More recently, Cai et al. [181] retrospectively looked at a single institution experience of 903 consecutive total joint arthroplasty cases who received the occlusive hydrofibre dressing and 875 consecutive cases who received standard gauze dressing. The incidence of infection was significantly lower in the new dressing group, and multivariate analysis showed it was an independent protective. Grosso et al. [182] just recently confirmed the favourable impact of such dressings. Analysing the charts of more than 1100 patients, they found a fourfold decrease in acute PJI with the use of occlusive silver-impregnated hydrofibre dressing. Body of evidence is not enough to make a strong recommendation regarding the additive value of silver, and aspects such as costs should be taken into consideration [183]. The addition of topical antibiotics is also probably beneficial in reducing the risk of infection in people with surgical wound healing by primary intention compared with no topical antibiotic, although the specific role of different antibiotic(s) or even its role in promoting antibiotic resistance or possible adverse reactions such as contact dermatitis are unclear [184].

4.3 Urinary Catheter

Indwelling urinary catheterization is often used to facilitate patient care in the first postoperative hours and days after TJA, and it has been shown to reduce the incidence of urinary retention [185]. However, urinary tract infection is a frequent minor complication after TJA especially in older females [186], and, as previously discussed, postoperative symptomatic UTI is an established risk factor for PJI [19, 84, 86].

Wald et al. [187] confirmed the empirical awareness that prolonged catheterization increases the risk of UTI and defined a threshold at 2 days. As such, surgeons must keep in mind that urinary catheterization is not without risks and efforts should be made to avoid it or minimize its length of stay. Stephan et al. [188] showed that a multifaceted prevention strategy can dramatically decrease both the frequency and duration of urinary catheterization thus decreasing urinary tract infection after surgery.

4.4 Duration of Hospital Stay

Prolonged hospital stay is an important risk factor for the occurrence of infection after hip replacement [11, 19, 26, 189]. Not only do these patients tend to have more medical comorbidities as they are also more exposed to nosocomial usually more virulent microorganisms. Decreasing the duration of hospital stay depends on many factors. Of course preoperative optimization of patient comorbidities is paramount, but also proper patient education, optimal pain management, blood-sparing strategies, adequate anticoagulation and early ambulation collectively known as “fast-track” surgery seem to play a major role in diminishing length of stay without increasing complications [190].

5 Prevention of Late Haematogenous Infections

Even after successful procedures with uneventful wound healing and rehabilitation, patients with any kind of joint arthroplasty are at risk of developing late infections [189, 191]. Late haematogenous PJI usually manifests itself with clear clinical and/or radiographical signs of infection occurring after an initial asymptomatic period [192]. They most often arise as a result of bacteraemia episodes and should be distinguished from those that result of intraoperative contamination.

The strongest evidence for an extra-articular source of PJI would be to culture the same pathogen both in the joint and the extra-articular site. Notwithstanding, that is not possible in a signifi-

cant proportion of cases, and presumed aetiology is therefore assumed [193]. Most late haematogenous infections are sequelae of *Staphylococcus aureus* sepsis, skin infection or urosepsis [70, 194–196]. It has been shown that the risk of developing PJI after a documented *S. aureus* bacteraemia may be as high as 30–40% [195, 196]. Naturally, other conditions such as infective endocarditis, pneumonia, gastrointestinal system inflammatory conditions, IV drug users and even dental abscesses have also been implicated [9, 197–199]. Any active bacterial infections in a patient bearing prosthetic joint(s) should be promptly diagnosed and treated to prevent bacterial seeding. Extra-articular sources that contribute to late PJI should be identified by obtaining clinical history and performing a thorough physical exam, laboratory testing, adequate imaging and examination by specialists whenever required.

Although cases described in the literature are exceptional, it is hypothetically believable that a small portion of these cases are caused by transient bacteraemia during invasive medical procedures. The question whether patients undergoing such procedures (e.g. dental, urologic or gastrointestinal) should undergo specific antibiotic prophylaxis is still matter of open debate. A recent International Consensus Meeting [47] acknowledged the conflicting evidence available and recommended the use of antibiotic prophylaxis on an individual basis, according to patient risk factors and the type and invasiveness of the procedure to be performed [47]. The risk of bacteraemia is, of course, directly related to the invasiveness of the procedure. Techniques such as dental extraction or scaling [200], oesophageal dilation or variceal sclerotherapy [201] and transurethral prostate resection [202] or transrectal prostate biopsy [203] pose higher risks than simple endodontic treatment, flexible colonoscopies, esophagogastroduodenoscopies or simple cystoscopy. Regarding dental procedures, the consensus recommends one dose of antibiotics be given about 1 h prior to the procedure in all patients within the first 2 years after surgery [47]. High- risk patients (e.g. previous prosthetic joint infection, inflammatory arthropathies, immunosuppression, diabetes, etc.) should consider doing it during their entire lifetime [47]. In gastrointestinal endoscopic procedures, prophylaxis is recommended routinely especially in high-risk patients [47]. The same is true for genitourinary procedures, especially in patients with bacteriuria that has been shown to significantly increase the risk of bacteraemia [204].

However, this recommendation is not consensual, and this is not surprising given the paucity of strong clinical evidence. The lack of clear evidence and the potential risks of antibiotic use such as toxicity, allergy and the promotion of microbial resistance have lead other experts to advise against routine antibiotic prophylaxis [205, 206]. Ultimately the decision relies on clinical judgement of the treating physician taking into consideration an individual patient risk/benefit analysis.

References

1. Kamath AF, Ong KL, Lau E, Chan V, Vail TP, Rubash HE, Berry DJ, Bozic KJ (2015) Quantifying the burden of revision total joint arthroplasty for periprosthetic infection. J Arthroplast 30(9):1492–1497
2. Norwegian National Advisory Unit on Arthroplasty and hip Fractures 2015 Annual Report. Report June 2015. http://nrlweb.ihelse.net/Rapporter/Report2015_english.pdf. Accessed 29 Apr 2017
3. National Joint Replacement Registry. Supplementary Report 2016—Revision Hip and Knee Arthroplasty. https://aoanjrr.sahmri.com/documents/10180/275107. Accessed 29 Apr 2017
4. Padegimas EM, Maltenfort M, Ramsey ML, Williams GR, Parvizi J, Namdari S (2015) Periprosthetic shoulder infection in the United States: incidence and economic burden. J Shoulder Elb Surg 24(5):741–746
5. National Joint Registry for England Wales Northern Ireland and the Isle of Man. 13th Annual Report. http://www.hqip.org.uk/media/NJR/NJR Annual Report 2016.pdf. Accessed 29 Apr 2017
6. Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J (2013) Periprosthetic joint infection increases the risk of one-year mortality. J Bone Joint Surg Am 95(24):2177–2184
7. Matsen Ko LJ, Yoo JY, Maltenfort M, Hughes A, Smith EB, Sharkey PF (2016) The effect of implementing a multimodal approach on the rates of periprosthetic joint infection after total joint arthroplasty. J Arthroplast 31(2):451–455
8. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD (2016) Patient-related risk factors for peripros-

thetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. PLoS One 11(3):e0150866
9. Cordero-Ampuero J, de Dios M (2010) What are the risk factors for infection in hemiarthroplasties and total hip arthroplasties? Clin Orthop Relat Res 468(12):3268–3277
10. Everhart JS, Altneu E, Calhoun JH (2013) Medical comorbidities are independent preoperative risk factors for surgical infection after total joint arthroplasty. Clin Orthop Relat Res 471(10):3112–3119
11. Maoz G, Phillips M, Bosco J, Slover J, Stachel A, Inneh I, Iorio R (2015) The otto aufranc award: modifiable versus nonmodifiable risk factors for infection after hip arthroplasty. Clin Orthop Relat Res 473(2):453–459
12. Tayton ER, Frampton C, Hooper GJ, Young SW (2016) The impact of patient and surgical factors on the rate of infection after primary total knee arthroplasty: an analysis of 64,566 joints from the New Zealand Joint Registry. Bone Joint J 98-B(3):334–340
13. Peersman G, Laskin R, Davis J, Peterson M (2001) Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Clin Orthop Relat Res 392:15–23
14. Bozic KJ, Ong K, Lau E, Berry DJ, Vail TP, Kurtz SM, Rubash HE (2013) Estimating risk in Medicare patients with THA: an electronic risk calculator for periprosthetic joint infection and mortality. Clin Orthop Relat Res 471(2):574–583
15. Berbari EF, Osmon D, Lahr B, Eckel-Passow JE, Tsaras G, Hanssen AD, Mabry T, Steckelberg J, Thompson R (2012) The Mayo prosthetic joint infection risk score: implication for surgical site infection reporting and risk stratification. Infect Control Hosp Epidemiol 33(8):774–781
16. Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ (2012) Patient-related risk factors for postoperative mortality and periprosthetic joint infection in Medicare patients undergoing TKA. Clin Orthop Relat Res 470(1):130–137
17. Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y (2015) Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. J Hosp Infect 89(2):82–89
18. Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, Berry DJ (2012) Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am 94(9):794–800
19. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J (2008) Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res 466(7):1710–1715
20. Marchant MH Jr, Viens NA, Cook C, Vail TP, Bolognesi MP (2009) The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am 91(7):1621–1629
21. Giori NJ, Ellerbe LS, Bowe T, Gupta S, Harris AH (2014) Many diabetic total joint arthroplasty candidates are unable to achieve a preoperative hemoglobin A1c goal of 7% or less. J Bone Joint Surg Am 96(6):500–504
22. Harris AH, Bowe TR, Gupta S, Ellerbe LS, Giori NJ (2013) Hemoglobin A1C as a marker for surgical risk in diabetic patients undergoing total joint arthroplasty. J Arthroplast 28(8 Suppl):25–29
23. Mraovic B, Suh D, Jacovides C, Parvizi J (2011) Perioperative hyperglycemia and postoperative infection after lower limb arthroplasty. J Diabetes Sci Technol 5(2):412–418
24. Stryker LS, Abdel MP, Morrey ME, Morrow MM, Kor DJ, Morrey BF (2013) Elevated postoperative blood glucose and preoperative hemoglobin A1C are associated with increased wound complications following total joint arthroplasty. J Bone Joint Surg Am 95(9):808–814
25. Hwang JS, Kim SJ, Bamne AB, Na YG, Kim TK (2015) Do glycemic markers predict occurrence of complications after total knee arthroplasty in patients with diabetes? Clin Orthop Relat Res 473(5):1726–1731
26. Urquhart DM, Hanna FS, Brennan SL, Wluka AE, Leder K, Cameron PA, Graves SE, Cicuttini FM (2010) Incidence and risk factors for deep surgical site infection after primary total hip arthroplasty: a systematic review. J Arthroplast 25(8): 1216–1222
27. Dowsey MM, Choong PF (2008) Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res 466(1):153–158
28. Lubbeke A, Zingg M, Vu D, Miozzari HH, Christofilopoulos P, Uckay I, Harbarth S, Hoffmeyer P (2016) Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthop 87(2):132–138
29. Watts C, Martin JR, Houdek M, Abdel M, Lewallen D, Taunton M (2016) Prior bariatric surgery may decrease the rate of re-operation and revision following total hip arthroplasty. Bone Joint J 98-B(9):1180–1184
30. Inacio MC, Paxton EW, Fisher D, Li RA, Barber TC, Singh JA (2014) Bariatric surgery prior to total joint arthroplasty may not provide dramatic improvements in post-arthroplasty surgical outcomes. J Arthroplast 29(7):1359–1364
31. Kulkarni A, Jameson S, James P, Woodcock S, Muller S, Ree MR (2011) Does bariatric surgery prior to lower limb joint replacement reduce complications? Surgeon 9(1):18–21
32. Smith TO, Aboelmagd T, Hing CB, MacGregor A (2016) Does bariatric surgery prior to total hip or knee arthroplasty reduce post-operative complications and improve clinical outcomes for obese patients? Systematic review and meta-analysis. Bone Joint J 98-B(9):1160–1166

33. Greene KA, Wilde AH, Stulberg BN (1991) Preoperative nutritional status of total joint patients. Relationship to postoperative wound complications. J Arthroplast 6(4):321–325
34. Marin LA, Salido JA, Lopez A, Silva A (2002) Preoperative nutritional evaluation as a prognostic tool for wound healing. Acta Orthop Scand 73(1):2–5
35. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, Abbas M, Atema JJ, Gans S, van Rijen M, Boermeester MA, Egger M, Kluytmans J, Pittet D, Solomkin JS (2016) New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 16(12):e276–ee87
36. Borghi B, Casati A (2000) Incidence and risk factors for allogenic blood transfusion during major joint replacement using an integrated autotransfusion regimen. The Rizzoli study group on Orthopaedic Anaesthesia. Eur J Anaesthesiol 17(7):411–417
37. Spahn DR (2010) Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology 113(2):482–495
38. Lee JJ, Patel R, Biermann JS, Dougherty PJ (2013) The musculoskeletal effects of cigarette smoking. J Bone Joint Surg Am 95(9):850–859
39. Singh JA, Houston TK, Ponce BA, Maddox G, Bishop MJ, Richman J, Campagna EJ, Henderson WG, Hawn MT (2011) Smoking as a risk factor for short-term outcomes following primary total hip and total knee replacement in veterans. Arthritis Care Res 63(10):1365–1374
40. Tonnesen H, Nielsen PR, Lauritzen JB, Moller AM (2009) Smoking and alcohol intervention before surgery: evidence for best practice. Br J Anaesth 102(3):297–306
41. Warner DO (2006) Perioperative abstinence from cigarettes: physiologic and clinical consequences. Anesthesiology 104(2):356–367
42. Thomsen T, Tonnesen H, Moller AM (2009) Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg 96(5):451–461
43. Wong J, Lam DP, Abrishami A, Chan MTV, Chung F (2012) Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. Can J Anaesth 59(3):268–279
44. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO (2011) Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med 124(2):144–154
45. Moller AM, Villebro N, Pedersen T, Tonnesen H (2002) Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet 359(9301):114–117
46. Harris AH, Reeder R, Ellerbe L, Bradley KA, Rubinsky AD, Giori NJ (2011) Preoperative alcohol screening scores: association with complications in men undergoing total joint arthroplasty. J Bone Joint Surg Am 93(4):321–327
47. Gehrke T, Parvizi J. Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection. 2013. https://www.efort.org/wp-content/uploads/2013/10/Philadelphia_Consensus.pdf. Accessed 29 Apr 2017
48. Ravi B, Croxford R, Hollands S, Paterson JM, Bogoch E, Kreder H, Hawker GA (2014) Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheum 66(2):254–263
49. Bongartz T, Halligan CS, Osmon DR, Reinalda MS, Bamlet WR, Crowson CS, Hanssen AD, Matteson EL (2008) Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Rheum 59(12):1713–1720
50. Ledford CK, Watters TS, Wellman SS, Attarian DE, Bolognesi MP (2014) Risk versus reward: total joint arthroplasty outcomes after various solid organ transplantations. J Arthroplast 29(8): 1548–1552
51. Grennan DM, Gray J, Loudon J, Fear S (2001) Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 60(3):214–217
52. Momohara S, Kawakami K, Iwamoto T, Yano K, Sakuma Y, Hiroshima R, Imamura H, Masuda I, Tokita A, Ikari K (2011) Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. Mod Rheumatol 21(5):469–475
53. Graham SM, Lubega N, Mkandawire N, Harrison WJ (2014) Total hip replacement in HIV-positive patients. Bone Joint J 96-B(4):462–466
54. Capogna BM, Lovy A, Blum Y, Kim SJ, Felsen UR, Geller DS (2013) Infection rate following total joint arthroplasty in the HIV population. J Arthroplast 28(8):1254–1258
55. Lin CA, Kuo AC, Takemoto S, Takemoto S (2013) Comorbidities and perioperative complications in HIV-positive patients undergoing primary total hip and knee arthroplasty. J Bone Joint Surg Am 95(11):1028–1036
56. Lin CA, Takemoto S, Kandemir U, Kuo AC (2014) Mid-term outcomes in HIV-positive patients after primary total hip or knee arthroplasty. J Arthroplast 29(2):277–282
57. Barrington JW, Barrington TA (2011) What is the true incidence of dental pathology in the total joint arthroplasty population? J Arthroplast 26(6 Suppl):88–91
58. Sousa R, Pereira A, Massada M, Vieira da Silva M, Lemos R (2010) Costa e Castro J. Empirical antibiotic therapy in prosthetic joint infections. Acta Orthop Belg 76(2):254–259

59. Price CS, Williams A, Philips G, Dayton M, Smith W, Morgan S (2008) Staphylococcus aureus nasal colonization in preoperative orthopaedic outpatients. Clin Orthop Relat Res 466(11):2842–2847
60. Lucet JC, Regnier B (2010) Screening and decolonization: does methicillin-susceptible Staphylococcus aureus hold lessons for methicillin-resistant S. aureus? Clin Infect Dis 51(5):585–590
61. Yano K, Minoda Y, Sakawa A, Kuwano Y, Kondo K, Fukushima W, Tada K (2009) Positive nasal culture of methicillin-resistant Staphylococcus aureus (MRSA) is a risk factor for surgical site infection in orthopedics. Acta Orthop 80(4):486–490
62. Kalmeijer MD, van Nieuwland-Bollen E, Bogaers-Hofman D, de Baere GA (2000) Nasal carriage of Staphylococcus aureus is a major risk factor for surgical-site infections in orthopedic surgery. Infect Control Hosp Epidemiol 21(5):319–323
63. Hacek DM, Robb WJ, Paule SM, Kudrna JC, Stamos VP, Peterson LR (2008) Staphylococcus aureus nasal decolonization in joint replacement surgery reduces infection. Clin Orthop Relat Res 466(6):1349–1355
64. Berthelot P, Grattard F, Cazorla C, Passot JP, Fayard JP, Meley R, Bejuy J, Farizon F, Pozzetto B, Lucht F (2010) Is nasal carriage of Staphylococcus aureus the main acquisition pathway for surgical-site infection in orthopaedic surgery? Eur J Clin Microbiol Infect Dis 29(4):373–382
65. Skramm I, Fossum Moen AE, Aroen A, Bukholm G (2014) Surgical site infections in orthopaedic surgery demonstrate clones similar to those in orthopaedic staphylococcus aureus nasal carriers. J Bone Joint Surg Am 96(11):882–888
66. Levy PY, Ollivier M, Drancourt M, Raoult D, Argenson JN (2013) Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis. Orthop Traumatol Surg Res 99(6):645–651
67. Bode LG, Kluytmans JA, Wertheim HFL, Bogaers D, Vandenbroucke-Grauls CMJE, Roosendaal R, Troelstra A, Box ATA, Voss A, van der Tweel I, van Belkum A, Verbrugh HA, Vos MC (2010) Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med 362(1):9–17
68. Kim DH, Spencer M, Davidson SM, Li L, Shaw JD, Gulczynski D, Hunter DJ, Martha JF, Miley GB, Parazin SJ, Dejoie P, Richmond JC (2010) Institutional prescreening for detection and eradication of methicillin-resistant Staphylococcus aureus in patients undergoing elective orthopaedic surgery. J Bone Joint Surg Am 92(9):1820–1826
69. Rao N, Cannella BA, Crossett LS, Yates AJ Jr, McGough RL 3rd, Hamilton CW (2011) Preoperative screening/decolonization for Staphylococcus aureus to prevent orthopedic surgical site infection: prospective cohort study with 2-year follow-up. J Arthroplast 26(8):1501–1507
70. Schweizer ML, Chiang HY, Septimus E, Moody J, Braun B, Hafner J, Ward MA, Hickok J, Perencevich EN, Diekema DJ, Richards CL, Cavanaugh JE, Perlin JB, Herwaldt LA (2015) Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. J Am Med Assoc 313(21):2162–2171
71. Sousa R, Barreira P, Leite P, Santos AC, Ramos MH, Oliveira A (2016) Preoperative Staphylococcus aureus screening/decolonization protocol before total joint arthroplasty-results of a small prospective randomized trial. J Arthroplast 31(1):234–239
72. Hetem DJ, Bootsma MC, Bonten MJ (2016) Prevention of surgical site infections: decontamination with mupirocin based on preoperative screening for staphylococcus aureus carriers or universal decontamination? Clin Infect Dis 62(5):631–636
73. Anderson MJ, David ML, Scholz M, Bull SJ, Morse D, Hulse-Stevens M, Peterson ML (2015) Efficacy of skin and nasal povidone-iodine preparation against mupirocin-resistant methicillin-resistant Staphylococcus aureus and S. aureus within the anterior nares. Antimicrob Agents Chemother 59(5):2765–2773
74. Torres EG, Lindmair-Snell JM, Langan JW, Burnikel BG (2016) Is preoperative nasal povidone-iodine as efficient and cost-effective as standard methicillin-resistant staphylococcus aureus screening protocol in total joint arthroplasty? J Arthroplast 31(1):215–218
75. Burton DS, Schurman DJ (1975) Hematogenous infection in bilateral total hip arthroplasty. Case report. J Bone Joint Surg Am 57(7):1004–1005
76. Cruess RL, Bickel WS, vonKessler KL (1975) Infections in total hips secondary to a primary source elsewhere. Clin Orthop Relat Res 106:99–101
77. Hall AJ (1974) Late infection about a total knee prosthesis. Report of a case secondary to urinary tract infection. J Bone Joint Surg (Br) 56(1):144–147
78. Irvine R, Johnson BL Jr, Amstutz HC (1974) The relationship of genitourinary tract procedures and deep sepsis after total hip replacements. Surg Gynecol Obstet 139(5):701–706
79. David TS, Vrahas MS (2000) Perioperative lower urinary tract infections and deep sepsis in patients undergoing total joint arthroplasty. J Am Acad Orthop Surg 8(1):66–74
80. Wymenga AB, van Horn JR, Theeuwes A, Muytjens HL, Slooff TJ (1992) Perioperative factors associated with septic arthritis after arthroplasty. Prospective multicenter study of 362 knee and 2,651 hip operations. Acta Orthop Scand 63(6):665–671
81. Ritter MA, Fechtman RW (1987) Urinary tract sequelae: possible influence on joint infections following total joint replacement. Orthopedics 10(3):467–469
82. Koulouvaris P, Sculco P, Finerty E, Sculco T, Sharrock NE (2009) Relationship between perioperative urinary tract infection and deep infec-

tion after joint arthroplasty. Clin Orthop Relat Res 467(7):1859–1867
83. Glynn MK, Sheehan JM (1984) The significance of asymptomatic bacteriuria in patients undergoing hip/knee arthroplasty. Clin Orthop Relat Res 185:151–154
84. Cordero-Ampuero J, Gonzalez-Fernandez E, Martinez-Velez D, Esteban J (2013) Are antibiotics necessary in hip arthroplasty with asymptomatic bacteriuria? Seeding risk with/without treatment. Clin Orthop Relat Res 471(12):3822–3829
85. Finnigan TKP, Bhutta MA, Shepard GJ (2012) Asymptomatic bacteriuria prior to arthroplasty: how do you treat yours? J Bone Joint Surg (Br) 94-B(Supp XXIX 58):23–29
86. Sousa R, Munoz-Mahamud E, Quayle J, Dias da Costa L, Casals C, Scott P, Leite P, Vilanova P, Garcia S, Ramos MH, Dias J, Soriano A, Guyot A (2014) Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? Clin Infect Dis 59(1):41–47
87. Juthani-Mehta M (2007) Asymptomatic bacteriuria and urinary tract infection in older adults. Clin Geriatr Med 23(3):585–594
88. Bailey RR, Peddie BA, Gorrie SI, Hume C, Gillespie WJ (1988) Prevalence of asymptomatic bacteriuria in patients presenting for total hip or knee replacement. N Z Med J 101(839):6
89. Ollivere BJ, Ellahee N, Logan K, Miller-Jones JCA, Allen PW (2009) Asymptomatic urinary tract colonisation predisposes to superficial wound infection in elective orthopaedic surgery. Int Orthop 33(3):847–850
90. Duncan RA (2014) Prosthetic joint replacement: should orthopedists check urine because it's there? Clin Infect Dis 59(1):48–50
91. Webster J, Osborne S (2015) Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. Cochrane Database Syst Rev 2:CD004985
92. Kapadia BH, Elmallah RK, Mont MA (2016) A randomized, clinical trial of preadmission chlorhexidine skin preparation for lower extremity total joint arthroplasty. J Arthroplast 31(12):2856–2861
93. Kapadia BH, Jauregui JJ, Murray DP, Mont MA (2016) Does preadmission cutaneous chlorhexidine preparation reduce surgical site infections after total hip arthroplasty? Clin Orthop Relat Res 474(7):1583–1588
94. Kapadia BH, Zhou PL, Jauregui JJ, Mont MA (2016) Does preadmission cutaneous chlorhexidine preparation reduce surgical site infections after total knee arthroplasty? Clin Orthop Relat Res 474(7):1592–1598
95. Tanner J, Norrie P, Melen K (2011) Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev 11:CD004122
96. Lange-Asschenfeldt B, Marenbach D, Lang C, Patzelt A, Ulrich M, Maltusch A, Terhorst D, Stockfleth E, Sterry W, Lademann J (2011) Distribution of bacteria in the epidermal layers and hair follicles of the human skin. Skin Pharmacol Physiol 24(6):305–311
97. Darouiche RO, Wall MJJ, Itani KMF, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH (2010) Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med 362(1):18–26
98. Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z (2015) Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Cochrane Database Syst Rev 4:CD003949
99. Swenson BR, TLl H, Metzger R, Bonatti H, Pruett TL, Sawyer RG (2009) Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. Infect Control Hosp Epidemiol 30(10):964–971
100. Sistla SC, Prabhu G, Sistla S, Sadasivan J (2010) Minimizing wound contamination in a 'clean' surgery: comparison of chlorhexidine-ethanol and povidone-iodine. Chemotherapy 56(4):261–267
101. Saltzman MD, Nuber GW, Gryzlo SM, Marecek GS, Koh JL (2009) Efficacy of surgical preparation solutions in shoulder surgery. J Bone Joint Surg Am 91(8):1949–1953
102. Johnson AJ, Daley JA, Zywiel MG, Delanois RE, Mont MA (2010) Preoperative chlorhexidine preparation and the incidence of surgical site infections after hip arthroplasty. J Arthroplast 25(6 Suppl):98–102
103. Dahl J, Wheeler B, Mukherjee D (1990) Effect of chlorhexidine scrub on postoperative bacterial counts. Am J Surg 159(5):486–488
104. Webster J, Alghamdi A (2015) Use of plastic adhesive drapes during surgery for preventing surgical site infection. Cochrane Database Syst Rev 4:CD006353
105. Pereira LJ, Lee GM, Wade KJ (1997) An evaluation of five protocols for surgical handwashing in relation to skin condition and microbial counts. J Hosp Infect 36(1):49–65
106. Parienti JJ, Thibon P, Heller R, Le Roux Y, von Theobald P, Bensadoun H, Bouvet A, Lemarchand F, Le Coutour X (2002) Hand-rubbing with an aqueous alcoholic solution vs traditional surgical handscrubbing and 30-day surgical site infection rates: a randomized equivalence study. J Am Med Assoc 288(6):722–727
107. Tanner J, Dumville JC, Norman G, Fortnam M (2016) Surgical hand antisepsis to reduce surgical site infection. Cochrane Database Syst Rev 1:CD004288
108. Merollini KM, Zheng H, Graves N (2013) Most relevant strategies for preventing surgical site infection after total hip arthroplasty: guideline recommendations and expert opinion. Am J Infect Control 41(3):221–226
109. Bosco JA, Bookman J, Slover J, Edusei E, Levine B (2015) Principles of antibiotic prophylaxis in total

joint arthroplasty: current concepts. J Am Acad Orthop Surg 23(8):e27–e35
110. van Kasteren ME, Mannien J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC (2007) Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 44(7):921–927
111. Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, Dellinger EP, Burke JP, Simmons B, Kritchevsky SB (2009) Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the trial to reduce antimicrobial prophylaxis errors. Ann Surg 250(1): 10–16
112. Friedman RJ, Friedrich LV, White RL, Kays MB, Brundage DM, Graham J (1990) Antibiotic prophylaxis and tourniquet inflation in total knee arthroplasty. Clin Orthop Relat Res 260:17–23
113. Soriano A, Bori G, Garcia-Ramiro S, Martinez-Pastor JC, Miana T, Codina C, Macule F, Basora M, Martinez JA, Riba J, Suso S, Mensa J (2008) Timing of antibiotic prophylaxis for primary total knee arthroplasty performed during ischemia. Clin Infect Dis 46(7):1009–1014
114. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, Gomes SM, Gans S, Wallert ED, Wu X, Abbas M, Boermeester MA, Dellinger EP, Egger M, Gastmeier P, Guirao X, Ren J, Pittet D, Solomkin JS (2016) New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 16(12):e288–e303
115. Wymenga AB, Hekster YA, Theeuwes A, Muytjens HL, van Horn JR, Slooff TJ (1991) Antibiotic use after cefuroxime prophylaxis in hip and knee joint replacement. Clin Pharmacol Ther 50(2):215–220
116. Tang WM, Chiu KY, Ng TP, Yau WP, Ching PTY, Seto WH (2003) Efficacy of a single dose of cefazolin as a prophylactic antibiotic in primary arthroplasty. J Arthroplast 18(6):714–718
117. Aujla RS, Bryson DJ, Gulihar A, Taylor GJ (2013) Trends in orthopaedic antimicrobial prophylaxis in the UK between 2005 and 2011. Ann R Coll Surg Engl 95(7):495–502
118. Brill MJ, Houwink AP, Schmidt S, Van Dongen EPA, Hazebroek EJ, van Ramshorst B, Deneer VH, Mouton JW, Knibbe CAJ (2014) Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. J Antimicrob Chemother 69(3):715–723
119. Ho VP, Nicolau DP, Dakin GF, Pomp A, Rich BS, Towe CW, Barie PS (2012) Cefazolin dosing for surgical prophylaxis in morbidly obese patients. Surg Infect 13(1):33–37
120. Darley ES, MacGowan AP (2004) Antibiotic treatment of gram-positive bone and joint infections. J Antimicrob Chemother 53(6):928–935
121. European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe. 2010–2011. http://ecdc.europa.eu/en/publications/Publications/SSI-in-europe-2010-2011.pdf. 2013 Accessed 30 Apr 2017
122. Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J 3rd (2014) The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. Iowa Orthop J 34:111–117
123. Tyllianakis ME, Karageorgos ACH, Marangos MN, Saridis AG, Lambiris EE (2010) Antibiotic prophylaxis in primary hip and knee arthroplasty: comparison between cefuroxime and two specific antistaphylococcal agents. J Arthroplast 25(7):1078–1082
124. Merrer J, Desbouchages L, Serazin V, Razafimamonjy J, Pauthier F, Leneveu M (2006) Comparison of routine prophylaxis with vancomycin or cefazolin for femoral neck fracture surgery: microbiological and clinical outcomes. Infect Control Hosp Epidemiol 27(12):1366–1371
125. Finkelstein R, Rabino G, Mashiah T, Bar-El Y, Adler Z, Kertzman V, Cohen O, Milo S (2002) Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. J Thorac Cardiovasc Surg 123(2):326–332
126. Smith EB, Wynne R, Joshi A, Liu H, Good RPI (2012) It time to include vancomycin for routine perioperative antibiotic prophylaxis in total joint arthroplasty patients? J Arthroplast 27(8 Suppl):55–60
127. Courtney P, Melnic CM, Zimmer Z, Anari J, Lee GC (2015) Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. Clin Orthop Relat Res 473(7):2197–2203
128. Sewick A, Makani A, Wu C, O'Donnell J, Baldwin KD, Lee GC (2012) Does dual antibiotic prophylaxis better prevent surgical site infections in total joint arthroplasty? Clin Orthop Relat Res 470(10):2702–2707
129. Saravolatz LD, Pawlak J, Johnson LB (2012) In vitro susceptibilities and molecular analysis of vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus isolates. Clin Infect Dis 55(4):582–586
130. Melo-Cristino J, Resina C, Manuel V, Lito L, Ramirez M (2013) First case of infection with vancomycin-resistant Staphylococcus aureus in Europe. Lancet 382(9888):205
131. Liu C, Kakis A, Nichols A, Ries MD, Vail TP, Bozic KJ (2014) Targeted use of vancomycin as perioperative prophylaxis reduces periprosthetic joint infection in revision TKA. Clin Orthop Relat Res 472(1):227–231
132. Kanellakopoulou K, Papadopoulos A, Varvaroussis D, Varvaroussis A, Giamarellos-Bourboulis EJ, Pagonas A, Stergiou A, Papadelis P, Nikolaidis V, Giamarellou H (2009) Efficacy of teicoplanin for the prevention of surgical site infections after total hip

or knee arthroplasty: a prospective, open-label study. Int J Antimicrob Agents 33(5):437–440
133. Periti P, Stringa G, Mini E (1999) Comparative multicenter trial of teicoplanin versus cefazolin for antimicrobial prophylaxis in prosthetic joint implant surgery. Italian Study Group for Antimicrobial Prophylaxis in Orthopedic Surgery. Eur J Clin Microbiol Infect Dis 18(2):113–119
134. Soriano A, Popescu D, Garcia S, Bori G, Martinez JA, Balasso V, Marco F, Almela M, Mensa J (2006) Usefulness of teicoplanin for preventing methicillin-resistant Staphylococcus aureus infections in orthopedic surgery. Eur J Clin Microbiol Infect Dis 25(1):35–38
135. Tornero E, Garcia-Ramiro S, Martinez-Pastor JC, Bori G, Bosch J, Morata L, Sala M, Basora M, Mensa J, Soriano A (2015) Prophylaxis with teicoplanin and cefuroxime reduces the rate of prosthetic joint infection after primary arthroplasty. Antimicrob Agents Chemother 59(2):831–837
136. Engesaeter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI (2003) Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. Acta Orthop Scand 74(6):644–651
137. Malchau H, Herberts P, Ahnfelt L (1993) Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978-1990. Acta Orthop Scand 64(5):497–506
138. Chiu FY, Chen CM, Lin CF, Lo WH (2002) Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees. J Bone Joint Surg Am 84-A(5):759–762
139. Chiu FY, Lin CF, Chen CM, Lo WH, Chaung TY (2001) Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus. A prospective, randomised study. J Bone Joint Surg (Br) 83(5):691–695
140. Namba RS, Chen Y, Paxton EW, Slipchenko T, Fithian DC (2009) Outcomes of routine use of antibiotic-loaded cement in primary total knee arthroplasty. J Arthroplast 24(6 Suppl):44–47
141. Hinarejos P, Guirro P, Leal J, Montserrat F, Pelfort X, Sorli ML, Horcajada JP, Puig L (2013) The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees. J Bone Joint Surg Am 95(9):769–774
142. Bohm E, Zhu N, Gu J, de Guia N, Linton C, Anderson T, Paton D, Dunbar M (2014) Does adding antibiotics to cement reduce the need for early revision in total knee arthroplasty? Clin Orthop Relat Res 472(1):162–168
143. Canadian Agency for Drugs and Technologies in Health. Antibiotic impregnated cement for primary hip or knee arthroplasty: a review of the clinical and cost-effectiveness. 2015
144. Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P (2014) No decreased infection rate when using antibiotic-impregnated cement in primary total joint arthroplasty. Orthopedics 37(12):839–845
145. Soares D, Leite P, Barreira P, Aido R, Sousa R (2015) Antibiotic-loaded bone cement in total joint arthroplasty. Acta Orthop Belg 81(2):184–190
146. Thomes B, Murray P, Bouchier-Hayes D (2002) Development of resistant strains of Staphylococcus epidermidis on gentamicin-loaded bone cement in vivo. J Bone Joint Surg (Br) 84(5):758–760
147. Hope PG, Kristinsson KG, Norman P, Elson RA (1989) Deep infection of cemented total hip arthroplasties caused by coagulase-negative staphylococci. J Bone Joint Surg (Br) 71(5):851–855
148. Stefansdottir A, Johansson D, Knutson K, Lidgren L, Robertsson O (2009) Microbiology of the infected knee arthroplasty: report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases. Scand J Infect Dis 41(11–12):831–840
149. Malhas AM, Lawton R, Reidy M, Nathwani D, Clift BA (2015) Causative organisms in revision total hip & knee arthroplasty for infection: increasing multi-antibiotic resistance in coagulase-negative staphylococcus and the implications for antibiotic prophylaxis. Surgeon 13(5):250–255
150. Cristina ML, Sartini M, Schinca E, Ottria G, Spagnolo AM (2016) Operating room environment and surgical site infections in arthroplasty procedures. J Prev Med Hyg 57(3):E142–EE48
151. Scaltriti S, Cencetti S, Rovesti S, Marchesi I, Bargellini A, Borella P (2007) Risk factors for particulate and microbial contamination of air in operating theatres. J Hosp Infect 66(4):320–326
152. Salassa TE, Swiontkowski MF (2014) Surgical attire and the operating room: role in infection prevention. J Bone Joint Surg Am 96(17):1485–1492
153. Mischke C, Verbeek JH, Saarto A, Lavoie MC, Pahwa M, Ijaz S (2014) Gloves, extra gloves or special types of gloves for preventing percutaneous exposure injuries in healthcare personnel. Cochrane Database Syst Rev 3:CD009573
154. Charnley J (1972) Postoperative infection after total hip replacement with special reference to air contamination in the operating room. Clin Orthop Relat Res 87:167–187
155. Der Tavitian J, Ong SM, Taub NA, Taylor GJS (2003) Body-exhaust suit versus occlusive clothing. A randomised, prospective trial using air and wound bacterial counts. J Bone Joint Surg (Br) 85(4):490–494
156. Pasquarella C, Pitzurra O, Herren T, Poletti L, Savino A (2003) Lack of influence of body exhaust gowns on aerobic bacterial surface counts in a mixed-ventilation operating theatre. A study of 62 hip arthroplasties. J Hosp Infect 54(1):2–9

157. Hooper GJ, Rothwell AG, Frampton C, Wyatt MC (2011) Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement?: the ten-year results of the New Zealand joint Registry. J Bone Joint Surg (Br) 93(1):85–90
158. Lidwell OM, Lowbury EJ, Whyte W, Blowers R, Stanley SJ, Lowe D (1982) Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study. Br Med J (Clin Res Ed) 285(6334):10–14
159. Miner AL, Losina E, Katz JN, Fossel AH, Platt R (2007) Deep infection after total knee replacement: impact of laminar airflow systems and body exhaust suits in the modern operating room. Infect Control Hosp Epidemiol 28(2):222–226
160. Brandt C, Hott U, Sohr D, Daschner F, Gastmeier P, Ruden H (2008) Operating room ventilation with laminar airflow shows no protective effect on the surgical site infection rate in orthopedic and abdominal surgery. Ann Surg 248(5):695–700
161. Ritter MA, Olberding EM, Malinzak RA (2007) Ultraviolet lighting during orthopaedic surgery and the rate of infection. J Bone Joint Surg Am 89(9):1935–1940
162. Sorensen AI, Sorensen TS (1991) Bacterial growth on suction drain tips. Prospective study of 489 clean orthopedic operations. Acta Orthop Scand 62(5):451–454
163. Drinkwater CJ, Neil MJ (1995) Optimal timing of wound drain removal following total joint arthroplasty. J Arthroplast 10(2):185–189
164. Zamora-Navas P, Collado-Torres F, de la Torre-Solis F (1999) Closed suction drainage after knee arthroplasty. A prospective study of the effectiveness of the operation and of bacterial contamination. Acta Orthop Belg 65(1):44–47
165. Manian FA, Meyer PL, Setzer J, Senkel D (2003) Surgical site infections associated with methicillin-resistant Staphylococcus aureus: do postoperative factors play a role? Clin Infect Dis 36(7):863–868
166. Parker MJ, Livingstone V, Clifton R, McKee A (2007) Closed suction surgical wound drainage after orthopaedic surgery. Cochrane Database Syst Rev 18(3):CD001825
167. Parker MJ, Roberts CP, Hay D (2004) Closed suction drainage for hip and knee arthroplasty. A meta-analysis. J Bone Joint Surg Am 86-A(6): 1146–1152
168. Weber EW, Slappendel R, Prins MH, van der Schaaf DB, Durieux ME, Strumper D (2005) Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. Anesth Analg 100(5):1416–1421
169. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB (1999) An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 81(1):2–10
170. Friedman R, Homering M, Holberg G, Berkowitz SD (2014) Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. J Bone Joint Surg Am 96(4):272–278
171. Frisch NB, Wessell NM, Charters MA, Yu S, Jeffries JJ, Silverton CD (2014) Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplast 29(9 Suppl):189–192
172. Kim JL, Park JH, Han SB, Cho IY, Jang KM (2017) Allogeneic blood transfusion is a significant risk factor for surgical-site infection following total hip and knee arthroplasty: a meta-analysis. J Arthroplast 32(1):320–325
173. Bianchi M, Vaglio S, Pupella S, Marano G, Facco G, Liumbruno GM, Grazzini G (2016) Leucoreduction of blood components: an effective way to increase blood safety? Blood Transfus 14(2):214–227
174. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC (2016) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 10:CD002042
175. Saleh K, Olson M, Resig S, Bershadsky B, Kuskowski M, Gioe T, Robinson H, Schmidt R, McElfresh E (2002) Predictors of wound infection in hip and knee joint replacement: results from a 20 year surveillance program. J Orthop Res 20(3):506–515
176. Jaberi FM, Parvizi J, Haytmanek CT, Joshi A, Purtill J (2008) Procrastination of wound drainage and malnutrition affect the outcome of joint arthroplasty. Clin Orthop Relat Res 466(6):1368–1371
177. Toon CD, Lusuku C, Ramamoorthy R, Davidson BR, Gurusamy KS (2015) Early versus delayed dressing removal after primary closure of clean and clean-contaminated surgical wounds. Cochrane Database Syst Rev 9:CD010259
178. Ravenscroft MJ, Harker J, Buch KA (2006) A prospective, randomised, controlled trial comparing wound dressings used in hip and knee surgery: aquacel and tegaderm versus cutiplast. Ann R Coll Surg Engl 88(1):18–22
179. Burke NG, Green C, McHugh G, McGolderick N, Kilcoyne C, Kenny P (2012) A prospective randomised study comparing the jubilee dressing method to a standard adhesive dressing for total hip and knee replacements. J Tissue Viability 21(3):84–87
180. Hopper GP, Deakin AH, Crane EO, Clarke JV (2012) Enhancing patient recovery following lower limb arthroplasty with a modern wound dressing: a prospective, comparative audit. J Wound Care 21(4):200–203
181. Cai J, Karam JA, Parvizi J, Smith EB, Sharkey PF (2014) Aquacel surgical dressing reduces the rate of acute PJI following total joint arthroplasty: a case-control study. J Arthroplast 29(6):1098–1100
182. Grosso MJ, Berg A, LaRussa S, Murtaugh T, Trofa DP, Geller JA (2016) Silver-impregnated occlusive dressing reduces rates of acute periprosthetic joint infection after total joint arthroplasty. J Arthroplast 32(3):929–932
183. Dumville JC, Gray TA, Walter CJ, Sharp CA, Page T, Macefield R, Blencowe N, Milne TK, Reeves BC,

Blazeby J (2016) Dressings for the prevention of surgical site infection. Cochrane Database Syst Rev 12:CD003091
184. Heal CF, Banks JL, Lepper PD, Kontopantelis E, van Driel ML (2016) Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. Cochrane Database Syst Rev 11:CD011426
185. Michelson JD, Lotke PA, Steinberg ME (1988) Urinary-bladder management after total joint-replacement surgery. N Engl J Med 319(6):321–326
186. Alvarez AP, Demzik AL, Alvi HM, Hardt KD, Manning DW (2016) Risk factors for postoperative urinary tract infections in patients undergoing total joint arthroplasty. Adv Orthop 2016:7268985
187. Wald HL, Ma A, Bratzler DW, Kramer AM (2008) Indwelling urinary catheter use in the postoperative period: analysis of the national surgical infection prevention project data. Arch Surg 143(6):551–557
188. Stephan F, Sax H, Wachsmuth M, Hoffmeyer P, Clergue F, Pittet D (2006) Reduction of urinary tract infection and antibiotic use after surgery: a controlled, prospective, before-after intervention study. Clin Infect Dis 42(11):1544–1551
189. Ong KL, Kurtz S, Lau E, Bozic KJ, Berry DJ, Parvizi J (2009) Prosthetic joint infection risk after total hip arthroplasty in the medicare population. J Arthroplast 24(6 Suppl):105–109
190. Glassou EN, Pedersen AB, Hansen TB (2014) Risk of re-admission, reoperation, and mortality within 90 days of total hip and knee arthroplasty in fast-track departments in Denmark from 2005 to 2011. Acta Orthop 85(5):493–500
191. Huotari K, Peltola M, Jamsen E (2015) The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. Acta Orthop 86(3):321–325
192. Tsukayama DT, Estrada R, Gustilo RB (1996) Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am 78(4):512–523
193. Rodriguez D, Pigrau C, Euba G, Cobo J, Garcia-Lechuz J, Palomino J, Riera M, Del Toro MD, Granados A, Ariza X (2010) Acute haematogenous prosthetic joint infection: prospective evaluation of medical and surgical management. Clin Microbiol Infect 16(12):1789–1795
194. Maderazo EG, Judson S, Pasternak H (1988) Late infections of total joint prostheses. A review and recommendations for prevention. Clin Orthop Relat Res 229:131–142
195. Murdoch DR, Roberts SA, Fowler VG Jr, Shah MA, Taylor SL, Morris AJ, Corey GR (2001) Infection of orthopedic prostheses after Staphylococcus aureus bacteremia. Clin Infect Dis 32(4):647–649
196. Sendi P, Banderet F, Graber P, Zimmerli W (2011) Periprosthetic joint infection following Staphylococcus aureus bacteremia. J Inf Secur 63(1):17–22
197. Wust J, Steiger U, Vuong H, Zbinden R (2000) Infection of a hip prosthesis by Actinomyces naeslundii. J Clin Microbiol 38(2):929–930
198. Lamas C, Boia M, Eykyn SJ (2006) Osteoarticular infections complicating infective endocarditis: a study of 30 cases between 1969 and 2002 in a tertiary referral centre. Scand J Infect Dis 38(6-7):433–440
199. Han Z, Burnham CA, Clohisy J, Babcock H (2011) Mycoplasma pneumoniae periprosthetic joint infection identified by 16S ribosomal RNA gene amplification and sequencing: a case report. J Bone Joint Surg Am 93(18):e103
200. Heimdahl A, Hall G, Hedberg M, Sandberg H, Soder PO, Tuner K, Nord CE (1990) Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. J Clin Microbiol 28(10):2205–2209
201. Nelson DB (2003) Infectious disease complications of GI endoscopy: Part I, endogenous infections. Gastrointest Endosc 57(4):546–556
202. Mohee AR, Gascoyne-Binzi D, West R, Bhattarai S, Eardley I, Sandoe JA (2016) Bacteraemia during transurethral resection of the prostate: what are the risk factors and is it more common than we think? PLoS One 11(7):e0157864
203. Zani EL, Clark OA, Rodrigues Netto N Jr (2011) Antibiotic prophylaxis for transrectal prostate biopsy. Cochrane Database Syst Rev 5:CD006576
204. Chihara S, Popovich KJ, Weinstein RA, Hota B (2010) Staphylococcus aureus bacteriuria as a prognosticator for outcome of Staphylococcus aureus bacteremia: a case-control study. BMC Infect Dis 10:225
205. Uckay I, Pittet D, Bernard L, Lew D, Perrier A, Peter R (2008) Antibiotic prophylaxis before invasive dental procedures in patients with arthroplasties of the hip and knee. J Bone Joint Surg (Br) 90(7):833–838
206. Zimmerli W, Sendi P (2010) Antibiotics for prevention of periprosthetic joint infection following dentistry: time to focus on data. Clin Infect Dis 50(1):17–19

Greater Wound and Renal Complications in Gout Patients Undergoing Total Joint Arthroplasty

Margaret V. Shields and Antonia F. Chen

1 Introduction

Gout is a fairly ubiquitous, inflammatory, degenerative arthritic condition that is known to be associated with several comorbidities. These comorbidities include hypertension, cardiovascular disease, renal dysfunction, diabetes mellitus, obesity, hyperlipidemia, and metabolic syndrome (MetS) [1]. Due to the prevalence of these comorbidities, it is important for orthopedic surgeons to be fully aware of the potential perioperative medical complications in patients with a history of gout and to take prophylactic measures to optimize patients for the best results. This chapter specifically focuses on wound and renal complications in patients with underlying gout who undergo total joint arthroplasty (TJA).

2 Gout Definition and Risk Factors

Gout is a condition that manifests as inflammatory arthritis that occurs from the causal precursor of serum uric acid elevation. The compound, uric acid, can crystallize into monosodium urate crystals in the joint region, producing acute severe pain. Following several episodes of acute gout, a person can develop chronic gout, which consists of persistent urate crystal tophi in the joints.

Interestingly, only humans can develop significant hyperuricemia, and this may be due to the lack of the uricase enzyme in humans [2]. Uricase is an enzyme that other animals use to degrade uric acid into a final soluble product called allantoin that can be excreted in the urine [3]. Without uricase, the result is urate levels in humans that are roughly ten times higher than that in other mammals [2].

There are a variety of factors that play a role in the accumulation of uric acid. The compound is accumulated either from exogenous purine consumption or endogenous purine nucleotide catabolism, and thus it is necessary to have a fine balance between dietary purine intake, endogenous purine breakdown, and excretion of uric acid. Uric acid has been found to be more prevalent in certain foods and drinks, such as meat, seafood, beer, liquor, and fructose- and sugar-sweetened soft drinks [2]. In fact, it has been found that men in the highest quintile of meat intake have a 41% higher chance of developing gout than men in the lowest quintile and men in the highest quintile of seafood intake have a 51% higher risk for gout [2]. While these foods increase the risk for hyperuricemia and gout, other purine-rich foods and vegetables are not associated with hyperuricemia and gout, such as oatmeal, peas, beans, lentils, spinach, mush-

M.V. Shields
Sidney Kimmel Medical College,
Thomas Jefferson University, Philadelphia, PA, USA
e-mail: antonia.chen@rothmaninstitute.com

A.F. Chen, M.D., M.B.A. (✉)
Brigham and Women's Hospital,
Harvard Medical School, Boston, MA, USA
e-mail: antonia.chen@rothmaninstitute.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_63, © Springer International Publishing AG
Published Online: 04 April 2018

rooms, and cauliflower [2]. Dairy products, coffee, and vitamin C appear to be protective against the development of gout [4].

Beyond food sources for gout, there are also certain medical conditions that have been associated with hyperuricemia. Obesity is independently linked to an increase in urate levels, and weight loss has been associated with a decrease in de novo purine synthesis [5]. Increased insulin resistance, as seen in the MetS, has been found to be inversely related to uric acid excretion by the kidneys and thus results in increased serum urate levels [5, 6]. Medical conditions that lead to high cell turnover in the body, such as proliferative and inflammatory conditions, can increase endogenous purine catabolism, leading to increased serum urate levels [2]. Hypertension is also an independent risk factor for gout, as patients with this condition have significantly decreased renal urate excretion relative to their glomerular filtration rate [7]. Some have suggested that the association between hypertension and gout may be due to a hypertensive process within the kidney called nephrosclerosis [7]. Sclerosis of the renal blood vessels, likely due to hypertension, makes it more difficult to excrete uric acid, resulting in increased serum urate levels.

Lastly, some medications have been found to increase uric acid levels. These medications include diuretics, salicylate at low doses, cyclosporine, tacrolimus, and beta-blockers [2]. While hyperuricemia is central to the pathogenesis of gout, it is not the sole factor associated with risk for acute gouty attacks. Some of the above-listed comorbidities and medications can independently precipitate a gouty attack, particularly hypertension, obesity, the use of thiazide and loop diuretics, and high alcohol intake.

3 Gout Epidemiology

The incidence of gout is increasing incidence worldwide. Prevalence of gout among US adults in 2007–2008 was estimated at 3.9% (5.9% among men, 2.0% among women), which is roughly a total of 8.3 million individuals [8]. The prevalence has more than doubled from the 1960s to the 1990s [8]. Data from China, the United Kingdom, and New Zealand all showed similar trends in the prevalence of gout within their communities [4]. In addition, approximately 21.4% (43.3 million) of US adults met criteria for hyperuricemia, which is defined as a serum urate level > 7 mg/dL for men and >5.7 mL/dL for women [8]. While gout is a problem that can occur at all ages, its prevalence also increases with age, occurring in about 9% of men and 6% of women older than 80 years [2]. This is of particular importance when considering the older age group of patients that typically undergo TJA.

4 Gout Comorbidities

Gout is commonly associated with major comorbidities, which are important to consider when assessing for surgical candidacy. The association with MetS, cardiovascular disease, and peripheral vascular disease has been the focus of recent literature [10]. In fact, recent data from a study of 5707 patients showed that 74% of gouty patients have hypertension, 71% have chronic kidney disease (CKD) > stage 2, 53% are obese, 26% have diabetes, 24% have nephrolithiasis, 14% have had a myocardial infarction, and 11% have heart failure [9]. In this same patient population, the highest urate levels (>10 mg/dL) were associated with CKD > stage 2 in 86% of patients, hypertension in 66%, obesity in 65%, heart failure in 33%, and diabetes in 33%. In another study of 2763 patients, similar associations were found in gout patients, including obesity (39%), type 2 diabetes (25%), hypercholesterolemia (72%), hypertriglyceridemia (40%), hypertension (68%), heart failure (7%), coronary heart disease (10%), and chronic renal failure (9%) [1]. In addition, this same study found that the duration of gout diagnosis was linked to significant increased risk of certain comorbidities, such as hypertension, dyslipidemia, MetS, and liver disorders. In contrast, the duration of gout was not associated with greater prevalence of diabetes, heart failure, coronary heart disease, or renal failure [1]. The presence of these comorbidities puts patients at an increased risk of cardiovascular mortality and morbidity resulting from myocardial infarction and peripheral vascular disease in the postoperative period [1].

One significant comorbid condition in gout, MetS, is of particular importance when considering

postoperative outcomes. MetS, also known as the insulin resistance syndrome, is characterized three or more of the following characteristics: (1) disturbed glucose (fasting >110 mg/dL), (2) increased waist circumference (>102 cm in men or >88 cm in women), (3) dyslipidemia (triglycerides >150 mg/dL, HDL < 40 mg/dL), and/or (4) hypertension (systolic blood pressure > 130 mmHg or diastolic >85 mmHg) [11, 12]. The presence of MetS leads to increased risk for development of type 2 diabetes mellitus and cardiovascular disease [11, 12]. A large cross-sectional study by NHANES III found that the prevalence of MetS in the general population was 25.4% compared to 62.8% in patients with gout [4].

5 Total Joint Arthroplasty Complications

The comorbidities associated with the diagnosis of gout are important to consider from a surgical standpoint, as they play a role in perioperative and postoperative complications. Before undergoing surgical procedures, such as TJA, gout patients should undergo a full systemic evaluation to assess for the presence of these comorbidities. If present, necessary prophylactic measures can be taken to control comorbidities in the hopes of decreasing perioperative and postoperative complications. Common postoperative complications for all patients following TJA include pulmonary embolism (PE), deep vein thrombosis (DVT), superficial wound infection, periprosthetic joint infection (PJI), and cardiovascular morbidity [13]. However, gout patients have specific complications that orthopedic surgeons should be aware of in order to properly counsel patients and their families about the risks of the surgery.

6 Gout and Total Joint Arthroplasty Complications

Gout patients are a unique patient population with specific complications to consider following TJA. While there are plenty of studies looking at outcomes after TJA on patients with other comorbidities, the data for gout patients is lacking. Some studies have shown that the combination of the inflammatory nature of gout, tophi deposition, and the comorbidities linked with gout all contribute to detrimental effects on soft tissue and wound healing, along with predisposing these patients to renal complications [10].

The complications associated with gout patients undergoing surgery are often secondary to the comorbidities linked with gout. Previous studies have found that patients with uncontrolled MetS have significantly more postoperative complications (48.6%), compared to patients with controlled MetS (7.9%) [13]. However, there was no difference in complications when comparing patients with controlled MetS to healthy patients, suggesting that if gout patients with MetS can achieve control of their MetS prior to surgery, they will be less likely to have complications [13]. Another study comparing MetS patients versus non-MetS patients undergoing TJA found that complications after surgery increased to 35.9% in MetS patients versus only 16.3% in control patients [13]. This same study also looked at obesity as a single risk factor and found that MetS patients had a significantly higher risk of complications after TJA compared to non-MetS patients, while obese patients who did not fit MetS criteria did not have a significantly higher risk [14].

7 Wound Complications in Gout TJA Patients

Wound complications are a major postoperative concern for all orthopedic patients, including gout patients, due to the high incidence of PJI in TJA patients following wound complications [15]. In addition, the presence of wound complications has been linked to longer hospital stays and subsequent hospital procedures, increasing the health-care economic burden [15].

Patients with gout who develop tophi in joints respond to the abnormal monosodium urate crystals by recruiting inflammatory cells. While this inflammation is intended to clear bacteria present in the joint, it can also lead to slower wound healing. In a mouse model, mice with depleted neutrophils healed faster than mice with inflammatory

cells present [16]. A similar study in rabbits found that subjects who were stimulated to make extra inflammatory cells in wounds had significantly delayed reepithelialization and increased scarring than subjects with normal levels of inflammatory cells [17]. The proposed mechanism for slower wound healing is due to the ability of neutrophils to secrete proteases and reactive oxygen species into healing tissue [17]. Considering the inflammatory nature of gout, this finding helps to explain the wound healing problems found in these patients after TJA.

Impaired wound healing is also associated with peripheral vascular disease (PVD), which is a comorbidity commonly associated with gout. PVD reduces blood flow to the extremities, leading to tissue hypoxia and decreased delivery of nutrients to healing tissue. The lack of oxygen and nutrients results in decreased neoangiogenesis and altered tissue remodeling that can have a detrimental effect on wound healing [10, 18]. In addition, decreased mobility in patients with PVD can create excess periods of unrelieved pressure on extremities, increasing the shearing force applied to wounds following surgery and thus making wound healing more difficult [18]. Thus, interventions prior to TJA in PVD patients may improve wound healing and reduce complications after surgery.

In addition to PVD, gout patients also have a higher risk of cardiovascular diseases, some of which require aggressive anticoagulation [1, 10]. Medications such as warfarin and rivaroxaban may lead to increased hematoma formation and can result in impaired wound healing. One study specifically reported a direct correlation between excessive anticoagulation and an increase in postoperative wound healing complications, which then resulted in increased PJI [19].

A recent study looking at 482 gout patient cases matched to 482 non-gout patients found that gout patients had significantly more wound healing problems and renal complications after TJA [10]. Of the gout patients undergoing TJA, 12.2% (59 patients) had wound complications compared to 5.0% (24 patients) of the non-gout TJA patients (Table 1). In the same study, medically treated gout patients had better outcomes than untreated gout patients, with trends toward decreased rates of wound complications (11.8% vs. 13.3%), renal complications (7.8% vs. 11.9%), and cardiovascular complications (4.3% vs. 5.9%), although the numbers were not significant. Lastly, the study revealed that gout patients undergoing TJA had significantly higher rates of 90-day readmission compared to non-gout patients. This study shows the importance of controlling gout with medical and lifestyle changes before TJA in order to decrease the rate of postoperative complications, especially wound complications and cardiovascular problems.

Table 1 Wound and renal complications following total joint arthroplasty comparing gout and non-gout patients

Patient characteristics	Gout	Non-gout	*p*-value
Patients, *n* (%)	482 (100)	482 (100)	1.00
Wound complications, *n* (%)			
Total	59	24 (5.0)	0.001[a]
Wound drainage—Oral antibiotics	(12.2)	15 (3.1)	
Superficial wound infections—Oral	33 (6.8)	3 (0.6)	
antibiotics	13 (2.7)	1 (0.2)	
Cellulitis—IV antibiotics	5 (1.0)	3 (0.6)	
Cellulitis—Oral antibiotics	3 (0.6)	1 (0.2)	
Persistent wound drainage—IV antibiotics	3 (0.6)	1 (0.2)	
Surgical irrigation and debridement due to hematoma	1 (0.2)	0	
Partial skin necrosis	1(0.2)		
Kidney complications (AKI), *n* (%)			
Total	43 (8.9)	15 (3.1)	0.0003[a]
Hypovolemia	30 (6.2)	9 (1.9)	
Perioperative hypotension	6 (1.2)	5 (1.0)	
Decompensated congestive heart failure	5 (1.0)	1 (0.2)	
Cardiac arrest	1 (0.2)	0	
Sepsis	1 (0.2)	0	

AKI acute kidney injury, *IV* intravenous.
[a]Statistically significant.

8 Renal Complications in Gout TJA Patients

While wound complications are a major concern for gout patients undergoing TJA, perioperative and postoperative renal problems are also important to consider. Gout patients have higher postoperative urinary and renal complications after TJA, including uric acid urolithiasis and renal impairment [10]. Increased serum uric acid levels are a risk factor for acute kidney injury (AKI) and CKD. A recent study demonstrated that gout patients undergoing TJA had a significantly increased risk of developing AKI, as 8.9% (43 patients) of gout TJA patients developed AKI versus 3.1% (15 patients) of matched TJA patients without gout (Table 1) [10]. Orthopedic surgeons operating on gout patients should be aware of the risk for kidney disease, often secondary to dehydration and under-resuscitation during surgery. Thus, prophylactic measures should be taken to reduce fluid depletion preoperatively, and close monitoring should occur perioperatively to watch for signs of dehydration so that intervention can be performed. Allowing gout patients to drink clear fluids 2–3 h prior to surgery may improve hydration and has been shown in the general surgery literature to be a safe option prior to surgery [20, 21].

Conclusions

Gout is associated with a variety of comorbidities that place these patients at a higher risk of postoperative complications after TJA. Specifically, comorbidities such as MetS, hypertension, and PVD put patients at an increased risk of wound and perioperative cardiovascular complications. In addition, the disease process of gout itself is also associated with increased risk of wound complications and AKI. Orthopedic surgeons should work with other medical specialists to attempt to achieve control of serum urate levels prior to surgery, especially in patients with coexisting MetS, diabetes, obesity, hypertension, and cardiac diseases. This can be accomplished by dietary modifications, weight loss, and taking urate-lowering medications to prevent gouty attacks and reduce gout-related postoperative complications. While these changes will be beneficial in lowering urate levels, they will also aid in controlling MetS symptoms and glucose levels, thus lowering potential perioperative complications. Future studies should be conducted to determine if specific preoperative serum uric acid levels correlate to perioperative and postoperative complications, which may provide a threshold for which TJA should be postponed until adequate control can be achieved.

References

1. Richette P, Clerson P, Périssin L, Flipo R-M, Bardin T (2013) Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis 74(1):142–147
2. Choi HK, Mount DB, Reginato AM, American College of Physicians; American Physiological Society (2005) Pathogenesis of gout. Ann Intern Med 143(7):499–516
3. Terkeltaub RA (2003) Gout. New Engl J Med 349(17):1647–1655
4. Roddy E, Choi HK (2014) Epidemiology of gout. Rheum Dis Clin N Am 40(2):155–175
5. Emmerson B (1998) Hyperlipidaemia in hyperuricaemia and gout. Ann Rheum Dis 57:509–510
6. Facchini F, Chen Y-D, Hollenbeck CB, Reaven GM (1991) Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. J Am Med Assoc 266:3008–3011
7. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG (1980) Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med 93:817–821
8. Zhu Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and nutrition examination survey 2007–2008. Arthritis Rheum 63(10):3136–3141
9. Zhu Y, Pandya BJ, Choi HK (2012) Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. Am J Med 125:679–687
10. Chen CL, Shao H, Block JL, Chen AF (2016) Greater wound and renal complications in gout patients undergoing total joint arthroplasty. J Arthroplast 31(7):1431–1436
11. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT (2002) The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. J Am Med Assoc 288(21):2709–2716
12. Tzimas P, Petrou A, Laou E, Milionis H, Mikhailidis DP, Papadopoulos G (2015) Impact of metabolic

syndrome in surgical patients: should we bother? Br J Anaesth 115(2):194–202
13. Zmistowski B, Dizdarevic I, Jacovides CL, Radcliff KR, Mraovic B, Parvizi J (2013) Patients with uncontrolled components of metabolic syndrome have increased risk of complications following total joint arthroplasty. J Arthroplast 28(6):904–907
14. Gage MJ, Schwarzkopf R, Abrouk M, Slover JD (2014) Impact of metabolic syndrome on perioperative complication rates after total joint arthroplasty surgery. J Arthroplast 29(9):1842–1845
15. Patel VP, Walsh M, Sehgal B, Preston C, DeWal H, Di Cesare PE (2007) Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. J Bone Joint Surg Am 89(1):33–38
16. Dovi JV, He LK, DiPietro LA (2003) Accelerated wound closure in neutrophil-depleted mice. J Leukoc Biol 73:448–455
17. Qian L-W, Fourcaudot AB, Yamane K, You T, Chan RK, Leung KP (2016) Exacerbated and prolonged inflammation impairs wound healing and increases scarring. Wound Repair Regen 24(1):26–34
18. Henry JC, Peterson LA, Schlanger RE, Go MR, Sen CK, Higgins RSD (2014) Wound healing in peripheral arterial disease: current and future therapy. J Vasc Med Surg 2:157
19. Parvizi J, Ghanem E, Sharkey P, Rothman R, Hozack W (2007) Does excessive anticoagulation predispose the patient to periprosthetic infection? J Arthroplast 22(2):24–28
20. Read MS, Vaughan RS (1991) Allowing pre-operative patients to drink: effects on patients' safety and comfort of unlimited oral water until 2 hours before anaesthesia. Acta Anaesthesiol Scand 35(7):591–595
21. Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammarqvist F, Almstrom C, Lindh A, Thorell A, Ljungqvist O (2001) A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg 93:1344–1350

Augmentation of Bone Healing in Delayed Union and Atrophic Nonunion of Fractures of Long Bones by Partially Decalcified Bone Allograft

Anuj Jain and Prateek Garg

1 Introduction

Ability to stimulate fracture repair and heal nonunions is a common goal among all orthopedic surgeons. Of all the fractures of long bone that occur annually, 5–10% end in delayed union or nonunion [1]. The standard treatment of delayed union and atrophic nonunion has been stable surgical fixation and augmentation of bone healing. Autogenous bone graft (autograft) from iliac crest has been considered as the gold standard for augmentation of bone healing. But due to disadvantages of autograft complications like fatigue fractures, growth impairment in children, osteomyelitis, peritoneal perforation, massive hematoma, and sacroiliac joint instability various studies are being done to find a suitable alternative [2]. Also autograft presents with problems like limited availability of graft available, increased surgical time, more blood loss, and donor-site morbidity. Allograft in different forms has been considered as good option. Allogenic bone graft can be freeze-dried, deep frozen, or partially decalcified. Freeze-dried and deep-frozen allograft bones need sophisticated equipment and a bone bank setup which are very expensive [3, 4]. Partially decalcified bone allograft (decal bone) is considered good economical alternative in benign cystic lesion of bones but their role in augmentation of bone healing is not well defined. When demineralization is carried out by 0.6 N hydrochloric acid (HCl) the matrix retains high levels of bone morphogenic protein (BMP) responsible for osteoinductive property of decal bone [5, 6].

Delayed Union: Union is considered delayed when healing has not advanced at the average rate for the location and type of fracture (usually 3–6 months) [7].

Nonunion: In 1986 the US Food and Drug Administration panel defined nonunion as "when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months." In general, the absence of any clinical or radiographic evidence of progression of fracture healing for 2–3 months after the expected time period for healing constitutes a nonunion [8]. Clinically nonunion presents as a painless abnormal mobility at fracture site.

2 Bone Grafting

A bone graft is used clinically to provide a bridge of osteogenic tissue, either in a part of the skeleton that is deficient or to establish bony fusion of diseased joint.

A. Jain (✉)
Department of Orthopaedics, UCMS and GTB Hospital, Delhi, India
e-mail: jain.doctor.anuj@gmail.com

P. Garg
Department of Orthopaedics, Sant Parmanand Hospital, Delhi, India

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_121, © Springer International Publishing AG
Published Online: 15 July 2018

Bone grafts are termed according to the source of origin:

1. Autograft: A graft obtained from one site and applied at the other site in the same individual
2. Allograft: Tissue transferred between two genetically dissimilar individuals of same species
3. Xenograft: Tissue obtained from one species and implanted into the member of another species
4. Isograft: The graft tissue obtained from identical twin

3 Biology of Incorporation of Bone Grafts

Bone grafts serve two functions, a mechanical function (osteoconduction) and a biologic function. The net biologic activity of a graft is the sum of its inherent biologic activity (osteogenesis) and its capacity to activate surrounding host tissues to relevant biologic activity (osteoinduction) which is mediated by bioactive factors within the matrix such as glycoprotein bone morphogenic protein (BMP) [9]. Bone grafts are remodeled in response to mechanical load to which they are subjected [10]. Table 1 shows the commonly used bone grafts in orthopedics.

4 Preparation of Partially Decalcified Bone Allograft

Decal bone was prepared from bones of the patients undergoing amputations or arthroplasties after taking informed consent. The guidelines of tissue procurement and bone banking were followed [11, 12]. After harvesting, bone was thoroughly cleaned of soft tissues and blood. Thereafter the bone was partially decalcified in freshly prepared solution of 0.6 N hydrochloric acid (HCl) for 24–48 h (Fig. 1). After decalcification sample of the bone was sent for aerobic, anaerobic, and fungal cultures. The allograft was

Table 1 Commonly used bone grafts in clinical orthopedics

	Fresh autogenous	Fresh unprocessed allogenic	Frozen/ freeze-dried allogenic	Partially decalcified allogenic	Deproteinized allogenic
Osteoinduction	++++	++	+	++	0
Osteoconduction	+++	++	++	+++	++
Osteogenic	++	0	0	0	0
Immunogenicity	0	+++	++	+	0
Mechanical strength	+++	+++	++	++	++
Cost	–	+	+++	+	+++

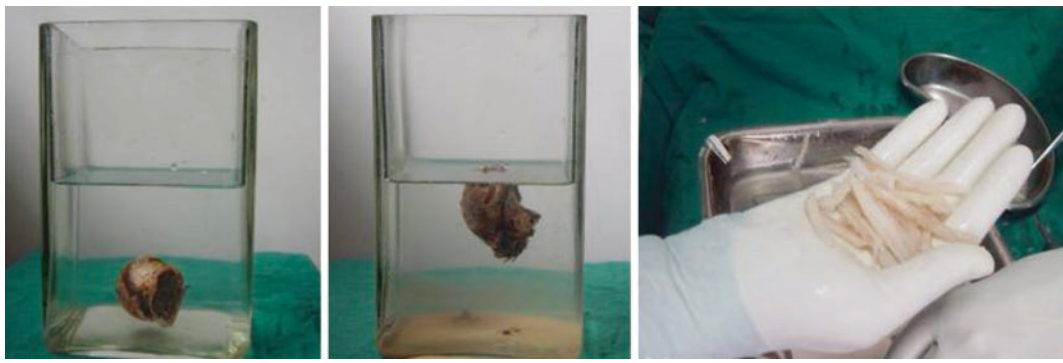


Fig. 1 Left: Preserved femoral head at the bottom of the jar filled with 0.6 N HCl. Middle: After partial decalcification floating femoral head in jar. Right: Slivers of decal bone prepared in theatre that are put across the fracture site

stored in 90% ethanol at 4° C in a domestic refrigerator. The stored allograft was taken out of the container in operation theatre and was thoroughly washed with normal saline. Thereafter piece of allograft was sent for culture. The allogenic bone was cut into 5 mm slivers and bridged across the fracture site (Fig. 1).

Osteoinductive capacity of allogenic decal bone depends on the agent used for demineralizing and extent of demineralization. When bone is demineralized with 0.6 N HCl, it remains osteoinductive and readily osteoconductive material without any appreciable local foreign-body reaction [13]. Decalcification using EDTA and nitric acid markedly decreases the osteoinductive capacity [14]. It has been reported that mineral content should be reduced to at least 40% of normal before a strong osteoinductive response can occur [15].

The biological process of incorporation of partially decalcified bone graft is similar to that of autograft. When graft is placed at the fracture site there is osteoclastic and phagocytic resorption of calcium hydroxyapatite and cellular debris. This makes the graft porous through which neovascularization propagates. Release of osteoinductive material (e.g., BMP) by the graft leads to conversion of osteoprogenitor cells to osteoblastic cells which lay down new bone on the porous matrix by the process of creeping substitution. In autografts the mineral and organic material must undergo resorption before creeping substitution starts whereas in decal bone resorption of demineralized matrix is faster because of the prior removal of minerals in the laboratory. Decal bone provides a permeable scaffolding structure which permits creeping substitution.

Various experimental studies have proven the osteoinductive potential of decal bone. Role of decal bone has been well established in benign cystic lesion of bones [16, 17]. But there is scanty literature on the role of decal bone in augmentation of fracture healing in humans. Saraf et al. [18] observed that allogenic bone shows high degree of osteoinduction and remodeling when used as bone strips and is less osteoinductive when used in the form of bone cylinders or bone powder. Tuli and Gupta reported the efficacy of partially decalcified bone in bridging of osteoperiosteal defects [19, 20]. Zhang et al. [21] used allogeneic decalcified bone graft taken from fresh corpse in 17 children with nonunion and showed successful outcome in 9 cases whereas 7 cases required 2 surgeries.

5 Authors' Results

A prospective study was conducted in the Department of Orthopedics, University College of Medical Science and associated Guru Teg Bahadur Hospital, Delhi, India. Patients with clinico-radiological diagnosis of delayed union or atrophic nonunion of long-bone fractures were included in the study. Patients at extreme of ages (<18 yrs. and > 60 years);with pathological fractures, metabolic bone diseases, infected nonunion, hypertrophic nonunion, and systemic illness like diabetes mellitus; and who are on drugs that impair fracture healing were excluded from the study. Out of 32 patients with delayed union and nonunion of fractures, 22 patients met the inclusion and exclusion criterion. Two patients were lost to follow-up. Hence 20 patients were included in the study and were assessed for the outcome (union and complications, if any).

Eight patients underwent open reduction and internal fixation with low contact dynamic compression plate and allografting, six patients had open reduction, intamedullay nailing, and allografting while another six patients underwent osteoperiosteal allografting (Table 2). Postoperatively patients were given antibiotics for 2 weeks and antihistaminic (tab cetirizine 10 mg HS) for 3 weeks. Patients were reviewed at 4-week interval for clinical and radiological signs of union. The clinical variables observed were redness, swelling, induration, raised temperature, and tenderness or discharge from the operative site to rule out postoperative infection and radiological parameters to assess the status and time of union of fracture. Fracture was labeled as united when clinically there was no local tenderness at the fracture site and radiologically bridging callus across the fracture site was observed in at least three cortices in two orthogonal views.

There were 20 patients with mean age of 34 years (range 18–55 years). There were 14

Table 2 Detail of the patients

	Age (Yrs)	Sex	Bone	Type of Nonunion	Duration (months)	Procedure	Duration of union (weeks)
A	55	M	Tibia	Atrophic nonunion	9	ORIF with ILN and allografting	12
B	24	M	Tibia	Delayed union	5	Osteoperiosteal allografting	12
C	29	M	Femur	Atrophic nonunion with implant in situ	11	Osteoperiosteal allografting	20
D	26	M	Humerus	Delayed union	5	ORIF with LCDCP and allografting	12
E	52	F	Humerus	Atrophic nonunion	7	ORIF with LCDCP and allografting	16
F	26	M	Femur	Delayed union with implant in situ	7	Osteoperiosteal allografting	16
G	28	M	Femur	Delayed union with implant in situ	8	Osteoperiosteal allografting	12
H	44	M	Tibia	Delayed union	9	ORIF with ILN and allografting	20
I	24	M	Humerus	Atrophic nonunion	13	ORIF with LCDCP and allografting	–
J	30	M	Tibia	Atrophic nonunion	14	ORIF with K nail and allografting	16
K	50	F	Humerus	Atrophic nonunion	12	ORIF with LCDCP and allografting	12
L	40	F	Humerus	Atrophic nonunion	7	ORIF with LCDCP and allografting	16
M	36	F	Humerus	Atrophic nonunion	9	ORIF with LCDCP and allografting	12
N	23	M	Tibia	Delayed union	8	ORIF with ILN and allografting	20
O	35	F	Humerus	Atrophic nonunion	5	ORIF with LCDCP and allografting	12
P	36	M	Femur	Delayed union with implant in situ	5	Osteoperiosteal allografting	12
Q	34	M	Femur	Delayed union with implant in situ	6	Osteoperiosteal allografting	20
R	26	M	Tibia	Atrophic nonunion	10	ORIF with ILN and allografting	16
S	44	M	Tibia	Delayed union	7	ORIF with ILN and allografting	20
T	18	F	Humerus	Atrophic nonunion	13	ORIF with LCDCP and allografting	8

ORIF open reduction and internal fixation, *ILN* interlock nailing, *LCDCP* limited-contact dynamic compression plate

males and 6 females. The bones involved were humerus (8/20), tibia (7/20), and femur (5/20). There were 11 patients with atrophic nonunion and 9 patients with delayed union (Table 2). 11 patients sustained injuries in road traffic accident, three patients had fall from height, and six patients had fall from stairs. Ten patients had a history of smoking and four patients had a history of alcohol abuse. Nineteen out of twenty fractures showed union in a mean duration of 14.9 weeks (8–20 weeks) (Figs. 2, 3, and 4). The mean time of union was 14 weeks in atrophic nonunion and 16 weeks in delayed union.

There were two major and eight minor complications in the study. One patient had persistent nonunion and one patient had postoperative wound infection. One patient with atrophic nonunion of humerus shaft did not unite. The failure of union was attributed to technical error of fixation. Rescue treatment was done for this patient in the form of repeat fixation and autologous bone grafting from iliac crest and the fracture united after 8 weeks of grafting. One patient developed purulent discharge from the operative site in the immediate postoperative period. Culture from the wound grew *Staphylococcus aureus*. Despite intravenous antibiotics patient continued to have purulent discharge from the operative site. At 3weeks postoperatively the patient was taken up for wound debridement and loose pieces of allograft were removed. The wound healed subsequently and fracture healed in 16 weeks (Fig. 5). Minor complication included serous discharge from the operative site of eight patients that subsided in most patients in 3 weeks. Like any allograft, decal bone transplanted in the recipient evokes an immunogenic reaction. Cancellous bone is considered to be more antigenic than cortical bone which can be attributed to greater cellularity, both osteogenic and hematopoietic. Though the exact mechanism may be unclear, it is well established that

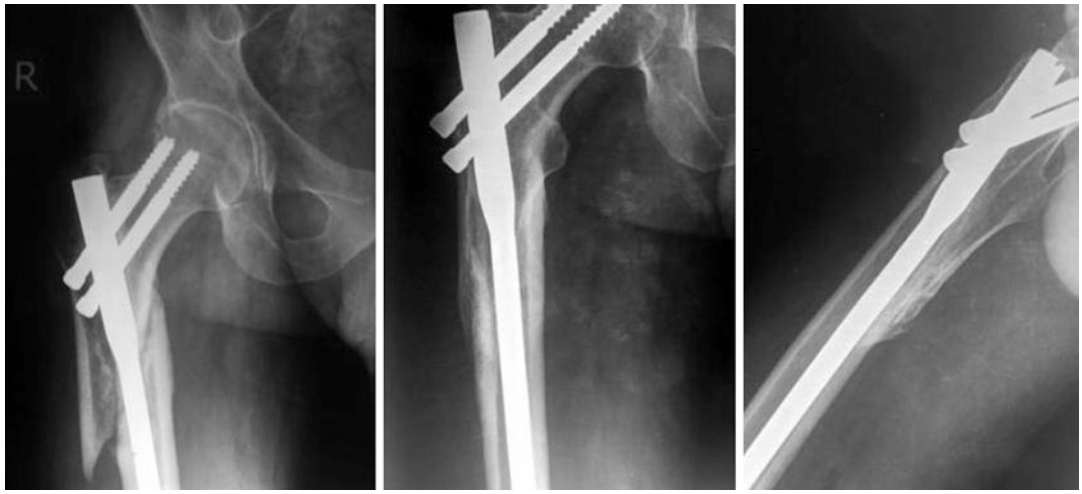


Fig. 2 Left: Surgically intervened nonunion proximal femur band. Middle: Follow-up anteroposterior radiograph. Right: Lateral radiograph showing union

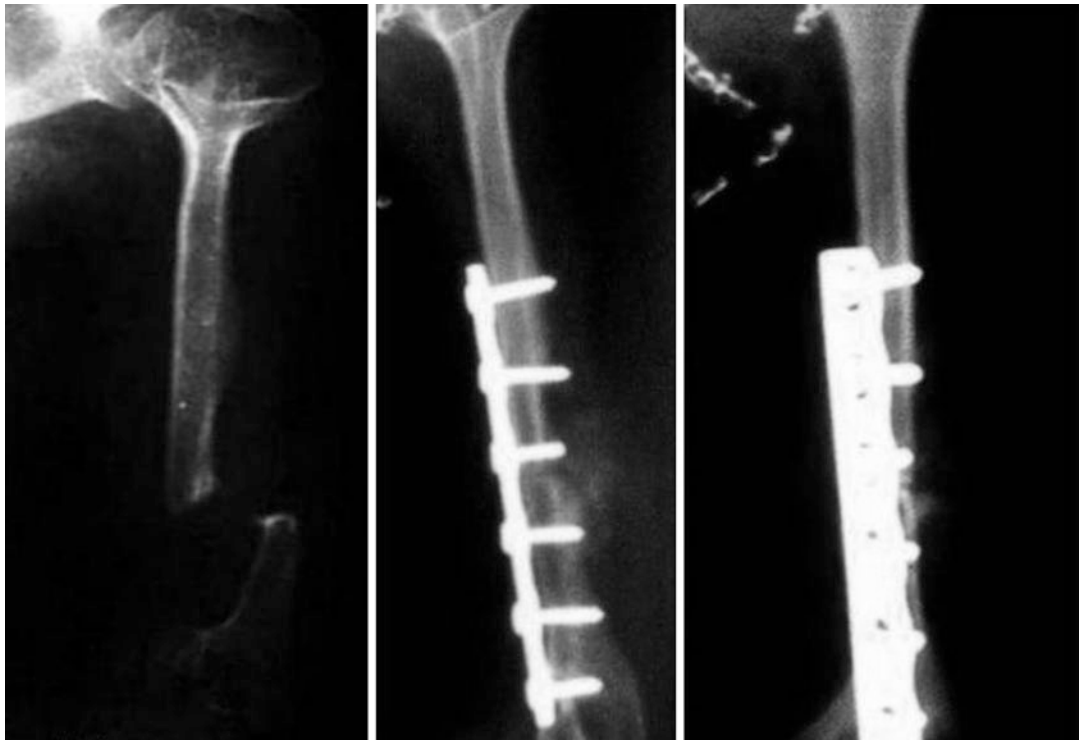


Fig. 3 Left: Atrophic nonunion of fracture of humerus. Middle: Follow-up anteroposterior and (right) lateral radiographs showing union

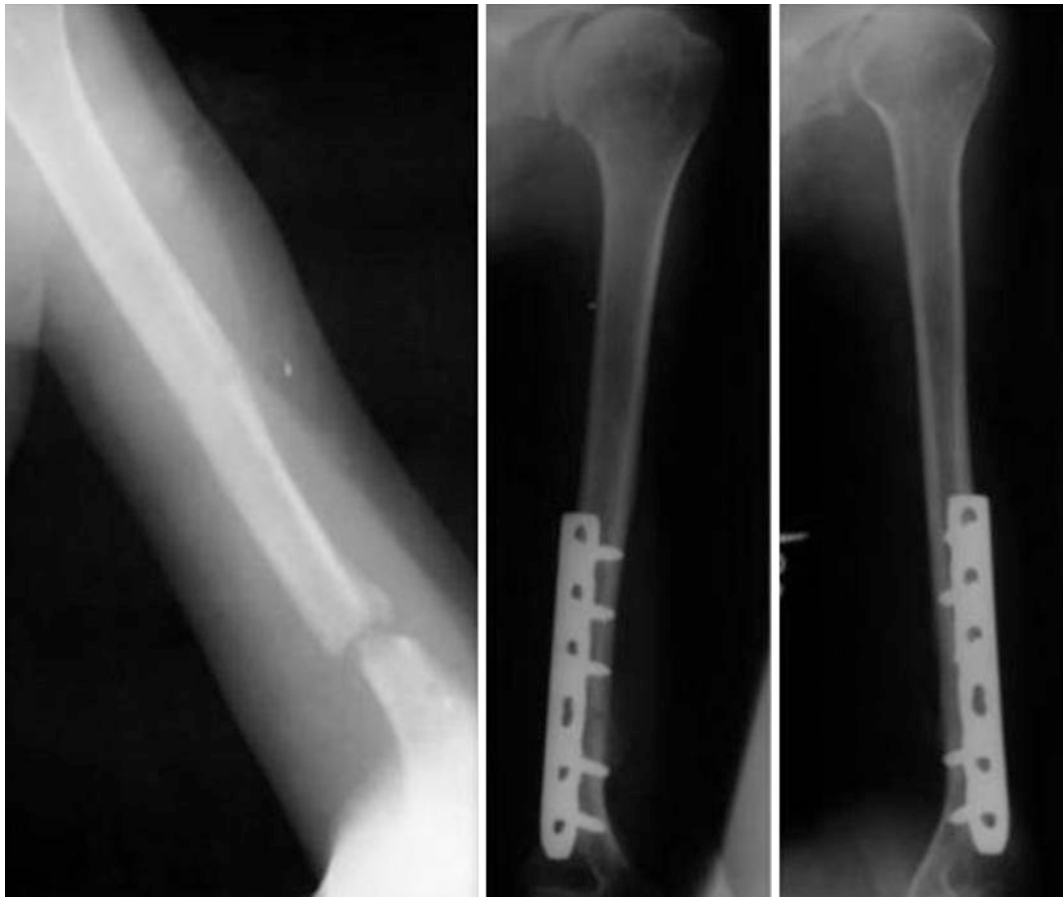


Fig. 4 Left: Atrophic nonunion of fracture of humerus. Middle: Follow-up anteroposterior and (right) lateral radiographs showing union

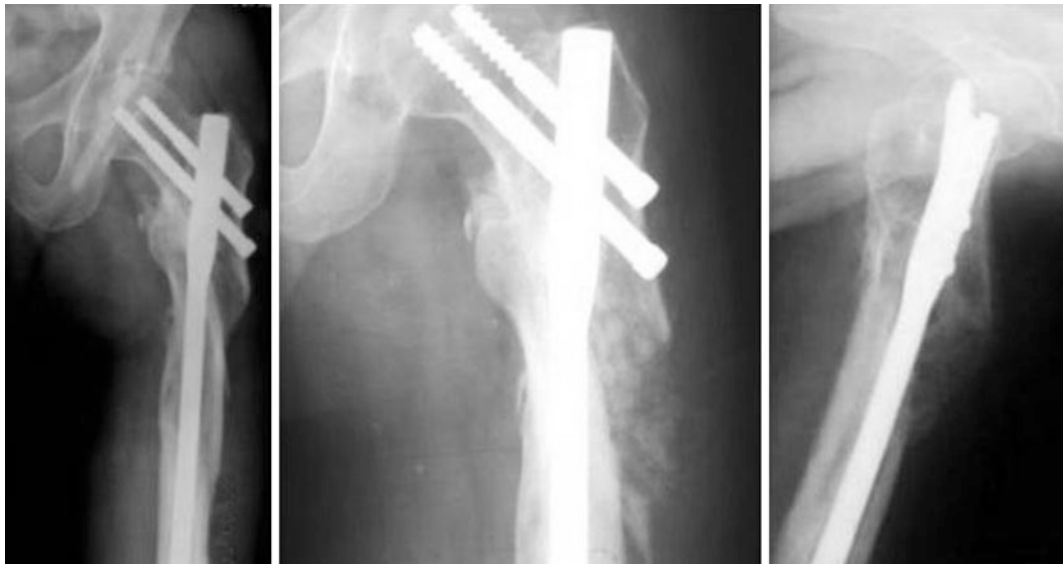


Fig. 5 Left: Surgically intervened nonunion proximal femur. Patient had postoperative infection. Union despite infection evident by bridging callus in both (middle) anteroposterior and (right) lateral radiographs

allograft bone carries immunogenic potential. Efforts are made to reduce and eliminate antigenicity of bone by processing of the allograft bone. Wang et al. showed immune response to allogenic bone in the sera of 32 patients out of 50 patients and complete graft healing in 30 of these patients [22]. A study on immunogenicity of decal bone by assessing type of cellularity (CD4 and CD8 cells) in perigraft area by FNAC concluded that decal bone did not excite an appreciably significant immunological response and partially decalcified allografts are a good substitute of autogenous bone grafts in clinical practice [23].

Conclusions

This study has given clinical evidence of efficacy of partially decalcified bone as an induction of bone healing in delayed union and atrophic nonunion of fractures of long bones but additional focused independent multicentric trials are required to accurately assess the efficacy of partially decalcified bone allograft in the induction of bone healing.

References

1. Wendy M, MaCalus V, Shawn M, William M (2008) Critical analysis of the evidence for current technologies in bone-healing and repair. J Bone Joint Surg Am 90:85–91
2. Kurz LT, Garfin SR, Booth RE (1989) Harvesting autogenous iliac bone grafts. A review of complications and techniques. Spine (Phila Pa 1976) 14:1324–1331
3. Tomford WW, Doppelt SH, Mankin HJ (1983) Bone bank procedures. Clin Orthop 174:15–21
4. Friedlaender GE (1976) Personnel and equipment required for "complete" tissue bank. Transplant Proc 8(2 Suppl 1):235–240
5. Urist MR, Silverman BF, Burking K, Dubuc FC, Rosenberg JM (1967) The bone induction principle. Clin Orthop 53:243–283
6. Urist MR (1994) The search for and discovery of bone morphogenetic protein. In: Urist MR, O'Connor BT, Burwell RG (eds) Bone grafts, derivatives and substitutes. Butterworth Heinemann Ltd, Waltham, Massachusetts, pp 315–362
7. Kevin B (2008) Delayed union and malunion of fractures. In: Canale ST, Beaty JH (eds) Campbell's operative Orthopaedics. Elsevier, Philadelphia, pp 3529–3530
8. Chapman MW (2001) Principles of treatment of nonunions and malunions. In: Chapman MW (ed) Chapman's Orthopaedic surgery. Lippincott Williams & Wilkins, Philadelphia, pp 1104–1105
9. de Boer HH (1988) The history of bone grafts. Clin Orthop 226:292–298
10. Kushner A (1940) Evaluation of Wolff's law of bone formation. J Bone Joint Surg 22:589–596
11. Friedlaender E, Mankin J (1979) Guidelines for the banking of musculoskeletal tissues. Newsletter Am Assn Tissue Banks 3:2–7
12. Friedlaender E, Mankin HJ (1981) Bone banking: current methods and suggested guidelines. Instr Course Lect 30:36–55
13. Goel SC, Tuli SM (1994) Use of decal bone in healing of osseous cystic defects. In: Urist MR, O'Connor BT, Burwell RG (eds) Bone grafts, derivatives and substitutes. Butterworth Heinemann Ltd, Waltham, Massachusetts, pp 210–219
14. Urist MR, Strates BS (1970) Bone formation implants and wholly demineralized bone matrix. Including observations on acetone-fixed intra and extracellular proteins. Clin Orthop 71:271–278
15. Hallfeldt KK, Stutzel H, Puhalman M, Kessler S, Schweiberer L (1995) Sterlization of partially demineralized bone matrix: the effects of different sterlization technique on osteogenetic properties. J Surg Res 59(5):614–620
16. Sethi A, Agrawal K, Sethi S, Kumar S, Marya SKS, Tuli SM (1993) Allograft in treatment of benign cystic lesions of bone. Arch Orthop Trauma Surg 112:167–170
17. Goel SC, Tuli SM, Singh HP, Sharma SV, Saraf SK, Srivastava TP (1992) Allogenic decalbone in the repair of benign cystic lesions of bone. Int Orthop 16(2):176–179
18. Saraf SK, Kumar A, Tuli SM, Khanna S (1994) Effect of size and shape of the allogenic bone grafts in bridging experimental ulnar gap in rabbits. Indian J Exp Biol 32(10):690–693
19. Gupta D, Tuli SM (1982) Osteoinductivity of partially decalcified alloimplants in healing of large osteoperiosteal defects. Acta Orthop Scand 53(6):857–865
20. Tuli SM, Gupta KB (1981) Bridging of large chronic osteoperiosteal gaps by allogeneic decalcified bone matrix implants in rabbits. J Trauma 21(10):894–898
21. Zhang D, Liu Z, Li M (2000) Treatment of nonunion in childhood by allogeneic decalcified bone graft. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 14:96–98
22. Wang H (1993) Study of antibody against protein in human allografts of decalcified bones. Zhonghua Wai Ke Za Zhi 31:177–180
23. Garg M, Dev G, Tuli SM, Kumar S (2000) Immunocellular responses of bone grafts in humans - a fine needle aspiration study. Ind J Orthopaed 34(3):135–137

Part II

Ophthalmology

Corneal Wound Healing and Laser Refractive Surgery

Leopoldo Spadea, Daniele Giammaria, and Claudia Ganino

1 Introduction

The cornea is a highly specialized tissue that offers a protective barrier for intraocular structures and simultaneously acts as a lens to focus images on the retina due to the regularity of its surfaces and to its transparency. Corneal traumas have the potential to affect the optical properties of tissue. This can be either through direct damage, resulting from the trauma itself, or indirect, arising from the process of tissue repair. Over the past 20 years, the spread of laser corneal refractive surgery has led to much more interest in the study of corneal "wound healing." The understanding of the complex interplay of phenomena that govern corneal healing at a cellular and molecular level has become an essential element in improving the effectiveness and safety of refractive surgery procedures.

2 Corneal Wound Healing: An "Epithelium-Stroma" Interaction

Epithelial wound healing passes through a series of different stages, carried out with a precise temporal order: the stage of sliding, in which the cells migrate to the surface and cover the damaged corneal surface; the phase of proliferation, in which there are increased cell divisions; and, finally, the stage of stratification, in which multilayers are reestablished in the epithelial structure [1].

There is a very early stage between the injury and the onset of epithelial cell migration characterized by cellular synthesis of cytoskeletal proteins such as vinculin [2], actin [3], talin, and other surface molecules such as integrins and CD44, the receptor for hyaluronic acid [4, 5]. These changes permit cells to migrate, establishing dynamic adhesion with other epithelial cells with extracellular matrix components. In the epithelial cells surrounding the wound edge, after 3 h of injury, there is an increased expression of CD44, and this expression reaches its peak after 18 h [5]. In the early stages of the process of epithelial healing, a local deposition of fibrin, fibronectin, and hyaluronic acid occurs at the level of the wound surface [6, 7]. Therefore, there is a temporary matrix that can support the migration of epithelial cells in the process of epithelial wound closure [8]. Our knowledge suggests that neural factors can deeply influence the process of corneal wound healing. The nerve fibers that innervate the corneal epithelium are positive for substance P [9]. This neuropeptide, in combination with the insulin-like growth factor-1 (IGF-1) or with the epidermal growth factor (EGF), is able to stimulate the migration of epithelial cells through the induction of adhesion molecules and

L. Spadea, M.D. (✉) · D. Giammaria, M.D.
C. Ganino, M.D.
Department of Ophthalmology, Ospedali Riuniti Marche Nord, Fano-Pesaro, Italy
e-mail: leopoldo.spadea@uniroma1.it

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_64, © Springer International Publishing AG
Published Online: 04 April 2018

cytoskeleton proteins [10]. After the migration of epithelial cells, the phase of proliferation begins. A progression of mitosis moves from the periphery to the wound site. This phase does not stop until the epithelial wound is closed and the thickness of the epithelium has returned to normal. Some studies suggest that many cytokines are involved in the healing process including epithelial EGF, the hepatocyte growth factor (HGF), the keratinocyte growth factor (KGF), and the transforming growth factor (TGF)-β (Fig. 1) [11–13]. Due to their mitogenic function, these cytokines are able to enhance the replicative activity of the epithelial cells. Growth factors are dissolved in the tear film and in many cases are produced by activated stromal keratocytes [14, 15].

The first observable phenomenon following a lesion of the corneal epithelium is the reduction of the number of keratocytes in the anterior stroma, just below the epithelial wound. The disappearance of keratocytes is via apoptosis [16]. Apoptosis of keratocytes is mediated by the release of proapoptotic molecules by the damaged epithelium; it becomes evident within a few minutes after the onset of epithelial damage and proceeds for several hours [17]. Several cytokines are involved in the induction of this process; among these interleukin-1 (IL-1) [17], Fas ligand [18], and the tumor necrosis factor (TNF)-α [19] are the most important. The majority of these cytokines are constitutively produced by cells of the corneal epithelium which may release them immediately when they are damaged.

After the first phase of apoptosis, the surviving keratocytes, nearest to the area affected by the epithelial lesion, begin to proliferate. The cells undergo a process of metabolic activation with increased size and content of cytoplasmic organelles and assume a morphology similar to fibroblasts [20]. For 24 h after the trauma, activated cells undergo rapid replication and acquire the ability to migrate, and they start to move toward the area of damaged tissue. In this phase the phenotypic change of keratocytes is realized at the molecular level through the reorganization of the cytoskeleton with the development of stress fibers and focal adhesion structures [21]. Several genes that encode a number of proteins involved in the processes of tissue repair, such as fibronectin, metalloproteinases, and integrins, are activated [22]. The deposition of these molecules in the matrix enhances cell migration and permits a rapid cell repopulation of the tissue. It seems that the platelet-derived growth factor (PDGF) plays a decisive role in inducing the proliferation and migration of keratinocytes [11]. This cytokine is produced by epithelial cells and normally is segregated at the level of the epithelial basal membrane. When a corneal injury involves both the epithelium and the basement membrane, PDGF can have access to the stroma and can

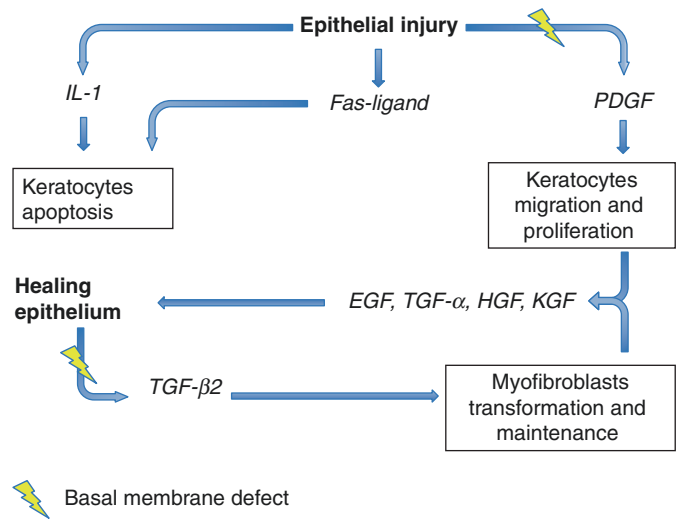


Fig. 1 Molecular regulation of epithelial cells and keratocytes in corneal wound healing

interact with the stromal keratocytes inducing its mitogenic effects [23]. The repair process continues, with a portion of fibroblasts acquiring a peculiar biological feature: a transformation of the cells into myofibroblasts. These cells are characterized by the expression of smooth muscle α-actin [24]. These cells, compared to other fibroblasts, have a greater size and a higher content of stress fibers and focal adhesion complexes. A part of corneal myofibroblasts seems to originate from cells derived from the bone marrow that penetrate the corneal stroma in response to the trauma [25]. Myofibroblasts are initially located in the portions of the superficial stroma below the epithelium. Then, they can extend deeper into the tissue. The appearance of myofibroblasts occurs in a progressive manner in the weeks following the onset of a corneal injury and, when it occurs, gives the healing process a strong ability to develop fibrotic tissue for repair [26]. In this phase stromal cell density increase and myofibroblasts cause the deposition of disorganized collagen and glycosaminoglycans [27]. The structure of the cytoskeleton of myofibroblasts confers their contractile capacity, and the interaction of these cells with the components of the matrix determines a contraction of the repairing tissue [21, 28]. The hypercellularity, the decrease of the crystallines, and the deposition of disorganized components of the matrix are important factors in determining the reduction of corneal transparency that occurs in this phase of wound healing [29]. A regulation system is present. Some studies show that TGF-β2 (transforming growth factor) is able to stimulate the fibroblasts to synthesize stress fibers and smooth muscle α-actin, a biological marker of myofibroblasts [24]. This cytokine is produced constitutively by the cells of the corneal epithelium, and the presence of the basal membrane prevents diffusion in the stroma. When the integrity of the basal membrane is compromised, TGF-β2 can diffuse in the stroma and interact with keratocytes [30]. Myofibroblasts produce cytokines that can regulate the proliferation, migration, and differentiation of cells of the overlying damaged epithelium. Among the most important factors are HGF and KGF (Fig. 1) [31]. The receptors for these cytokines are located on the epithelium and are upregulated in response to a corneal injury [31]. In a period of time between several weeks and several months, myofibroblasts tend to gradually disappear. It was observed that IL-1 causes apoptosis of myofibroblasts when the levels of TGF-β2 present in the corneal stroma are reduced, following the restoration of the integrity of the basal membrane [32]. The disappearance of the myofibroblasts indicates the exhaustion of corneal reparative processes and marks the beginning of the remodeling phase of tissue [22]. In this phase, the cornea tends to restore a morphology and a normal transparency. Consequently there is a progressive regularization of the diameter of the collagen fibrils and a spatial reorganization of stromal fibrils [33]. The remodeling process can take years before it is concluded definitively. At this stage the collagen turnover is much higher compared to what happens in a normal cornea [34]. This seems linked to a change in the expression of matrix metalloproteinases (collagenase, gelatinase A) triggered by the processes of wound healing [35]. These proteins are a family of proteolytic enzymes normally present in low concentrations in the corneal stroma where they play a homeostatic function by degrading abnormal or damaged collagen fibrils [36]. The synthesis of metalloproteinases occurs in response to the activity of cytokines, growth factors, and inflammatory mediators [37].

The influence of corneal wound healing on laser refractive surgery is regression and haze.

Corneal wound healing is one of the most important factors that accounts for the predictability of laser refractive surgery. The refractive outcome after procedures such as photorefractive keratectomy (PRK), laser-assisted subepithelial keratomileusis (LASEK), and laser-assisted in situ keratomileusis (LASIK) and its stability over the time are strongly influenced by the biological response of the corneal tissue. Understanding corneal wound healing processes improves precision and safety of refractive procedures.

Many studies show a loss of surgical outcome after these procedures [38, 39], and the main cause of this loss seems to be the regression. Refractive regression is defined as a grad-

ual, partial, or complete loss of the attempted correction that limits any prediction in all types of refractive surgery. In both PRK and LASIK, the refractive regression is mainly due to epithelial hyperplasia and stromal remodeling [40–42], two processes related to corneal wound healing that compromise the refractive accuracy and stability after surgery. The tendency for regression occurs more frequently after PRK than LASIK, although in both cases a persistent increase of epithelial thickness is noted in a percentage ranging from 15 to 20% [43, 44]. In particular, epithelial changes in LASIK occur within 1 week after surgery and persist for about 3 years; in PRK, the initial epithelial thinning caused by debridement is followed by a gradual thickening that occurs up to 12 months after surgery [44]. After PRK significant differences are reported between patients treated for mild myopia and patients treated for high myopia: apoptosis, keratocyte proliferation, and myofibroblast cellular density have proved to be most intense processes following treatment for high myopia compared to treatments for mild myopia [45]. Consequently, a regression is more common following PRK for high myopia compared to PRK for mild myopia [46, 47]. Ivarsen et al. [44] showed that both PRK and LASIK caused stromal regrowth during the first year after treatment. However, for the same myopic correction, wound repair after PRK gave rise to significantly more stromal tissue deposition than did LASIK, and the increase in stromal thickness correlated with the postoperative regression. Interestingly, stromal regrowth in LASIK involved only the stromal bed without any changes on the flap.

A clinically significant reduction of corneal transparency (haze) occurs in 1–4% of all laser surface ablation procedures [46, 48]. Corneal haze is a consequence of corneal wound healing: keratocytes differentiate into myofibroblasts, and there is a disorderly deposition of collagen. Patients who develop haze complain of worsening of visual acuity that occurs about 2–3 months after surgery. Anterior segment biomicroscopy shows a corneal opacity just beneath the epithelium. Usually this opacity disappears completely after 6–9 months but in some cases can remain for a longer time.

3 Several Clinical Factors Have Been Correlated with Haze Formation

3.1 Degree of Myopia

Haze onset is rare for myopic corrections below six diopters, although it may still occur. Its incidence typically increases for more than six diopters of myopia. A study by Møller-Pedersen showed that onset and duration of haze increase proportionally with the increase of ablation depth [49].

3.2 Stromal Surfaces Irregularities After Treatment

Stromal surface irregularities are related to persistent defects of basal membrane that facilitates the passage of TGF-beta in the underlying stroma. As evidenced in some studies in animal models, by the time the stromal irregularities are reduced and stromal basement membrane defects closed, it prevents the TGF-β from promoting the myofibroblasts survival [50].

3.3 Type of Laser

The new excimer lasers with a small spot create a more regular ablation reducing the probability of developing corneal haze [51].

3.4 Ablation Procedure

Corneal haze is more common after PRK compared to LASIK due to the disruption of basal membrane that occurs in ablation surface procedures [30]. After PRK, two types of haze may occur: a type appears after 1–3 months and is rarely associated with symptoms; it typically disappears after about 1 year following

the surgery [52]. Another type of haze, reported by Meyer et al. and Lipshitz et al. [53, 54], is defined as "late-onset corneal haze" and tends to appear from 2 to 5 months after surgery and persist for more than 3 years until it disappears. Following LASIK instead, we can observe a circumferential haze that follows the edge of the flap: this is due to breakage of the basal membrane that occurs at the edge of the flap. The fibrotic response that occurs at the edge of the flap is associated with myofibroblasts transformation and involves the cytokine TGF-β [55]. The epithelial flap in LASEK may minimize the onset of haze. In fact, a reduced release of TGF-β was reported in the tear film of patients undergoing this ablation procedure, compared to PRK patients [56].

3.5 Debridement Technique

In LASEK an ethanol solution is used to promote the separation between epithelium and stroma; stromal hydration changes with the variation of the time of exposure to ethanol. Furthermore, this alcohol may cause the necrosis of the anterior keratocytes, especially when is used at high concentration and for a longer time [57]. In PRK, mechanical debridement seems to generate a greater amount of haze compared to laser transepithelial ablation. In a recent study by Celik et al. [58], it was reported that the healing time and the onset of postoperative haze are significantly lower in eyes treated with transepithelial PRK compared to those treated with PRK and mechanical debridement. Probably, as reported by Helena et al. [59], it is related to a lower level of keratinocyte apoptosis caused by transepithelial ablation. However, Møller-Pedersen et al. [49] reported a greater inflammatory response with an increased activation of keratocytes after transepithelial ablation. The healing of the corneal epithelium seems to be faster in eyes undergoing transepithelial ablation than in eyes undergoing mechanical and alcoholic debridement [58, 60]. However, Clinch et al. [61] did not report this difference.

3.6 UV Radiation Exposure

Stojanovic et al. in 2001 [62] released a study to evaluate the association between high ultraviolet (UV) radiation exposure and late-onset corneal haze (LOCH) in PRK patients. They reported that an environment with high levels of UV radiation may increase the risk of LOCH. The authors suggested the use of UV-protective eyewear during the first year after surgery in these patients.

4 Pharmacological Modulation of Corneal Wound Healing

Mitomycin C (MMC) belongs to a family of chemotherapy antibiotics derived from *Streptomyces caespitosus* and was isolated for the first time in 1956 [63]. It is classified as alkylating agent although the mechanism of action has not been fully established yet. Once activated by enzymes such as cytochrome 450 reductase [64], MMC may interact with DNA through the formation of covalent bonds between residues of adenine and guanine during the G1 and S phases of the cell cycle. Consequently, the alkylation of DNA is able to block DNA synthesis and cell mitosis with the arrest of the cell cycle [65, 66].

Due to its antimitotic properties, MMC is widely used in ophthalmic surgery to delay tissue healing and reduce the fibrotic response. This drug is commonly used in glaucoma surgery, pterygium surgery, and corneal-conjunctival neoplasm [67–69]. In refractive surgery, MMC is widely used as an intraoperative adjuvant agent for surface ablation procedures due to its ability in reducing the onset of subepithelial haze, especially in high myopia corrections and in retreatments [70–72]. The underlying mechanism of this effect may be the inhibition of mitosis of cells that aim to repopulating the anterior stroma after ablation [71]. In particular, MMC seems to inhibit the activation and proliferation of keratocytes and their differentiation in myofibroblasts [73]. Over the recent years, the reduction of concentration and time of exposure in the use of MMC is the trend in refractive surgery. Currently, the most used concentration is 0.2 mg/mL

(0.02%); lower concentrations may not be effective in reducing the onset of haze in high degrees of myopia [74, 75]. The time exposure of this drug varies from 12 s to a minute, depending on the depth of ablation [71, 76, 77]. Variations in the exposure time affect the penetration of this drug in the cornea and in the anterior chamber less in comparison to changes in its concentration [78, 79]. Some authors recommend the intraoperative use of MMC for high degrees of myopia (greater than −6.00 diopters) [71] or when ablation laser depth is included between 50 and 100 μm [76, 80, 81].

The use of MMC in refractive surgery with dosages and methods described in the literature is considered safe and effective [82]. A recent study by Kremer et al. [83] reported a delay on reepithelization in 3.5% of patients treated with PRK and MMC. Some studies show a decrease of cellular density in anterior stroma, in patients treated with MMC 1 month after surgery and the following 6 months [71, 84]. Several animal studies showed the existence of a potential toxicity on corneal endothelium depending on dosage and exposure time [78, 85]. However, human clinical trials performed with dosages and exposure times actually used in refractive surgery have not shown a significant endothelial toxicity [77, 82].

Inflammatory response related to corneal wound healing after PRK is due mainly to a stromal infiltration of macrophages [86]. Macrophages remove cell debris and dead cells after laser ablation and contribute to reorganize corneal tissue. Along with cells of the corneal epithelium, macrophages can release TGF-β, modulating differentiation of keratocytes in myofibroblasts [87, 88]. Corticosteroids may inhibit macrophage activity and corneal fibroblasts proliferation [86, 89]. By delaying the overall wound healing processes, steroids decrease the risk of haze onset after PRK. However, as reported by Nien et al. [90] in a rabbit study, the corticosteroids anti-haze effect seems to run out over time after discontinuation of treatment. Currently, steroids continue to represent the most used drug for modulation of postoperative corneal wound healing after laser ablation.

Conclusions

While laser refractive surgery offers the promise to correct visual refractive errors permanently and predictably, variability and complications continue to hinder widespread acceptance. To explain variations a lot of studies have focused on the role of corneal wound healing in modulating refractive outcomes, playing a pivotal role in defining the results of refractive surgery. Therefore a better understanding of the corneal cellular and molecular biology is mandatory if refractive surgery is ever to achieve predictable and safe refractive results.

References

1. Lu L, Reinach PS, Kao WW (2001) Corneal epithelial wound healing. Exp Biol Med (Maywood) 226(7):653–664
2. Soong HK (1987) Vinculin in focal cell-to-substrate attachments of spreading corneal epithelial cells. Arch Ophthalmol 105(8):1129–1132
3. Nakagawa S, Nishida T, Manabe R (1985) Actin organization in migrating corneal epithelium of rabbits in situ. Exp Eye Res 41(3):335–343
4. Päällysaho T, Williams DS (1991) Epithelial cell-substrate adhesion in the cornea: localization of actin, talin, integrin, and fibronection. Exp Eye Res 52(3):261–267
5. FX Y, Guo J, Zhang Q (1998) Expression and distribution of adhesion molecule CD44 in healing corneal epithelia. Invest Ophthalmol Vis Sci 39(5):710–717
6. Allen-Hoffmann BL, Schlosser SJ, Brondyk WH, Fahl WE (1990) Fibronectin levels are enhanced in human fibroblasts overexpressing the c-sis protooncogene. J Biol Chem 265(9):5219–5225
7. Asari A, Morita M, Sekiguchi T, Okamura K, Horie K, Miyauchi S (1996) Hyaluronan, CD44 and fibronectin in rabbit corneal epithelial wound healing. Jpn J Ophthalmol 40(1):18–25
8. Watanabe K, Nakagawa S, Nishida T (1988) Chemotactic and haptotactic activities of fibronectin for cultured rabbit corneal epithelial cells. Invest Ophthalmol Vis Sci 29(4):572–577
9. Tervo K, Tervo T, Eränkö L, Vannas A, Cuello AC, Eränkö O (1982) Substance P-immunoreactive nerves in the human cornea and iris. Invest Ophthalmol Vis Sci 23(5):671–674
10. Nishida T, Nakamura M, Ofuji K, Reid TW, Mannis MJ, Murphy CJ (1996) Synergistic effects of substance P with insulin-like growth factor-1 on epithelial migration of the cornea. J Cell Physiol 169(1):159–166

11. Imanishi J, Kamiyama K, Iguchi I, Kita M, Sotozono C, Kinoshita S (2000) Growth factors: importance in wound healing and maintenance of transparency of the cornea. Prog Retin Eye Res 19(1):113–129
12. Kandarakis AS, Page C, Kaufman HE (1984) The effect of epidermal growth factor on epithelial healing after penetrating keratoplasty in human eyes. Am J Ophthalmol 98(4):411–415
13. FS Y, Yin J, Xu K, Huang J (2010) Growth factors and corneal epithelial wound healing. Brain Res Bull 81(2-3):229–235
14. Vesaluoma M, Teppo AM, Gronhagen-Riska C, Tervo T (1997) Release of TGF-beta 1 and VEGF in tears following photorefractive keratectomy. Curr Eye Res 16(1):19–25
15. Nishimura T, Toda S, Mitsumoto T, Oono S, Sugihara H (1998) Effects of hepatocyte growth factor, transforming growth factor-beta1 and epidermal growth factor on bovine corneal epithelial cells under epithelial-keratocyte interaction in reconstruction culture. Exp Eye Res 66(1):105–116
16. Wilson SE, Kim WJ (1998) Keratocyte apoptosis: implications on corneal wound healing, tissue organization, and disease. Invest Ophthalmol Vis Sci 39(2):220–226
17. Wilson SE, He YG, Weng J, Li Q, McDowall AW, Vital M, Chwang EL (1996) Epithelial injury induces keratocyte apoptosis: hypothesized role for the interleukin-1 system in the modulation of corneal tissue organization. Exp Eye Res 62(4):325–327
18. Mohan RR, Liang Q, Kim WJ, Helena MC, Baerveldt F, Wilson SE (1997) Apoptosis in the cornea: further characterization of Fas/Fas ligand system. Exp Eye Res 65(4):575–589
19. Mohan RR, Mohan RR, Kim WJ, Wilson SE (2000) Modulation of TNF-alpha induced apoptosis in corneal fibroblasts by transcription factor NF-kappaB. Invest Ophthalmol Vis Sci 4(6):1327–1336
20. Zieske JD, Guimarães SR, Hutcheon AE (2001) Kinetics of keratocyte proliferation in response to epithelial debridement. Exp Eye Res 72(1):33–39
21. Desmouliere A, Chaponnier C, Gabbiani G (2005) Tissue repair, contraction, and the myofibroblast. Wound Repair Regen 13(1):7–12
22. Fini ME (1999) Keratocyte and fibroblast phenotypes in the repairing cornea. Prog Retin Eye Res 18(4):529–551
23. Kim WJ, Mohan RR, Mohan RR, Wilson SE (1999) Effect of PDGF, IL-1 alpha, and BMP2/4 on corneal fibroblast chemotaxis: expression of the platelet-derived growth factor system in the cornea. Invest Ophthalmol Vis Sci 40(7):1364–1372
24. Jester JV, Petroll WM, Cavanagh HD (1999) Corneal stromal wound healing in refractive surgery: the role of myofibroblasts. Prog Retin Eye Res 18(3):311–356
25. Barbosa FL, Chaurasia SS, Cutler A, Asosingh K, Kaur H, de Medeiros FW, Agrawal V, Wilson SE (2010) Corneal myofibroblast generation from bone marrow-derived cells. Exp Eye Res 91(1):92–96
26. Jester JV, Petroll WM, Barry PA, Cavanagh HD (1995) Expression of alpha-smooth muscle (alpha-SM) actin during corneal stromal wound healing. Invest Ophthalmol Vis Sci 36(5):809–819
27. Karamichos D, Guo XQ, Hutcheon AE, Zieske JD (2010) Human corneal fibrosis: an in vitro model. Invest Ophthalmol Vis Sci 51(3):1382–1388
28. Jester JV, Petroll WM, Barry PA, Cavanagh HD (1995) Temporal, 3-dimensional, cellular anatomy of corneal wound tissue. J Anat 186(Pt 2):301–311
29. Jester JV, Brown D, Pappa A, Vasiliou V (2012) Myofibroblast differentiation modulates keratocyte crystallin protein expression, concentration, and cellular light scattering. Invest Ophthalmol Vis Sci 53(2):770–778
30. Stramer BM, Zieske JD, Jung JC, Austin JS, Fini ME (2003) Molecular mechanisms controlling the fibrotic repair phenotype in cornea: implications for surgical outcomes. Invest Ophthalmol Vis Sci 44(10):4237–4246
31. Sotozono C, Kinoshita S, Kita M, Imanishi J (1994) Paracrine role of keratinocyte growth factor in rabbit corneal epithelial cell growth. Exp Eye Res 59(4):385–391
32. Barbosa FL, Chaurasia SS, Kaur H, de Medeiros FW, Agrawal V, Wilson SE (2010) Stromal interleukin-1 expression in the cornea after haze-associated injury. Exp Eye Res 91(3):456–461
33. Cintron C, Hassinger LC, Kublin CL, Cannon DJ (1978) Biochemical and ultrastructural changes in collagen during corneal wound healing. J Ultrastruct Res 65(1):13–22
34. Cionni RJ, Katakami C, Lavrich JB, Kao WW (1986) Collagen metabolism following corneal laceration in rabbits. Curr Eye Res 5(8):549–558
35. Ando H, Twining S, Yue BY, Zhou X, Fini ME, Kaiya T, Higginbotham EJ, Sugar J (1993) MMPs and proteinase inhibitors in the human aqueous humor. Invest Ophthalmol Vis Sci 34(13):3541–3548
36. Fini ME, Girard MT, Matsubara M (1992) Collagenolytic/gelatinolytic enzymes in corneal wound healing. Acta Ophthalmol Suppl 202:26–33
37. Strissel KJ, Rinehart WB, Fini ME (1997) Regulation of paracrine cytokine balance controlling collagenase synthesis by corneal cells. Invest Ophthalmol Vis Sci 38(2):546–552
38. Aliò JL, Muftuoglu O, Ortiz D, Artola A, Pérez-Santonja JJ, de Luna GC, Abu-Mustafa SK, Garcia MJ (2008) Ten-year follow-up of photorefractive keratectomy for myopia of more than −6 diopters. Am J Ophthalmol 145(1):37–45
39. Kato N, Toda I, Hori-Komai Y, Sakai C, Tsubota K (2008) Five-year outcome of LASIK for myopia. Ophthalmology 115(5):839–844
40. Balestrazzi E, De Molfetta V, Spadea L, Vinciguerra P, Palmieri G, Santeusanio G, Spagnoli L (1995) Histological, immunohistochemical and ultrastructural findings in human corneas after photorefractive keratectomy. J Refract Surg 11(3):181–187

41. Spadea L, Fasciani R, Necozione S, Balestrazzi E (2000) Role of the corneal epithelium in refractive changes following laser in situ keratomileusis for high myopia. J Refract Surg 16(2):133–139
42. Reinstein DZ, Silverman RH, Sutton HF, Coleman DJ (1999) Very high frequency ultrasound corneal analysis identifies anatomic correlates of optical complications of lamellar refractive surgery: anatomic diagnosis in lamellar surgery. Ophthalmology 106(3):474–482
43. Ambrósio R Jr, Wilson S (2003) LASIK vs LASEK vs PRK: advantages and indications. Semin Ophthalmol 18(1):2–10
44. Ivarsen A, Fledelius W, Hjortdal JØ (2009) Three-year changes in epithelial and stromal thickness after PRK or LASIK for high myopia. Invest Ophthalmol Vis Sci 50(5):2061–2066
45. Mohan RR, Hutcheon AE, Choi R, Hong J, Lee J, Mohan RR, Ambrósio R Jr, Zieske JD, Wilson SE (2003) Apoptosis, necrosis, proliferation, and myofibroblast generation in the stroma following LASIK and PRK. Exp Eye Res 76(1):71–87
46. Williams DK (1997) Multizone photorefractive keratectomy for high and very high myopia: long term results. J Cataract Refract Surg 23(7):1034–1041
47. Kim JH, Sah WJ, Park CK, Hahn TW, Kim MS (1996) Myopic regression after photorefractive keratectomy. Ophthalmic Surg Lasers 27(5 Suppl):S435–S439
48. Rajan MS, Jaycock P, O'Brart D, Nystrom HH, Marshall J (2004) A long-term study of photorefractive keratectomy; 12-year follow-up. Ophthalmology 111(10):1813–1824
49. Møller-Pedersen T, Cavanagh HD, Petroll WM, Jester JV (1998) Corneal haze development after PRK is regulated by volume of stromal tissue removal. Cornea 17(6):627–639
50. Netto MV, Mohan RR, Sinha S, Sharma A, Dupps W, Wilson SE (2006) Stromal haze, myofibroblasts, and surface irregularity after PRK. Exp Eye Res 82(5):788–797
51. Fiore T, Carones F, Brancato R (2001) Broad beam vs. flying spot excimer laser: refractive and videokeratographic outcomes of two different ablation profiles after photorefractive keratectomy. J Refract Surg 17(5):534–541
52. Netto MV, Mohan RR, Ambrósio R Jr, Hutcheon AE, Zieske JD, Wilson SE (2005) Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. Cornea 24(5):509–522
53. Meyer JC, Stulting RD, Thompson KP, Durrie DS (1996) Late onset of corneal scar after excimer laser photorefractive keratectomy. Am J Ophthalmol 121(5):529–539
54. Lipshitz I, Loewenstein A, Varssano D, Lazar M (1997) Late onset corneal haze after photorefractive keratectomy for moderate and high myopia. Ophthalmology 104(3):369–373
55. Ivarsen A, Laurberg T, Møller-Pedersen T (2003) Characterisation of corneal fibrotic wound repair at the LASIK flap margin. Br J Ophthalmol 87(10):1272–1278
56. Lee JB, Choe CM, Kim HS, Seo KY, Seong GJ, Kim EK (2002) Comparison of TGF-beta1 in tears following laser subepithelial keratomileusis and photorefractive keratectomy. J Refract Surg 18(2):130–134
57. Espana EM, Grueterich M, Mateo A, Romano AC, Yee SB, Yee RW, Tseng SC (2003) Cleavage of corneal basement membrane components by ethanol exposure in laser-assisted subepithelial keratectomy. J Cataract Refract Surg 29(6):1192–1197
58. Celik U, Bozkurt E, Celik B, Demirok A, Yilmaz OF (2014) Pain, wound healing and refractive comparison of mechanical and transepithelial debridement in photorefractive keratectomy for myopia: results of 1 year follow-up. Cont Lens Anterior Eye 37(6):420–426
59. Helena MC, Baerveldt F, Kim WJ, Wilson SE (1998) Keratocyte apoptosis after corneal surgery. Invest Ophthalmol Vis Sci 39(2):276–283
60. Lee HK, Lee KS, Kim JK, Kim HC, Seo KR, Kim EK (2005) Epithelial healing and clinical outcomes in excimer laser photorefractive surgery following three epithelial removal techniques: mechanical, alcohol, and excimer laser. Am Ophthalmol 139(1):56–63
61. Clinch TE, Moshirfar M, Weis JR, Ahn CS, Hutchinson CB, Jeffrey JH (1999) Comparison of mechanical and transepithelial debridement during photorefractive keratectomy. Ophthalmology 106(3):483–489
62. Stojanovic A, Nitter TA (2001) Correlation between ultraviolet radiation level and the incidence of late-onset corneal haze after photorefractive keratectomy. J Cataract Refract Surg 27(3):404–410
63. Hata T, Hoshi T, Kanamori K, Matsumae A, Sano Y, Shima T, Sugawara R (1956) Mitomycin, a new antibiotic from Streptomyces I. J Antibiot 9(4):141–146
64. Crowston JG, Chang LH, Constable PH, Daniels JT, Akbar AN, Khaw PT (2002) Apoptosis gene expression and death receptor signaling in mitomycin C-treated human Tenon capsule fibroblasts. Invest Ophthalmol Vis Sci 43(3):692–699
65. Galm U, Hager MH, Van Lanen SG, Ju J, Thorson JS, Shen B (2005) Antitumor antibiotics: bleomycin, enediynes, and mitomycin. Chem Rev 105(2):739–758
66. Mladenov E, Tsaneva I, Anachkova B (2007) Activation of the S phase DNA damage checkpoint by mitomycin C. J Cell Physiol 211(2):468–476
67. Oguz H (2003) Mitomycin C and pterygium excision. Ophthalmology 110(11):2257–2258
68. Pinilla I, Larrosa JM, Polo V, Honrubia FM (1998) Subconjunctival injection of low doses of mitomycin C: effects on fibroblast proliferation. Ophthalmologica 212(5):306–309
69. Abraham LM, Selva D, Casson R, Leibovitch I (2006) Mitomycin: clinical applications in ophthalmic practice. Drugs 66(3):321–340
70. Wilson SE, Chaurasia SS, Medeiros FW (2007) Apoptosis in the initiation, modulation and termination of the corneal wound healing response. Exp Eye Res 85(3):305–311

71. Netto MV, Mohan RR, Sinha S, Sharma A, Gupta PC, Wilson SE (2006) Effect of prophylactic and therapeutic mitomycin C on corneal apoptosis, cellular proliferation, haze, and long-term keratocyte density in rabbits. J Refract Surg 22(6):562–574
72. Schipper I, Suppelt C, Gebbers JO (1997) Mitomycin C reduces scar formation after excimer laser (193 nm) photorefractive keratectomy in rabbits. Eye 11(Pt 5):649–655
73. Xu H, Liu S, Xia X, Huang P, Wang P, Mitomycin WX (2001) C reduces haze formation in rabbits after excimer laser photorefractive keratectomy. J Refract Surg 17(3):342–349
74. Thornton I, Xu M, Krueger RR (2008) Comparison of standard (0.02%) and low dose (0.002%) mitomycin C in the prevention of corneal haze following surface ablation for myopia. J Refract Surg 24(1):S68–S76
75. Thornton I, Puri A, Xu M, Krueger RR (2007) Low dose mitomycin C as a prophylaxis for corneal haze in myopic surface ablation. Am J Ophthalmol 144(5):673–681
76. Lacayo GO 3rd, Majmudar PA (2005) How and when to use mitomycin-C in refractive surgery. Curr Opin Ophthalmol 16(4):256–259
77. Lee DH, Chung HS, Jeon YC, Boo SD, Yoon YD, Kim JG (2005) Photorefractive keratectomy with intraoperative mitomycin-C application. J Cataract Refract Surg 31(12):2293–2298
78. Song JS, Kim JH, Yang M, Sul D, Kim HM (2006) Concentrations of mitomycin C in rabbit corneal tissue and aqueous humor after topical administration. Cornea 25(10 Suppl 1):S20–S23
79. Song JS, Kim JH, Yang M, Sul D, Kim HM (2007) Mitomycin-C concentration in cornea and aqueous humor and apoptosis in the stroma after topical Mitomycin-C application: effects of Mitomycin-C application time and concentration. Cornea 26(4):461–467
80. Mirza MA, Qazi MA, Pepose JS (2004) Treatment of dense subepithelial corneal haze after laser-assisted subepithelial keratectomy. J Cataract Refract Surg 30(3):709–714
81. DeBenito-Llopis L, Teus MA, Sánchez-Pina JM (2008) Comparison between LASEK with mitomycin C and LASIK for the correction of myopia of - 7.00 to – 13.75 D. J Refract Surg 24(5):516–523
82. Spadea L, Verrecchia V (2011) Effectiveness of scraping and mitomycin C to treat haze after myopic photorefractive keratectomy. Open Ophthalmol J 5:63–65
83. Kremer I, Ehrenberg M, Levinger S (2012) Delayed epithelial healing following photorefractive keratectomy with mitomycin C treatment. Acta Ophthalmol 90(3):271–276
84. Kim TI, Tchah H, Lee SA, Sung K, Cho BJ, Kook MS (2003) Apoptosis in keratocytes caused by mitomycin C. Invest Ophthalmol Vis Sci 44(5):1912–1917
85. Nassiri N, Farahangiz S, Rahnavardi M, Rahmani L, Nassiri N (2008) Corneal endothelial cell injury induced by mitomycin-C in photorefractive keratectomy: nonrandomized controlled trial. J Cataract Refract Surg 34(6):902–908
86. O'Brien TP, Li Q, Ashraf MF, Matteson DM, Stark WJ, Chan CC (1998) Inflammatory response in the early stages of wound healing after excimer laser keratectomy. Arch Ophthalmol 116(11):1470–1474
87. Saika S (2004) TGF-beta signal transduction in corneal wound healing as a therapeutic target. Cornea 23(8 Suppl):S25–S30
88. Saika S, Yamanaka O, Sumioka T, Miyamoto T, Miyazaki K, Okada Y, Kitano A, Shirai K, Tanaka S, Ikeda K (2008) Fibrotic disorders in the eye: targets of gene therapy. Prog Retin Eye Res 27(2):177–196
89. Nguyen KD, Lee DA (1992) Effect of steroids and nonsteroidal antiinflammatory agents on human ocular fibroblast. Invest Ophthalmol Vis Sci 33(9):2693–2701
90. Nien CJ, Flynn KJ, Chang M et al (2011) Reducing peak corneal haze after photorefractive keratectomy in rabbits: prednisolone acetate 1.00% versus cyclosporine a 0.05%. J Cataract Refract Surg 37(5):937–944

Corneal Epithelial Wound Healing and Management Strategies

Leyla Asena, Hosamadden Alkayid, and Dilek Dursun Altınörs

1 Introduction

Corneal epithelial integrity is essential for maintaining its barrier function against infective microorganisms and normal stromal hydration and providing a transparent refractive surface. Therefore, careful treatment of corneal epithelial defects is essential. Delayed reepithelialization due to the slow regeneration of the basal membrane complexes may lead to persistent epithelial defects, corneal ulcers and infections. The first step of wound healing consists of a significant increase in cell proliferation to cover the denuded area which continues for 24–30 h after the injury [1]. Cell proliferation, cell migration and adequate cell-to-substrate adhesion are also necessary for epithelial healing. Some observations suggest that cell proliferation, adhesion and migration at early stages of differentiation and apoptosis at late stages of wound healing are controlled by several growth-modulating cytokines including platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor alpha (TGF-α) and tumour necrosis factor beta (TNF-β), as well as fibronectin and vitamin A [1, 2]. Artificial tears, autologous serum eye drops, topical umbilical cord serum, topical human breast milk, epidermal growth factor (EGF), tissue adhesives like fibronectin, anti-inflammatory agents like corticosteroids and keeping away from the traumatic agent may enhance reepithelialization [3, 4]. Topical treatment with human breast milk may be helpful as well, since it contains many anti-infective agents and growth factors that may enhance epithelial wound healing [5]. In this chapter, corneal structure, corneal epithelial wound healing and treatment of corneal epithelial wounds with a special emphasis on the effect of human breast milk drops will be discussed.

2 Corneal Structure

The cornea is the transparent anterior segment of the eye that refracts light onto the retina. It is the first element in the eye's optical system, contributing two-thirds of the eye's total refractive power, and must remain essentially clear for optimal vision to be achieved. The cornea acts as the eye's outermost lens, which plays an important role in focusing our vision in addition to its protective function. To maintain transparency, the cornea must remain avascular and unscarred and preserve its highly regular organized internal structure. The cornea is also the most sensitive tissue in the body. The epithelium and interstitial

L. Asena, M.D. (✉) · D.D. Altınörs
Department of Ophthalmology, Baskent University Faculty of Medicine, Ankara, Turkey
e-mail: leylaerk@yahoo.com

H. Alkayid
Department of Ophthalmology, Jordanian Royal Medical Services, Amman, Jordan

Department of Ophthalmology, Baskent University Faculty of Medicine, Ankara, Turkey

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_65, © Springer International Publishing AG
Published Online: 01 May 2018

layers of the cornea are innervated by the trigeminal nerve and sympathetic nerves, which are considered to play important roles not only in sensory transmission but also in maintenance for the viability of corneal epithelial cells [6].

The human cornea is made of five layers: the outermost corneal regenerable *epithelium, *Bowman's membrane, *stroma (which is populated by keratocytes, being the thickest layer), *Descemet's membrane (DM) and the inner *corneal endothelium, which is a monolayer of neural crest-derived endothelial cells (Fig. 1). Recently a novel, well-defined, acellular, strong layer in the pre-Descemet's cornea was described by Dua HS et al. (Dua's layer) [7]. All of the above-mentioned layers extend laterally to the limbus which marks the transition zone from corneal epithelium to conjunctival epithelium anteriorly. Externally the epithelium is coated by a thin, continuously renewed layer of tears, while internally the endothelium is in constant contact with the aqueous humour that fills the anterior chamber of the eye [8].

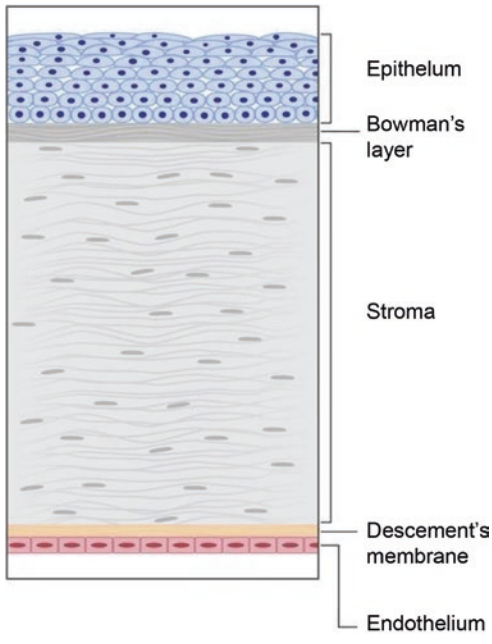


Fig. 1 Anatomy of the corneal layers. The outermost corneal regenerable *epithelium, *Bowman's membrane, *stroma(which is populated by keratocytes, being the thickest layer), *Descemet's membrane (DM) and the inner *corneal endothelium

2.1 Tear Film

In the healthy eye, tear film is a thin fluid layer of approximately 10 μm coating the surface of the cornea [9]. Tear fluid contains water, mucin, lipids, lysozyme, lactoferrin, lipocalin, lacritin, immunoglobulins, glucose, urea, sodium and potassium. The precorneal film has three distinct layers: lipid layer, aqueous layer and mucous layer. Tears are formed by secretions from the lacrimal glands with contributions from the Meibomian glands and goblet cells. These are mixed and spread over the cornea by the regular action of the blink. The tear film serves the epithelium by preserving its optical quality, delivering nutrients, facilitating the transport of signalling proteins, providing a pathway for access of leukocytes and acting as a reservoir for topically applied medications. Additionally the richness of the tears in antimicrobial factors and the high frequency of tear film renewal help to protect the cornea from infection and toxic substances [10].

2.2 Corneal Epithelium

The major roles of the corneal epithelium are to act as a barrier, to assist in maintaining a constant level of stromal hydration and to serve as an optical interface. The barrier function of the epithelium is directed against physical trauma, pathogens and chemicals. All of these are a threat to the underlying stroma that may lose its transparency if damaged. By preventing the diffusion of water and solutes from the tear film into the cornea, the epithelium also enables relatively dehydrated state of the stroma to persist. By remaining smooth and clear, the epithelium transmits refracted light from the tear film uninterrupted into the eye [11]. The corneal epithelium consists of five to seven layers of non-keratinized squamous stratified-type epithelial cells with an approximate thickness of 50 μm (Fig. 1). The cells of this layer can be distinguished morphologically into basal columnar cells, wing cells and superficial squamous cells. The squamous cells of the ocular surface desquamate relatively frequently to be washed away into the tear film over the course of the blink. The transition of a cell

from basal, to wing, then squamous cell that is shed takes 1–2 weeks. This regular turnover contributes to the protective role of the epithelium as any infected or damaged cells are quickly replaced [8, 12]. Epithelial cells attach to each other and the extracellular matrix through junctional and non-junctional adhesions. Junctional adhesions are structures where cytoskeletal, transmembrane and in some cases extracellular proteins aggregate to form a complex with distinct morphology under the electron microscope. In the corneal epithelium, there are zonula occludens junctions, gap junctions, adherens junctions, desmosomes and hemidesmosomes. Nonjunctional adhesions are ligand-receptor interactions that are not visible without immunochemical staining. The surface-exposed apical aspect of the squamous cells expresses glycocalyx that interacts with tear film mucin to maintain the cornea's wettability. This supports an even distribution of tear film across the surface of the cornea. Cells of this layer are terminally differentiated and will desquamate into the tear film within a week. Squamous corneal epithelial cells of the superficial layers form zonula occludens junctions with surrounding cells contributing significantly to the epithelium's barrier function [13]. The intercellular junctions of the wing cells contribute significantly to structural integrity of the corneal epithelium. The basal cells are the only mitotic layer in the corneal epithelium with their stem cells located in the limbal region. As a basal cell divides, it gives rise to a daughter cell that moves upwards and towards the central cornea as it differentiates into a wing cell. Basal cells are interconnected by gap junctions that maintain a fixed distance between adjacent cells and form pores through which the cytoplasm of adjacent cells can communicate [14]. These junctions are believed to be important to cell differentiation and development. Hemidesmosomes are cell-to-substrate adhesion junctions that anchor the basal cells to the stroma and basal lamina. They are located within the basal aspect of the cell and are associated with cytoskeletal and transmembrane protein complexes. These complexes attach anchoring filaments that join to anchoring fibrils in the basement membrane which in turn terminate in anchoring plaques located 0.6 μm beyond the epithelial basement membrane within the stroma, firmly fixing the epithelium to the underlying cornea [15]. Epithelial basement membrane is a 0.2 μm thick layer separating the cellular epithelium from the stroma. It is primarily composed of collagen type IV, the sulphated proteoglycan heparin, laminin and ectactin [16].

2.3 Stroma

The stroma is the thickest layer of the cornea (80% of total corneal thickness), which is "sandwiched" between the outer epithelium and the inner endothelium. It is composed of approximately 200 parallel laminae of densely packed connective tissue and cells (keratocytes) [8]. The collagen fibrils in the stroma are made of a mixture of type I and type V collagens. These heterodimer fibrils with a consistent diameter are regularly spaced by their association with sulphated proteoglycans [17]. These proteoglycans are relatively hygroscopic, thus making the stroma prone to swelling; however to maintain its transparency, the stroma must remain at a constant thickness and in a deturgescent state. This is achieved by the tight junctions of the epithelium anteriorly and the leaky tight junctions combined with the ion pump of the endothelium posteriorly. This structure prevents a net influx of fluid from either surface. In the human stroma, the anterior 18 μm of the collagen fibres are irregularly packed into an acellular layer referred to as Bowman's layer [8].

2.4 Dua's Layer

A new layer was suggested by Harminder Singh Dua et al. [18] from the University of Nottingham, who suggested a previously undetected thin and very strong corneal layer located between stroma and Descemet's membrane.

2.5 Endothelium and Descemet's Membrane

Descemet's is the collagenous basement membrane of the endothelium. It is secreted by the

endothelial cells onto the posterior stroma, reaching a thickness of up to 10 μm [19]. The endothelial cells form a monolayer upon Descemet's membrane appearing flat in transverse sections but hexagonal when viewed from above, forming a honeycomb-like network. In humans this layer becomes non-proliferative after birth. Endothelial cells are joined by gap junctions and "leaky" tight junctions [20]. These "leaky" junctions allow the movement of fluid between the stroma and anterior chamber, a process vital for nutrient supply to the stroma. The ion pumps of the endothelial cells continuously transport ions from the stroma into the aqueous humour, resulting in osmotic movement of fluid from the stroma into the hypertonic aqueous humour. This mechanism maintains a clear, relatively dehydrated cornea.

2.6 The Limbus

The limbus is the border ring between the cornea and conjunctiva, which contains limbal stem cells that are required for maintenance of the corneal epithelium. The epithelium in this transitional zone is about 10–12 layers thick and contains melanocytes, Langerhans cells and a network of blood vessels. The limbal stroma with its overlying epithelium is arranged in radial fibrovascular elevations, termed the palisades of Vogt, which alternate with epithelial rete ridges. These palisades are present all around the cornea but are most defined inferiorly and superiorly. The population density of basal cells is maximal in the palisade region [21].

3 Corneal Epithelial Wound Healing

Corneal wound injuries are common and major reason for emergency department visits. Wounds on the surface of cornea are usually self-limiting and do not require hospitalization.

To gain insight into how corneal epithelial renewal occurs, wound closure models have been employed by many investigators. They involve making a defined central epithelial wound and characterizing the kinetics of the healing response. The healing of epithelial wounds can be divided into four distinct but continuous phases: the first phase is referred to as the latent phase or lag phase as there is no cell movement or change in cell numbers [22]. During this time there is an increase in metabolic activity and a reorganization of the cell structure in preparation for the next phase. The second phase is migration; this is characterized by the cells surrounding the wound sliding over and covering the denuded surface. This is followed by the proliferation phase where the cells begin to divide and differentiate, restoring the epithelium's original structure and intercellular junctions. The final phase is the return of the cell-substrate attachments present in nonmotile epithelium. Often a subsequent phase will begin before the completion of the prior phase; however the sequence of the phases is maintained. Thus in the corneal epithelium, wound healing progresses through four overlapping phases that first enable cell movement then coverage of the wound area before restoring the original cell density and reforming cell attachments.

3.1 Latency

The lag phase is a delay immediately following corneal epithelial injury, while the cells and the ocular surface transform to facilitate cell migration. Those cells that were damaged by the wound stimulus undergo apoptosis and are shed into the tear film. Fibronectin polymerizes onto the wound bed forming a provisional extracellular matrix over which the cells can later more easily move. Adherens junctions and gap junctions are lost [14]. Basal cells in the area surrounding the wound dismantle their hemidesmosome attachments to the substrate. This phase may continue without the initiation of migration for up to several hours.

3.2 Migration

During the migration phase, cells move over the wound area to cover the defect. Following the delay of the latent phase, cells at the wound margin flatten and spread into a monolayer. Those cells at the

leading edge of the wound are observed to send out filopodia and have the characteristic ruffled appearance of migrating epithelia [23]. Focal contacts bind to ligands on the fibronectin provisional matrix, and cell movement is enabled by the cytoskeletal contractile mechanisms of the actin stress fibres interacting with the adhesion complexes [24]. Following this single layer of sliding cells, a multilayered mass movement of cells is observed, and there is no cell proliferation in or around the wound area during this migration phase [25].

3.3 Proliferation

This phase restores the epithelial cell density and occurs in conjunction with cell differentiation. Mitosis is delayed within the wound area until after the cell migration phase is complete. Cell mitosis is thus initially limited to the basal transient amplifying cells that are distant from the wound and to the limbus where the stem cells are located [25]. As the area of proliferation progresses centrally, daughter cells are displaced inwards and upwards towards the more superficial layers, differentiating into wing then squamous cells to restratify the epithelium [25]. The first junctions to reform are the zonula occludens, appearing behind the leading edge of the wound, restoring the epithelial barrier function even before migration is complete. The basement membrane is remodelled by the migrated epithelium, secreting laminin within 24 h that can attach to integrin αvβ6 of the cell membrane [14].

3.4 Attachment

In this phase a firm adherence of the epithelial layer to the underlying substrate occurs after formation of hemidesmosomes which are necessary for the strong attachment of the basal epithelial cells to the underlying basement membrane and stroma [26]. This process begins once the overlying epithelium has stratified but may not be complete until up to a year after the original injury. In the recurrent erosion disorders, the absence of hemidesmosomes seem to be the main cause [27].

4 Regulation of Corneal Epithelial Wound Healing

All of the above-mentioned phases are regulated by a number of signalling pathways and complex mechanisms. Cytokines released during injury play a key role in the orchestration of the wound healing response, particularly interleukin (IL)-1 and IL-6. These cytokines are able to influence the expression of the growth factors such as epithelial growth factor (EGF), keratocyte growth factor (KGF), hepatocyte growth factor (HGF), transforming growth factor (TGF) and platelet-derived growth factor (PDGF) [2]. These growth factors and cytokines together regulate the healing processes including cellular apoptosis, migration, proliferation and differentiation. Closure of the wound also involves activation of proteases and changes to extracellular matrix proteins and is influenced by neural factors [14]. Thus wound healing in the corneal epithelium is regulated by a range of cytokines, growth factors, matrix proteins and proteases.

The nervous system also contributes to the process of corneal epithelial wound healing. The importance of neural inputs to the corneal wound healing process is suggested by the delayed wound healing in cases with corneal hypoesthesia that is characteristic of altered trigeminal nerve function associated with herpetic eye disease, fifth nerve lesions, topical anaesthetic abuse and diabetes mellitus [28].

Extracellular matrix interactions with the epithelium regulate phases of corneal healing as well. Focal contact proteins are upregulated in the presence of fibronectin, and this suggests that the extracellular matrix initiates and facilitates epithelial cell migration during the wound healing process [11].

5 Treatment of Corneal Epithelial Wounds

The first step in the management of any epithelial abnormality is to determine the aetiology of the disease. The definitive management of ocular surface disease (OSD) secondary to

exposure keratopathy from thyroid eye disease, for example, may be vastly different from a patient with OSD who suffers from graft-versus-host disease or limbal stem cell deficiency from an alkali burn. In these cases, treatment of the underlying processes is necessary in order for local therapy for the OSD to be successful.

Numerous standard therapies can be used in an attempt to heal persistent corneal epithelial defects. Additionally, a number of new therapies have recently been introduced, and there are promising alternatives in the pipeline. Conventional therapies for corneal epithelial wounds include frequent lubrication, prophylactic antibiotics, eye patching and bandage contact lenses. Punctal occlusion, therapeutic contact lenses and surgical treatment options are reserved for selected cases. However, delayed healing in some patients leading to prolonged discomfort and risk of vision loss brings forth the need for therapeutic agents that are able to support the healing process. To date a wide range of substances or their combinations have been investigated. The classes of these agents can be generally divided into lubricants, anti-inflammatories, growth factors, cytokines, proteins, saccharides and antioxidants.

The basic mode of action by which reepithelialization is accelerated by these agents is either an increase in the cell's proliferation rate and/or migration rate. They may also aid wound healing by creating a more favourable environment through secondary mechanisms such as modulating inflammation, countering toxic substances, or facilitating attachment of cells at the wound site. Below, these therapeutic agents, some of which are still experimental and others widely adopted in clinical practice, will be discussed.

5.1 Aggressive Lubrication

In general, traditional medical therapy of corneal epithelial wounds starts with aggressive lubrication using preservative-free artificial tears and ointments.

5.2 Discontinuation of Medications

On occasion, epithelial defects fail to heal because the patient is using topical medications that contain preservatives toxic to the corneal epithelium, such as benzalkonium chloride. Common offenders tend to be antibiotics, antivirals and anti-glaucoma medications. Although discontinuation of the offending agent may not be medically indicated given the ocular circumstance, if indicated, however, shifting to a different agent or stopping altogether may prove to be curative [29].

5.3 Punctal Occlusion

If the ocular surface can be freed from the toxic effect of unnecessary medications, then punctal plugging can augment the beneficial effects of aggressive lubrication by keeping the lubrication on the eye for a longer time. It is not recommended to plug the puncta when toxic medications are still being used because this will keep the toxicity in contact with the ocular surface for even longer.

5.4 Bandage Soft Contact Lens

Bandage soft contact lenses are effective devices for treating corneal epithelial wounds. They can protect the fragile, healing epithelium from sloughing because of blinking. It is important, however, to keep the eye lubricated to protect the lens from drying out and sticking to the ocular surface. Therefore, it is recommended for all patients using bandage soft contact lenses to apply preservative-free artificial tears every 1–2 h. Furthermore, there is a known risk of infectious keratitis with contact lens use, so it is recommended to prescribe a broad-spectrum topical antibiotic drop such as a fourth-generation fluoroquinolone or polymyxin B-trimethoprim combination. Even with antibiotic prophylaxis, infectious keratitis can occur, so patients should be educated regarding the warning signs of infec-

tious keratitis, and frequent follow-up in these patients is of utmost importance.

5.5 Pressure Patching

Pressure patching is an alternative to bandage soft contact lenses. Although in routine corneal epithelial defects, pressure patching is a popular treatment method, it has been found in some studies to actually inhibit the healing process [30]. Additionally, as persistent epithelial defects often require extended time to heal, prolonged patching is inconvenient and impractical. Patching for longer than 48 h at a time is generally not recommended. It should also be noted that infectious keratitis can occur with patching.

5.6 Debridement

On many occasions, the epithelial cells at the leading edge of the persistent epithelial defect become stagnant and thicken, inhibiting further migration of the cells. When standard medical therapies fail, debridement of the leading edges of the epithelial defect can remove these stagnant cells and promote the more peripheral epithelium to migrate and heal the defect.

5.7 Tarsorrhaphy

Less frequently implemented but highly effective is the use of temporary or permanent tarsorrhaphy in the management of the persistent epithelial defects. This therapy limits corneal exposure and permits repair even in the harshest environments. Simple lid taping, especially in the evening, is effective for 24–48 h at a time, while lid opposition with cyanoacrylate glue may last up to 5 days. Temporary suture tarsorrhaphy with bolsters may last up to 6 weeks which can be less intimidating for the patient concerned about cosmetic appearance from a permanent procedure (Fig. 2). Some specialists advocate for the injection of botulinum toxin A into the levator muscle to keep the surface covered for months at a time still permitting frequent ocular examination, if needed, but without the need to surgically close the eyelids [31].

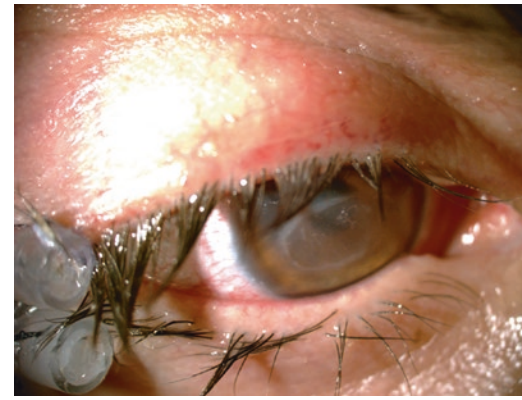


Fig. 2 Anterior segment of a patient with a temporary suture tarsorrhaphy with bolsters

5.8 Growth Factors

Growth factors are produced locally in ocular tissues and have a homeostatic role in the maintenance of the ocular surface. Studies on the wound healing properties of growth factors have demonstrated that several are able to promote either proliferation or migration of corneal epithelial cells, such as epidermal growth factor (EGF). Unfortunately a number of these growth factors also have other growth-like effects that may be unwanted in a therapeutic agent used on the cornea. For example, while transforming growth factor-β2 (TGF-β2) accelerates wound closure, it also has angiogenic properties [32]. TGF-β2 and other wound healing growth factors such as FGF overstimulate the healing process to the point of promoting stromal fibrosis. PDGF promotes cell migration and proliferation but requires the presence of fibronectin [33]. The majority of growth factors have only been tested in animal models. These appear promising, but without a trial using a control, it is difficult to interpret the clinical utility. EGF however has been tested in a multicentre randomized controlled trial (RCT) [34], and it was found to accelerate wound closure in patients with abrasions.

5.9 Cytokines

As with the growth factors, most of the cytokines that have been investigated for wound healing are naturally occurring in the eye and are released following corneal epithelial injury and appear to initiate the healing response. IL-1, for example, has been proposed as the master regulator of the corneal response to injury by modulating keratocyte apoptosis, leukocyte infiltration and angiogenesis [35]. However as with a number of other cytokines, it is also pro-inflammatory increasing the risk of wound vascularization and neutrophil-mediated tissue damage [36]. IL-6 also has been shown to promote cell migration [37]; however, none of the signalling molecules have been clinically trialled, presumably due to the anticipated inflammatory adverse events.

5.10 Proteins, Glycoproteins and Saccharides

During the epithelial healing process, there is a significant increase in the rate of protein, in particular glycoprotein, synthesis. Blocking the synthesis of protein or asparagine-linked glycoproteins inhibits cell migration. Galectins are a family of widely distributed carbohydrate-binding proteins defined by their affinity for the β-galactoside-containing glycans which are present on various cell surface and extracellular matrix glycoproteins. Galectin-3 and galectin-7 have been shown to promote cell migration and corneal reepithelialization [38]. Studies have revealed that exogenous galectin-3 advances reepithelialization of wounds in rat corneas, monkey corneas as well as in a rat dry eye model. Galectin-7 expression is upregulated substantially in mouse corneas upon injury, and exogenous galectin-7 was shown to stimulate corneal wound reepithelialization in organ culture specimens.

An agent best supported by a number of case series as a treatment for persistent epithelial defects is fibronectin with in vitro data suggesting it promotes adhesion and migration of corneal epithelial cells and clinical studies showing enhanced reepithelialization in persistent corneal epithelial defects [39]. Other agents such as lactoferrin, vitronectin and pigment epithelial-derived factor show promise in animal models but are yet to be tested clinically.

Another agent-promoting corneal epithelial healing is trehalose. Trehalose is a nonreducing disaccharide of glucose, naturally produced and accumulated in many living organisms, but not in mammals. It was identified as a key response element needed to protect the cells against a great number of environmental stresses, such as desiccation, dehydration, cold, heat and oxidation. Among these functions, the protection against desiccation was widely studied in ophthalmic research, as exogenous trehalose protects corneal epithelial cells from experimental drying, and was shown to be effective in the treatment of moderate-to-severe human dry eye. Furthermore, during desiccation in vivo, it was also demonstrated that trehalose could effectively suppress apoptotic cell death on the ocular surface [40].

5.11 Antioxidants

Ascorbic acid has been shown to have protective effects in cornea disease repair in animals and in clinic, such as in UV irradiation, chemical corneal burns, corneal neovascularization and inflammation. The function of ascorbic acid in corneal epithelium could possibly be attributed to its role as an antioxidant that suppresses the intracellular reactive oxygen species level. Ascorbic acid is also well known for its effect on enhancing cell proliferation and extracellular matrix production. In a recent study, direct therapeutic benefits of ascorbic acid on mouse corneal epithelial wound healing were shown in vivo [41]. There have also been small clinical trials on the use of N-acetylcysteine and combined vitamin A and vitamin E for recovery from refractive surgery. While the benefit of N-acetylcysteine appears to be mostly reduced inflammation, high-dose vitamins A and E were able to accelerate reepithelialization.

Another topical agent for enhancement of corneal wound healing is coenzyme Q10, a vitamin-

like benzoquinone compound which has been evaluated in recent years and accepted in clinical practice by many ophthalmologists [42]. Coenzyme Q10 is an organic molecule composed of a hydrophobic tail and a redox-active quinone ring. It is present in biological membranes, particularly in mitochondria, and acts as an effective antioxidant and free radical scavenger to protect against oxidative damages to the mitochondrial and lipid membranes. It has been shown that CoQ10 can influence epithelial wound healing by several different mechanisms. CoQ10 can improve the viability of corneal epithelial cell culture and the mitochondrial bioenergetics, and administration of CoQ10 after corneal epithelium removal promotes corneal wound healing.

5.12 Human Serum-Derived and Plasma-Derived Therapies

Human serum-derived and plasma-derived therapies have become increasingly popular in the treatment of ocular surface disorders, with mounting clinical and scientific evidence suggesting good safety and efficacy profiles. These therapies may be considered for various ocular surface conditions, such as dry eye syndrome and corneal epithelial wounds such as persistent epithelial defects (Fig. 3), when conservative management does not suffice [43].

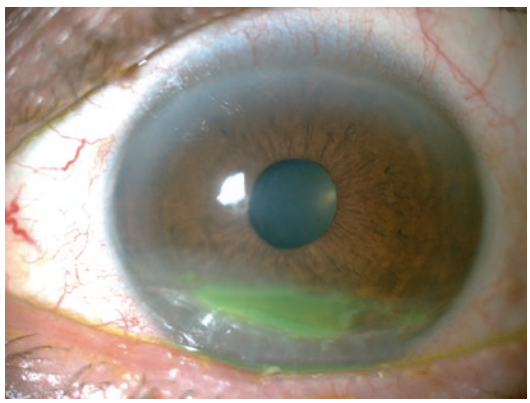


Fig. 3 Anterior segment of a patient with a persistent corneal epithelial defect

1. Autologous serum eye drops (ASE). The biochemical properties of ASE are similar to those of human tears [44]. Epidermal growth factor, which increases migration and proliferation of corneal epithelial cells, and TGF-β are the most important components of tears. Fibronectin, vitamin A and a variety of chemokines, growth factors and nutrients further contribute to the tear film milieu that maintains the ocular surface. Fibronectin is present at a concentration of 205 μg/mL in serum compared with a tear film concentration of 21 ng/mL. EGF concentrations are similar in serum (0.7–10 ng/mL) and tears (0.5 ng/ mL), while vitamin A concentrations are much higher in serum (46 mg/mL) than in tears (0.02 mg/mL). More importantly, TGF-β concentrations are five times higher in serum than in tears. Therefore, many ophthalmologists prefer to use a 20% dilution of ASE to more closely match the TGF-β concentration in natural tears in order to prevent problems with epithelial cell proliferation. Based on the current literature, ASE therapy seems to be quite effective in the treatment of persistent epithelial defects, but study sample sizes have been very small. As ASE preparations usually do not contain preservative, one must pay heed to the theoretically increased infection risk that could arise with a serum-derived product in the setting of an epithelial defect [45, 46].
2. Umbilical cord serum (UCS). UCS contains many of the same growth factors and components as natural tears, including EGF and vitamin A. UCS may serve as a viable alternative in patients who are not good candidates for ASE therapy, such as those with graft-versus-host disease or Sjogren's syndrome, where pro-inflammatory cytokines could be present in the serum. A comparison study of UCS versus ASE and artificial tears in the treatment of ocular chemical burns found UCS-treated patients to require significantly less days to complete corneal epithelialization than those treated with ASE or artificial tears [47]. Vajpayee et al. [4] suggested that umbilical cord serum is associated with a faster reepithelialization rate when compared with autol-

ogous serum because of higher concentration of growth factors which stimulate a faster growth of stem cells. Since one sample of UCS may be distributed to many patients, preparation of samples can be done in advance and made readily available to patients. However, UCS samples must be rigorously screened for blood-borne infections prior to donation.

5.13 Human Breast Milk Drops (HBMD)

Human milk contains many distinct bioactive molecules that protect against infection and inflammation and contribute to immune maturation, organ development and healthy microbial colonization in infants [48]. It contains lactoperoxidase, lactoferrin, immunoglobulin A and lysozyme which have bactericidal effects. It also contains complementary substances which enhance the phagocytosis of microorganisms and cell migration in damaged tissues such as fibronectin, interleukin-6, epidermal growth factor, tumour necrosis factor-α and substances that have a role in epithelial and stromal wound healing such as transforming growth factor-β, insulin-like growth factor, lipids and vitamins. In fact, human breast milk shows marked similarity to the composition of natural tears.

Lactoferrin is an important component of the human breast milk, which has been investigated extensively as a novel therapeutic agent. These investigations have been advanced by the use of recombinant lactoferrin or bovine lactoferrin, due to its high homology with human lactoferrin [48]. Lactoferrin is a potent activator of natural killer cells playing an important role in primary defence against microbial and viral infections and also has antioxidant properties [49]. It has been shown that bovine lactoferrin stimulates human corneal epithelial wound healing in vitro at 2.5 and 5 mg/mL and this stimulation is mediated through the upregulation of PDGF or IL-6 [50]. Human breast milk also contains xanthine oxidase which inhibits bacterial growth and catalyses the formation of peroxynitrite—a powerful bactericidal agent—from nitrite, in the presence of oxygen [51]. This may be the reason why breast milk has been used with favourable outcomes in the treatment of neonatal conjunctivitis and infections secondary to nasolacrimal duct obstruction previously [52].

Fibronectin is another metabolic hormone found in natural tears, autologous serum, chord serum and also in human breast milk. It appears at the site of the wound and disappears after the healing process and has an important role in corneal wound healing by promoting migration, cell adhesion and differentiation and by increasing the phagocytic activity [53].

In a recent study, it has been shown that human breast milk enhances corneal epithelial wound healing without any obvious side effects in mice. HBMDs qid led to a faster and better epithelialization when compared with autologous serum and artificial tears. Moreover, it is much easier to obtain when compared with autologous serum and chord serum [5]. The most important concern is the risk of disease transmission and contamination which can be eliminated with screening of milk donors and pasteurization techniques. The rich content of human breast milk may be an alternative to epithelial healers and artificial tears.

Conclusions

Although corneal wounding is common, it does not always result in major sequelae, and the corneal epithelium heals itself in 24–48 h. However, under circumstances such as traumatic eye injury, toxic insults, ongoing trauma or infection, healing is compromised, and vision may be threatened. For these reasons, several therapeutic agents can be used to facilitate wound healing, and several new types are being actively investigated in laboratory models. The rich content of human breast milk may be an alternative to epithelial healers and artificial tears. Breast milk may be obtained from human milk banks, found in some countries including Brazil, the United States, Canada, Spain and Portugal. Furthermore, it does not require a time-consuming or complex preparation process before usage. The most important concern is the risk of disease transmission and contamination which can be

eliminated with screening of milk donors and pasteurization techniques. Future research should focus on experimental and clinical studies evaluating the safety of topical treatment with breast milk and mechanisms of action on corneal wound healing and pasteurization techniques, as well as proper preservation, concentration and application frequency in the treatment of corneal epithelial defects.

Acknowledgements This chapter is derived in part from an article published in Current Eye Research 2017 April, available online: doi: 10.1080/02713683.2016.1223318.

References

1. Lu L, Reinach PS, Kao WW (2001) Corneal wound healing. Exp Biol Med 226:653–664
2. FS Y, Yin J, Xu K, Huang J (2010) Growth factors and corneal epithelial wound healing. Brain Res Bull 81:229–235
3. Schulze SD, Sekundo W, Kroll P (2006) Autologous serum for the treatment of corneal epithelial abrasions in diabetic patients undergoing vitrectomy. Am J Ophthalmol 142:207–211
4. Vajpayee RB, Mukerji N, Tandon R, Sharma N, Pandey RM, Biswas NR et al (2003) Evaluation of umbilical cord serum therapy for persistent corneal epithelial defects. Br J Ophthalmol 87:1312–1316
5. Asena L, Suveren EH, Karabay G, Dursun Altinors D (2016) Human breast milk drops promote corneal epithelial wound healing. Curr Eye Res 19:1–7
6. Imanishi J, Kamiyama K, Iguchi I, Kita M, Sotozono C, Kinoshita S (2000) Growth factors: ımportance in wound healing and maintenance of transparency of the cornea. Prog Retin Eye Res 19(1):113–129
7. Dua HS, Faraj LA, Said DG, Gray T, Lowe J (2013) Human corneal anatomy redefined: a novel pre-Descemet's layer (Dua's layer). Ophthalmology 120(9):1778–1785
8. DelMonte DW, Kim T (2011) Anatomy and physiology of the cornea. J Cataract Refract Surg 37:588–598
9. Holly FJ (1987) Tear film physiology. Int Ophthalmol Clin 27:2–6
10. Paulsen F (2008) Functional anatomy and immunological interactions of ocular surface and adnexa. Dev Ophthalmol 41:21–35
11. Suzuki K, Saito J, Yanai R, Yamada N, Chikama T, Seki K, Nishida T (2003) Cell-matrix and cell-cell interactions during corneal epithelial wound healing. Prog Retin Eye Res 22:113–133
12. Beuerman RW, Pedroza L (1996) Ultrastructure of the human cornea. Microsc Res Tech 33:320–335
13. Ban Y, Dota A, Cooper LJ, Fullwood NJ, Nakamura T, Tsuzuki M, Mochida C, Kinoshita S (2003) Tight junction-related protein expression and distribution in human corneal epithelium. Exp Eye Res 76:663–669
14. Suzuki K, Tanaka T, Enoki M, Nishida T (2000) Coordinated reassembly of the basement membrane and junctional proteins during corneal epithelial wound healing. Invest Ophthalmol Vis Sci 41:2495–2500
15. Stepp MA (2006) Corneal integrins and their functions. Exp Eye Res 83:3–15
16. Rousselle P, Lunstrum GP, Keene DR, Burgeson RE (1991) Kalinin: an epithelium specific basement membrane adhesion molecule that is a component of anchoring filaments. J Cell Biol 114:567–576
17. Knupp C, Pinali C, Lewis PN, Parfitt GJ, Young RD, Meek KM, Quantock AJ (2009) The architecture of the cornea and structural basis of its transparency. Adv Protein Chem Struct Biol 78:25–49
18. Dua HS, Said DG (2016) Clinical evidence of the pre-Descemets layer (Dua's layer) in corneal pathology. Eye (Lond) 30:1144–1145
19. Joyce NC (2003) Proliferative capacity of the corneal endothelium. Prog Retin Eye Res 22:359–389
20. Bonanno JA (2012) Molecular mechanisms underlying the corneal endothelial pump. Exp Eye Res 95:2–7
21. Townsend WM (1991) The limbal palisades of Vogt. Trans Am Ophthalmol Soc 89:721–756
22. Agrawal VB, Tsai RJ (2003) Corneal epithelial wound healing. Indian J Ophthalmol 51:5–15
23. Crosson CE, Klyce SD, Beuerman RW (1986) Epithelial wound closure in the rabbit cornea. A biphasic process. Invest Ophthalmol Vis Sci 27:464–473
24. Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. Cell 69:11–25
25. Kuwabara T, Perkins DG, Cogan DG (1976) Sliding of the epithelium in experimental corneal wounds. Investig Ophthalmol 15:4–14
26. Gipson IK (1992) Adhesive mechanisms of the corneal epithelium. Acta Ophthalmol Suppl 202:13–17
27. Gipson IK, Spurr-Michaud S, Tisdale A, Keough M (1989) Reassembly of the anchoring structures of the corneal epithelium during wound repair in the rabbit. Invest Ophthalmol Vis Sci 30:425–434
28. Müller LJ, Marfurt CF, Kruse F, Tervo TM (2003) Corneal nerves: structure, contents and function. Exp Eye Res 76:521–542
29. Katzman LR, Jeng BH (2014) Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol 28(3):168–172
30. Campanile TM, St Clair DA, Benaim M (1997) The evaluation of eye patching in the treatment of traumatic corneal epithelial defects. J Emerg Med 15(6):769–774
31. Yucel OE, Arturk N (2012) Botulinum toxin-A-induced protective ptosis in the treatment of lagophthalmos associated with facial paralysis. Ophthal Plast Reconstr Surg 28(4):256–260
32. Sakamoto T, Ueno H, Sonoda K, Hisatomi T, Shimizu K, Ohashi H, Inomata H (2000) Blockade of TGF-beta by in vivo gene transfer of a soluble TGF-beta type II receptor in the muscle inhibits corneal opacification, edema and angiogenesis. Gene Ther 7:1915–1924
33. Kamiyama K, Iguchi I, Wang X, Imanishi J (1998) Effects of PDGF on the migration of rabbit corneal fibroblasts and epithelial cells. Cornea 17: 315–325

34. Pastor JC, Calonge M (1992) Epidermal growth factor and corneal wound healing. A multicenter study. Cornea 11:311–314
35. Wilson SE, Esposito A (2009) Focus on molecules: interleukin-1: a master regülatör of the corneal response to injury. Exp Eye Res 89:124–125
36. Davies BW, Panday V, Caldwell M, Scribbick F, Reilly CD (2011) Effect of topical immunomodulatory interleukin 1 receptor antagonist therapy on corneal healing in New Zealand white rabbits (Oryctolagus cunniculus) after photorefractive keratectomy. Arch Ophthalmol 129(7):909–913
37. Arranz-Valsero I, Soriano-Romaní L, García-Posadas L, López-García A, Diebold Y (2014) IL-6 as a corneal wound healing mediator in an in vitro scratch assay. Exp Eye Res 125:183–192
38. Cao Z, Saravanan C, Chen WS, Panjwani N (2015) Examination of the role of galectins in cell migration and re-epithelialization of wounds. Methods Mol Biol 1207:317–326
39. Nishida T (2010) Translational research in corneal epithelial wound healing. Eye Contact Lens 36(5):300–304
40. Aragona P, Colosi P, Rania L, Colosi F, Pisani A, Puzzolo D, Micali A (2014) Protective effects of trehalose on the corneal epithelial cells. Sci World J 2014:717835
41. Chen J, Lan J, Liu D, Backman LJ, Zhang W, Zhou Q, Danielson P (2017) Ascorbic acid promotes the stemness of corneal epithelial stem/progenitor cells and accelerates epithelial wound healing in the cornea. Stem Cells Transl Med 6(5):1356–1365
42. Mencucci R, Favuzza E, Boccalini C, Lapucci A, Felici R, Resta F, Chiarugi A, Cavone L (2014) CoQ10-containing eye drops prevent UVB-induced cornea cell damage and increase cornea wound healing by preserving mitochondrial function. Invest Ophthalmol Vis Sci 55(11):7266–7271
43. Soni NG, Jeng BH (2016) Blood-derived topical therapy for ocular surface diseases. Br J Ophthalmol 100(1):22–27
44. Pan Q, Angelina A, Zambrano A, Marrone M, Stark WJ, Heflin T, Tang L, Akpek EK (2013) Autologous serum eye drops for dry eye. Cochrane Database Syst Rev 2:CD009327
45. Chiang CC, Chen WL, Lin JM, Tsai YY (2009) Allogeneic serum eye drops for the treatment of persistent corneal epithelial defect. Eye (Lond) 23: 290–293
46. Jeng BH, Dupps WJ Jr (2009) Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. Cornea 28:1104–1108
47. Sharma N, Goel M, Velpandian T, Titiyal JS, Tandon R, Vajpayee RB (2011) Evaluation of umbilical cord serum therapy in acute ocular chemical burns. Invest Ophthalmol Vis Sci 52:1087–1092
48. Ballard O, Morrow AL (2013) Human milk composition: nutrients and bioactive factors. Pediatr Clin N Am 60(1):49–74
49. Kanyshkova TG, Babina SE, Semenov DV, Isaeva N, Vlassov AV, Neustroev KN, Kul'minskaya AA, Buneva VN, Nevinsky GA (2003) Multiple enzymic activities of human milk lactoferrin. Eur J Biochem 270:3353–3361
50. Pattamatta U, Willcox M, Stapleton F, Cole N, Garrett Q (2009) Bovine lactoferrin stimulates human corneal epithelial alkali wound healing in vitro. Invest Ophthalmol Vis Sci 50:1636–1643
51. Hancock JT, Salisbury V, Ovejero-Boglione MC, Cherry R, Hoare C, Eisenthal R, Harrison R (2002) Antimicrobial properties of milk: dependence on presence of xanthine oxidase and nitrite. Antimicrob Agents Chemother 46(10):3308
52. Verd S (2007) Switch from antibiotic eye drops to instillation of mother's milk drops as a treatment of infant epiphora. J Trop Pediatr 53:68–69
53. Fukuda M, Fullard RJ, Willcox MDP, Baleriola-Lucas C, Bestawros F, Sweeney D, Holden BA (1996) Fibronectin in the tear film. Invest Ophthalmol Vis Sci 37:459–467

Traumatic Wound Dehiscence Following Penetrating and Deep Anterior Lamellar Keratoplasty

Jay J. Meyer

1 Introduction

Corneal transplantation is the most common form of organ transplantation in the United States with over 20,000 penetrating and lamellar keratoplasties performed each year. Penetrating keratoplasty (PK) involves the creation of a full- thickness, 360° surgical wound by trephining the cornea and suturing a donor corneal button to the host rim. Deep anterior lamellar keratoplasty (DALK) is performed in a similar fashion; however, the trephination is partial, and the wound is approximately 90–99% of the corneal depth. Because DALK is a relatively newer technique that has historically been performed much less frequently than PK, the majority of published literature describes traumatic wound dehiscence (TWD) following PK.

Traumatic ruptures have been reported following many ocular surgeries, including PK [1–24], DALK [9, 10, 25–28], radial keratotomy [29–32], cataract extraction [33–35], and laser in situ keratomileusis (LASIK) [36–39]. The wound following PK is more susceptible to traumatic dehiscence than wounds created during other types of ocular surgery, such as cataract extraction [5]. In an eye that has had prior surgery, traumatic rupture occurs at the site of the original surgery, usually following blunt trauma. In contrast, eyes that have never had surgery usually develop a rupture at the corneoscleral limbus or at the site of muscle insertions onto the sclera [40].

2 Epidemiology and Risk Factors

The reported incidence proportions (number of dehiscences divided by number of grafts performed during the study period) following PK have ranged from <1% to 5.8% [1–3, 5, 10, 11, 14, 18, 22, 23, 41, 42]. One study calculated an incidence rate of 2.3 per 1000 person-years after incorporating the duration of time at risk for each graft into the rate [13].

TWD may occur at any time in the postoperative course and has been reported to occur as early as a few days and as late as 33 years following keratoplasty [4, 11]. The first 1–2 years following surgery is the highest risk period for TWD [10, 11, 13, 22, 43]. This is likely due to the weakness of the wound in the early postsurgical period despite having sutures in situ. Another possible explanation is increased physical activity attributable to improved visual acuity following surgery [18]. The period immediately following suture removal is another high-risk period [5].

A bimodal age distribution has been reported with younger individuals often receiving trauma

J.J. Meyer, M.D., M.P.H. (✉)
Department of Ophthalmology, University of Auckland, Auckland, New Zealand
e-mail: Jay_meyer@rocketmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_66, © Springer International Publishing AG
Published Online: 26 April 2018

(accidental or deliberate) and older individuals frequently involved in falls [14]. Elderly patients, in particular, may be more prone to dehiscence from relatively minor trauma, such as self-instillation of topical medication [1, 14]. The graft-host junction of older patients may heal more slowly as wound leaks following suture removal occur more frequently in older patients [44]. Wound dehiscence has even been reported to occur spontaneously following suture removal or a forceful Valsalva [2, 13, 44–47]. The majority of accidental traumatic graft ruptures occur during routine daily activities [13].

Males have been found to be at higher risk for TWD compared to females [1, 3–6, 11, 17, 18, 20, 22]. For younger males, this may be due to a higher risk of assault compared to females or other age groups [48].

Perhaps, unsurprisingly, poor bilateral vision may be a risk for trauma and subsequent dehiscence [23]. Reduced contralateral visual acuity before wound rupture has also been shown to be a risk factor in some studies [13, 22, 41].

Keratoconus was the most common indication for keratoplasty in eyes that experience TWD in several studies, including populations where keratoconus was not the most common indication overall [3, 5, 9, 11, 13, 14, 23]. There are several possible explanations for this association. This could be due to the younger transplantation age of patients with keratoconus compared to other indications resulting in a longer period of risk for trauma and a higher level of physical activity. Keratoconus causes thinning and protrusion of the cornea which often results in a donor corneal button of normal thickness being sutured to a thinner host rim. This creates a mismatch in the size of the wound edges and subsequent misalignment of the anterior and/or posterior margins of the wound which may reduce the strength of the wound. Also, corneal grafts performed for keratoconus are less likely to vascularize, a process that would hasten healing and strengthen the wound [3]. Patients with keratoconus also frequently rub their eyes which could impair wound healing and/or wound stability through chronic low-grade blunt trauma.

Graft size has not been identified as a definite risk factor for dehiscence [3], possibly because there is generally little variation in graft sizes performed. Incisions in the periphery of the cornea heal more quickly than those in the center [49]. As such, dehiscence might be expected to occur more frequently in smaller grafts due to slower wound healing compared to larger grafts which are located closer to the limbal vasculature. Conversely, a larger graft theoretically has a longer scar that could be more vulnerable to dehiscence.

The globe is less protected by the orbital rim inferiorly and temporally, and blunt trauma at these sites would be expected to produce dehiscence at the opposite sides through a contrecoup mechanism or superiorly and nasally, respectively. While one study found more frequent dehiscences superiorly [6], other studies have not identified a predilection for dehiscence of a specific quadrant [13, 22]. Dehiscence often involves one to three quadrants and rarely can result in complete (360°) dehiscence and loss of the corneal button [22].

3 Pathophysiology/Wound Healing

A corneal wound has reduced tensile strength compared to that of normal cornea, even years following surgery. This is the case for both full- thickness corneal wounds, as occurring in PK, and partial- thickness wounds as occurring in radial keratotomy or DALK [5, 10, 34, 49–54]. Many factors have been proposed to contribute to weakness of the graft- host junction. These include avascularity of the tissue interface, prolonged treatment with topical corticosteroids, poor apposition of wound edges, and suture complications such as breakage or premature removal [11, 14]. Other possible associations include elevated intraocular pressure and corneal edema [2, 7].

In a rabbit study involving full-thickness, central, corneal wounds, there was no measurable tensile strength within the first 6 days, increasing to approximately 50% of that of normal intact tissue by 3 months [49]. In human studies, this same level of strength is not achieved until 2–3 years postoperatively [16, 55]. Holographic stress testing has confirmed that the graft-host

junction continues to be a potentially weak site over a year after PK [56]. This is in contrast to skin tissue, in which the tensile strength of wounds approximates that of intact skin by the twenty-first postoperative day [57]. Corneal wounds are unique due to the avascularity of the tissue in the undiseased state. The tensile strength of corneal wounds has been noted to be reduced to a similar degree as wounds of the lumbosacral aponeurosis, likely due to the avascularity of both of these tissues [49].

Monofilament 10–0 nylon sutures are typically used to circumferentially suture the donor graft to the host rim. This material is unlikely to induce an inflammatory reaction that could incite neovascularization and subsequent rejection of the transplant. However, lack of a significant inflammatory response may reduce the overall strength of the wound. Three main suturing techniques are used: interrupted, continuous, and combined interrupted and continuous sutures. Dehiscence has been reported to occur following suturing with each of these techniques [2, 13]. Sutures are frequently left in place for 1–2 years following keratoplasty. The presence of sutures does not fully protect against TWD during this time period, although the extent of dehiscence may be reduced while sutures are in place [13]. In cases of TWD with sutures in situ, the trauma is sufficient to cause breakage of the 10–0 nylon sutures (Fig. 1). Studies have shown that 10–0 nylon sutures are able to contain a stress of 650 ± 15 M pascals although the suture strength degrades over time [40, 58].

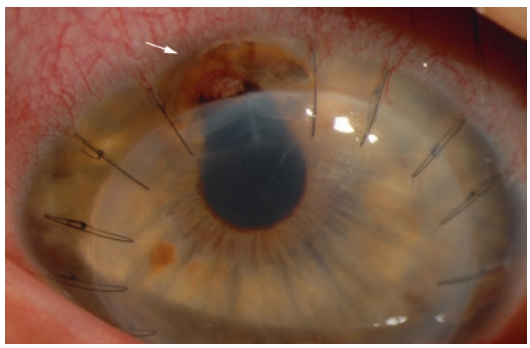


Fig. 1 Small, focal, 1 clock-hour dehiscence (white arrow) with prolapse of iris tissue at the site of a previous suture that was broken during trauma. The eye had been poked accidentally by a small child

Primary closure of the graft-host junction is effected by an epithelial plug that extends down wherever the tips of the wound are not apposed [59]. Keratocytes migrate and undergo transformation into fibroblasts and begin scar formation. Fibroplasia only accounts for approximately 20% of the final tensile strength of the wound with collagen formation contributing a greater component [59, 60]. Collagen fibrils are produced which do not run in parallel bundles and develop a more normal configuration with time [49, 60]. This tangle of new collagen fibrils intercalates the adjacent stromal lamellae to connect the lamellar cut ends of the graft- host junction [16, 61]. Eyes with a history of PK examined post-mortem showed wound irregularities leading to incomplete healing that was visible microscopically at the graft-host interface in over 80% of eyes [51].

The stroma to stroma adhesions of the graft-host junction likely contribute relatively little to the overall strength of the wound. This is supported by the observation that LASIK flaps can be surgically relifted even years after surgery, despite a wide surface area of the stromal wound [16]. Clinically, even years after transplantation, the graft-host junction can often be pulled open using two pairs of forceps without any sharp dissection required, and the majority of the wound adhesion appears and feels to be superficial, at the epithelial/subepithelial level. In addition, the graft following DALK can be peeled from the host bed even years later with little resistance from the adhesions of the bed.

Following surgery, topical corticosteroids are routinely prescribed to reduce the risk of rejection of the transplant and are often tapered off over the subsequent 1–2 years. However, corticosteroids slow down the healing of corneal tissue and contribute to the weakness of the wound during this time period.

Loose or broken sutures occur prior to planned suture removal in roughly one-third of grafts following PK and DALK with the highest rate seen in grafts performed for keratoconus [13]. This may increase the susceptibility of the graft to TWD in the region of missing sutures during the

early postoperative period. In addition, it can allow anteroposterior misalignment of the wound edges which may decrease the long-term strength of the wound (Fig. 2).

4 Outcomes

The visual outcomes following dehiscence repair range widely from acuity levels of 20/20 to complete loss of vision, with enucleation required in some cases. Overall, the prognosis is poor. Loss of the lens [10] and posterior segment injuries [1, 5, 9, 17, 18, 20, 22, 27] are associated with a worse prognosis. Final visual acuity is also inversely correlated with the extent of wound separation, likely due to a higher risk of posterior segment damage with increasing prolapse of intraocular contents through the wound (Fig. 3) [13, 22].

A TWD is generally repaired acutely using the same graft since even quite edematous grafts often clear with time. Additional procedures may

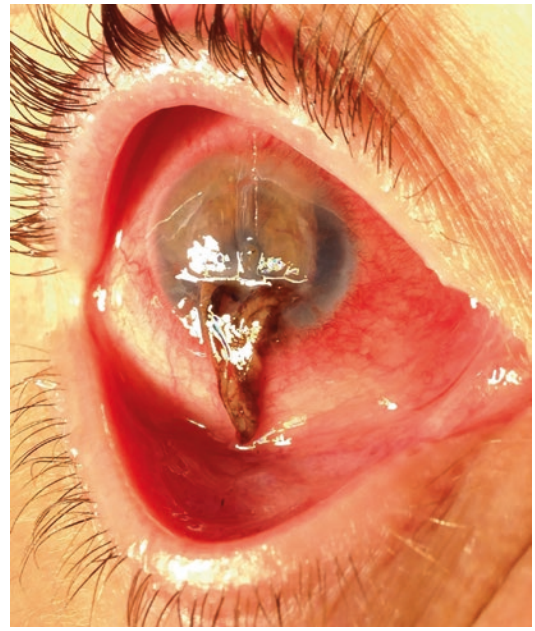


Fig. 3 Inferior traumatic wound dehiscence with partial avulsion and prolapse of the iris (Photo courtesy of Christian Hester, M.D.)

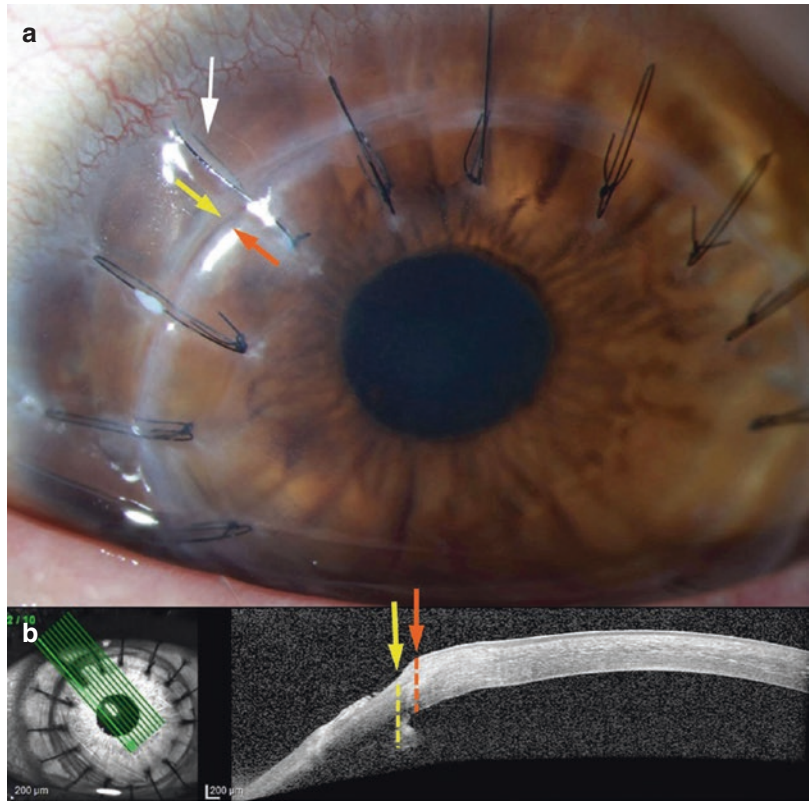


Fig. 2 (**a**) Slit lamp photo of a patient with severe allergies and eye rubbing that resulted in keratolysis and loosening of a suture (white arrow) with poor apposition and misalignment of the graft (red arrow) and host (yellow arrow) wound edges underlying the suture. (**b**) Ocular coherence tomography image of the graft- host junction at the site of the loose suture demonstrates misalignment with the graft (red arrow) edge sitting more anterior than the host (yellow arrow) wound edge

be required at the time of initial repair, such as anterior vitrectomy and lens repositioning or lensectomy. Postoperatively, there is a high risk of retinal detachment and a risk of graft failure that may require further surgical procedures as well.

5 Prevention

Patients should be counseled preoperatively regarding the risk of TWD and should be reminded postoperatively, particularly during the first 1–2 years following keratoplasty. Advice should be given regarding precautions to avoid accidents such as finger pokes and fall reduction strategies. Suggestions for protection include 24-h eyewear (shield or glasses) during the first month, daytime eyewear for 6 months following keratoplasty and following suture removal, and lifelong eyewear during risk activities [5]. Patients should be advised to avoid high- risk activities, such as contact sports, for the remainder of their life.

Traditionally, the trephination of the host and donor tissue has been performed using a reusable or disposable metal trephine. The use of a femtosecond laser to perform donor and host trephination has allowed the creation of nonlinear wound profiles, such as "mushroom" and "zigzag" configurations [62]. These profiles allow the donor and host wound edges to "interlock" and may reduce the occurrence of poor apposition or wound slippage of the host and donor rim edges. Theoretically, this could strengthen the wound and reduce the risk of dehiscence. However, because laser trephination is relatively new and has not been widely adopted, it is unknown whether there is a reduced risk of dehiscence with these techniques.

Deep anterior lamellar keratoplasty (DALK) is a technique that is an alternative to PK for cases with an intact and healthy endothelium. In contrast to PK where the incision is full corneal thickness, this technique leaves the Descemet's membrane, with or without a thin (<50–100 μm) layer of overlying stroma, intact. A possible advantage of DALK may be greater structural integrity that is more resistant to dehiscence or that does not result in full-thickness dehiscence and prolapse of intraocular contents [28]. There is insufficient data to conclusively determine whether DALK results in clinically lower rates of TWD. Some series have shown very low rates in eyes following DALK (0–0.5%) [10, 13], while another found a rate (3.2%) similar to PK. It is possible that the exact DALK technique also influences the structural integrity and techniques that do not bare Descemet's membrane and leave some residual stroma might retain more integrity, assuming good wound alignment. Eyes with dehiscence following DALK may have a better visual prognosis compared to post-PK eyes [9].

Conclusions

TWD may occur at any time in the postoperative course due to the poor tensile strength of the wound. Overall, the visual outcomes are poor and loss of vision is not uncommon following this injury. Patients should be counseled regarding the lifelong risk of wound dehiscence, even from relatively minor trauma. Protective eyewear should be encouraged during the early postoperative period, and patients should be instructed to avoid any high- risk activities throughout their lifetime. Newer keratoplasty techniques such as femtosecond laser enabled keratoplasty, and DALK might provide increased protection from traumatic dehiscence in the future.

References

1. Agrawal V, Wagh M, Krishnamachary M, Rao GN, Gupta S (1995) Traumatic wound dehiscence after penetrating keratoplasty. Cornea 14(6):601–603
2. Binder PS, Abel R Jr, Polack FM, Kaufman HE (1975) Keratoplasty wound separations. Am J Ophthalmol 80(1):109–115
3. Bowman RJ, Yorston D, Aitchison TC, McIntyre B, Kirkness CM (1999) Traumatic wound rupture after penetrating keratoplasty in Africa. Br J Ophthalmol 83(5):530–534
4. Das S, Whiting M, Taylor HR (2007) Corneal wound dehiscence after penetrating keratoplasty. Cornea 26(5):526–529
5. Elder MJ, Stack RR (2004) Globe rupture following penetrating keratoplasty: how often, why, and what can we do to prevent it? Cornea 23(8):776–780

6. Foroutan AR, Gheibi GH, Joshaghani M, Ahadian A, Foroutan P (2009) Traumatic wound dehiscence and lens extrusion after penetrating keratoplasty. Cornea 28(10):1097–1099
7. Friedman AH (1973) Late traumatic wound rupture following successful partial penetrating keratoplasty. Am J Ophthalmol 75(1):117–120
8. Hiratsuka Y, Sasaki S, Nakatani S, Murakami A (2007) Traumatic wound dehiscence after penetrating keratoplasty. Jpn J Ophthalmol 51(2):146–147
9. Jafarinasab MR, Feizi S, Esfandiari H, Kheiri B, Feizi M (2012) Traumatic wound dehiscence following corneal transplantation. J Ophthal. Vis Res 7(3):214–218
10. Kawashima M, Kawakita T, Shimmura S, Tsubota K, Shimazaki J (2009) Characteristics of traumatic globe rupture after keratoplasty. Ophthalmology 116(11):2072–2076
11. Lam FC, Rahman MQ, Ramaesh K (2007) Traumatic wound dehiscence after penetrating keratoplasty-a cause for concern. Eye 21(9):1146–1150
12. Maheshwari S, Saswade M, Thool A (2003) Traumatic wound dehiscence 14 years following penetrating keratoplasty. Indian J Ophthalmol 51(3):259–260
13. Meyer JJ, McGhee CN (2016) Incidence, severity and outcomes of traumatic wound dehiscence following penetrating and deep anterior lamellar keratoplasty. Br J Ophthalmol 100(10):1412–1415
14. Nagra PK, Hammersmith KM, Rapuano CJ, Laibson PR, Cohen EJ (2006) Wound dehiscence after penetrating keratoplasty. Cornea 25(2):132–135
15. Oshry T, Lifihitz T (2001) Traumatic wound dehiscence after corneal graft. Ophthalmic Surg Lasers 32(6):470–473
16. Pettinelli DJ, Starr CE, Stark WJ (2005) Late traumatic corneal wound dehiscence after penetrating keratoplasty. Arch Ophthalmol 123(6):853–856
17. Raber IM, Arentsen JJ, Laibson PR (1980) Traumatic wound dehiscence after penetrating keratoplasty. Arch Ophthalmol 98(8):1407–1409
18. Rehany U, Rumelt S (1998) Ocular trauma following penetrating keratoplasty: incidence, outcome, and postoperative recommendations. Arch Ophthalmol 116(10):1282–1286
19. Steinberg J, Eddy MT, Katz T, Fricke OH, Richard G, Linke SJ (2012) Traumatic wound dehiscence after penetrating keratoplasty: case series and literature review. Eur J Ophthalmol 22(3):335–341
20. Topping TM, Stark WJ, Maumenee E, Kenyon KR (1982) Traumatic wound dehiscence following penetrating keratoplasty. Br J Ophthalmol 66(3):174–178
21. Tran TH, Ellies P, Azan F, Assaraf E, Renard G (2005) Traumatic globe rupture following penetrating keratoplasty. Graefes Arch Clin Exp Ophthalmol 243(6):525–530
22. Tseng SH, Lin SC, Chen FK (1999) Traumatic wound dehiscence after penetrating keratoplasty: clinical features and outcome in 21 cases. Cornea 18(5):553–558
23. Williams MA, Gawley SD, Jackson AJ, Frazer DG (2008) Traumatic graft dehiscence after penetrating keratoplasty. Ophthalmology 115(2):276–278; e1
24. Watson AP, Simcock PR, Ridgway AE (1987) Endothelial cell loss due to repeated traumatic wound dehiscence after penetrating keratoplasty. Cornea 6(3):216–218
25. Chaurasia S, Ramappa M (2011) Traumatic wound dehiscence after deep anterior lamellar keratoplasty. J AAPOS 15(5):484–485
26. Lee WB, Mathys KC (2009) Traumatic wound dehiscence after deep anterior lamellar keratoplasty. J Cataract Refract Surg 35(6):1129–1131
27. Sari ES, Koytak A, Kubaloglu A, Culfa S, Erol MK, Ermis SS, Özertürk Y (2013) Traumatic wound dehiscence after deep anterior lamellar keratoplasty. Am J Ophthalmol 156(4):767–772
28. Zarei-Ghanavati S, Zarei-Ghanavati M, Sheibani S (2010) Traumatic wound dehiscence after deep anterior lamellar keratoplasty: protective role of intact descemet membrane after big-bubble technique. Cornea 29(2):220–221
29. Lee BL, Manche EE, Glasgow BJ (1995) Rupture of radial and arcuate keratotomy scars by blunt trauma 91 months after incisional keratotomy. Am J Ophthalmol 120(1):108–110
30. Glasgow BJ, Brown HH, Aizuss DH, Mondino BJ, Foos RY (1988) Traumatic dehiscence of incisions seven years after radial keratotomy. Am J Ophthalmol 106(6):703–707
31. McDonnell PJ, Lean JS, Schanzlin DJ (1987) Globe rupture from blunt trauma after hexagonal keratotomy. Am J Ophthalmol 103(2):241–242
32. Forstot SL, Damiano RE (1988) Trauma after radial keratotomy. Ophthalmology 95(6):833–835
33. Hurvitz LM (1999) Late clear corneal wound failure after trivial trauma. J Cataract Refract Surg 25(2):283–284
34. Swan KC, Meyer SL, Squires E (1978) Late wound separation after cataract extraction. Ophthalmology 85(10):991–1003
35. Ball JL, McLeod BK (2001) Traumatic wound dehiscence following cataract surgery: a thing of the past? Eye 15(Pt 1):42–44
36. Xiao J, Jiang C, Zhang M, Jiang H, Li S, Zhang Y (2014) When case report became case series: 45 cases of late traumatic flap complications after laser-assisted in situ keratomileusis and review of Chinese literature. Br J Ophthalmol 98(9): 1282–1286
37. Iskander NG, Peters NT, Anderson Penno E, Gimbel HV (2001) Late traumatic flap dislocation after laser in situ keratomileusis. J Cataract Refract Surg 27(7):1111–1114
38. Melki SA, Talamo JH, Demetriades AM, Jabbur NS, Essepian JP, O'Brien TP, Azar DT (2000) Late traumatic dislocation of laser in situ keratomileusis corneal flaps. Ophthalmology 107(12):2136–2139
39. Kim HJ, Silverman CM (2010) Traumatic dislocation of LASIK flaps 4 and 9 years after surgery. J Refract Surg 26(6):447–452
40. Cherry PM (1972) Rupture of the globe. Arch Ophthalmol 88(5):498–507

41. Rohrbach JM, Weidle EG, Steuhl KP, Meilinger S, Pleyer U (1996) Traumatic wound dehiscence after penetrating keratoplasty. Acta Ophthalmol Scand 74(5):501–505
42. Murata N, Yokogawa H, Kobayashi A, Yamazaki N, Sugiyama K (2013) Clinical features of single and repeated globe rupture after penetrating keratoplasty. Clin Ophthalmol 7:461–465
43. Kartal B, Kandemir B, Set T, Kugu S, Keles S, Ceylan E, Akmaz B, Apil A, Ozertürk Y (2014) Traumatic wound dehiscence after penetrating keratoplasty. Ulus Travma Acil Cerrahi Derg 20(3):181–188
44. Crawford AZ, Meyer JJ, Patel DV, Ormonde SE, McGhee C (2016) Complications related to sutures following penetrating and deep anterior lamellar keratoplasty. Clin Exp Ophthalmol 44(2):142–143
45. Brown SI, Tragakis MP (1971) Wound dehiscence with keratoplasty: complication of the continuous-suture technique. Am J Ophthalmol 72(1):115–116
46. Spigelman AV, Doughman DJ, Lindstrom RL, Nelson JD (1988) Visual loss following suture removal post-keratoplasty. Cornea 7(3):214–217
47. Abou-Jaoude ES, Brooks M, Katz DG, Van Meter WS (2002) Spontaneous wound dehiscence after removal of single continuous penetrating keratoplasty suture. Ophthalmology 109(7):1291–1296
48. Scherer M, Sullivan WG, Smith DJ Jr, Phillips LG, Robson MC (1989) An analysis of 1,423 facial fractures in 788 patients at an urban trauma center. J Trauma 29(3):388–390
49. Gasset AR, Dohlman CH (1968) The tensile strength of corneal wounds. Arch Ophthalmol 79(5):595–602
50. Binder PS, Waring GO 3rd, Arrowsmith PN, Wang C (1988) Histopathology of traumatic corneal rupture after radial keratotomy. Arch Ophthalmol 106(11):1584–1590
51. Lang GK, Green WR, Maumenee AE (1986) Clinicopathologic studies of keratoplasty eyes obtained post mortem. Am J Ophthalmol 101(1):28–40
52. Larson BC, Kremer FB, Eller AW, Bernardino VB Jr (1983) Quantitated trauma following radial keratotomy in rabbits. Ophthalmology 90(6):660–667
53. Luttrull JK, Jester JV, Smith RE (1982) The effect of radial keratotomy on ocular integrity in an animal model. Arch Ophthalmol 100(2):319–320
54. Viola RS, Kempski MH, Nakada S, del Cerro M, Aquavella JVA (1992) New model for evaluating corneal wound strength in the rabbit. Invest Ophthalmol Vis Sci 33(5):1727–1733
55. Simonsen AH, Andreassen TT, Bendix K (1982) The healing strength of corneal wounds in the human eye. Exp Eye Res 35(3):287–292
56. Calkins JL, Hochheimer BF, Stark WJ (1981) Corneal wound healing: holographic stress-test analysis. Invest Ophthalmol Vis Sci 21(2):322–334
57. Howes EL, Sooy JW, Harvey SC (1929) The healing of wounds as determined by their tensile strength. J Am Med Assoc 92:42
58. Rennie L, Fleming W, Clark D, Ellerton C, Bosanquet R (1994) Some mechanical properties of 10/0 monofilament nylon sutures. Eye 8(Pt 3):343–345
59. Lemp MA (1976) Cornea and sclera. Arch Ophthalmol 94(3):473–490
60. Kitano S, Goldman JN (1966) Cytologic and histochemical changes in corneal wound repair. Arch Ophthalmol 76(3):345–354
61. Maurice DM (1987) The biology of wound healing in the corneal stroma. Castroviejo lecture. Cornea 6(3):162–168
62. Asota I, Farid M, Garg S, Steinert RF (2013) Femtosecond laser-enabled keratoplasty. Int Ophthalmol Clin 53(2):103–114

Boston Type I Keratoprosthesis in Ocular Chemical Burns

Jiaqi Chen, Jianjun Gu, and Jiajie Zhai

1 Introduction

Ocular surface is a complex unit that is comprised of many components acting in an integrated fashion to achieve excellent vision for the patient. A healthy lid and blink mechanism are essential for the proper spread of tear films and the protection of the cornea. The tear film provides lubrication, nutrition, and antimicrobial defense. The conjunctival and corneal epithelial compartments constitute the physical ocular surface. Chemical burns may produce severe and extensive damage to the ocular surface. In chronic chemical burns, structural disorders of the lids such as entropion, trichiasis, and lagophthalmos could lead to non-healing epithelial defects, secondary corneal ulceration, and evaporative dry eye. These disorders must be addressed prior to attempting surgery on the ocular surface. Symblepharon in chemical burns results in tethering of the lids to the globe and restricts the movement of both structures. It also results in failure of replenishment of the tear film on the ocular surface. To restore the normal anatomy, thorough release of the symblepharon includes excision of fibrotic scar tissues and transplantation of amniotic membrane or conjunctival substitute such as oral mucosa.

J. Chen, M.D. (✉) · J. Gu · J. Zhai
Cornea Service, Zhongshan Ophthalmic Center,
Sun Yat-Sen University, Guangzhou,
People's Republic of China
e-mail: docjiaqi@163.com

Various surgical techniques have been tried for the restoration of vision in eyes with Roper-Hall grade III/IV ocular chemical burns. Lamellar keratoplasty may have difficulties in reestablishing useful vision due to the presence of residual stromal haze and interface vascularization. Penetrating keratoplasty is often associated with problems of graft rejection and glaucoma [1, 2]. The poor prognosis of penetrating keratoplasty in chemical burns results from a combination of immunologic and nonimmunologic factors. The immunologic risk is attributed to the extensive vascularization that is seen in most cases of chemical burns. Nonimmunologic graft failure can be caused by tear deficiency and lid abnormality [3] or by limbal stem cell loss that leads to persistent epithelia defects and chronic corneal ulceration [4]. Limbal stem cell transplantation has a success rate of 10–50% with a follow-up of 5 years [5]. However, a second-stage central penetrating keratoplasty may be required for visual rehabilitation. The disadvantages include the need for two separate operations, exposure of the patient to two separate antigenic challenges, and a longer period of visual rehabilitation [6]. Besides, immunological responses against the transplanted cornea remain the major cause of graft failure. Postoperative systemic immunosuppression is known as the treatment of choice in immunologic high-risk transplants as ocular chemical burns. However, ophthalmologists are cautious about administering potentially toxic systemic immunosuppressive agents, even in

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_67, © Springer International Publishing AG
Published Online: 26 April 2018

those patients in whom a surviving graft would allow vision in the only eye [7].

Keratoprosthesis in cases of severe chemical burns is a useful surgical procedure to clear the visual axis in selected circumstances. The concept of an artificial cornea is not novel. It was first described by Guillaume Pellier de Quengsy, a French doctor in 1789. But no significant progress was made until the observance of the new biocompatible material of polymethyl methacrylate (PMMA) in the middle of the last century. Of the various types of keratoprosthesis currently in wide use include the AlphaCor artificial cornea [8], the osteo-odonto-keratoprosthesis (OOKP) [9], and the Boston keratoprosthesis (KPro) [10]. Each has its advantages and disadvantages in specific conditions, and therefore the indications for each device should be taken into consideration by the surgeons.

KPro was developed at the Massachusetts Eye and Ear Infirmary and the Schepens Eye Research Institute [11]. The Boston Type I Keratoprosthesis is the most widely used device. Since its approval by the US Food and Drug Administration in 1992, over 12,000 implants have been performed worldwide [12]. It is a collar button design consisting of two plates sandwiched around a donor cornea. The front plate has a 3.2 mm stem that connects to a 5.5 mm front plate whose refractive power can be selected. Sixteen holes of the backplate allow for communication with the aqueous for nutrition and hydration of the corneal graft. The whole assemble is locked together with a titanium locking ring (Fig. 1). KPro I is the device chosen for patients with graft failure, aniridia, and trauma. KPro II, whose design has a 2-mm-long anterior nub off the front plate, is used in severe dry eye conditions, like Stevens-Johnson syndrome, ocular cicatricial pemphigoid, etc. [13].

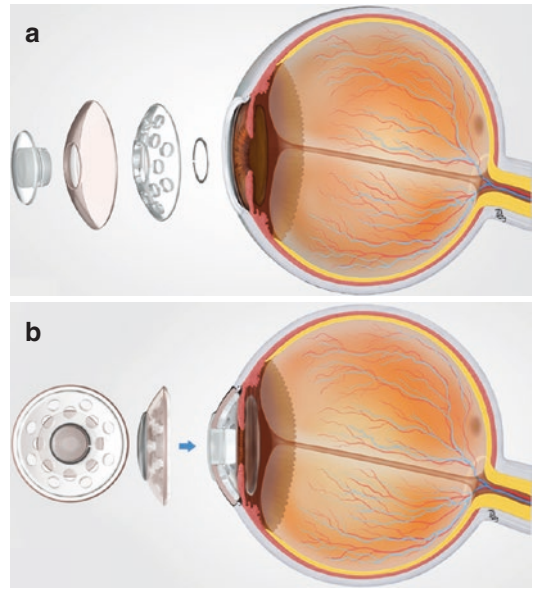


Fig. 1 Schematic of the Boston Type I Keratoprosthesis. (**a**) Three components (front part containing optics, backplate with 16 holes, titanium locking ring) and the donor cornea. (**b**) An assembled Boston keratoprosthesis with a PMMA backplate is implanted into an aphakic eye

2 Surgical Indications

Potential recipients of ocular chemical burns of KPro I should have access to the hospital, understand prophylactic and follow-up medication regimen, and be willing to adhere to regular follow-up schedule. Preoperative visual acuity should range from 20/100 to light perception. Glaucoma that may affect visual potential should be controlled prior to KPro I implantation. A stable ocular surface with minimum inflammation needs to be achieved in order to create as normal an ocular environment as possible.

3 Contraindications

KPro I surgery should not be considered for patients who are good candidates for penetrating keratoplasty. KPro I surgery is contraindicated in patients with severe dry eye, end-stage glaucoma, dense amblyopia, or retinal pathology. Patients with autoimmune diseases (i.e., Stevens-Johnson syndrome, ocular cicatricial pemphigoid) are a relative contraindication for this procedure.

4 Preoperative Assessment

The preoperative screening of a KPro I implantation should include the routine work-up for a full-thickness penetrating keratoplasty. The visual acuity should be assessed on a Snellen's visual acuity chart, and a detailed examination of the lids and the ocular surface should be performed. An evaluation of the tear film status could be done by using Schirmer's test, tear breakup time, and fluorescein staining. Ultrasound biomicroscopy and anterior segment optical coherence tomography (AS-OCT) could be used to assess the status of various anterior segment structures and angle anatomy in eyes with opaque cornea (Fig. 2). Glaucoma is not uncommon in severe ocular chemical burns and may not be evaluated by tonometers. A rough estimate of intraocular pressure (IOP) is obtained by digital palpation of the globe. Preoperative glaucoma was also evaluated by ultrasound findings suggestive of an increased cup/ratio (Fig. 3) or nasal defect of visual field testing. Corneal vascularization, corneal sensation, and the status of the corneal epithelium should also be examined for the postoperative outcomes.

Chemical burns not only affect the cornea and ocular surface but may also affect the eyelids. Eyelid abnormalities that can be seen include trichiasis, entropion, ectropion, foreshortening, eyelid defect, and lagophthalmos. These abnormal lid conditions can lead to exposure keratitis, epithelial defects, and disability to retain a bandage contact lens (Fig. 4). It is vital to address any eyelid abnormalities surgically before KPro I surgery, because proper lid anatomy and blink function are important to maintain a hydrated ocular surface and retain a bandage contact lens to improve ocular surface stability.

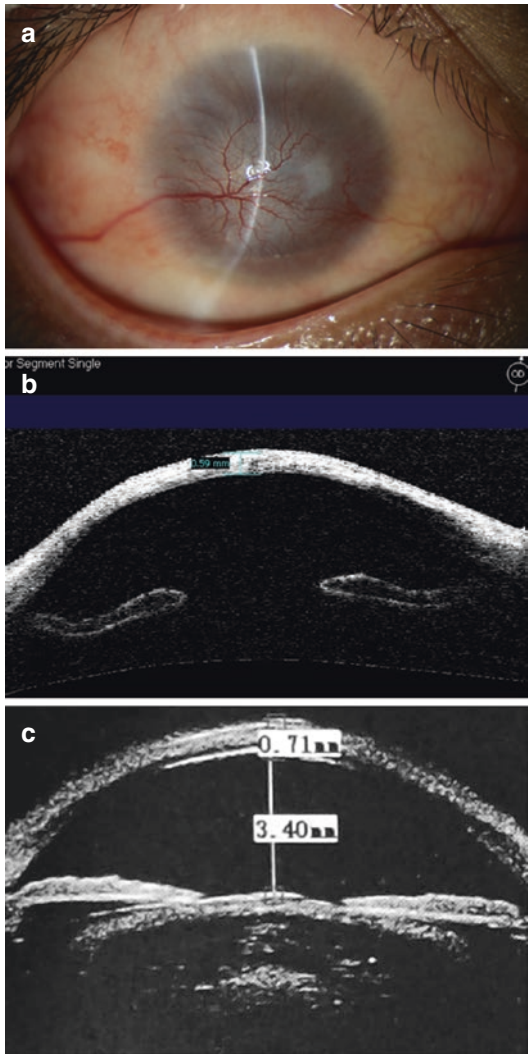


Fig. 2 Preoperative evaluation of anterior segment in keratoprosthesis candidates. (**a**) Slit lamp of a patient with ocular alkali burns. (**b**) Anterior segment OCT of the same eye with corneal opacity; note the lens could not be clearly defined. (**c**) Ultrasound biomicroscopy reveals the anterior chamber depth and the lens with hyper-reflective echoes

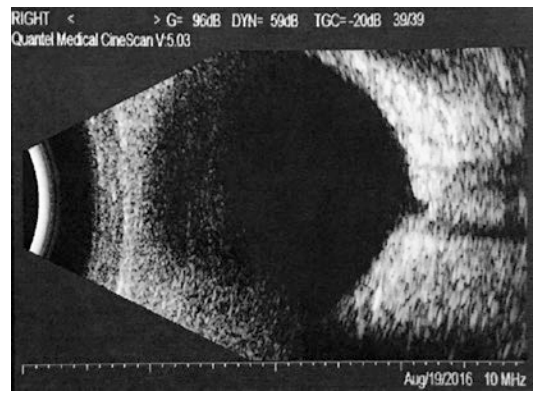


Fig. 3 B-scan ultrasonography in ocular chemical burns revealed abnormality of cup-to-disc ratio of the optic nerve head

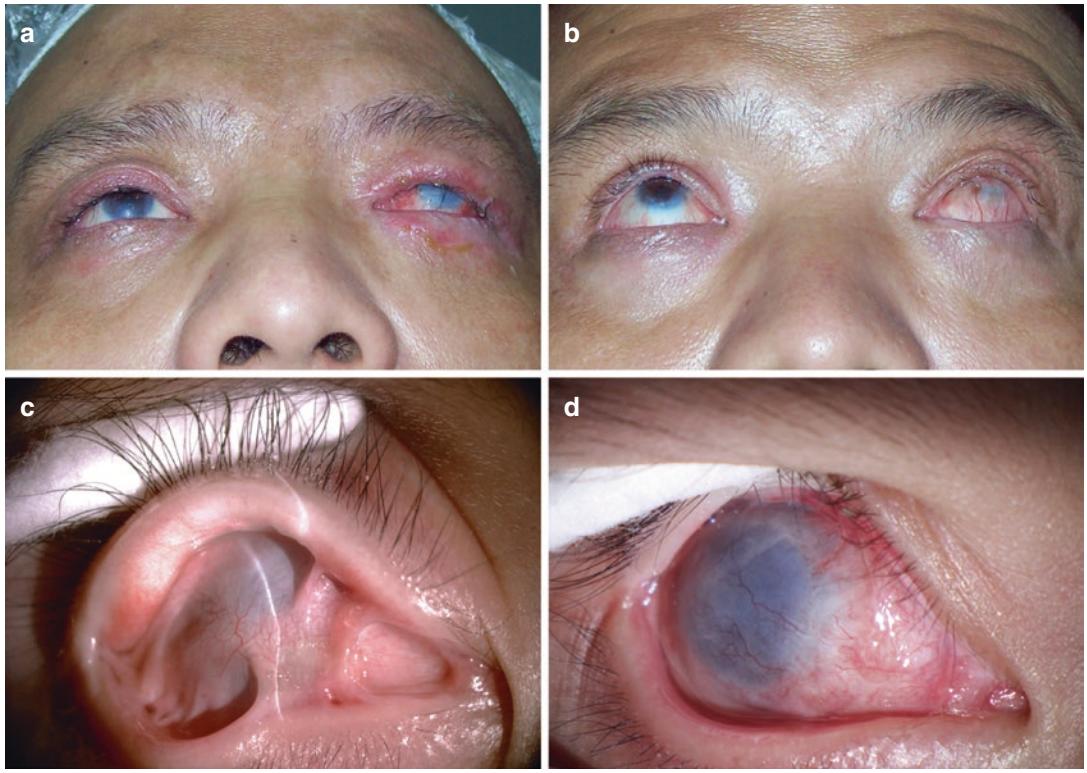


Fig. 4 Mechanical eyelid problems in ocular chemical burns. Preoperative photograph of bilateral cicatricial upper eyelid entropion and trichiasis following (**a**) acid burns and (**b**) postoperatively. Preoperative slit lamp of a 34-year-old patient with symblepharon in the right eye as a result of an (**c**) alkali injury and (**d**) postoperatively

5 Preoperative Procedures

All patients should be provided with educational information. There are more potential long-term complications with a KPro I than with standard cornea transplant. The KPro I patient must adhere indefinitely to postoperative procedures, such as lifetime topical antibiotic prophylaxis and lifetime glaucoma management.

Patients should be admitted to the hospital for a minimum of 3 days preoperatively. Biometry should be performed with confirmation of phakic, pseudophakic, aphakic status to determine KPro type and focal length.

A course of intramuscular injection of vitamin K1 1 mg for 3 days is recommended known to be prophylaxis of hemorrhage in the vascularized ocular surface in our hospital. Patients should receive a preoperative course of topical steroids to be anti-inflammatory.

6 Surgical Technique

6.1 Technique of Implantation

General anesthesia is preferred for KPro I implantation. We usually administer two drops of 5% povidone-iodine preoperatively. After prepping and draping the patient's eye in the usual sterile fashion for intraocular surgery, a 360° conjunctival peritomy is performed, and the conjunctiva is retracted posteriorly from the limbus all around. Any symblepharon present over the cornea is also released. If the limbus is difficult to define, a transillumination is performed to note the location of the limbus.

A Flieringa ring is sutured to the eye using 6–0 sutures. The donor cornea is trephinated in the usual fashion to be 8.5–9.0 mm in diameter, usually intended for an 8.0 mm bed, because the recipient beds in chemical burn cases often con-

tract following trephination. Using the supplied 3.0 mm dermatological punch, a central 3.0 mm hole is created in the center of the donor button. The anterior plate is secured on the table by a double-sided adhesive which is provided by the manufacturer. The donor button with 3 mm opening is lowered over the stem until the epithelial side contacts the back of the front plate. Viscoelastic material is applied to the corneal button's endothelium to increase lubrication. The backplate is slid over the front plate stem and pushed down onto the donor cornea using index fingers without any rotating movement. The titanium locking ring clicks into place by applying downward pressure with a white locking pin, which accompanies the device. The locking pin should be at 90° from the front plate when pressing down. The entire assembly is inspected under operating microscope to ensure the backplate and locking ring are properly assembled. The complete composition is then removed from the adhesive placed into the storage solution while the patient's host bed is being prepared.

A forceps is used to grasp the Flieringa ring, and an open-bladed, disposable trephine is held in the opposite hand and first pressed on the cornea and then rotated approximately three-fourths of the way into the recipient bed. Any bleeding in the host bed can usually be controlled by topical epinephrine drops or microcautery to the bleeding vessels. The patient's cornea is removed by a No. 15 blade and corneal scissors. Viscoelastic material is injected into the anterior chamber to counteract posterior pressure and create space between the cornea and iris. Synechiae between the iris and the cornea are lysed meticulously with viscoelastic or a spatula. Corectopia is handled with iridoplasty to clear the visual axis obstruction through the KPro I optic. If the patient is phakic, usually cataract is present in severe ocular chemical burns, a lensectomy shall be performed. If the patient is aphakic and vitreous presents, an anterior core vitrectomy needs to be performed. In aphakic eyes, the axial length of the eyes is used to calculate the refractive power of the KPro I. The KPro-graft is sutured into position with interrupted 10–0 sutures. All suture knots are buried, and the graft-host junction should be examined to make sure it is water tight. At the completion of the surgery, a soft contact lens (Kontur Kontact Lens Co., Hercules, CA), which accompanies the device, is placed over the eye and remains in place postoperatively.

7 Postoperative Management

The patients should be followed up meticulously, weekly for the first month and 1–2 months thereafter, because chemical burn patients are at increased risk of developing suture-related complications like loose or vascularized sutures (Fig. 5). Visual acuity, slit-lamp examination, funduscopy, and IOP management were performed at each visit. Postoperatively, topical vancomycin and tobramycin dexamethasone are administered four times per day for 1 month. Then the topical steroid of fluoroquinolone is tapered to twice daily every day over a 3-month period, and daily antibiotic prophylaxis with topical levofloxacin is used indefinitely. Because the Kontur Kontact Lens is not available in China, the contact lens was replaced with a disposable soft bandage contact lens (Optix; Ciba Vision) at each visit.

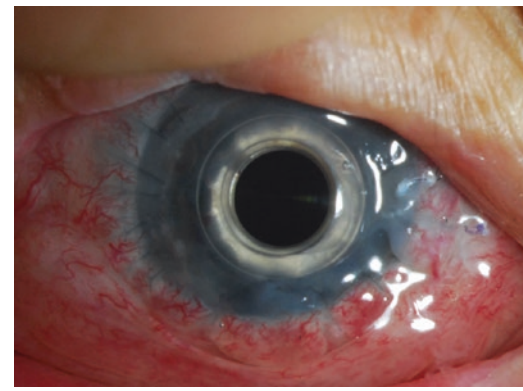


Fig. 5 A loose suture is noted at 3 o'clock 4 months after KPro I implantation

8 Outcomes

In a series of 19 eyes which was done in our hospital [14], the preoperative best-corrected visual acuity was less than finger counter in all eyes. The mean age of the patients undergoing KPro I for chemical burns was 42.7 ± 11.3 years (range 29–62 years). All patients in this study were male. The mean duration between injury and KPro I surgery was 6.6 ± 5.2 years (range 2–25.6 years). The mean follow-up time was 41.3 ± 5.5 months (range 36–56 months). Postoperatively, 17 patients (89.4%) achieved at least 20/200 once, and 7 patients (36.8%) achieved at least 20/200 and maintained this visual acuity until the last follow-up (Fig. 6). The initial KPro I was retained in 14 (73.6%) eyes and successfully replaced in 1 eye.

The cause of poor postoperative vision following KPro I includes glaucoma, retinal detachment, retroprosthetic membrane (RPM), and corneal melt.

Fabiano et al. reported data collected from 28 eyes of 23 patients who underwent KPro implantation [15]. Their follow-up ranged from 1 month to 162 months (median, 57 months). The patient age was 46 (SD ± 15) years. Sixteen eyes had alkaline burn, and 12 eyes had acid burn. The authors reported a retention rate of 75%. Of the remaining seven KPros implanted, six had the KPro replaced once, and one had it replaced twice. Functional results were analyzed as postoperative best-corrected visual acuity ranged from no light perception to 20/20. Among eyes at the last follow-up, vision was >20/60 in nine (32%) eyes.

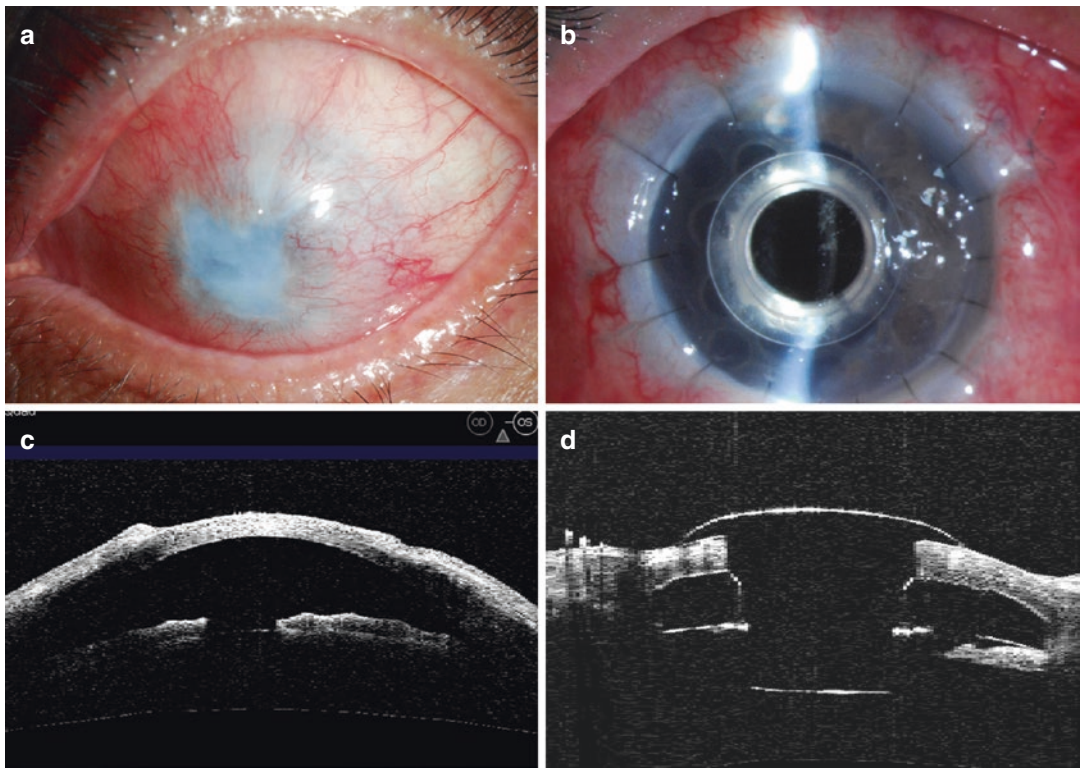


Fig. 6 A 52-year-old patient with bilateral corneal blindness from alkali chemical burns. Slit-lamp photographs show the appearance of the left eye (**a**) preoperatively and (**b**) 6 months postoperatively. Vision improved from hand movement to 20/40 at 6 months. (**c**) Anterior segment optical coherence tomography (AS-OCT) showing an open anterior chamber angle preoperatively. (**d**) AS-OCT revealing a closed angle with iridocorneal adhesion 6 months postoperatively

Fernanda et al. [16] reported the results of ten patients who underwent KPro placement between 2008 and 2010. The mean follow-up was 25.7 ± 10.8 months. In the majority of patients, visual acuity improved. The number of patients with BCVA 20/200 or better went from 0% preoperatively to 90% postoperatively. Sixty percent had postoperative vision of 20/60 or better. The anatomical retention rate was 90% after 24 months of follow-up.

David et al. [17], in a series of nine patients of severe chemical and thermal injury, reported six eyes were ≥20/70 after a mean follow-up period of 40.7 months (29–60 months). Retention of the initial KPro was 77.8% (seven eyes) and was successfully replaced in the other two eyes (Table 1).

9 Complications

The major complications that affect the visual acuity after KPro I implantation include (1) corneal necrosis adjacent to the stem of KPro, (2) glaucoma, (3) RPM, and (4) retinal detachment. Progress in the field had resulted in decrease of the occurrence of the complications. These improvements include design of KPro and materials (holes in backplate, locking ring, titanium backplate), contact lens use, prophylactic antibiotics, and glaucoma drainage devices (GDDs) for control of glaucoma associated with KPro implantation and Nd:YAG laser membranectomy [19].

9.1 Retroprosthetic Membrane

This membrane may occur in association with prolonged intraocular inflammation. In our study, 47% patients developed RPM postimplantation (Fig. 7) [14]. Other authors also reported higher incidence of RPM development in chemical burns [20]. The occurrence of RPM emphasizes the importance of postoperative anti-inflammatory therapy. Once formed, some of them could be treated with Nd:YAG laser (Fig. 8). Nd:YAG laser pulses with power energy above 2.0 mJ should be avoided because the optical portion of the device can crack. If the membrane cannot be cut with laser, a vitrectomy and membranectomy are needed [21].

9.2 Corneal Melt

Corneal melt after KPro I implantation may be caused by action of proteolytic enzymes [22] and presence of eyelid abnormalities and RPM. The incidence of corneal melt after implantation was once over 50% [23]. It has been significantly decreased with the modification of the device, together with the use of a bandage contact lens to prevent ocular surface desiccation. If the patients are vulnerable to persistent epithelial defect and corneal melt due to eyelid abnormalities and difficulty in retaining the bandage contact lens, a conjunctival flap covering KPro I has been studied

Table 1 Results of Boston keratoprosthesis case series for chemical burns

	Diagnosis	# of eyes	KPro I, %	Device retention rate, %	Postoperative VA	Follow-up, mean (range)
Cade [15]	100% chemical burns	28	82	78 (type I) 60 (type II)	79% ≥ 20/200(BA) 46% ≥ 20/200(LF)	57 months (1–162 months)
Harissi-Dagher [18]	70% chemical burns	30	100	90	77% ≥ 20/200(BA) 53% ≥ 20/60(BA)	35 months (1–108 months)
Magalhães [16]	90% chemical burns	10	100	90	90% ≥ 20/200(BA) 40% ≥ 20/200(LF)	25 months (13–41 months)
Phillips [17]	89% chemical burns	9	100	78	100% ≥ 20/200(BA) 33% ≥ 20/200(LF)	41 months (29–60 months)
Gu [14]	100% chemical burns	19	100	74	89% ≥ 20/200(BA) 37% ≥ 20/200(LF)	41 moths (36–56) months

VA vision acuity, *BA* best achieved, *LF* last follow-up

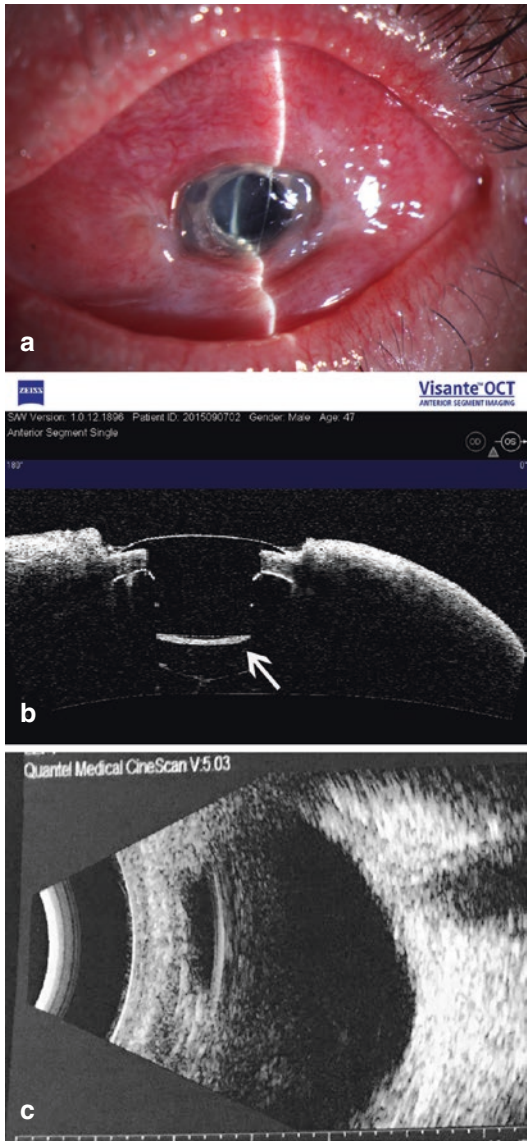


Fig. 7 Retroprosthetic membrane (RPM) after KPro I surgery. (**a**) Slit lamp demonstrated RPM 5 months after KPro I implantation in a patient injured by alkali chemical burns 18 years ago. (**b**) Anterior segment optical coherence tomography showing a thick RPM (arrow). (**c**) B-scan ultrasonography showing the presence of sterile vitritis after ruling out infection

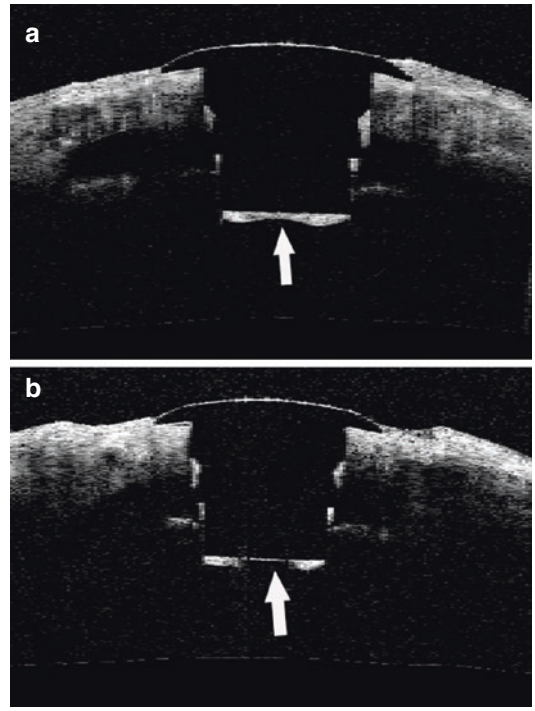


Fig. 8 Serial AS-OCT imaging of a patient with RPM treated with Nd:YAG laser. (**a**) Cross-sectional AS-OCT scan demonstrating a thick RPM (arrow) posteriorto the stem preoperatively. (**b**) AS-OCT image of the same eye showing the absence of RPM (arrow) after Nd:YAG laser treatment

[24]. It seemed that a conjunctival flap acts as biologic patches, conferring a trophic effect. Blood vessels will supply nutrients, and the α2-macroglobulins in the blood may inhibit the proteolytic enzymes [25]. This technique is useful, and the flap can serve as "poor man's contact lens" in developing countries like China where Kontur contact lens are not available (Fig. 9).

Corneal melt also developed in patients with evidence of RPM. It has been reported that RPM thickness correlates with the risk of corneal melt [26]. The mechanism of corneal melt may be the limit of communication between the corneal graft and aqueous which provide nutrition to the cornea. In our experience, cells in the RPM stained positive with antibodies against CD68, identifying these cells as macrophages, which are considered part of the innate immune response. An infiltration of T lymphocytes (CD3) was also observed in the RPM. Thus, we have provided evidence of some type of adaptive system that was locally related to the KPro (Fig. 10).

In case of full-thickness corneal melt around the stem, choroidal detachments can also develop due to hypotony (Fig. 11). We recommend it is more reliable to make KPro replacement or

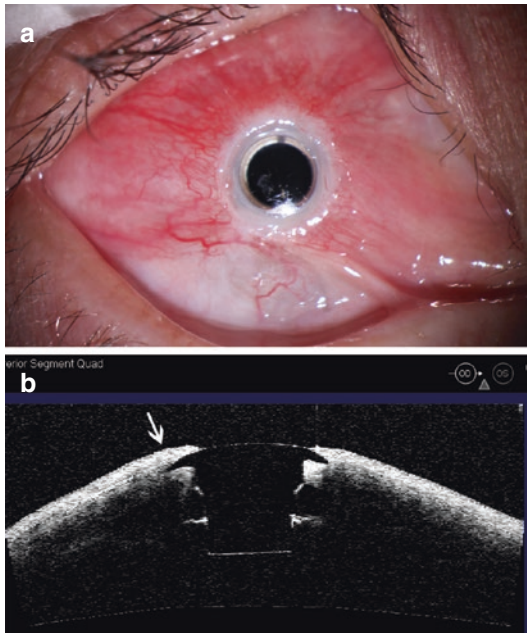


Fig. 9 Total conjunctival flap in KPro I. (**a**) Slit lamp of total conjunctival flap in KPro I 18 months postoperatively; note the symblepharon in the lower eyelid. (**b**) AS-OCT scan revealing epithelial tissue of conjunctiva extends onto the KPro I front plate (arrows)

explanation with penetrating keratoplasty to decrease the risk of infectious endophthalmitis.

9.3 Glaucoma

Glaucoma occurs in up to 75% of eyes with severe chemical burns [15]. High-pressure intraocular spikes can occur immediately after chemical burns and can persist indefinitely [27]. It may be caused by multiple mechanisms, including pupillary block, accumulation of inflammatory debris in the trabecular meshwork, and direct damage to the trabecular meshwork [28]. In addition, the ganglion cell layer of the retina has been damaged by deep diffusion in alkali injuries, setting it at a new level of sensitivity to pressure [29]. The development or aggravation of glaucoma in KPro I patients may have several causes, including a compromise of the angle by a crowded anterior chamber, the routine use of topical steroids, or an accumulation of inflammatory debris in the trabecular meshwork. After the KPro I is implanted, the aggravation of glaucoma or glaucoma de novo is based on the examination

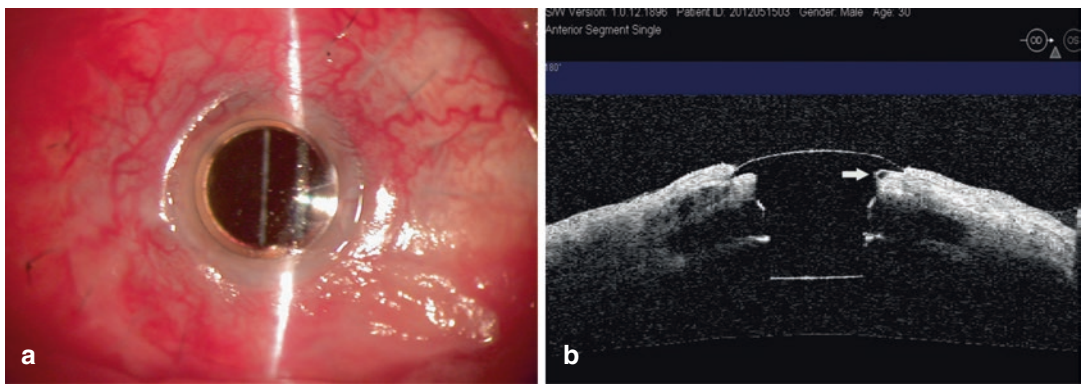


Fig. 10 Progression of corneal melting. (**a**) Slit lamp of a patient implanted with KPro I 3 months postoperatively. (**b**) Horizontal AS-OCT of the same eye showing corneal melting at 3 o'clock (arrow). (**c**) Slit lamp 26 months postoperatively. (**d**) AS-OCT obtained on 26 months postoperatively showing corneal melting at 3 and 9 o'clock (arrows) and RPM. (**e**) Slit lamp at 30 months postoperatively showing the extrusion of the KPro I with RPM formation. (**f**) Horizontal AS-OCT of the same eye showing extrusion of the backplate at 9 o'clock (arrow) and dense formation of RPM. (**g**) Hematoxylin and eosin staining of the RPM revealing a foreign body giant cell (arrow), plasma cells, lymphocytes, macrophages, and fibroblasts in the mixed inflammatory infiltrate (×200). (**h**) Micrograph of CD3 staining with positive labeling of T lymphocytes in the RPM (×200). (**i**) CD68 staining labeling macrophages in the RPM tissue adjacent to the KPro I (×200)

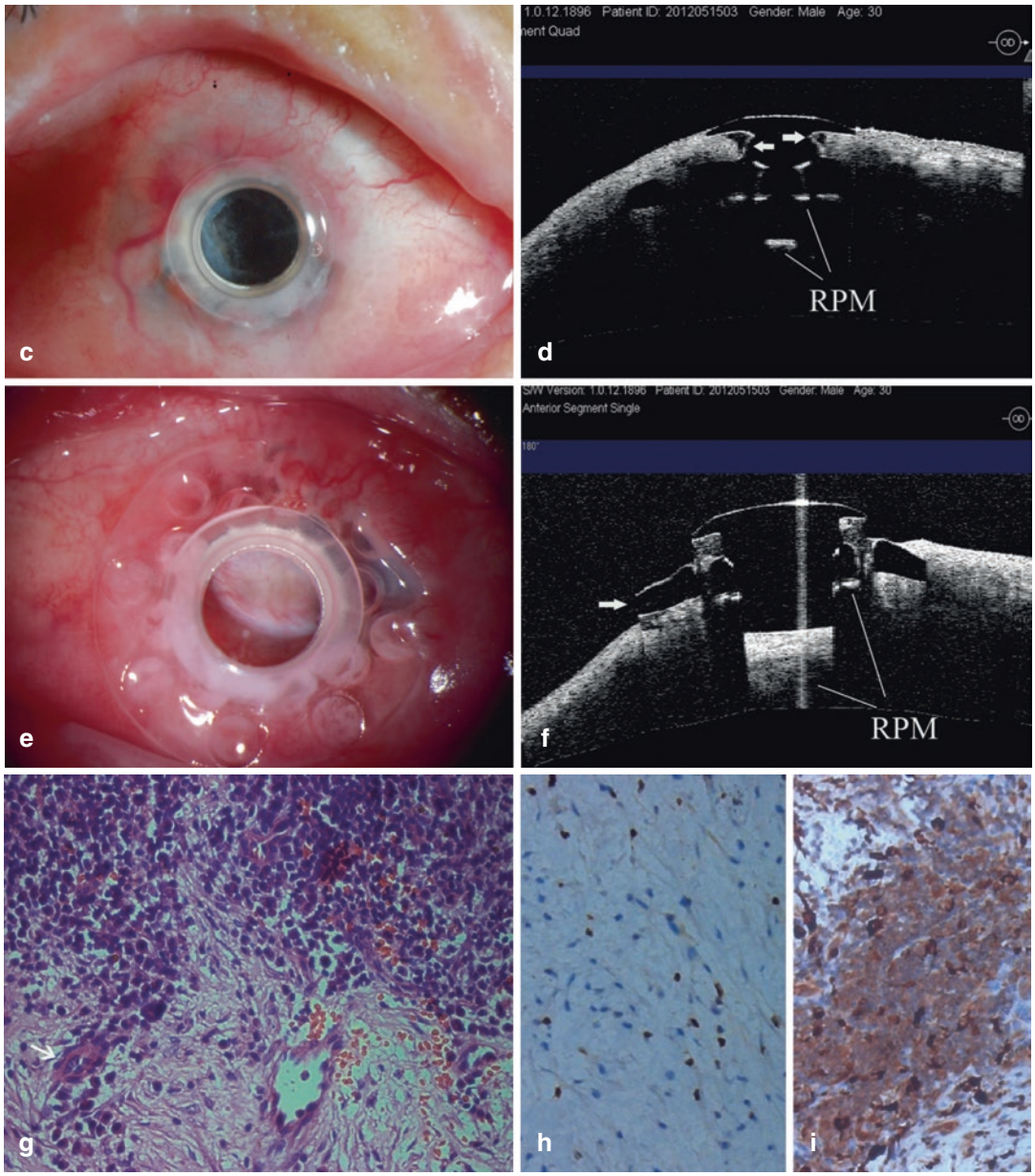


Fig. 10 continued

of the intraocular pressure by palpation, the optic nerve, the visual field, and the retinal thickness by optical coherence tomography. GDDs are a useful alternative to medical therapy for the management of glaucoma (Fig. 12) [30]. In cases GDDs are not feasible to implant, trans-scleral cyclophotocoagulation should be considered to control glaucoma with KPro [31].

9.4 Retinal Detachment

The incidence of retinal detachment in our KPro I patients was 10.5% (2 of 19 patients) [14], which is comparable with those reported in previous studies [18, 32]. Retinal detachment after KPro I implantation can be rhegmatogenous or tractional in nature. It may be due to vitreoretinal

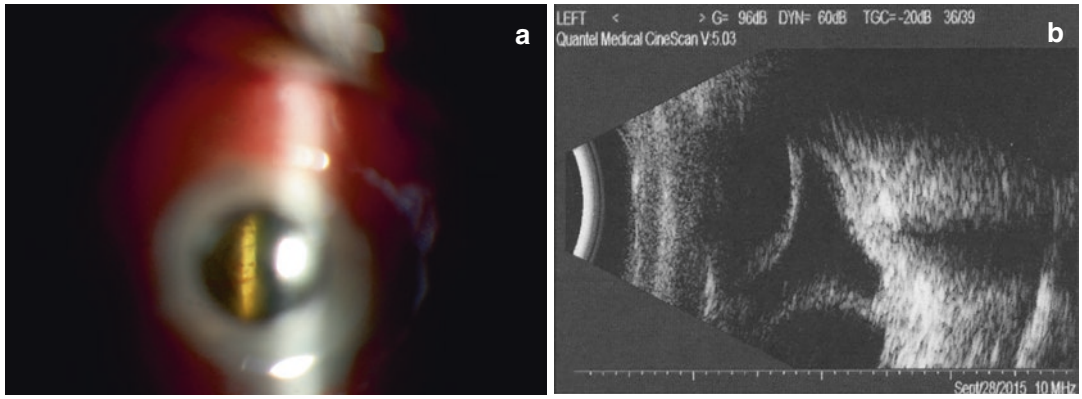


Fig. 11 Corneal necrosis around the prosthetic implant resulting in hypotony. (**a**) Slit lamp of choroidal detachment viewed through KPro I. (**b**) Ultrasound of choroidal detachment on KPro I

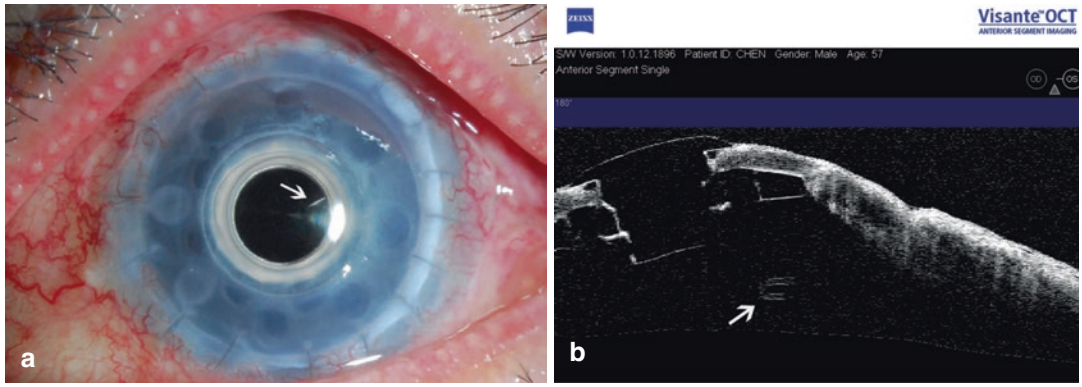


Fig. 12 Glaucoma drainage device (GDD) surgery for control of glaucoma associated with KPro I surgery. (**a**) Slit lamp of the right eye of a patient that underwent prior GDD and KPro I. Note the tube at 3 o'clock behind the stem of KPro I (arrow). (**b**) AS-OCT showing the tube of the GDD behind the KPro I (arrow)

traction secondary to chronic inflammation or aphakic status. Diagnosis is by direct visualization or B-scan ultrasonography. Treatment typically includes vitrectomy plus tamponade with silicone oil [21, 33]. The prognosis for vision recovery is ominous.

10 Discussion

Restoration of vision after chemical burns has never been straightforward. Developing countries carry the largest burden yet are the least able to afford the costs [34, 35], so it is urgent to provide a possibility in the visual rehabilitation of chemical burns. We suggest that KPro I may be used for eyes injured by severe chemical burns.

This procedure is easy to perform using the same technique as for penetrating keratoplasty. Furthermore, good visual acuity results could be achieved in eyes with chemical burns due to recovery of visual axis and the absence of corneal astigmatism. KPro I implantation is a promising surgical modality in eyes with severe chemical burns. Good patient selection and in-depth patient follow-up have a critical impact on patient outcomes.

References

1. Sundmacher R, Reinhard T, Althaus C (1997) Homologous central limbo-keratoplasty in limbus stem cell damage. Retrospective study of 3 years' experience. Ophthalmologe 94(12):897–901

2. Redbrake C, Buchal V (1996) Keratoplasty with scleral rim after the most severe chemical eye burns of the anterior eye segment. Klin Monatsbl Augenheilkd 208(3):145–151
3. Kramer SG (1983) Late numerical grading of alkali burns to determine keratoplasty prognosis. Trans Am Ophthalmol Soc 82:97–106
4. Mattax JB, McCulley JP (1988) Corneal surgery following alkali burns. Int Ophthalmol Clin 28(1):76–82
5. Tan DT, Ficker LA, Buckley RJ (1996) Limbal transplantation. Ophthalmology 103(1):29–36
6. Tims S, Lee B (2013) Keratoplasty in ocular surface disease. In: Holland EJ, Mannis MJ, Lee B (eds) Ocular surface disease. Elsevier, London, pp 397–402
7. Slegers T, Daly M, Larkin P (2006) Corneal transplant rejection. In: Reinhard T, Larkin D (eds) Cornea and external eye disease. Springer, Berlin, pp 73–81
8. Hicks CR, Crawford GJ, Dart JK, Grabner G, Holland EJ, Stulting RD, Tan DT, Bulsara M (2006) AlphaCor: clinical outcomes. Cornea 25(9):1034–1042
9. De La Paz MF, De Toledo JÁ, Charoenrook V, Sel S, Temprano J, Barraquer RI, Michael R (2011) Impact of clinical factors on the long-term functional and anatomic outcomes of osteo-odonto-keratoprosthesis and tibial bone keratoprosthesis. Am J Ophthalmol 151(5):829–839
10. Homayounfar G, Grassi CM, Al-Moujahed A, Colby KA, Dohlman CH, Chodosh J (2016) Type 1 Boston keratoprosthesis: outcomes at two Canadian centres. Can J Ophthalmol 51(2):76–82
11. Dohlman CH, Schneider H, Doane MG (1974) Prosthokeratoplasty. Am J Ophthalmol 77:694–700
12. Ahmad S, Akpek E (2016) Comparing repeat donor corneal transplantation to boston keratoprosthesis in patients with previous graft failure. Boston KPro News 12:1–3
13. Lee R, Khoueir Z, Tsikata E, Chodosh J, Dohlman CH, Chen TC (2017) Long-term visual outcomes and complications of boston keratoprosthesis type II implantation. Ophthalmology 124(1):27–35
14. Gu J, Zhai J, Zhou S, Chen J (2016) Boston keratoprosthesis outcomes in severe ocular chemical burns in southern China: a retrospective study. Adv Ther 33(5):760–773
15. Cade F, Grosskreutz CL, Tauber A, Dohlman CH (2011) Glaucoma in eyes with severe chemical burn, before and after keratoprosthesis. Cornea 30(12):1322–1327
16. Magalhães FP, Hirai FE, de Sousa LB, de Oliveira LA (2013) Boston type 1 keratoprosthesis outcomes in ocular burns. Acta Ophthalmol 91(6):e432–e436
17. Phillips DL, Hager JL, Goins KM, Kitzmann AS, Greiner MA, Cohen AW, Welder JD, Wagoner MD (2014) Boston type 1 keratoprosthesis for chemical and thermal injury. Cornea 33(9):905–909
18. Harissi-Dagher M, Dohlman CH (2008) The Boston Keratoprosthesis in severe ocular trauma. Can J Ophthalmol 43(2):165–169
19. Salvador-Culla B, Kolovou PE (2016) Keratoprosthesis: a review of recent advances in the field. J Funct Biomater 7(2):13
20. Todani A, Ciolino JB, Ament JD, Colby KA, Pineda R, Belin MW, Aquavella JV, Chodosh J, Dohlman CH (2011) Titanium back plate for a PMMA keratoprosthesis: clinical outcomes. Graefes Arch Clin Exp Ophthalmol 249(10):1515–1518
21. Ray S, Khan BF, Dohlman CH, D'Amico DJ (2002) Management of vitreoretinal complications in eyes with permanent keratoprosthesis. Arch Ophthalmol 120(5):559–566
22. Dohlman CH (1983) Biology of complications following Keratoprosthesis. Cornea 2(3):175–176
23. Hannush SB (2011) Postoperative management of keratoprosthesis. In: Krachmer JH, Mannis MJ, Holland EJ (eds) Cornea, 3rd edn. Mosby Elsevier, St. Louis, MO, pp 1699–1704
24. Al-Merjan J, Sadeq N, Dohlman CH (2000) Temporary tissue coverage of keratoprosthesis. Mid East Afr J Ophthalmol 8:12
25. Dohlman CH (2016) Total conjunctival flap in KPro surgery. Boston KPro news, XII 2016. Massachusetts Eye and Ear Infirmary
26. Sivaraman KR, Hou JH, Allemann N, de la Cruz J, Cortina MS (2013) Retroprosthetic membrane and risk of sterile keratolysis in patients with type I Boston Keratoprosthesis. Am J Ophthalmol 155(5):814–822
27. Paterson CA, Pfister RR (1973) Ocular hypertensive response to alkali burns in the monkey. Exp Eye Res 17(5):449–453
28. Fish R, Davidson RS (2010) Management of ocular thermal and chemical injuries, including amniotic membrane therapy. Curr Opin Ophthalmol 21(4):317–321
29. Dohlman CH, Cade F, Pfister R (2011) Chemical burns to the eye: paradigm shifts in treatment. Cornea 30(6):613–614
30. P N, Chopra V (2014) Glaucoma management in Boston keratoprosthesis type I recipients. Curr Opin Ophthalmol 25(2):134–140
31. Rivier D, Paula JS, Kim E, Dohlman CH, Grosskreutz CL (2009) Glaucoma and keratoprosthesis surgery: role of adjunctive cyclophotocoagulation. J Glaucoma 18(4):321
32. de Oliveira LA, Pedreira Magalhães F, Hirai FE, de Sousa LB (2014) Experience with Boston keratoprosthesis type 1 in the developing world. Can J Ophthalmol 49(4):351–357
33. Goldman DR, Hubschman JP, Aldave AJ, Chiang A, Huang JS, Bourges JL, Schwartz SD (2013) Postoperative posterior segment complications in eyes treated with the Boston type I keratoprosthesis. Retina 33(3):532–541
34. Ilsar M, Chirambo M, Belkin M (1982) Ocular injuries in Malawi. Br J Ophthalmol 66(2):145–148
35. Umeh RE, Umeh OC (1997) Causes and visual outcome of childhood eye injuries in Nigeria. Eye (Lond) 11(Pt 4):489–495

Part III

Plastic Surgery

Variations in Treatment of Plastic Aesthetic Surgery Complications

Melvin A. Shiffman

1 Introduction

As with any surgical procedure, there are variations in the techniques for handling the different complications that may occur. Some alternatives are good and others may have problems that need to be identified. Certain aesthetic procedures are identified where there can be differences in opinions of how to solve postoperative problems.

2 Abdominoplasty

The rather common complication with abdominoplasty is necrosis of the abdominal flap (Fig. 1). Causes of the necrosis can be too-tight closure of the flap at the transverse incision sutured to the pubic area, liposuction of the abdomen (especially the center of the upper abdomen) prior to abdominoplasty, prior scars in the subcostal area from cholecystectomy or gastric surgery, and smoking. The areas of necrosis vary from the suprapubic area to the umbilicus. When the necrosis involves the area superior to the umbilicus, the cause is smoking, prior liposuction of the upper abdomen, or preoperative subcostal scars.

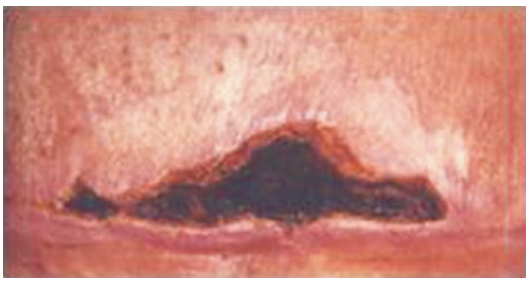


Fig. 1 Usual area of necrosis after abdominoplasty when the closure is too tight

The treatment is to allow the eschar to form and ultimately slough, and then the underlying granulation tissue will slowly pull the normal skin down to the pubis (Fig. 2).

The scar may have to be revised, but this can be a very good result. If there is infection, the necrotic tissue has to be debrided and the wound kept clean with saline or antibiotic solution until granulations have formed. Again the granulation area is kept clean with daily dressing changes until healing has occurred. Some surgeons prefer to use split-thickness grafts to hasten the closure, and the result is the abnormal appearing grafts that will be permanent.

I have had patients with large defects that close completely over months without anything but clean dressings on a daily basis, and the scars were only at the transverse suprapubic area. If a large scar results, revision is easier because the resulting scar is smaller than having had skin grafts.

M.A. Shiffman, M.D., J.D.
Tustin, CA, USA
e-mail: shiffmanmdjd@gmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_68, © Springer International Publishing AG
Published Online: 03 May 2018

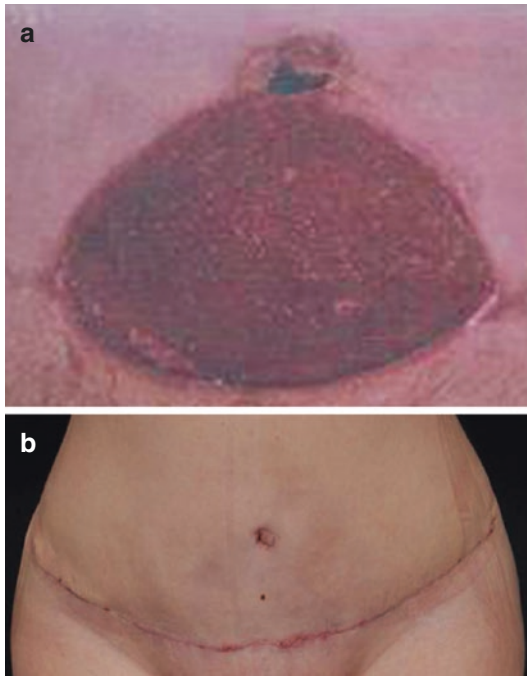


Fig. 2 (**a**) Smoker with necrosis of flap including the area around the umbilicus. (**b**) One and a half years after healing by secondary intention and revision of the transverse scar with several indentations

3 Blepharoplasty

In performing lower eyelid blepharoplasty, occasionally too much skin is removed resulting in ectropion. Some physicians do nothing and wait for healing to improve the problem especially after removal of suture. One can try massage to stretch the skin or may inject steroids into the scar. Still others may perform skin graft that will usually correct the deformity.

Lower lid ectropion is usually visible at the end of surgery and if possible should be corrected at that time. I release all the sutures and allow the wound to open and then allow secondary healing. This usually solves the problem with a resultant thin scar.

4 Breast Augmentation

A so-called double bubble can arise when implants for breast augmentation are placed in the subpectoral position (Fig. 3). This can occur from the attachment of the original inframammary fold

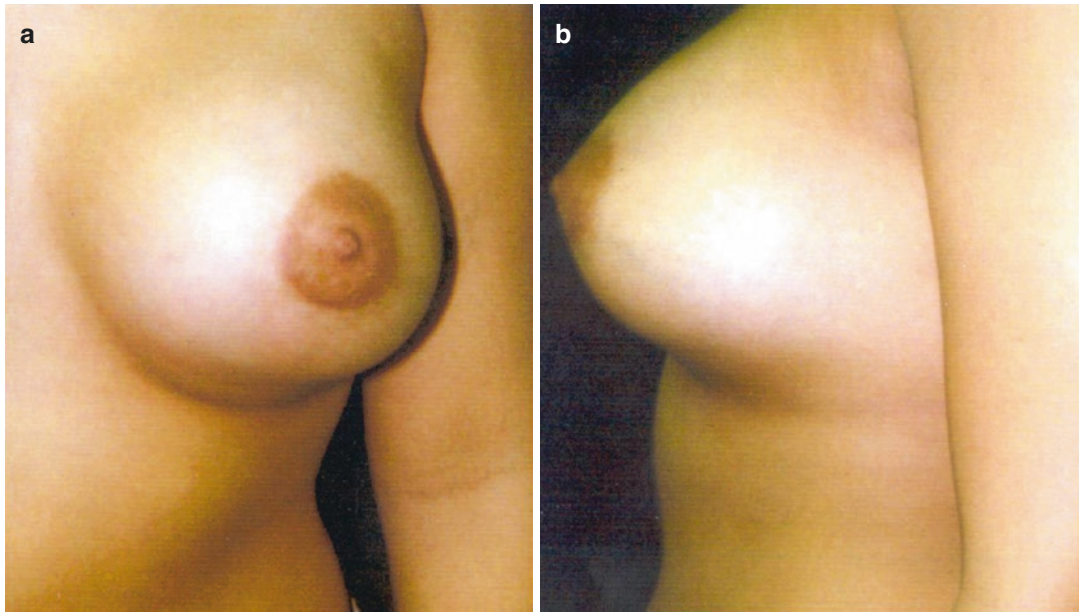


Fig. 3 (**a**) Double bubble. (**b**) One month after hand compression

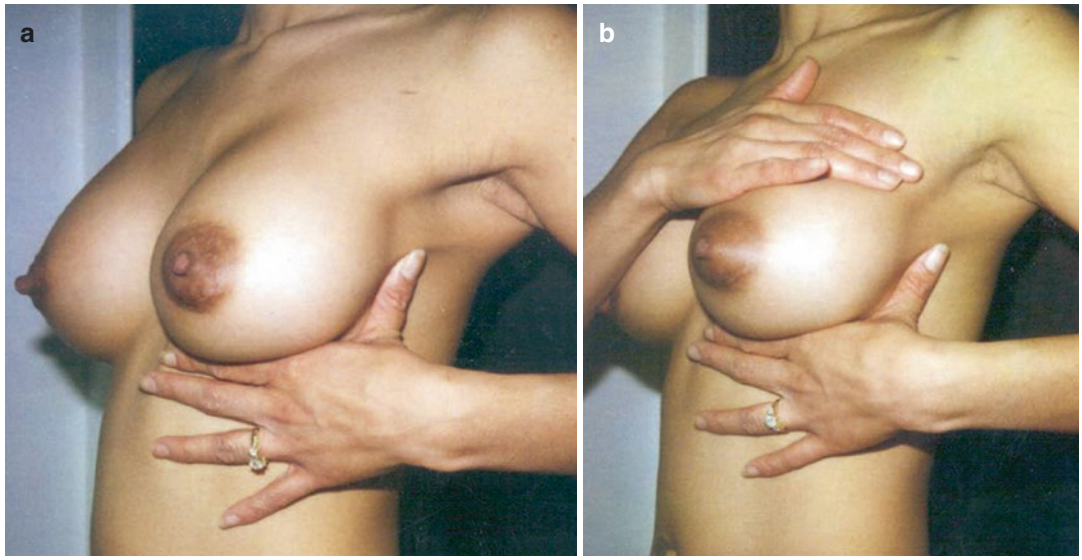


Fig. 4 (**a**) Placing hand under the breast to support the inframammary fold. (**b**) Placing the contralateral hand on the top of the breast and implant for compression

with its subdermal fibrosis at that fold to the underlying fascia. Failure to adequately transect the fibrotic area and stretch the fold can result in the "double bubble" effect. Downward compression of the implant with the contralateral hand and the other hand compressing the bottom of the inframammary fold to prevent downward movement of the implant will solve the problem if done five to ten times a day for several months (Fig. 4). If the patient is dissatisfied, placing the implant in a subglandular position will solve the problem. Some surgeons have suggested to patients that a piece of Gore-Tex will block the scar from recurring. The author prefers not to use more foreign bodies in a wound than are necessary.

5 Facelift

Necrosis of the facelift flap can occur if the flap is too thin and pulled too tight in closure or the patient is a smoker. The wound will heal quite well by leaving the eschar until it sloughs. The final scar will be along the facelift incision near the ear if the flap is not debrided and no skin grafts are applied. Some surgeons may use split-thickness skin grafts to close the defect, but this leaves a large permanent scar on the face.

In one patient who had a large necrosis of the flap, the surgeon, who was out of town, referred the patient to a burn specialist. This specialist treated the flap by resecting the eschar and used a graft from the center of the scalp. He had taken many photographs of the procedure that were surprisingly vivid of large wounds of the face and scalp. When a lawsuit was initiated, settlement was made for a large amount because of the probable emotional impact the photos would make to a jury.

6 Nose

The nasal cartilages are soft and malleable. Therefore, when removing lesions of the nose over the cartilages, care must be taken not to have any tension in the closure. Skin grafts should be made slightly larger than the defect to prevent contraction that will cause deformation by buckling of the cartilages.

A case of removal of a basal cell carcinoma with skin graft coverage on the dome of the nose was complicated by incomplete removal of the cancer. The pathologist suggested re-excision of the residual tumor. The skin (2 mm) around the graft was removed and the defect sutures closed. This resulted in buckling of the underlying cartilage (Fig. 5). Another case had resection of a basal cell carcinoma over the right lateral cartilage. A composite graft after resection was placed but ultimately failed. The pathologist said there was residual carcinoma (the author did not think there was residual because the pathologist was not informed that the two portions of the cancer were actually one circular excision but not properly marked by the nurse after surgery). The patient had a dermatologic surgeon perform Mohs surgery and no cancer was found. The wound was allowed to heal by secondary intention and is now virtually invisible (Fig. 6).

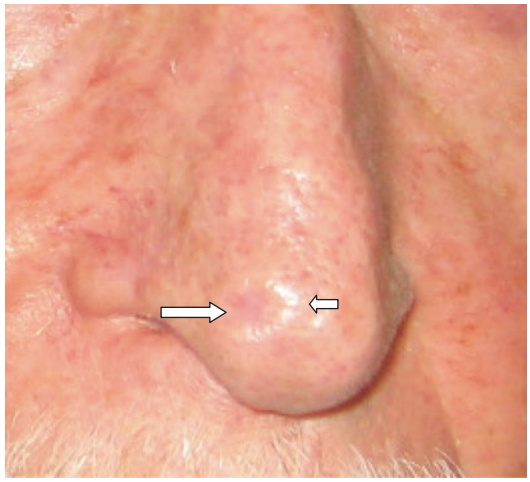


Fig. 5 Buckling of the dome cartilage because of tension. Small arrow shows protruding cartilage and long arrow shows graft with depression

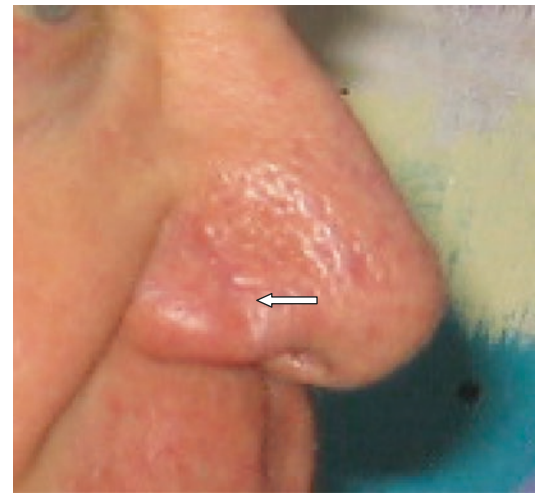


Fig. 6 Virtually invisible scarring after open wound allowed to close by secondary intention over the right lateral cartilage. Arrow shows area of scar

Reconstructive Surgery Following Bisphosphonate-Related Osteonecrosis of the Jaws: Evolving Concepts

Giuseppe Spinelli, Francesco Arcuri, Domenico Valente, Mirco Raffaini, and Tommaso Agostini

1 Introduction

Bisphosphonates are synthetic analogues of the endogenous substance pyrophosphate (a normal constituent of the bone matrix), which inhibit bone resorption and thus have a hypocalcemic effect [1–3]. Bisphosphonates are a relatively novel class of agents that have been increasingly recommended for use in patients suffering osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, osteolytic bone metastases, and osteolytic lesions of multiple myeloma [1–12]. Several medicines are available in the United States with different indications, dosage, administration, and potency (Table 1). Despite the benefits related to their use, osteonecrosis of the jaws represents a complication in a subset of patients receiving these treatments, especially when administered intravenously and following dentoalveolar surgery [8–22]. In this condition, the affected bones become friable, nonviable, and eventually exposed [22–37]. The oral complications can have negative impact on quality of life by affecting eating, speaking, and maintenance of oral hygiene [18]. The first complications were described in 2003, few years later their approval, and nowadays, although more than 950 articles have been published, pathophysiology remains to be well elucidated [23]. In 2003, Marx described 36 cases of exposed necrotic bone in patients suffering tumors who had been treated with intravenous bisphosphonates, and in 2004, Ruggiero reported further 63 cases [23, 24, 38, 39]. Several cells are implicated in bone metabolism including osteoblasts, osteoclasts, and osteocytes, and at this time osteoclasts represent the main cellular target; specifically bisphosphonates provide downregulation of osteoclasts thus repressing bone remodeling, but their effects on osteocytes remain controversial [12–24]. It is accepted that osteoblasts activity remains unalterated. The basic premise of this hypothesis is that the jaw has a high remodeling rate and bisphosphonates suppress remodeling [40–45]. It is also clear that remodeling within the intracortical envelope is considerably higher in the jaw compared with other skeletal sites. As a consequence the bisphosphonate-related osteonecrosis (BRON) follows the idea that since remodeling is higher in the jaw and bisphosphonates suppress remodeling, then this plays a role in the pathophysiology of osteonecrosis [45–50]. Intravenous bisphosphonate treatment seems to pose a greater risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ) than oral administration, though oral treatment longer than 3 years may increase the risk [50–53]. Since dentoalveolar

G. Spinelli · F. Arcuri · D. Valente · M. Raffaini
T. Agostini (✉)
Department of Maxillo-Facial Surgery, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
e-mail: tommasoagostini@ymail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_70, © Springer International Publishing AG
Published Online: 07 June 2018

Table 1 Medicines available in the United States with different indications, dosage, administration, and potency

Active ingredient (Drug's name)	Indication to use	Nitrogen	Administration	Dose	Relative potency
Etidronate (Didronel)	Paget's Disease	No	Oral	300–750 mg daily for 6 months	1
Tiludronate (Skelid)	Paget's Disease	No	Oral	400 mg daily for 3 months	50
Alendronate (Fosamax)	Osteoporosis	Yes	Oral	10 mg/day 70 mg/week	1.000
Risedronate (Actonel)	Osteoporosis	Yes	Oral	5 mg/day 35 mg/week	1.000
Ibandronate (Boniva)	Osteoporosis	Yes	Oral	2.5 mg/day 150 mg/month	1.000
			Intravenous	3 mg every 3 months	
Pamidronate (Aredia)	Bone metastasis	Yes	Intravenous	90 mg/3 weeks	1.000–5.000
Zoledronate					10.000
(Zometa)	Bone Metastasis	Yes	Intravenous	4 mg/3 weeks	
(Reclast)	Osteoporosis	Yes	Intravenous	5 mg/year	

surgery is a precipitating factor, preventive measures include maintaining good oral hygiene and undertaking any necessary dental treatment before beginning a course of intravenous bisphosphonate treatment [30–35]. Some clinical guidelines recommend that people at risk of BRONJ should take a 3-month break from oral bisphosphonates before and after dental treatment [37–39]. Greater drug strength, longer duration of use, older age, and a history of inflammatory dental disease are associated with a higher risk of BRONJ. The true incidence of BRONJ is unknown. Reported rates range from 0.028% to 18.6% depending on indication for treatment, study population, and sample size [53]. Osteonecrosis is found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as lingual and palatal tori, bony exostoses, and the mylohyoid ridge [1–7]. The following factors are thought to be risk factors for BRONJ: corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs [53].

2 Diagnostic Criteria

According to the American Association of Oral and Maxillofacial Surgeons Position Paper, patients can be considered suffering BRONJ if all the following three characteristics are present at the same time:

1. Current or previous treatment with bisphosphonates
2. Exposed bone in the maxillofacial area persisting for more than 8 weeks
3. No history of radiotherapy to the jaws [1]

Differential diagnosis remains the main topic in order to identify the proper treatment, and in particular the following conditions must be excluded: alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders [1, 53]. BRONJ may be asymptomatic or present with pain, swelling, loose teeth, and altered sensation [1]. Other medications (denosumab, bevacizumab, cabozantinib, sunitinib) have also been associated with jaw osteonecrosis, the condition then being called medication-related osteonecrosis of the jaw (MRONJ) [53]. Beyond clinical assessment according to the above criteria, radiographic exams are necessary to stage the disease, and in particular orthopantomography, CT scans of the maxillofacial skeleton with contrast medium and magnetic resonance imaging are recommended [1–11].

3 Osteonecrosis Management

There is currently no "gold standard" of treatment for BRONJ [1, 53]. Interventions used to treat this complication are diverse, controversial, and largely empirical. Three broad categories of interventions have been described: classical

"wound-healing" conservative treatment, diverse surgical techniques, and different "add-on" treatments [1, 53]. These three approaches are often used in combination, either at the same time or in succession, and are elucidated in Table 2. Strategies for the management of patients suffering BRON have been defined by the American Association of Oral and Maxillofacial Surgeons in the Position Paper on Bisphosphonates-Related Osteonecrosis of the Jaw and approved by the Board of Trustees in September 2006 [1]. The position paper was developed by a task force appointed by the Board and composed of clinicians with extensive experience in treating these patients and basic science researchers. The knowledge base and experience in addressing BRON have expanded, thus requiring modifications and refinements to the original paper [1–4]. The task force was then called again in 2008 to revise the recommendations previously published in 2006. This update contains revisions to the diagnosis and staging and management strategies and highlights the status of basic science research (Table 3). Despite this, these recommendations are not widely followed, and several therapeutic strategies have been recommended in the literature according to the severity of this complication, ranging from strictly conservative to aggressive surgical approaches [53]. At-risk patients and asymptomatic patients have been identified including proper prophylactic measurements as listed in Tables 4 and 5, respectively. The treatment of BRONJ is still under debate, and most reports show different outcomes. For this reason, a systematic review of the available literature was made in order to assess which treatment has a higher success rate in patients diagnosed with BRONJ by Comas-Calonge and co-workers [53]. In this research the author considered the treatment successful when the patient improved the stage of the disease or when there was absence of bone exposure with proper healing and the patient remained asymptomatic without any clinical signs of infection. They referred several limitations including the lack of standardized success criteria and treatment protocols, the use of different surgical approach (sequestrectomy vs. bone resection), and the association of several antibiotics and antiseptics. Nonetheless the success rates of BRONJ surgical treatment vary between 58% and 100%. The main advantage of sequestrectomy is an expected superior healing process since unaffected periosteum is preserved. Tension-free closure of the wound and an adequate bone resection are key factors for the treatment prognosis [53]. Although it is extremely difficult to quantify the amount of bone that should be removed, bleeding is considered a sign of healthy bone [45–53]. Some authors proposed a more aggressive management, based in bone resections, to treat BRONJ patients, in the idea that, regardless of the stage of the disease, areas of the necrotic bone that are a constant source of soft tissue irritation should be removed in order to allow a proper healing [50–53].

Table 2 Three approaches often used in combination, either at the same time or in succession

Conservative treatments	Surgical treatments	Adjuvant non-surgical treatments
Disinfectant mouth rinses (saline, chlorhexidine, chlorine, peroxide)	Surgical debridement, sequestrum removal, surgical sinus drainage procedures (antrostomy)	Hyperbaric oxygen therapy
Antibiotic therapy (local, systemic, or both)	Extraction of teeth within osteonecrotic bone, management of implants	Pentoxifylline and tocopherol (vitamin E)
Antifungal therapy	Bone resection	Ozone therapy
	Surgical wound closure, reconstructive surgery, grafts	Low level laser therapy (LLLT) for biostimulation, pain relief anti-inflammatory treatment (erbium-doped yttrium aluminium garnet (Er:YAG); neodymium-doped yttrium aluminium garnet (Nd:YAG), natrium-doped yttrium aluminium perovskite (Nd:YAP), etc.
	Laser-assisted surgery	Platelet-rich plasma
	Fluorescence-assisted surgery	Parathyroid hormone and teriparatide
		Bone morphogenetic protein (BMP)

Table 3 Revisions to the diagnosis and staging and management strategies and highlights the status of basic science research

Bron stage[a]	Signs and symptoms	Management[b,c,d]
At risk	No apparent necrotic bone in patterns who have been treated with either oral or IV bisphosphonates	• No treatment indicated
		• Patient education
0	No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	• Systemic management, including the use of pain medication and antibiotics
1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse
		• Clinical follow-up on a quarterly basis
		• Patient education and review of indications for continued bisphosphonate therapy
2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	• Symptomatic treatment with oral antibiotics
		• Oral antibacterial mouth rinse
		• Pain control
		• Superficial debridement to relieve soft tissue irritation
3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxilliary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	• Antibacterial mouth rinse
		• Antibiotic therapy and pain control
		• Surgical debridement/resection for longer term palliation of infection and pain

[a]Exposed bone in the maxillofacial region without resolution in 8–12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws

[b]Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process

[c]Discontinuation of the IV bisphosphonates shows no short-term benefit. However, if systemic conditions permit, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient

[d]Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient

Table 4 At-risk patients and management

	Risk stratification	Management
1	Patients who have taken oral bisphosphonates for less than three years and have no clinical risk factors (corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs)	• No alteration or delay in the planned surgery is necessary
		• If implants are placed, informed consent should be provided related to possible implant failure and possible osteonecrosis of the jaws if the patient continues taking oral bisphosphonates
		• It is advisable to contact the practitioner who initially prescribed the oral bisphosphonate and suggest monitoring such patients and considering either alternate dosing of the bisphosphonate, drug holidays, or an alterative to bisphosphonate therapy
		• Implant patients should be on a regular recall schedule
2	Patients who have taken oral bisphosphonates for less than three years and have also taken corticosteroids concomitantly or have any of the other risk factors listed above	• The prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery (if systemic conditions permit)
		• The bisphosphonate should not be restarted until osseous healing has occurred
3	Patients who have taken oral bisphosphonates for more than three years with or without concomitant steroid medication or other risk factors	• The prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery, if systemic conditions permit
		• The bisphosphonate should not be restarted until osseous healing has occurred
4	Patients with an established diagnosis of Bisphosphonate-Related Osteonecrosis of the Jaws (BRON)	• Treatment objectives are to eliminate pain, control infection of the hard and soft tissues, and minimize the progression or occurrence of bone necrosis
		• Surgical treatment is less predictable than with the established surgical algorithms for osteomyelitis or osteoradionecrosis; therefore, surgery should be delayed if possible
		• Areas of necrotic bone that are a constant source of irritation should be removed or recontoured without exposure of additional bone
		• Loose segments of bony sequestrum should be removed with exposed/necrotic bone in patients with pain
		• Patients should avoid elective dentoalveolar surgical procedures
		• The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process

Table 5 Asymptomatic patients and management

Type	Asymptomatic patient's status	Management
A	Patients about to initiate intravenous bisphosphonate therapy	• If systemic conditions permit, initiation of IV bisphosphonate therapy should be delayed until dental health is optimized
		• Non-restorable teeth and those with a poor prognosis should be extracted. Other elective dentoalveolar surgery necessary should be done at this time
		• Patients with full or partial dentures should be examined for areas of mucosal trauma (lingual flange, palatal or mandibular tori, or other exostoses). These areas should be treated if necessary prior to bisphosphonate therapy
		• If systemic conditions permit, bisphosphonate therapy should be delayed until the extraction site has mucosalized (14–21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control, and conservative restorative dentistry on an ongoing basis are necessary to maintain functionally sound teeth
B	Asymptomatic patients receiving intravenous bisphosphonate treatment	• Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by crown removal and endodontic treatment of the remaining roots
		• Placement of dental implants should be avoided in patients exposed to the more potent IV bisphosphonates (zoledronate "Zometa" and pamidronate "Aredia" on a frequent dosing schedule [4–12 times per year])
C	Asymptomatic patients receiving oral bisphosphonate therapy	• Appear to be at risk of developing Bisphosphonate-Related Osteonecrosis of the Jaws (BRON) to a much lesser degree than those people treated with IV bisphosphonates
		• BRON can develop spontaneously or after minor trauma
		• These patients seem to have less severe manifestations of necrosis, and respond more readily to stage specific treatment regimens
		• Elective dentoalveolar surgery does not seem to be contraindicated in this group
		• Patients should be informed of the small risk of compromised bone healing. The risk of BRON may be associated with increased duration of treatment with oral bisphosphonates, i.e., greater than three years, and other risk factors including concomitant use of corticosteroids, chemotherapy, diabetes, smoking, excessive alcohol use, and poor oral hygiene

4 Reconstructive Microsurgery

For the management of exposed necrotic bone, additional surgical debridement or sequestrectomy with primary mucosal closure seems to be effective in most cases [3–23]. If there are recurrences at the conservative treatment, then osteotomies should be considered as it seems to be more successful than wound debridement alone [33–43]. The reconstruction of subtotal mandibulectomy defects requires the vascularized bone to promote healing and provide adequate soft tissue support and oral competence [34]. Patients with reasonable life expectancy with regard to their malignant disease should be considered for microvascular tissue transfer after aggressive resection of the affected region [5]. The effect of the transferred flap with a new input of blood supply might be one of the reasons for the uneventful postoperative in all patients; moreover the cutaneous component provides additional health tissue useful to achieve successful reconstruction by establishing a tension-free closure of the intraoral defect [52]. Finally it gives also the opportunity of oral prosthetic rehabilitation using dental implants, as described by Ferrari et al. (2008) [15]. After an observation period of 12 months from microsurgical reconstruction of

the jaws, high survival rates can be expected with few recurrences of osteonecrosis [53]. This, in turn, means that vascularized fibula flap has been a well-accepted method to reconstruction, and despite the limited number of publications, this treatment appears to be practicable in BRONJ-resected patients and doesn't seem to influence the natural course of the primary disease [45–53].

According to the best of our knowledge, there have been 37 cases of stage III BRONJ treated with free-flap reconstruction in the published literature (Table 6). Radiographic imaging with CT, cone beam, and/or orthopantomogram was obtained during follow-up in all patients. Flap failure occurred in two cases from the fibula, and a second flap was constructed from additional tissue during a second procedure [44, 50]. Fistulas formed in four cases making it the most common complication observed across studies [44]; BRONJ recurred in the contralateral jaw in two cases [12, 30]. Nonunion as reported by Nocini et al. [30] can occur because the resected margins were not free of disease; this finding was not

Table 6 37 cases of stage III BRONJ treated with free-flap reconstruction in the published literature

Reference	Patients (n), years	Medical history	Pharmacological therapy	Bone involvement, reconstruction	Follow-up	Postoperative complications
Engroff and Kim (2007) [12]	2, 56.6 y	2 Breast cancer	1 Pz. IV Zoledronate 1 Pz. OS Pamidronate	Partially, FFF	12 months	– Postoperative hematoma – Contralateral BRONJ, managed conservatively
Ferrari et al. (2008) [15]	1, 66 y	1 Multiple myeloma	IV Pamidronate and Zoledronate	Totally, FFF	12 months	No
Mucke et al. (2009) [29]	1, 60 y	1 Multiple myeloma	IV Zoledronate	Partially, FFOCF	12 months	No
Nocini et al. (2009) [30]	7, 61 y	5 Breast cancer 1 1 Prostate cancer 1 1 Multiple myeloma	5 Pz. IV Pamidronate and Zoledronate; 2 Pz. IV Zoledronate	2 Partially, FFF 6 Totally, FFOCF	6–36 months	– 1 Shortterm recurrence at resection margin, managed conservatively
Seth et al. (2010) [44]	11, 61.3 y	5 Breast cancer 2 Prostate cancer 2 Multiple myeloma 2 osteoporosis	6 Pz. IV Zoledronate 2 Pz. OS Alendronate 2 Pz. OS Ibandronate 1 Pz. IV Etidronate	11 Partially, FFOCF	2 weeks to 31 months	4 Fistula 1 Infection 1 Flap loss
Bedogni et al. (2011) [50]	3, NA	NA	NA	Partially, FFF	NA	1 Flap loss
Ghazali et al. (2013) [49]	1,82 y	Osteoporosis	OS Alendronate	Partially, FFF	NA	No
Colletti et al. (2014) [48]	2, NA	NA	NA	Partially, FFF	NA	NA
Spinelli et al. (2014) [51]	8, 64.7 y	3 Breast cancer 1 Prostate cancer 4 Multiple myeloma	5 Pz. IV Pamidronate 6 Pz. IV Zoledronate	3 Partially, FFF 5 Totally, FFOCF	29 months	No
Neto et al. (2016) [53]	1, 54 y	Lung cancer	IV Zoledronate	Partially, FFF	48 months	No

evident during surgery and was found during histological evaluation of the resected tissue.

Some authors have stated that "aggressive" surgery, in this case resection and reconstruction with a free flap, is inappropriate because of the diminished life expectancy, poor general condition, and concomitant medications, such as steroids or chemotherapy, that can interfere with the postoperative result of patients with advanced BRONJ and the overall success of conservative measures and minimal surgical procedures [53]. Diminished life expectancy is certainly a theoretical concern given that most people who received intravenous bisphosphonates in our and others' reviews had metastatic cancer to the bone or malignancy-related hypercalcemia [52, 53].

The main concerns, just theoretical, regard the possible transfer of sicked tissue into the oral cavity in patients suffering disseminated disease, but this is not been described yet. Indeed, one patient in the Seth et al. series died 8 weeks after reconstruction surgery in consequence of cancer-related complications [50–53]. On the other hand, most patients among published reports survived at least 12 months and many for at least several years after surgery suggesting that health status alone should not be an absolute contraindication to this procedure.

5 Outcome Measurements

Primary outcomes of proper management include healing of the osteonecrosis as indicated by one or more of the six indicators listed in Table 7; secondary outcomes are important indicators and listed in Table VII. Patients need close follow-up every 3 months for monitoring intraoral or extraoral symptoms along with radiographic examination (Table 8).

Table 7 Primary and secondary outcomes

	Primary outcome	Secondary outcome
1	Improvement in the clinical grade of the lesions according to the American Academy of Oral and Maxillofacial Surgeons staging or BRONJ	Mortality rate and cause of death.
2	Wound healing (yes or no)	Pam: presence and level of pain, use of analgesia during the first two weeks after intervention, use of analgesics, duration of pain, per cent pain relief.
3	Improvement in exposed bone quality (judged clinically on inspection of the mouth by a dentist or a dental/oral surgeon as exposed bone that is less friable, less devitalised, less necrotic).	Improvement of pre-existing accompanying symptoms other than pain, such as mucosal oedema, super-infection. purulent discharges, fistulae to skin, or inflammatory reactions including fever.
4	Halt in bone disease progression as per imaging techniques such as: X-ray examination (improvement of sclerotic changes, mottling and bone fragmentation, improvement of formed sequestrum or persistent extraction sockets), computed tomography (CT) scan, magnetic resonance imaging (MRI) (surface area of the bone disease, localisation, evidence of bone marrow disease), positron emission tomography (PET)/CT imaging (decreased abnormal focal uptake)	Improvement in nutritional intake or in the ability of eating different types of food (normal diet, blended or pureed foods, liquid diets).
5	Halt in bone disease progression as visualised with doxycycline viable bone fluorescence (surface area of the bone disease, localisation, evidence of bone marrow disease)	Quality of life
6	Healing of sinus tract or deep periodontal pockets.	Health economic measures, such as effect on healthcare consumption, number or length of hospitalisations, health resource use.

Table 8 Symptoms of biphosphonate-related osteonecrosis

Intraoral	Extraoral
Pain, dental mobility, cutaneous fistula, halitosis, gingival recession, pathological fractures, oro-antral communication, dehiscence, phlogoses, decubitus, abscess	Abscess, edema, erythema, retraction, cervical mass, trismus, limited/extended sinusitis

6 Proposed Flowchart

Our flowchart to surgical management differs according to the mandible and maxilla (Fig. 1). For bisphosphonate-related osteonecrosis stage 0 and stage 1, we propose curettage, sequestrectomy, and marginal mandibulectomy according to the extension of bone resection, and this is applied both to mandible and maxilla. Stage 2 and stage 3 are managed according to site (maxillary/mandible) and patient's performance status; mandible bisphosphonate-related osteonecrosis stage 2 and stage 3 affecting patients with poor performance status are managed with segmental mandibulectomy without reconstruction (Figs. 2, 3, and 4); in case of good performance status, reconstruction is performed with free fibula flap for longer defects (Figs. 5, 6, and 7) and with medial femoral condylar flap for small defects (Figs. 7, 8, and 9). Maxillary stage 2 and

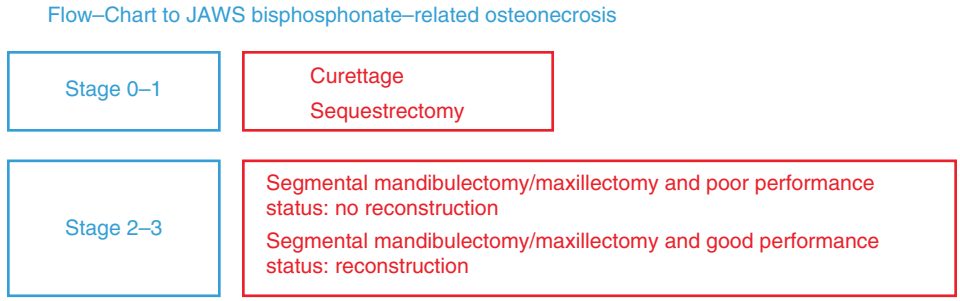


Fig. 1 Flowchart to bisphosphonate-related osteonecrosis

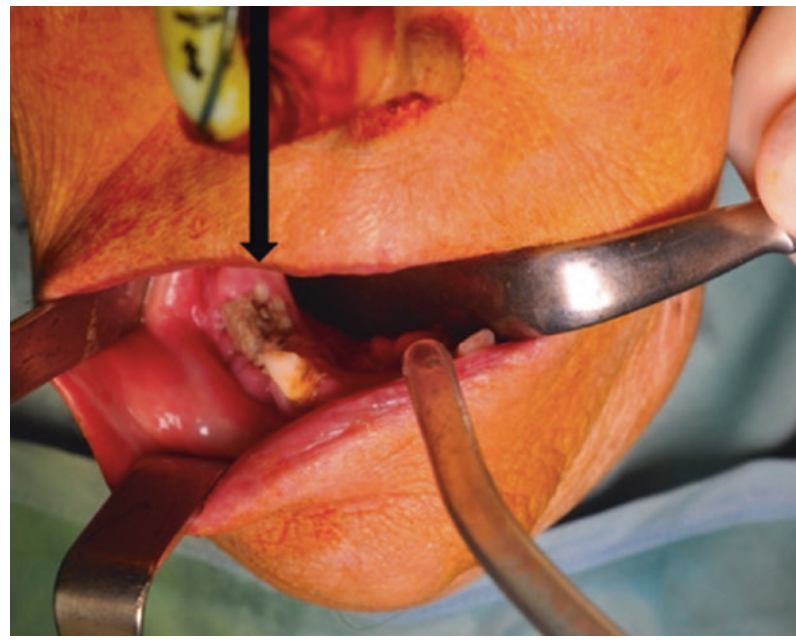


Fig. 2 A 78-year-old patient suffering breast cancer and right mandibular osteonecrosis (stage 2)

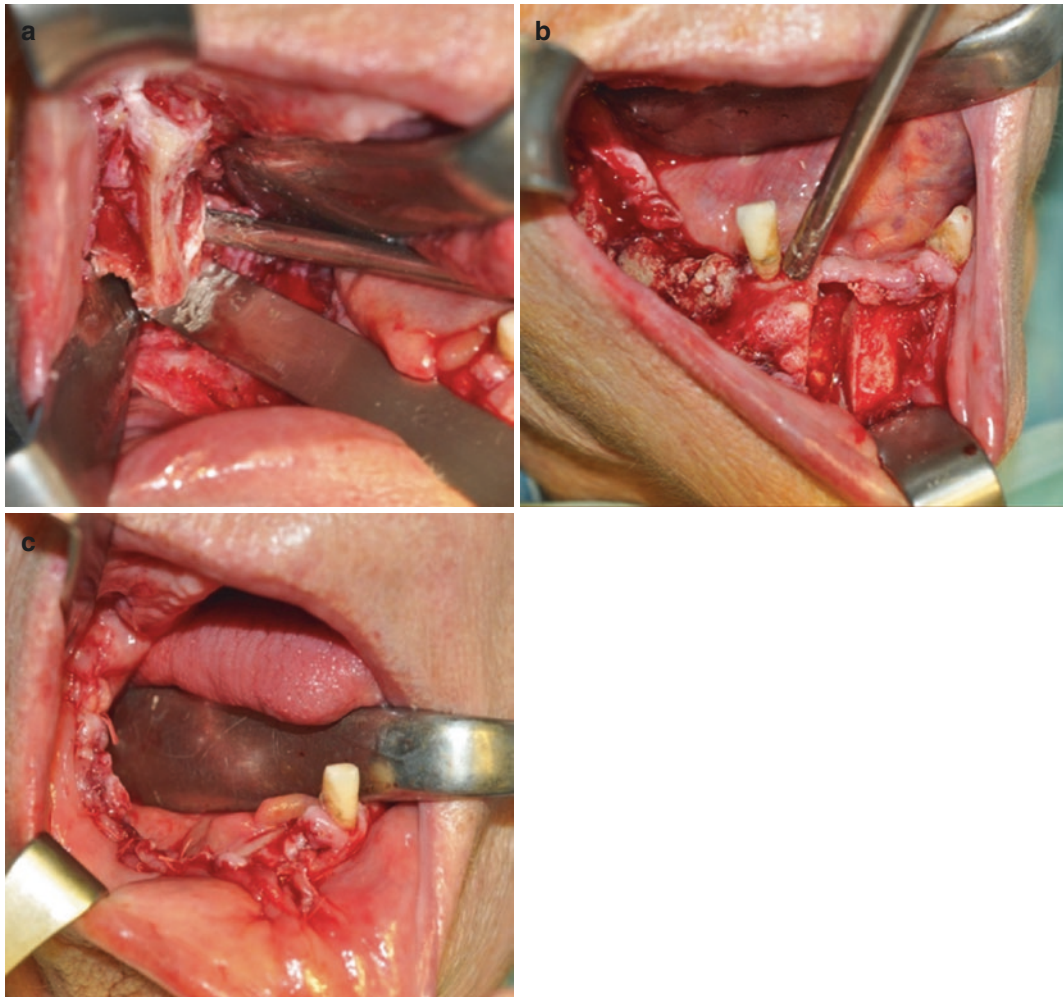


Fig. 3 (**a**–**c**) Due to poor performance status, she underwent right segmental mandibulectomy without reconstruction

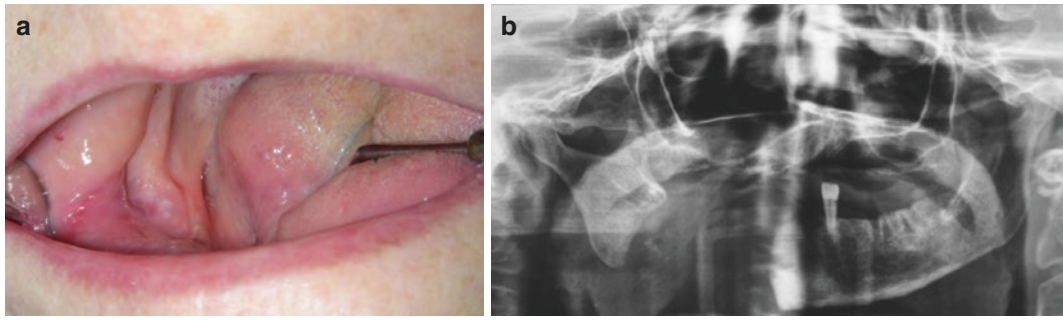


Fig. 4 (**a**, **b**) Postoperative control 6 months later showing good clinical and angiographic control

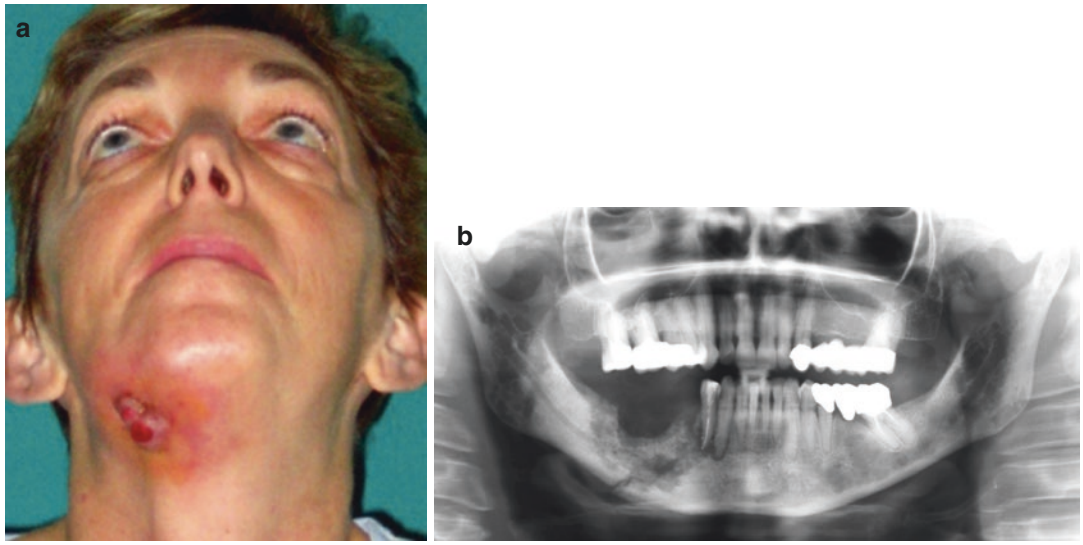


Fig. 5 (**a**, **b**) A 68-year-old patient suffering breast cancer and right mandibular osteonecrosis with cutaneous fistula (stage 3)

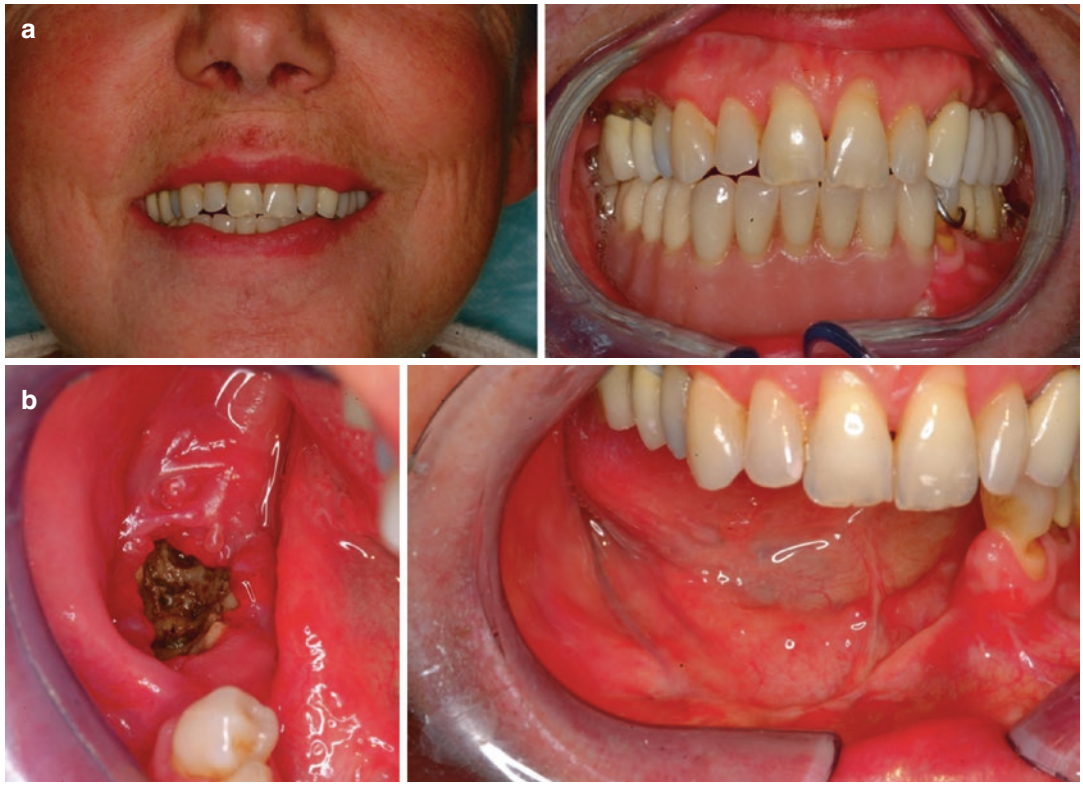


Fig. 6 (**a**, **b**) On the left the preoperative status and on the right the postoperative outcome after reconstruction. Due to good performance status, she underwent reconstruction with osteocutaneous fibula flap; the skin was used to restore the cervical skin

stage 3 are managed with hemimaxillectomy and Bichat fat flap/temporalis muscle flap in case of good performance status (Figs. 9 and 10).

7 Future Research

The National Institute of Health has provided fundings to researchers in order to elucidate the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw. The researchers focused on different aspects of this entity including but not limited to (a) the effect of bisphosphonates on intraoral soft tissue healing, (b) alveolar bone hemostasis, (c) antiangiogenic properties of bisphosphonate, (d) pharmacogenetic research, and (e) risk assessment tools. Novel strategies to improve prevention and treatment of BRON need to be developed and discussed in a proper manner. In the meantime, the 2014 update favors the term medication-related osteonecrosis of the jaw instead of BRONJ to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies. Denosumab is an antiresorptive agent that exists as a fully humanized antibody against receptor activator of nuclear factor kappa B ligand and inhibits osteoclast function and associated bone resorption. It is administered subcutaneously every 6 months to decrease the risk of vertebral, nonvertebral, and hip fractures in osteoporotic patients and administered monthly in metastatic bone disease from solid tumors. Denosumab is superior to zoledronic acid in preventing complications for patients with bone metastases. However, further studies are still needed to assess longer-term safety and efficacy of denosumab [53].

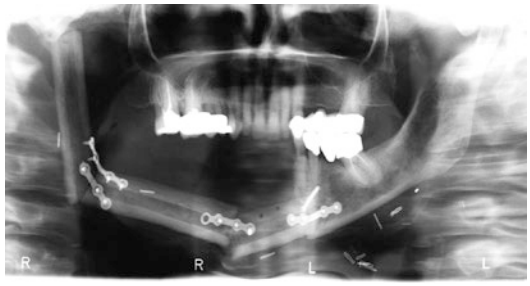


Fig. 7 Postoperative radiographic control a three months of the case presented in Figs. 5 and 6

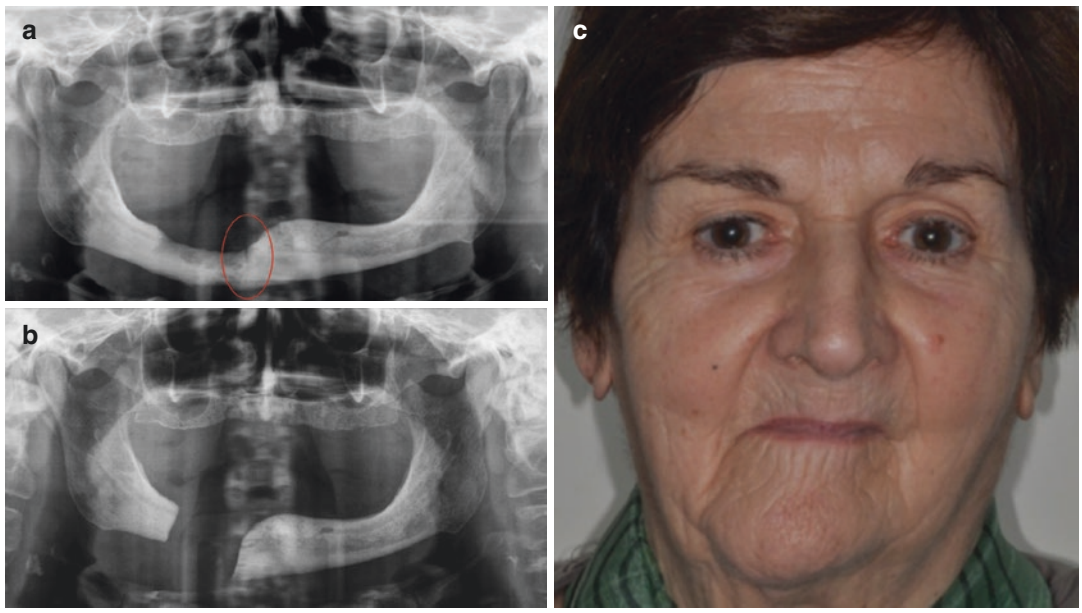


Fig. 8 (**a**–**c**) Preoperative radiographs showing pathological fracture on the right mandible (stage 3) of a 73-year-old patient suffering osteoporosis. She underwent segmental mandibulectomy without immediate reconstruction

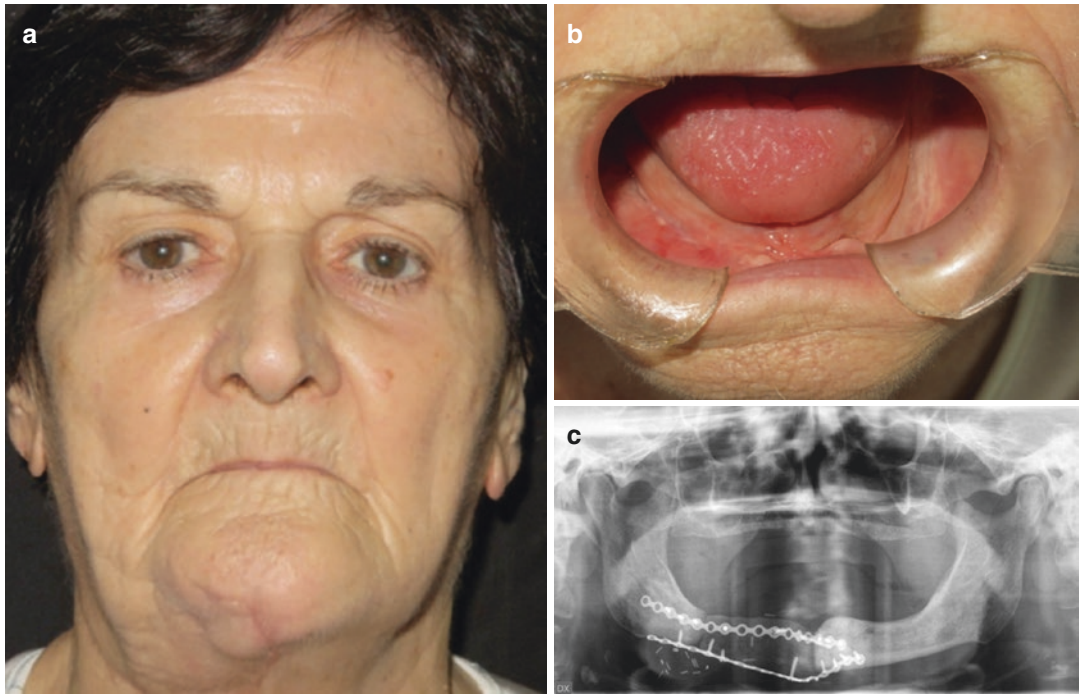


Fig. 9 (**a**–**c**) Postoperative outcome 6 months later showing symmetry, local disease control into the oral cavity, and good reconstruction outcome using a medial femoral condylar flap

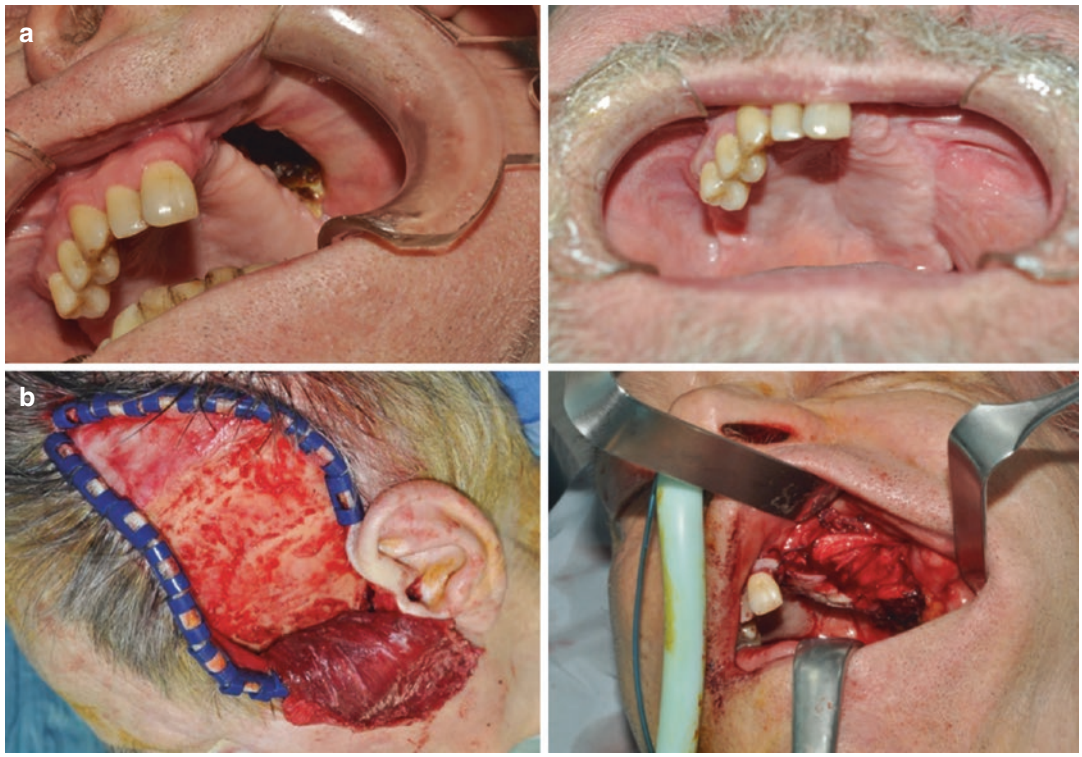


Fig. 10 (**a**, **b**) A 71-year-old patient suffering prostate cancer and left maxillary osteonecrosis with good reconstructive outcome after 3 months. He underwent reconstruction with a temporalis muscle flap due to good performance status

References

1. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. America Association of Oral and Maxillofacial Surgeons (2007) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65:369–376
2. Agrillo A, Ungari C, Filiaci F, Priore P, Iannetti G (2007) Ozone therapy in the treatment of avascular bisphosphonate-related jaw osteonecrosis. J Craniofac Surg 18(5):1071
3. Allen MR, Burr DB (2008) Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. J Oral Maxillofac Surg 66:987–994
4. Allen MR, Follet H, Khurana M, Sato M, Burr DB (2006) Antiremodeling agents influence osteoblast activity differently in modeling and remodelling sites of canine rib. Calcif Tissue Int 79:255–261
5. Allen MR, Iwata K, Phipps R, Burr DB (2006) Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. Bone 39:872–879
6. Anthony JP, Foster RD (1996) Mandibular reconstruction with the fibula osteocutaneous free flap. Oper Tech Plast Reconstr Surg 3(4):233–240
7. Arantes HP, Silva AG, Lazaretti-Castro M (2010) Bisphosphonates in the treatment of metabolic bone diseases. Arq Bras Endocrinol Metab 54:206–212
8. Assael LA (2007) New foundations in understanding osteonecrosis of the jaws. J Oral Maxillofac Surg 62:125–126
9. Boyce RW, Paddock CL, Gleason JR, Sletsema WK, Eriksen EF (1995) The effects of risedronate on canine cancellous bone remodeling: three-dimensional kinetic reconstruction of the remodeling site. J Bone Miner Res 10:211–221
10. Buchbinder D, St. Hilaire H (2006) The use of free tissue transfer in advanced osteoradionecrosis of the mandible. J Oral Maxillofac Surg 64:961–964
11. Duncan MJ, Manktelow RT, Zuker RM, Rosen IB (1985) Mandibular reconstruction in the radiated patient: the role of osteocutaneous free tissue transfers. Plast Reconstr Surg 76:829–840
12. Engroff LS, Kim DD (2007) Treating bisphosphonate osteonecrosis of the jaws: is there a role for resection and vascularized reconstruction? J Oral Maxillofac Surg 65:2374–2385
13. Eriksen EF, Melsen F, Sod E, Barton I, Chines A (2002) Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone 31:620–625
14. Farrugia MC, Summerlin DJ, Krowiak E, Huntley T, Freeman S, Borrowdale R, Tomich C (2006) Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscope 116:115–120
15. Ferrari S, Bianchi B, Savi A, Poli T, Multinu A, Balestreri A (2008) Fibula free flap with endosseous implants for reconstructing a resected mandible in bisphosphonate osteonecrosis. J Oral Maxillofac Surg 66:999–1003
16. Gliklich R, Wilson J (2009) Epidemiology of bisphosphonate-related osteonecrosis of the jaws: the utility of a national registry. J Oral Maxillofac Surg 67(Sp. Iss. 5):71–74
17. Goodacre TE, Walker CJ, Jawad AS, Jackson AM, Brough MD (1990) Donor site morbidity following osteocutaneous free fibula transfer. Br J Plast Surg 43:410–412
18. Greenberg MS (2004) Intravenous bisphosphonates and osteonecrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 98:259–260
19. Griz L, Caldas G, Bandeira C, Assunção V, Bandeira F (2006) Paget's disease of bone. Arq Bras Endocrinol Metabol 50:814–822
20. Hsu CC, Chuang YW, Lin CY, Huang YF (2006) Solitary fibular metastasis from lung cancer mimicking stress fracture. Clin Nucl Med 31:269–271
21. Iwata K, Li J, Follet H, Phipps RJ, Burr DB (2006) Bisphosphonates suppress periosteal osteoblast activity independently of resorption in rat femur and tibia. Bone 39:1053–1058
22. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG et al (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22:1479–1491
23. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61:1115–1117
24. Marx RE, Cillo JE Jr, Ulloa JJ (2007) Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 65:2397–2410
25. Marx RE, Sawatari Y, Fortin M, Broumand V (2005) Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 63:1567–1575
26. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB (2000) Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 15(4):613–620
27. McDonald MM, Dulai S, Godfrey C, Amanat N, Sztynda T, Little DG (2008) Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling. Bone 43:653–662
28. Migliorati CA (2003) Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 21:4253–4254
29. Mücke T, Haarmann S, Wolff KD, Hölzle F (2009) Bisphosphonate related osteonecrosis of the jaws treated by surgical resection and immediate osseous

microvascular reconstruction. J Craniomaxillofac Surg 37:291–297
30. Nocini PF, Saia G, Bettini G, Ragazzo M, Blandamura S, Chiarini L, Bedogni A (2009) Vascularized fibula flap reconstruction of the mandible in bisphosphonate-related osteonecrosis. Eur J Surg Oncol 35:373–379
31. Plotkin LI, Aguirre JI, Kousteni S, Manolagas SC, Bellido T (2005) Bisphosphonates and estrogens inhibit osteocyte apoptosis via distinct molecular mechanisms downstream of extracellular signal-regulated kinase activation. J Biol Chem 280:7317–7325
32. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T (1999) Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest 104:1363–1374
33. Reiriz AB, De Zorzi PM, Lovat CP (2008) Bisphosphonates and osteonecrosis of the jaw: a case report. Clinics (Sao Paulo) 63:281–284
34. Rodan GA, Fleisch HA (1996) Bisphosphonates: mechanisms of action. J Clin Invest 97:2692–2696
35. Rosen HN, Moses AC, Garber J, Iloputaife ID, Ross DS, Lee SL, Greenspan SL (2000) Serum CTX: a new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy. Calcif Tissue Int 66:100–103
36. Rosen HN, Moses AC, Garber J, Ross DS, Lee SL, Greenspan SL (1998) Utility of biochemical markers of bone turnover in the follow-up of patients treated with bisphosphonates. Calcif Tissue Int 63:363–368
37. Rosenberg TJ, Ruggiero S, Mehrotra O, Engroff SL (2003) Osteonecrosis of the jaws associated with the use of bisphosphonates. J Oral Maxillofac Surg 61(Suppl 1):60
38. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B (2009) Task force on bisphosphonate-related osteonecrosis of the jaws, American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update. J Oral Maxillofac Surg 35:119–130
39. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 62:527–534
40. Russell RG, Watts NB, Ebetino FH, Rogers MJ (2008) Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 19:733–759
41. Russell RG, Xia Z, Dunford JE, Oppermann U, Kwaasi A, Hulley PA, Kavanagh KL, Triffitt JT, Lundy MW, Phipps RJ, Barnett BL, Coxon FP, Rogers MJ, Watts NB, Ebetino FH (2007) Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. Ann N Y Acad Sci 1117:209–257
42. Santamaria M Jr, Fracalossi AC, Consolaro MF, Consolaro A (2010) Influence of bisphosphonates on alveolar bone density: a histomorphometric analysis. Braz Oral Res 24:309–315
43. Sarathy AP, Bourgeois SL Jr, Goodell GG (2005) Bisphosphonate-associated osteonecrosis of the jaws and endodontic treatment: two case reports. J Endod 31:759–763
44. Seth R, Futran ND, Alam DS, Knott PD (2010) Outcomes of vascularized bone graft reconstruction of the mandible in bisphosphonate-related osteonecrosis of the jaws. Laryngoscope 120:2165–2171
45. Urken ML (1991) Composite free flaps in oromandibular reconstruction. Review of the literature. Arch Otolaryngol Head Neck Surg 117:724–732
46. Vescovi P, Merigo E, Meleti M, Fornaini C, Nammour S, Manfredi M (2007) Nd:YAG laser biostimulation of bisphosphonate-associated necrosis of the jawbone with and without surgical treatment. Br J Oral Maxillofac Surg 45:628–632
47. Wang J, Goodger NM, Pogrel MA (2003) Osteonecrosis of the jaws associated with cancer chemotherapy. J Oral Maxillofac Surg 61:1104–1107
48. Colletti G, Autelitano L, Rabbiosi D, Biglioli F, Chiapasco M, Mandalà M, Allevi F (2014) Technical refinements in mandibular reconstruction with free fibula flaps: outcome-oriented retrospective review of 99 cases. Acta Otorhinolaryngol Ital 34(5):342–348
49. Ghazali N, Collyer JC, Tighe JV (2013) Hemimandibulectomy and vascularized fibula flap in bisphosphonate-induced mandibular osteonecrosis with polycythaemia rubra vera. Int J Oral Maxillofac Surg 42:120–123
50. Bedogni A, Saia G, Bettini G, Tronchet A, Totola A, Bedogni G, Ferronato G, Nocini PF, Blandamura S (2011) Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. Oral Oncol 47:420–424
51. Spinelli G, Torresetti M, Lazzeri D, Zhang YX, Arcuri F, Agostini T, Grassetti L (2014) Microsurgical reconstruction after bisphosphonate-related osteonecrosis of the jaw: our experience with fibula free flap. J Craniofac Surg 25:788–792
52. Sacco R, Sacco G, Acocella A, Sale S, Sacco N, Baldoni E (2011) A systematic review of microsurgical reconstruction of the jaws using vascularized fibula flap technique in patients with bisphosphonate-related osteonecrosis. J Appl Oral Sci 19:293–300
53. Neto T, Horta R, Balhau R, Coelho L, Silva P, Correia-Sá I, Silva Á (2016) Resection and microvascular reconstruction of bisphosphonate-related osteonecrosis of the jaw: the role of microvascular reconstruction. Head Neck 38(8):1278–1285

Antibiotic Susceptibility of Wound Isolates in Plastic Surgery Patients at a Tertiary Care Centre

Surendra B. Patil and Shree Harsh

1 Introduction

1.1 Background

Till the late eighteenth century, there was no significant work on control of infection [1]. In the nineteenth century, the observations by Ignaz Semmelweis of increased puerperal fever in teaching ward and reduced mortality by a simple practice of washing hands in chlorinated water are amongst the earliest documented evidence on surgical site infection [2]. In the late nineteenth century, Louis Pasteur for his "germ theory", Joseph Lister for his work on carbolic acid and Robert Koch for his work on culture of *Bacillus anthracis* and developing Koch's postulate were of paramount importance [1].

Koch's postulates had four components:

1. The organism should be present in the disease and absent in healthy subjects.
2. The suspected pathogen should be isolated from the diseased host and grown in vitro.
3. Cells from pure culture of suspected organism should cause disease in healthy host.
4. The suspected organism should be reisolated from the newly diseased host and have the same characteristics of the original organism (added by Loeffler) [3]. They hold importance with regard to surgical infections.

Staining of microorganisms started in the latter half of the nineteenth century. Though the principles of infection prevention were established, treatment of infection by antibiotics came in the middle of the century. Prontosil discovered by Gerhard Domagk was amongst the first effective antibacterial. It was an azo derivative. He won the Nobel Prize in Medicine in 1939 for demonstrating its antibacterial effects [4].

Antibiotic era is known by the names of Paul Ehrlich for his discovery of Salvarsan also known as "magic bullet" for syphilis and Sir Alexander Fleming's discovery of penicillin in 1928 [5]. He won the Nobel Prize in Physiology/Medicine in 1945 [6]. In his words, "When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did".

In the later part of the twentieth and twenty-first century, many new microbes were discovered and many chemotherapeutic agents developed. As the use of antibiotics increased, so did the rate of antibiotic resistance. For proper management of the wound infection, it is

S.B. Patil, M.S., M.Ch. (✉) · S. Harsh, M.Ch.
Department of Plastic and Maxillofacial Surgery, Government Medical College and Hospital, Maharashtra University of Health Sciences, Nagpur, India
e-mail: drsurendrapatil@yahoo.in; patilsurendrakumar@gmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_71, © Springer International Publishing AG
Published Online: 05 May 2018

important to know the organism involved in the disease process. It is done by collecting the sample from the wound and growing the same on culture media for identification.

2 Collecting the Sample from the Wound

2.1 Technique

For proper determination of the growth of microbes, it is necessary that the wound isolates are collected in a proper fashion. There are various methods described in literature for obtaining a proper specimen for culture. It should be done prior to the start of antibacterial therapy.

The wound is cleaned with normal saline, sterile water or a soap-based wound cleanser. Debridement of devitalized tissue is done prior to sample collection. The method of sample collection is debatable. The most accurate method has not been identified [7]. The swab can be taken as a broad Z covering the whole of the wound bed. The Levine technique described uses swab over 1 cm of tissue for 5 s along with application of enough pressure so as to extract enough tissue fluid [8]. Though historically tissue biopsy was considered as gold standard [9], it is not frequently practiced as it is invasive, painful, causes damage to the tissues and more expensive. Swab method is preferred to tissue biopsy or curetted sample as it is less invasive and the results obtained are similar to tissue biopsy or curette [10]. For antibiotic resistant wounds and for monitoring the response to treatment, biopsy can be used as the preferred method of sample collection [11]. In the absence of bony involvement in diabetic foot, swab cultures are reliable method to identify the pathogens [12].

In the authors' technique, a set of questions are asked (Table 1) relating to prior history of medication, duration of wound and type of injury/event leading to wound after taking a written informed consent in the patient's/guardian's language. The wound surface is routinely cleaned with normal saline to avoid contamination. Pus or profuse discharge along with the irrigation fluid is discarded. Sample collection is done bedside under all antiseptic precautions after debridement of devitalized tissue by senior resident surgeon. Wound specimen is taken from depth of wound with the help of sterile wound swab sticks. One swab stick per wound site is taken per patient. The collected specimen is stored in a sterile saline filled vial and sent to the microbiology lab within 1 h.

Table 1 Questions asked

S. No.	
Name	
Age/sex	
Type of injury	
Duration of wound	
Antibiotic treatment	

In the lab, the collected swab is streaked on blood agar and MacConkey's agar with sterile inoculation loops. Agar plates are incubated at 37° centigrade for a period of 24 to 48 h. Gram staining is then performed on the agar plate which undergoes biochemical tests for identification of the organism.

3 Wound in Plastic Surgery Patients

A wound is loss of skin coverage and may include subcutaneous tissue, muscle tendon and bones. They can be associated with trauma and disease process or may be iatrogenic. Increase in complex wounds seen in plastic surgery patients has resulted in increased financial burden to the patient and health-care provider. These complex wounds include extensive wounds, infected, those with compromised viability, associated with systemic pathology which hamper normal healing [13].

Specialized care has to be given for some wounds like burns, diabetic wounds, pressure ulcers, chronic venous ulcers, post-necrotic infections and those related to vasculitis and immunosuppressive therapy. Surgically created wounds can be complicated by dehiscence of wound, ischemia, infection, patient's general condition and compromised immune status [14].

When dealing with wounds, the concept of reconstructive ladder can be utilized [15]. It starts with the use of simple dressings and primary suturing for simple wounds to microvascular free-tissue transfer for complex three-dimensional

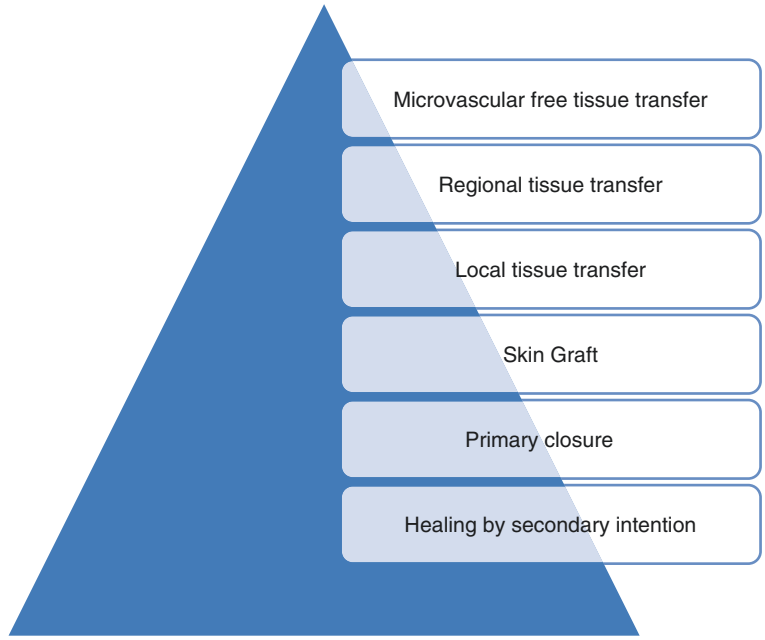


Fig. 1 Reconstructive ladder

defects (Fig. 1). The reconstructive ladder can be skipped by approaching a higher option first over an option lower down the ladder like a local flap that can be used in place of a graft for superior aesthetic results in areas of the face and so on. This was popularized by Gottlieb and Krieger and is known as reconstructive elevator [16]. As the complexity of the procedure increases, the results are better.

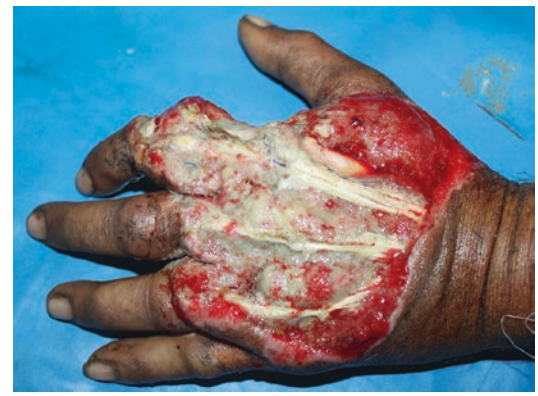


Fig. 2 Degloving injury of the hand

4 Discussion

4.1 Wound Infection in Plastic Surgery Patients

Wound can be classified into clean, clean-contaminated, contaminated or dirty. Clean wounds have less than 2% chance of infection. Clean-contaminated wounds involve those of oral, nasal cavity, axilla or perineal area that can carry an infection rate of about 10%. Contaminated wounds include post traumatic wounds of less than 4 h duration and raw areas and have about 20% infection rate. Dirty wounds are those which are grossly contaminated with dead and devitalized tissue with pus discharge and associated inflammation. They have the highest rate of infection of up to 40% [17].

Most patients in plastic surgery are contaminated or dirty wounds (Figs. 2, 3, 4, and 5).

Wound infection can depend on general condition of the patient, immune status, co-morbid illness, length of surgery and length of hospital stay. In clean plastic surgery cases like augmentation mammoplasty, the infection rate has been reported between 1% and 7% [18]. Wound infection in reduction mammoplasty can vary between 6.8% and 8.5% [19]. In abdominoplasty, the infection rate can be about 7.3% [20]. Benefit of prophylactic antibiotics in these cases is debatable [19, 21, 22].

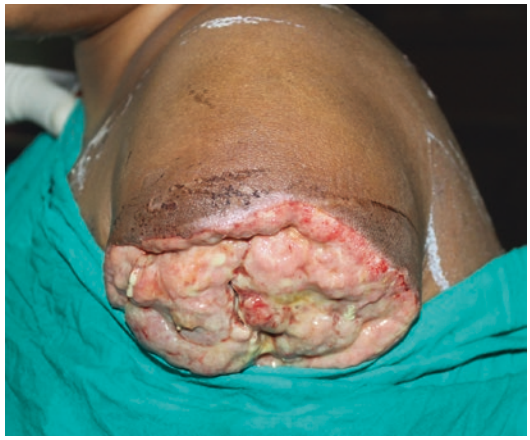


Fig. 3 Raw area above elbow amputation stump

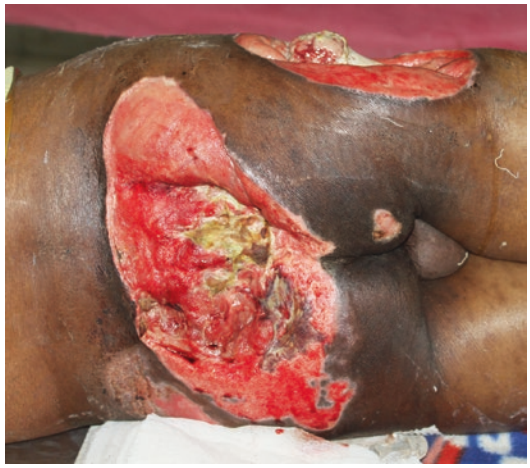


Fig. 4 Multiple pressure sores

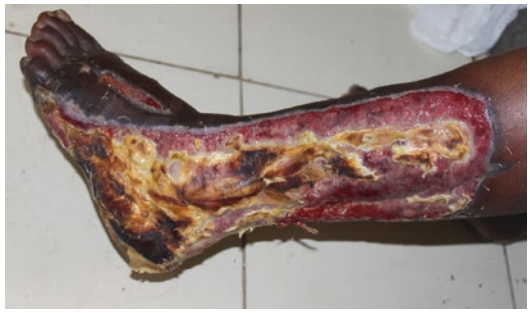


Fig. 5 Raw area leg after necrotising fasciitis

In clean-contaminated cases involving nasal or oral cavities, the use of prophylactic antibiotics has shown a reduction in the infection rate in the postoperative period [23]. For contaminated cases, there is a decrease in infection rate following the use of prophylactic antibiotics [24] which should be extended to complete the course of antibiotic therapy.

4.2 Antibiotic Susceptibility

The ability of an antibiotic to inhibit bacterial growth is measured by its susceptibility assessment. The potency of an antibiotic is measured by its degree of susceptibility against an organism. The minimal inhibitory concentration (MIC) [25] is the minimum amount of drug at which inhibitory activity occurs against the microorganism. Proper antibiotic selection helps in better wound management. After identification of the microbe, for institution of antibiotic, we need to consider many factors: the effect of drug on body, effect of body on drug, its side effects, interaction with other drugs, its cost and clinical status of the patient, previous antibiotic use and the pattern of antibiotic susceptibility of the institute.

Susceptibility testing can be done by qualitative methods such as Kirby-Bauer and quantitative testing by tube dilution and E-test. The reference test is the quantitative assessment of inhibitory activity and bactericidal activity tested by broth microdilution method [26].

4.3 Understanding the Pharmacokinetics

It is concerned with what body does to the drug such as absorption, distribution and elimination of the drug. An antibiotic when given by intravenous route has rapid absorption with peak level reaching almost immediately. When taken by oral route, not only the peak is delayed and absorption

is less; it is dependent on many factors like sepsis, local bowel pathology, the food consumed and administration of any other drug. After intramuscular injections, absorption is dependent on physiological conditions of the patient. After absorption, its concentration in plasma is dependent on the volume in which it is distributed. It is governed by the following equation:

Volume of distribution = Amount of drug present/Plasma concentration.

Volume of distribution can be affected in conditions like fever, sepsis, pregnancy and congestive heart failure. Here due to increased volume of distribution [27], the serum level of the drug is low resulting in lower efficacy. Distribution of the drug requires it to be delivered at the site of infection through circulation and the movement of antibiotic to the site of infection from the circulation. There are many factors like permeability of capillaries, protein binding [28] and lipid solubility of the drug and the presence of enzymes that have an effect on drug. Thereafter the drug is eliminated which also depends on a number of factors like protein binding, tubular secretion in kidneys for drugs which have renal excretion and normal liver function for those excreted by liver.

4.4 Understanding the Pharmacodynamics

It is the effect the drug has on the bacteria. There is a decrease in the level of bacterial count when the unbound drug exceeds the level of minimum bactericidal concentration (MBC) for a bactericidal drug. As the drug level decreases below MBC but still more than MIC, the count of bacteria may remain stable or decrease as a result of host immunity [29]. In case of a bacteriostatic drug, the bacterial count decreases when the level is above MIC due to host defences. Thereafter on further decrease of drug level to below MIC, the antibacterial effect can be due to postantibiotic effect (PAE) [30] and postantibiotic leucocyte enhancement (PALE) [31].

Choosing a drug depends on its microbiological as well as pharmacokinetic properties. The microbiological criteria include MIC, PAE, MBC, bacterial titre and the bactericidal rate. Amongst the pharmacokinetic criteria, we should see peak serum concentration at a steady state, area under the concentration time curve and the time duration for which serum concentration of the drug is more than a particular amount [32]. The best indicator to monitor drug therapy is by clinical status of the patient. Measurement of serum level of the drug can also help in the same as well as in monitoring the toxicity. Schlichter test can be used to monitor the serum bactericidal activity.

4.5 Wound Isolates in Plastic Surgery Patients and Experience at the Authors' Centre

Wound isolates can be monomicrobial [33, 34] or polymicrobial [35]. They vary from one place to another. Some studies have shown *Staphylococcus aureus* to be the commonest pathogen [36, 37] while it was *Pseudomonas* as the commonest offender in our series [34]. Flora of the wound can change with duration. This could be due to regional and geographical variation of the flora. We found that about 91% of patients in our series were found to be in the age group of 20–30 years, with a male preponderance. Most patients were post-traumatic (Fig. 3) affecting mostly the legs (44%).

Fourteen percent patients in our series were culture negative. Gram-negative organisms predominated our study (78%). Sensitivity of the microbes gradually decreases to routine antibiotics with duration of treatment. Antibiotic resistance can be a nuisance when dealing with wounds which can go to as high as 55% [38]. We had done the sensitivity pattern of isolates in detail (Tables 2 and 3) [34].

Table 2 Antibiotic sensitivity of Gram-negative isolates (Reproduced from Antibiotic susceptibility pattern of wound isolates in Plastic Surgery patients at a tertiary care centre [34])

		Antibiotics—number (%)									
Gram-negative isolates (number)	Reaction	A	AK	C	T	Cx	G	I	L	M	P
Pseudomonas (46)	S	–	33 (71.7)	26 (56.5)	31 (67.4)	33 (71.7)	28 (60.9)	39 (34.8)	30 (65.2)	24 (52.2)	35 (76.1)
	R	46 (100)	13 (28.3)	20 (43.5)	15 (32.6)	13 (28.3)	18 (39.1)	07 (15.2)	16 (34.8)	22 (47.8)	11 (23.9)
Klebsiella (28)	S	11 (39.3)	18 (64.3)	16 (57.1)	22 (78.6)	22 (78.6)	14 (50)	26 (92.9)	28 (100)	12 (42.9)	–
	R	17 (60.7)	10 (35.7)	12 (42.9)	06 (21.4)	06 (21.4)	14 (50)	02 (7.1)	–	16 (57.1)	–
Proteus (22)	S	12 (54.5)	14 (63.6)	10 (45.5)	10 (45.5)	14 (63.6)	11 (50)	19 (86.4)	18 (81.8)	14 (63.6)	–
	R	10 (45.5)	08 (36.4)	12 (54.5)	12 (54.5)	08 (36.4)	11 (50)	03 (13.6)	04 (18.2)	08 (36.4)	–
E. coli (15)	S	10 (66.7)	12 (80)	11 (73.3)	11 (73.3)	13 (86.7)	10 (66.7)	14 (99.3)	13 (86.7)	10 (66.7)	–
	R	05 (33.3)	03 (20)	04 (26.7)	04 (26.7)	02 (13.3)	05 (33.3)	01 (6.7)	02 (13.3)	05 (33.3)	–
Total (111)	S	33 (29.7)	77 (69.4)	63 (56.8)	74 (66.7)	82 (73.9)	63 (56.8)	98 (88.3)	89 (80.2)	60 (54)	35 (76.1)
	R	78 (70.3)	34 (30.6)	48 (43.2)	37 (33.3)	29 (26.1)	48 (43.2)	13 (11.7)	22 (19.8)	05 (46)	11 (23.9)

S sensitive, *R* resistance, – zero
A ampicillin, *AK* amikacin, *C* ciprofloxacin, *T* cefotaxime, *Cx* ceftriaxone
G gentamycin, *I* imipenem, *L* levofloxacin, *M* metronidazole, *P* piperacillin

Table 3 Antibiotic sensitivity of Gram-positive isolates (Reproduced from Antibiotic susceptibility pattern of wound isolates in Plastic Surgery patients at a tertiary care centre [34])

		Antibiotics								
Gram-positive isolates	Reaction	A	AK	C	T	Cx	G	I	L	M
Staphylococcus aureus (24)	S	04 (16.7)	24 (100)	21 (87.5)	22 (91.7)	21 (87.5)	18 (75)	24 (100)	24 (100)	15 (62.5)
	R	20 (83.3)	–	3 (12.5)	02 (8.3)	03 (12.5)	06 (25)	–	–	09 (37.5)
Coagulase-negative staphylococci (08)	S	03 (37.5)	08 (100)	06 (75)	08 (100)	08 (100)	05 (62.5)	08 (100)	08 (100)	04 (50)
	R	05 (62.5)	–	02 (25)	–	–	03 (37.5)	–	–	04 (50)
Total (32)	S	08 (25)	32 (100)	27 (84.4)	30 (93.8)	29 (90.6)	23 (71.9)	32 (100)	32 (100)	19 (59.4)
	R	25 (75)	–	05 (15.6)	02 (6.2)	03 (9.4)	09 (28.1)	–	–	13 (40.6)

Conclusions

Wound infection in plastic surgery patients like other specialities increases the morbidity of the patient. The choice of antibiotic administration depends on the wound isolate, condition of the patient and the pharmacokinetic and dynamic properties of the drug. Every hospital should have an antibiotic administration policy and should carry out sensitivity pattern on regular intervals. It not only helps in deciding the type of antibiotic to be administered on empirical basis but also determines and documents the pattern of antibiotic resistance in the institute, decreases the financial burden of the health seeker and the provider and helps in faster and better wound healing.

References

1. Watts JMK, McDonald PJ, O'Brien PE, Marshall VR, Finlay Jones JJ (eds) (1981) Infection in surgery: basic and clinical aspects. Churchill Livingstone, New York, p 27
2. Nuland SB (2003) The doctor's plague: germs, childbed fever, and the strange story of ignaz semmelweis. WW Norton and Co., New York, p 1
3. Tabrah F (2011) L Koch's postulates, carnivorous cows and tuberculosis today. Hawaii Med J 70(7):144–148
4. Wainwright M, Kristiansen JE (2011) On the 75th anniversary of prontosil. Dyes Pigments 88(3):231–234
5. Aminov RI (2010) A brief history of the antibiotic era: lessons learnt and challenges for the future. Front Microbiol 1:134
6. Tan SY, Tatsumura Y (2015) Alexander fleming (1881–1955): discoverer of penicillin. Singap Med J 56(7):366–367
7. Rondass AA, Schols JM, Halfens RJ, Stobberingh EE (2013) Swab versus biopsy for the diagnosis of chronic infected wounds. Adv Skin Wound Care 26(5):211–219
8. Angel DE, Lloyd P, Carville K, Santamaria N (2011) The clinical efficacy of two semi-quantitative wound swabbing techniques in identifying the causative organism(s) in infected cutaneous wounds. Int Wound J 8(2):176–185
9. Bill TJ, Ratliff CR, Donovan AM, Knox LK, Morgan RF, Rhodeheaver GT (2001) Quantitative swab culture versus tissue biopsy: a comparison in chronic wounds. Ostomy Wound Manage 47(1):34–37
10. Smith ME, Robinowitz N, Chaulk P, Johnson K (2014) Comparison of chronic wound culture techniques: swab versus curetted tissue for microbial recovery. Br J Community Nursing 19(90):s22–s26
11. Copeland Halperin LR, Kaminsky AJ, Bluefeld N, Miraliakbari R (2016) Sample procurement for culture of infected wounds: a systematic review. J Wound Care 25(4):s4-6–s8-10
12. Slater RA, Lazarovitch T, Boldur I, Ramot Y, Buchs A, Weiss M, Hindi A, Rapoport MJ (2004) Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. Diabet Med 21(7):705–709
13. Ferreira MC, Junior PT, Carvalho VF, Kamamoto F (2006) Complex wounds. Clinics (Sao Paulo) 61(6):571–578
14. Coltro PS, Ferreira MC, Bastia BPSN, Nakamoto HA, Milcheski DA, Tuma Junior P (2011) Role of plastic surgery on the treatment complex wounds. Rev Col Bras Cir 38(6):381–386
15. Boyce DE, Shokrollahi K (2006) Reconstructive surgery. BMJ 332(7543):710–712
16. Neligen PC, Gurtner GC (eds) (2013) Plastic surgery. Elsevier, New York, p 536
17. Hsu P, Bullock J, Matthews M (2006) Infection prophylaxis update. Semin Plast Surg 20(4):241–248
18. LeRoy J, Given KS (1991) Wound infection in breast augmentation: the role of prophylactic perioperative antibiotics. Aesthet Plast Surg 15(4):303–305
19. Serletti JM, Devenport MS, Herrera HR, Caldwell EH (1994) Efficacy of prophylactic antibiotics in reduction mammoplasty. Ann Plast Surg 33(5):476–480
20. Grazer FM, Goldwyn RM (1977) Abdominoplasty assessed by survey, with emphasis on complications. Plast Reconstr Surg 59(4):513–517
21. Kompatscher P, Von Planta A, Spicher I, Seifert B, Vetter S, Minder J, Beer GM (2003) Comparison of the incidence of the predicted risk of early surgical site infections after breast reduction. Aesthet Plast Surg 27(4):308–314
22. Soundararajan V, Hart NB, Royston CM (1995) Abdominoplasty following vertical banded gastroplasty for morbid obesity. Br J Plast Surg 48(6):423–427
23. Chole RA, Yee J (1987) Antibiotic prophylaxis for facial fractures. A prospective, randomized clinical trial. Arch Otolaryngol Head Neck Surg 113(10):1055–1057
24. Becker GD (1981) Chemoprophylaxis for surgery of the head and neck. Ann Otol Rhinol Laryngol Suppl 90(3Pt3):8–12

25. Nkang AO, Okonko IO, Majeha OK, Adewale OG, Udeze AO, Fowotade A, Fajobi EA, Adedeji O, Babalola ET (2009) Assessment of antibiotics susceptibility profiles of some selected clinical isolates from laboratory in Nigeria. J Microbiol Antimicrobials 1(2):19–26
26. Belkum AV, Dunne WM (2013) Next generation antimicrobial susceptibility testing. J Clin Microbiol 51(7):2018–2024
27. Turnidge J (2003) Pharmacodynamics and dosing of aminoglycosides. Infect Dis Clin N Am 17: 503–528
28. Scheife RT (1989) Protein binding: what does it mean? DCIP 23(7–8 Suppl):S27–S31
29. Levison ME, Levison JH (2009) Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin N Am 23(4):791–815
30. Spivey JM (1992) The postantibiotic effect. Clin Pharm 11(10):865–875
31. McDonald PJ, Wetherall BL, Pruul H (1981) Postantibiotic leucocyte enhancement: increased susceptibility of bacteria pretreated with antibiotics to activity of leucocytes. Rev Infect Dis 3(1):38–44
32. Sanchez NA, Sanchez RMM (1999) Basis of anti-infective therapy: pharmacokinetic-pharmacodynamic criteria and methodology for dual dose individualisation. Clin Pharmacokinet 37(4):289–304
33. Manikandan C, Amsath A (2013) Antibiotic susceptibility of bacterial strains isolated from wound infection patients in Pattukkottai, Tamil Nadu, India. Int J Curr Microbiol App Sci 2(6):195–203
34. Patil SB, Paramne A, Harsh S (2016t) Antibiotic susceptibility pattern of wound isolates in plastic surgery patients at a tertiary care centre. Indian J Plast Surg 49(2):198–205
35. Mama M, Abdissa A, Sewunet T (2014) Antimicrobial susceptibility pattern of bacterial isolates from wound infection and their sensitivity to alternative topical agents at Jimma University specialized hospital, south West Ethiopia. Ann Clin Microbiol Antimicrob 13:14
36. Goswami N, Trivedi HR, Goswami AP (2011) Antibiotic sensitivity profile of bacterial pathogens in postoperative wound infections at a tertiary care hospital in Gujrat, India. Aust J Pharm 2:158–164
37. Mulu A, Moges F, Tessema B, Kassu A (2006) Pattern and multiple drug resistance of bacterial pathogens isolated from wound infection at University of Gondar Teaching Hospital, northwestern Ethiopia. Ethiop Med J 44(2):125–131
38. Mwambete KD, Rugemalila D (2015) Antibiotic resistance profiles of bacteria isolated from surgical wounds in tertiary hospitals, Tanzania. Int J Curr Microbiol App Sci 4(1):448–455

Reconstructive Management of Facial Gunshot Wounds

Raffi Gurunluoglu and Antonio Rampazzo

1 Introduction

Firearm-related facial injuries are caused by a wide variety of weapons and projectiles in military and civilian populations [1]. The type and extent of treatment required should be based on an understanding of the various mechanisms contributing to tissue damage and wound assessment.

The kinetic energy ($E = 1/2$ mass $\times v^2$) of the penetrating projectile defines its ability to disrupt and displace tissue. The actual tissue damage is determined by the mode of energy release during the projectile-tissue interaction and the biologic characteristics of the tissues involved and the distance to the target. Certain projectile factors, such as caliber, configuration, construction, stability, and velocity, greatly influence the rate of energy transfer to the tissues along the wound track. As the velocity of the projectile significantly impacts the energy transferred, GSWs have been classically divided into low-velocity injuries (<300 m/s) caused by handguns (except Magnum loads), and high-velocity injuries (>300 m/s) caused by rifles, and shotgun blasts.

In high-energy GSWs, two zones of tissue damage can be identified, the permanent cavity created by the passage of the bullet and a potential area of contused tissue surrounding it, produced mainly by temporary cavitation which is a manifestation of effective high-energy transfer to tissue [2, 3].

The gunshot injuries may involve various parts in the face and have also been classified according to the involved anatomic areas [4]. They can be associated with serious ocular and brain injuries that require urgent neurosurgical and ophthalmologic interventions. Self-inflicted GSWs typically involve the lower half and anterior portion of the face that includes the mandible, maxilla, nose, and anterior cranial base.

In general, high-velocity and high-energy injuries result in more severe facial destruction compared to the low-velocity and low-energy-type injuries. Thus, facial GSWs may range from minor soft tissue injuries and/or bone fractures to devastating soft tissue and bone destruction and defects. The management depends on the type and location of the injury. Table 1 shows patient demographics, type of weapon involved, associated injuries, and reconstructive procedures. The following cases demonstrate the reconstructive surgical approach in various facial gunshot wound scenarios.

1.1 Case 1

A 58-year-old male sustained facial GSWs with an unknown handgun (Figs. 1, 2, 3, 4, and 5). After initial management and stabilization,

R. Gurunluoglu (✉) · A. Rampazzo
Department of Plastic Surgery,
Cleveland Clinic, Cleveland, OH, USA
e-mail: gurunlr@ccf.org; RAMPAZA@ccf.org

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_139, © Springer Nature Switzerland AG
Published Online: 13 October 2018

Table 1 Patient demographics, type of weapon involved, associated injuries, and reconstructive procedures

Patients	$n = 29$
M:F ratio	5:1
Age range	14–77 years
Average age	36.1 years
Self-inflicted	$n = 13$
Assault	$n = 16$
Permanent brain injury	$n = 4$
Bilateral blindness	$n = 2$
Unilateral blindness	$n = 4$
Handguns	$n = 15$
357 Magnum handgun	$n = 2$
Shotgun 12-gauge	$n = 6$
High-powered rifle	$n = 4$
Unknown	$n = 2$
Anterior skull base reconstruction	$n = 5$
ORIF of mandible fracture	$n = 6$
ORIF of midface fracture	$n = 8$
ORIF of orbital fracture	$n = 9$
Tongue repair	$n = 8$
Facial nerve sural nerve grafting	$n = 1$
Free fibula osteocutaneous flap (mandible and floor of the mouth: 10, maxilla/palate: 2)	$n = 12$
Free radial forearm flap (lower lip: 3, palate 3, nose:3, cheek:1)	$n = 10$
Free anterolateral thigh flap (lower lip/chin)	$n = 1$
Free rectus abdominis flap (midface)	$n = 1$
Free dorsalis pedis flap (lower lip)	$n = 1$
Free gracilis muscle flap (lower lip)	$n = 5$
Pedicled pectoralis major myocutaneous flap (floor of the mouth/chin and mandibular plate coverage)	$n = 2$
Maximum number of free flap in one patient	$n = 4$

patient underwent left frontotemporoparietal craniotomy, evacuation of subdural hematoma and debridement of GSW to left frontal lobe, frontal sinus cranialization (Fig. 6), rigid fixation of the anterior table of the frontal sinus, dura repair with pericranial graft, and temporalis muscle to skull base (Fig. 7). In the same operative setting, he also underwent adequate but limited debridement of soft tissue injuries, and primary repair of floor of the mouth, tongue and submental wounds, intraoperative maxillomandibular wire fixation, and open reduction and internal rigid fixation (ORIF) of mandible fractures (Fig. 8).

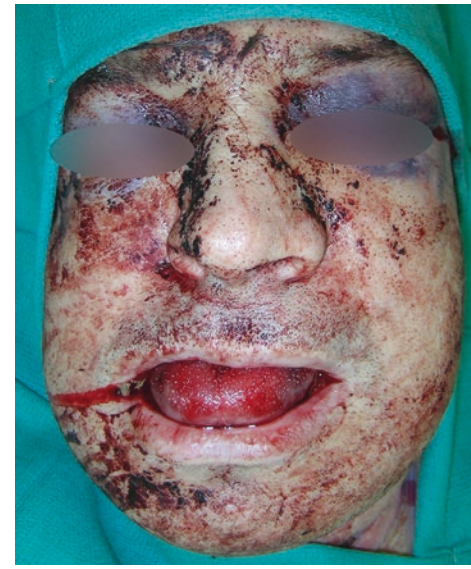


Fig. 1 Frontal view of the patient who sustained a submental GSW

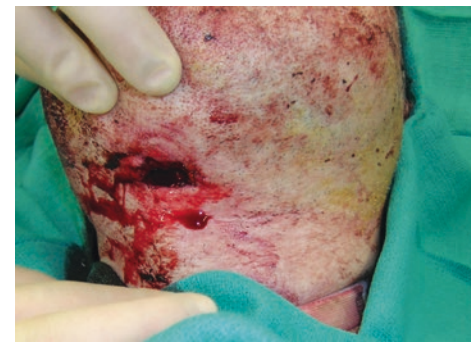


Fig. 2 The submental gunshot wound extending to the floor of the mouth created a full-thickness avulsion defect of the anterior tongue

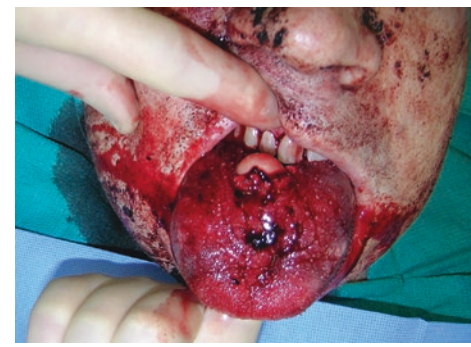


Fig. 3 The full-thickness avulsion defect of the anterior tongue

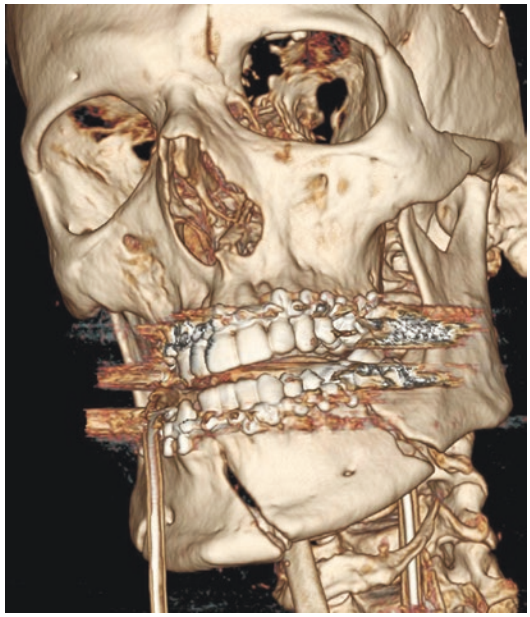


Fig. 4 3D CT (left oblique view) demonstrating the displaced right body and symphyseal mandible fractures

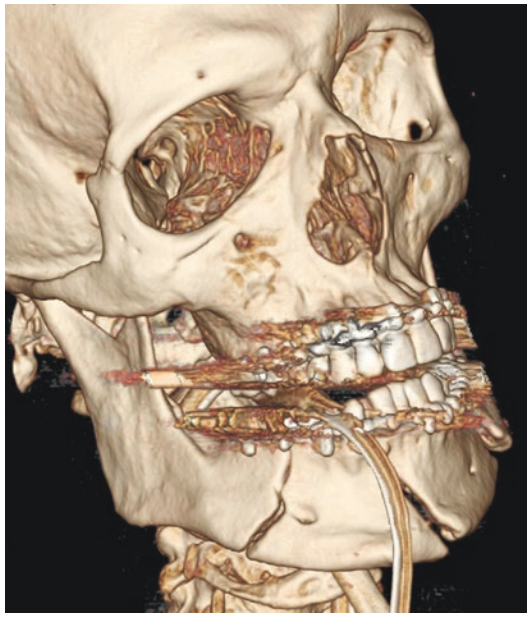


Fig. 5 3D CT (left oblique view) demonstrating the displaced left body and symphyseal mandible fractures

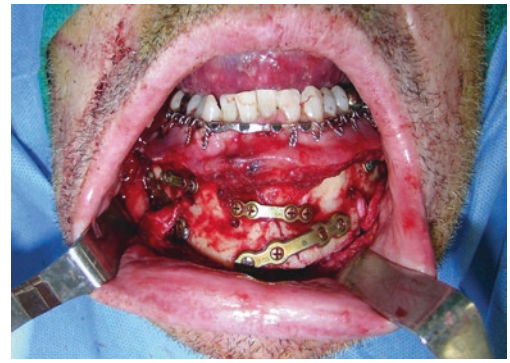


Fig. 6 Cranialization of frontal sinus, intraoperative view

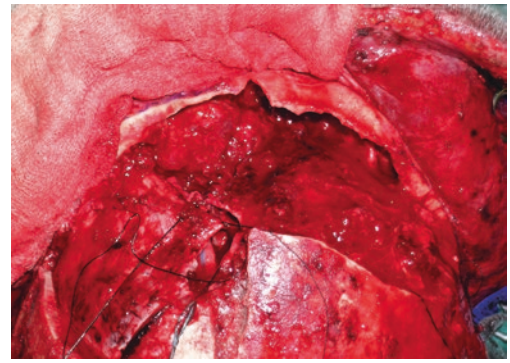


Fig. 7 3D postoperative CT (frontal view, right) and (left oblique view, left) demonstrating the rigid fixation of mandible fractures and craniotomy bone flap fixation

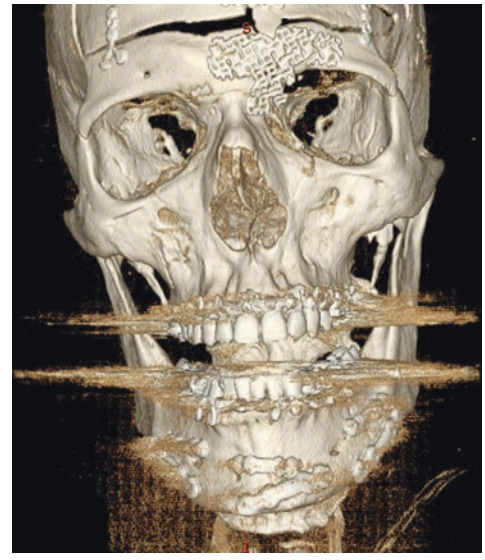


Fig. 8 Intraoperative view: Open reduction and internal fixation of mandible fractures using intraoral approach

1.2 Case 2

A 77-year-old male sustained self-inflicted facial GSWs with an unknown gun. The projectile resulted in an injury splitting his face as it traveled through the soft tissues involving the chin, lower and upper lips as well as the nose with avulsion of nasal soft tissues (Fig. 9). Complex repair was performed after adequate debridement (Fig. 10). Subsequently he received a nasal reconstruction in an elective setting using paramedian forehead flap (Fig. 11).

1.3 Case 3

A 59-year-old male sustained self-inflicted facial wounds with a 45 caliber handgun. Despite the low-velocity and low-energy nature of the projectile, he had extensive soft tissue and bone destruction resulting in both soft tissue and

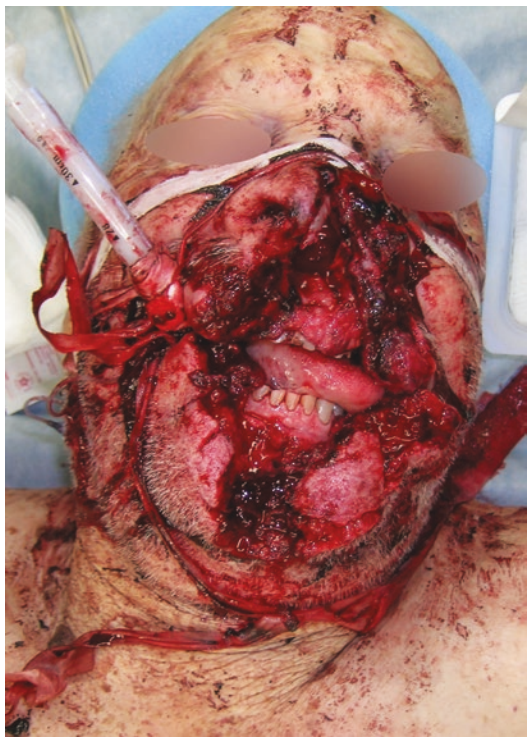


Fig. 9 GSW sustained by self-inflicted injury, splitting the soft tissues with tissue loss involving the chin, lower and upper lips as well as the nose

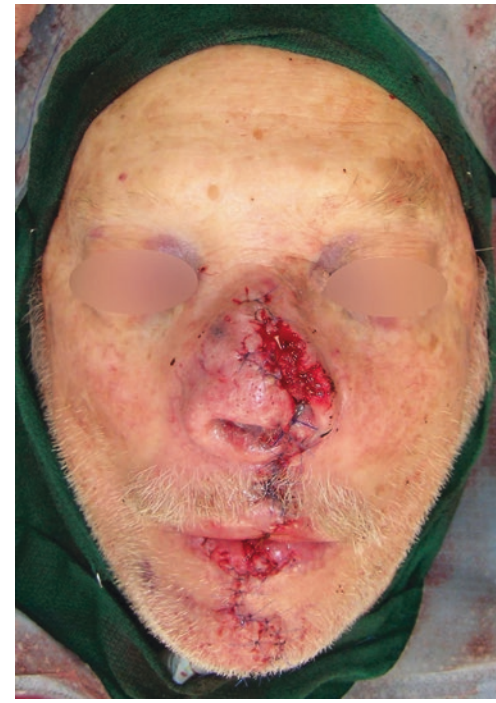


Fig. 10 Intraoperative view after complex repair following adequate debridement

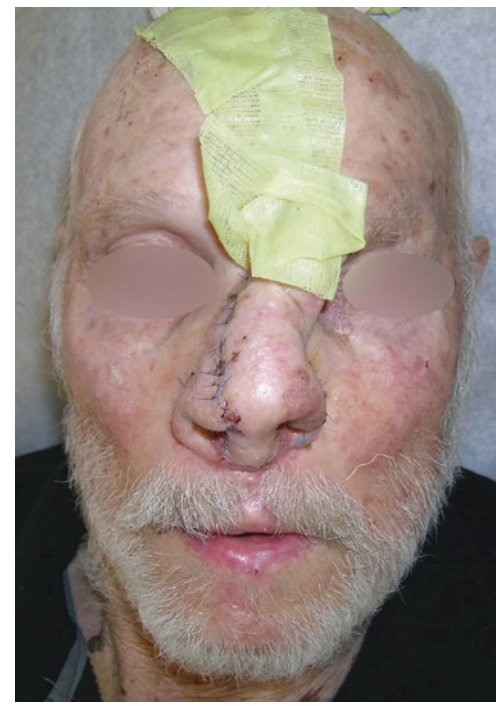


Fig. 11 First stage paramedian forehead flap for nasal reconstruction

bone defects in the maxilla as well as in the mandible (Fig. 12). 3D CT, remaining teeth and alveolar arches were used for optimal alignment and fixation of the mandible and maxilla. This was accomplished by collaboration and cooperation with maxillofacial surgery prior to surgery. Patient underwent debridement of devitalized tissues, open reduction internal fixation of bilateral orbital fractures, polyethylene implant placement to right orbital medial wall, right canthoplasty with transosseous wiring, and ORIF of nasal fractures. Three days after the initial surgery, he underwent a free osteocutaneous flap for maxilla reconstruction (Figs. 13 and 14), and subsequently in 1 week, another free osteocutaneous flap for mandible reconstruction (Fig. 15). Bilateral Karapandzic flaps were used for lower lip reconstruction at the same stage (Fig. 16). The cutaneous fistula that developed in the lower lip was then reconstructed using radial forearm free flap (Fig. 17). Figure 18 demonstrates postoperative 3D CT after the maxilla and mandible reconstruction using free fibular flaps, and ORIF of midface and orbital fractures.

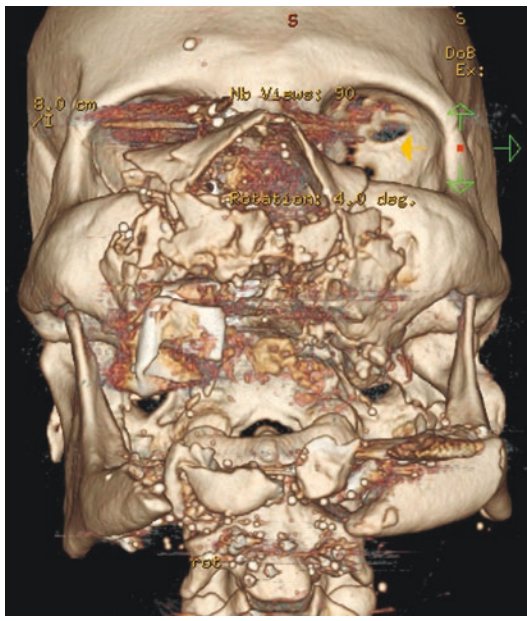


Fig. 12 3D CT (frontal view) demonstrating extensive bone destruction

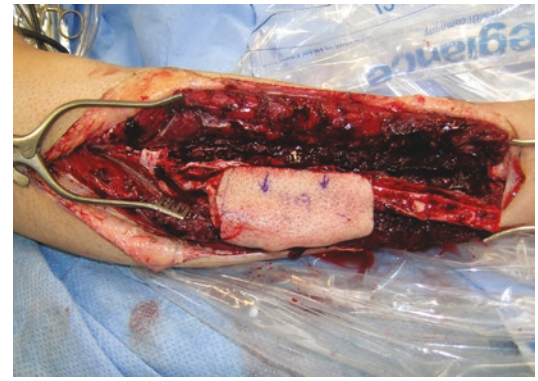


Fig. 13 Free fibular osteocutaneous flap dissected for maxilla reconstruction

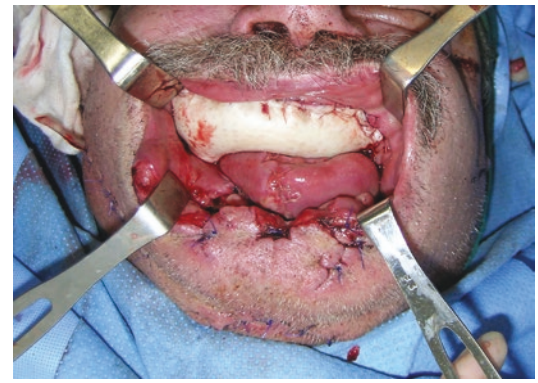


Fig. 14 Free fibular osteocutaneous flap for maxilla reconstruction. Right-sided facial vessels were used as recipient

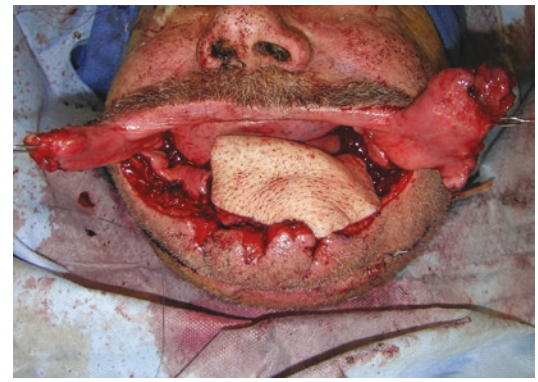


Fig. 15 Free fibular osteocutaneous flap for mandible reconstruction. Left-sided superior thyroid artery and facial vein were used as recipient

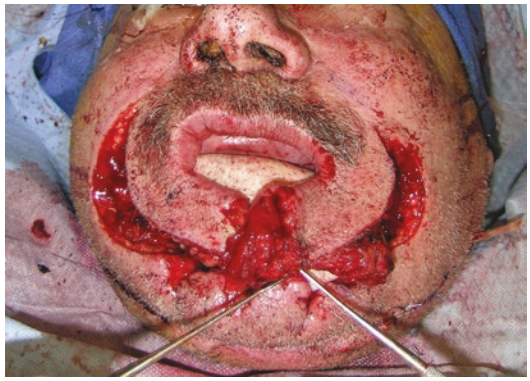


Fig. 16 Lower lip reconstruction using bilateral Karapandzic flaps

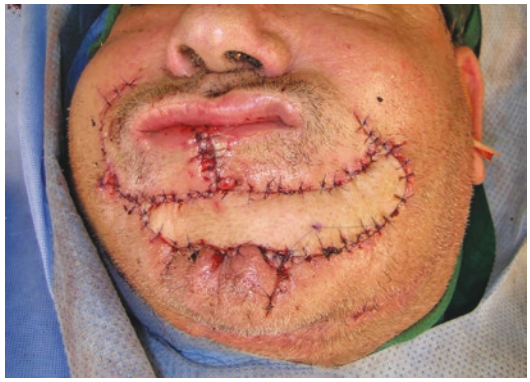


Fig. 17 Free radial forearm for reconstruction of orocutaneous fistula that developed at the junction of the lower lip and chin area

1.4 Case 4

A 54-year-old male patient sustained self-inflicted facial wounds with 12-gauge Shotgun. The injury resulted in loss of composite lower lip and the anterior segment of the mandible (Figs. 19, 20, and 21). Patient underwent a staged free osteocutaneous flap for composite mandible reconstruction (Fig. 22) and a free innervated gracilis muscle flap for functional total lower lip reconstruction 1 week thereafter (Fig. 23).

1.5 Case 5

A 46-year-old male patient sustained GSW to the left side of his face with shrapnel pieces

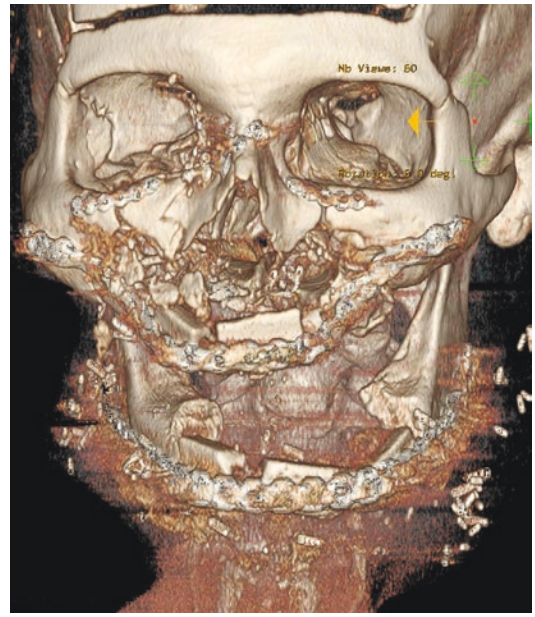


Fig. 18 Postoperative 3D CT (frontal view) demonstrating maxilla and mandible reconstruction using free fibular flaps and open reduction internal fixation of midface and nasal fractures

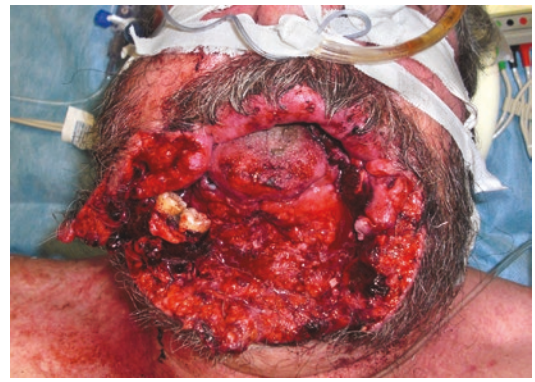


Fig. 19 Self-inflicted facial GSW that resulted in loss of anterior mandible and total lower lip

entering at the left retroauricular and mastoid area (Fig. 24) with an AR 16. He presented to plastic surgery clinic at 3 weeks after the initial injury that resulted in complex comminuted fractures of the left mandible angle, subcondylar region, and coronoid process. The left facial nerve was also injured. Inability to raise left eyebrow (Fig. 25), loss of eyelid closure (Fig. 26), and asymmetric smile and facial deviation to the

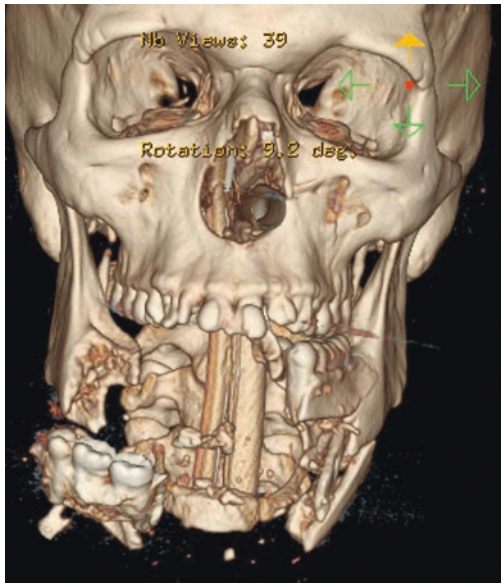


Fig. 20 3D CT demonstrating the extensive bone destruction with mandible defect

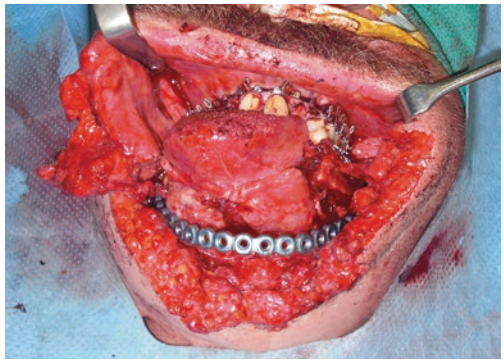


Fig. 21 Mandible reconstruction plate was placed to stabilize the remaining bone

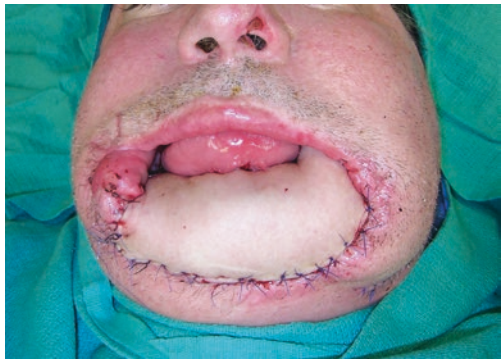


Fig. 22 Mandible reconstruction using free osteocutaneous flap

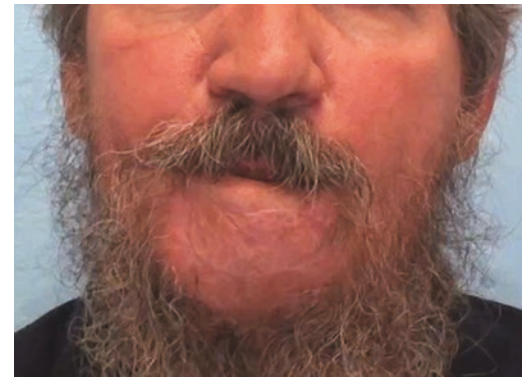


Fig. 23 The total lip was reconstructed using an innervated gracilis muscle flap. The muscle was resurfaced with a skin graft harvested from the scalp (12 months after reconstruction)

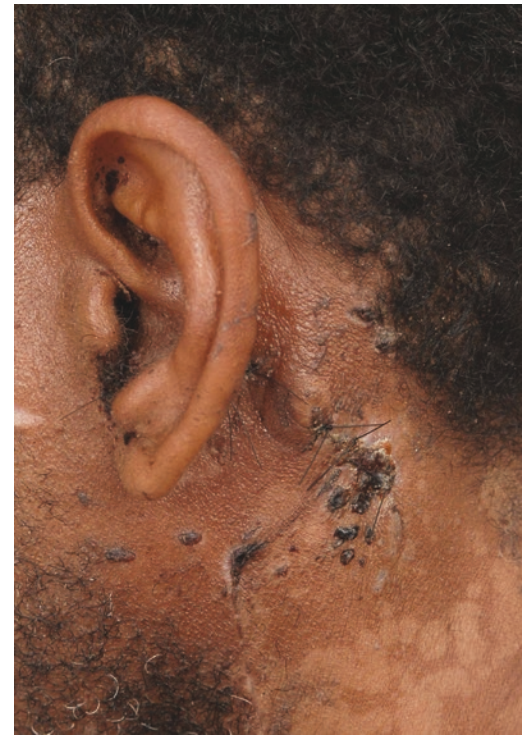


Fig. 24 GSW sustained at the level of left mastoid and retroauricular area

unaffected right side were noted (Fig. 27). The stapedius reflex was intact. Sensation to his ear was not altered. He had normal taste in the anterior 2/3 of his tongue. EMG study showed fibrillation and active denervation in all the facial

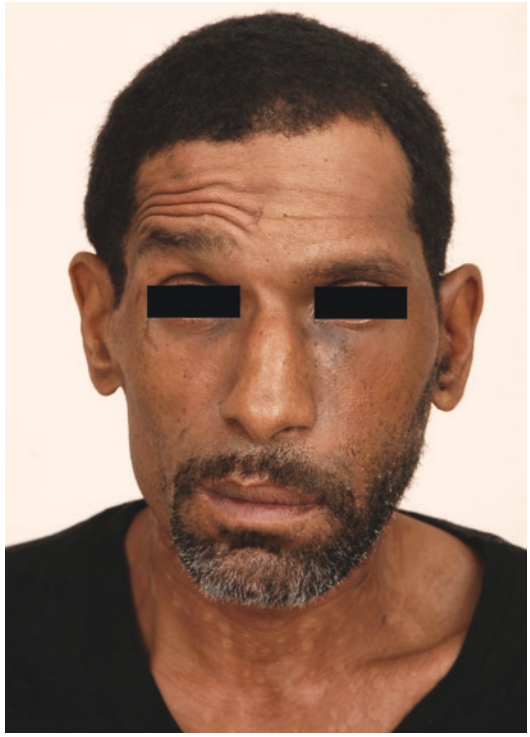


Fig. 25 Facial GSW that resulted in left-sided facial nerve injury. Note inability to raise eyebrow on the left side

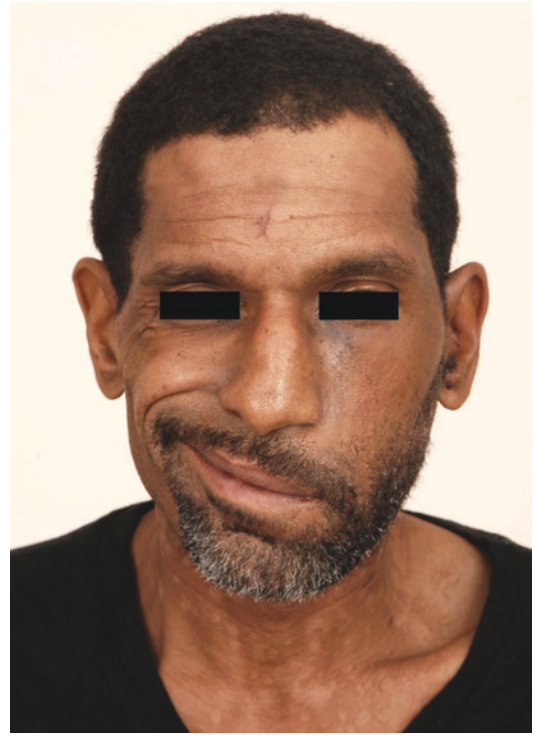


Fig. 27 Facial GSW that resulted in left-sided facial nerve injury. Note deviation of smile to the unaffected side

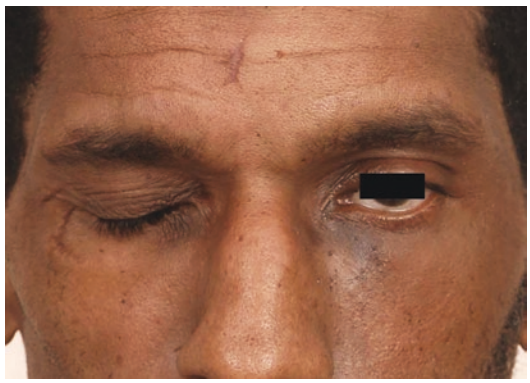


Fig. 26 Facial GSW that resulted in left-sided facial nerve injury. Note inability to close the left upper lid

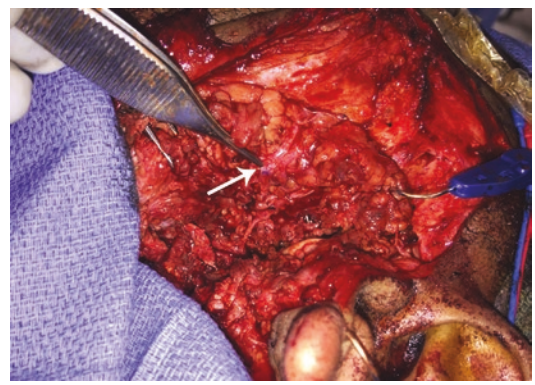


Fig. 28 Facial nerve exploration through preauricular incision. The arrow indicates the level of healthy distal branch where the sural nerve graft will be coapted distally

nerve innervated muscles on the left side and voluntary activation in all the muscles except left mentalis muscle. The injury appeared to be in the region of left retromandibular and mastoid area after the nerve exit from the stylomastoid foramen.

Patient underwent ORIF of mandible fractures and left facial nerve exploration. The facial nerve and its branches were explored (Fig. 28). Distal nerve branches were further explored after superficial parotidectomy. The

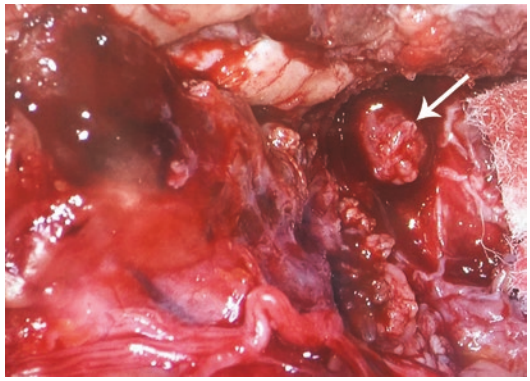


Fig. 29 Facial nerve main trunk was sharply debrided until healthy nerve stump. Proximal facial nerve (close-up view under microscope, arrow) stump 1 cm distal to the stylomastoid foramen

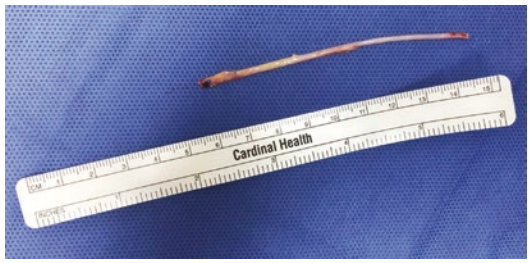


Fig. 30 Sural nerve graft for direct facial nerve grafting

main trunk and its divisions were in continuity but there was no facial nerve activity using nerve stimulator or facial nerve monitoring. The facial nerve main trunk was sharply debrided until healthy nerve fascicles were obtained proximally, 1 cm distal to the stylomastoid foramen (Fig. 29). The damaged nerve branches were sharply excised and direct nerve grafting was performed using two sural nerve cable grafts between the proximal stump and the inferior and superior divisions of the nerve distally (Figs. 30 and 31).

2 Discussion

No two maxillofacial GSWs are the same even if the same type of weapon causes them. In low-energy injuries there is usually limited damage to facial soft tissues and the underlying skeleton. A more straightforward therapeutic approach is

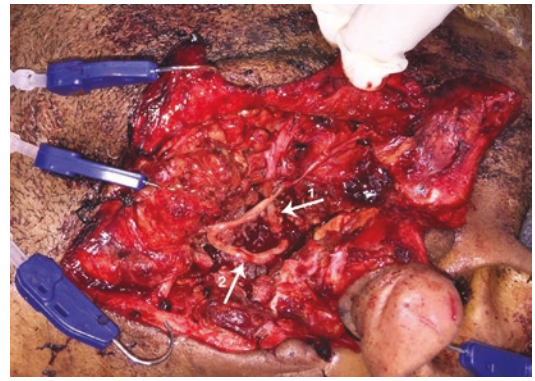


Fig. 31 Two cable nerve grafts were used between the proximal nerve trunk and lower (arrow 1) and upper (arrow 2) divisions of the facial nerve branches distally

required to repair such soft tissue and/or bone injuries using the basic craniofacial principles [5].

On the other hand, high-energy injuries are associated with extensive hard and soft tissue disruption, and are characterized by a surrounding zone of damaged tissue that is prone to progressive necrosis as a result of compromised blood supply and wound sepsis [6]. Current treatment protocols for these injuries emphasize the importance of serial debridement for effective wound control while favoring early definitive reconstruction [7]. Regardless of type of energy and tissue disruption, patients who sustained maxillofacial GSWs require the following:

- Emergency evaluation and management (BLS, ATLS, and trauma center protocols).
- Multidisciplinary approach when and if necessary (neurosurgery, OMFS, plastic and reconstructive surgery, ophthalmology, psychiatry).
- Acute surgical management (adequate debridement, early repair of soft tissue and/or bone injuries).
- Early reconstruction of soft tissue and/or bone defects for optimal functional restoration and appearance.

Multidisciplinary care is required from prehospital admission to discharge [8]. Determination of priorities and orchestration of a surgical plan with other surgical disciplines is mandatory. Neurosurgical and ophthalmologic emergencies

have precedence over facial injuries. Patients who sustained GSWs, in particular those with self-inflicted injuries, need immediate psychiatric evaluation and extensive rehabilitation thereafter.

After life-threatening injuries are overcome and stabilization of patient, we prefer to repair and/or reconstruct soft tissue as well as bone defects as early as patient status allows. Delayed repairs are associated with increased wound infection, scarring/contracture, respiratory problems, nutritional derangement, and overall poor functional as well as aesthetic outcomes. Early repair/reconstruction of soft tissue and/or bone injuries/defects provide optimal functional and aesthetic outcome. In complex soft tissue and/or bone destruction, staging of reconstructive procedures may be done to allow excessively long operative hours allowing patient recovery and avoiding surgeon fatigue. The interval between major reconstructive surgeries should be relatively short (preferably few days—1 week) to avoid scar tissue and contracture [9, 10].

Regional and local flaps may be utilized for soft tissue reconstruction but they have limited value in complex facial GSWs with large soft tissue and bone defects. They should be carefully planned as the zone of injury may negate their use. In patients who are not good candidates for free tissue transfer, pectoralis major may be helpful for soft tissue reconstruction in the lower half of the face. Pedicled temporalis muscle flap is useful in palate, maxilla, and midface area. Pedicled trapezius and sternocleidomastoid muscle flaps may be useful in select patients but have limited reach and use in most maxillofacial GSW reconstruction. Bone grafts may be used in relatively small bone defects (less than 5 cm) as long as adequate bone debridement and stable soft tissue coverage can be achieved.

When free tissue transfer is indicated, the flap choice should be based on patient comorbidities, potential flap donor site morbidity, type and extent of tissue loss. Goals should include functional reconstruction as well as restoration of acceptable and satisfactory appearance. Complex facial defects with significant amount of soft tissue and bone loss may require more than one free tissue transfer. While the face does have robust vascular supply through enormous amount of vascular connections among main branches of the external carotid artery feeding the face, a careful planning is mandatory for recipient site selection. This selection should be carefully made not to jeopardize the vascularity of the face as well as of the previously transferred flap(s).

Our choice for bone defects (more than 5 cm) in the setting of GSWs with inadequate soft tissue coverage is vascularized bone flaps. The free fibular flap is the preferred vascularized flap for mandible and/or maxilla reconstruction. Scapular flap is a viable option for maxilla or mandible reconstruction but the need for patient repositioning poses a significant disadvantage in these complex cases. Iliac bone flap may be used for osteocutaneous defects following maxillofacial GSW, but donor site morbidity and relatively rigid skin paddle make this option less favorable.

Use of virtual surgical planning may be useful for complex maxillofacial reconstruction, in particular with more than one simultaneous free flaps to be performed reliably and successfully. The use of prefabricated jigs and pre-contoured plates eases osteocutaneous flap molding and inset, allowing for a more complex procedure to be successful [11, 12]. Virtual planning and intraoperative imaging in management of ballistic mandibular and maxillary injuries are helpful but are not absolutely necessary to obtain good outcomes. In most level I trauma centers in the USA, these sophisticated options are not available.

In patients with total full-thickness lower lip defects, our choice is innervated gracilis muscle flap. The cutaneous coverage may be provided with the skin paddle or a skin graft harvested from the scalp [13, 14]. Figure 32 summarizes the reconstructive approach in patients undergoing reconstruction for composite mandible defect and functional total lower lip reconstruction in terms of timing and staging these procedures. In the majority of patients with self-inflicted injuries, facial nerve branches remain intact and marginal mandibular nerve may be used to innervate the obturator nerve of the gracilis flap. Our

Reconstructive Surgical Approach	Timing	Procedures
Acute Surgery	within 24 hours	Exploration and debridement of soft tissue and bone, ORIF, stabilization of the mandibular segments with reconstruction plate (MMF to guide proper teeth alignment, if feasible).
Composite Mandibular Defect Reconstruction	within 1 week	Further debridement, adjustment and revision of the mandibular plate (if necessary), fibular osteocutaneous flap *
Functional Lower lip Reconstruction	within 1 week after the fibular transfer	Innervated gracilis muscle flap **
Minor surgeries	2-3 months after the major surgeries	Scar revision, vermilion reconstruction, vermilion tattoo, intraoral flap debulking, dental rehabilitation

ORIF: Open reduction and internal fixation, MMF: Maxillo-mandibular using Erich Arch bars and interdental wiring. ** The gracilis muscle was harvested from the thigh ipsilateral to the selected facial vessels. * This was contralateral to the site used for fibular transfer.

Fig. 32 The reconstructive approach in patients undergoing reconstruction for composite mandible defect and functional total lower lip reconstruction in terms of timing and staging these procedures

experience using this technique in five patients has been favorable and oral competence was achieved in all patients. However, anterolateral thigh flaps with fascia grafts as well as radial forearm flap with palmaris longus have also been shown to provide satisfactory outcomes [15–19].

GSW patients having evidence of facial nerve injury should be thoroughly assessed to determine the level and the site of injury. Clinical examination should include evaluation of eyelid closure, eyebrow elevation, smile, and lip depressors and elevators. Schirmer test of tearing (to assess lacrimal gland function), taste examination in the anterior two-thirds of the tongue (chorda tympani), salivary flow (chorda tympani), and the sensation of ear (auricular branch) are essential tools to detect the anatomical site of the lesion. Further studies include needle EMG, blink reflex, and audiology (stapedius reflex). In addition, the high spatial resolution of multi-sliced CT and/or MRI is often required to support the clinical level of nerve injury. Presence of motor unit potentials in EMG may predict the recovery. Therefore exploration should be held in such cases, clinical findings during follow-up and repeat electrical assessment (monthly) should dictate the necessity of surgical exploration. Substantial clinical improvement supported by EMG may avoid an unnecessary surgical exploration and intervention. No improvement at the end of the third month by monthly electrical and clinical assessments warrants surgical intervention [20].

Clinical judgment is made based on the clinical findings and diagnostic studies whether facial nerve exploration is required. When the decision is made for exploration, within the first 72 h after the injury, distal nerve branches can still be stimulated, as they have not been yet depleted of neurotransmitters within the nerve terminals. Use of a nerve stimulator and/or intraoperative monitoring of facial nerve branches may assist in rapid and accurate identification of ends of facial nerves during surgical exploration [21, 22].

If the facial nerve injury was caused by a blast injury, the surgeon must be cognizant of nerve injury proximal and distal to the site of transection. The extent of the injury may be difficult to determine even using operating microscope. The repair may be delayed for 3 weeks or until the wound permits. Anatomic exploration of nerve branches and intraoperative judgment using the operating microscope to obtain healthy nerve branches proximally and distally will guide the repair. Intraoperative nerve biopsies may be helpful to identify healthy nerve fascicles. Nerve stimulator and/or facial nerve monitoring are still adjunct tools for assessment of neural function, in particular when the nerve is in continuity.

For injuries past the stylomastoid foramen, proximally a healthy facial nerve trunk may be obtained to source the facial nerve branches. The damaged facial nerve branches distally should be sharply excised and interpositional nerve grafts should be used between the main trunk and two

divisions of the facial nerve or the distal facial nerve branches, as needed.

For facial nerve injuries in the temporal bone, where the proximal nerve is not available, cross face nerve grafts (CFNGs) using the sural nerve in single or two stages, which are directed to resume eye closure, smile, and oral competency, may provide satisfactory functional outcomes, when done within 6 months after the onset of injury [23]. For later cases (over 6 months–2½ years), the two-stage "babysitter" procedure can be employed: the first stage involves the use of 40% of the ipsilateral hypoglossal nerve, which provides powerful motor fibers to the affected facial nerve preserving the facial muscle bulk. At the same time, several CFNGs are placed which are connected to selected branches of the unaffected facial nerve. The second stage, usually 9–12 months later, involves secondary microcoaptations between CFNGs and selected distal branches of the affected facial nerve [23].

Treatment of acute facial nerve injury requires a detailed understanding of anatomy, accurate clinical examination, and timely and appropriate diagnostic studies. Reconstruction depends on the extent and timing of injury and availability of the proximal stump.

Most patients with complex maxillofacial ballistic injuries will require revision procedures, as needed for both functional and cosmetic improvement. These include intraoral flap debulking, dental rehabilitation, scar revision, commissuroplasty, lip vermilion reconstruction, additional local, or free flap reconstructions if deemed necessary (Fig. 32).

In conclusion, facial ballistic injuries may result in severe soft tissue and/or bone destruction. Reconstructive management is dependent on the type and amount of tissue destruction and loss. Early reconstruction of soft tissue component and bone defects should be performed for optimal outcome.

References

1. Guevara C, Pirgousis P, Steinberg B (2016) Maxillofacial gunshot injuries: a comparison of civilian and military data. J Oral Maxillofac Surg 74(4):795.e1–795.e7
2. Stefanopoulos PK, Filippakis K, Soupiou OT, Pazarakiotis VC (2014) Wound ballistics of firearm-related injuries—part 1: missile characteristics and mechanisms of soft tissue wounding. Int J Oral Maxillofac Surg 43(12):1445–1458
3. Vasconez HC, Shockley ME, Luce EA (1996) High energy gunshot wounds to the face. Ann Plast Surg 36(1):18–25
4. Clark N, Birely B, Manson PN, Slezak S, Kolk CV, Robertson B, Crawley W (1996) High energy ballistic and avulsion facial injuries: classification, patterns, and an algorithm for primary reconstruction. Plast Reconstr Surg 98(4):583–601
5. Peleg M, Sawatari Y (2010) Management of gunshot wounds to the mandible. J Craniofac Surg 21(4):1252–1256
6. Christensen J, Sawatari Y, Peleg M (2015) High-energy traumatic maxillofacial injury. J Craniofac Surg 26(5):1487–1491
7. Stefanopoulos PK, Soupiou OT, Pazarakiotis VC, Filippakis K (2015) Wound ballistics of firearm-related injuries—part 2: mechanisms of skeletal injury and characteristics of maxillofacial ballistic trauma. Int J Oral Maxillofac Surg 44(1):67–78
8. Sinnott JD, Morris G, Medland PJ, Porter K (2016) High-velocity facial gunshot wounds: multidisciplinary care from prehospital to discharge. BMJ Case Rep
9. McLean JN, Moore CE, Yellin SA (2005) Gunshot wounds to the face—acute management. Facial Plast Surg 21(3):191–198
10. Glapa M, Kourie J, Doll D, Degiannis E (2007) Early management of gunshot injuries to the face in civilian practice. World J Surg 31(11):2104–2110
11. Saad A, Winters R, Wise MW, Dupin CL, St Hilaire H (2013) Virtual surgical planning in complex composite maxillofacial reconstruction. Plast Reconstr Surg 132(3):626–633
12. Kupfer P, Cheng A, Patel A, Amundson M, Dierks EJ, Bell RB (2017) Virtual surgical planning and intraoperative imaging in management of ballistic facial and mandibular condylar injuries. Atlas Oral Maxillofac Surg Clin North Am 25(1):17–23
13. Gurunluoglu R, Glasgow M, Williams SA, Gurunluoglu A, Antrobus J, Eusterman V (2012) Functional reconstruction of total lower lip defects using innervated gracilis flap in the setting of high-energy ballistic injury to the lower face: preliminary report. J Plast Reconstr Aesthet Surg 65(10):1335–1342
14. Sacak B, Gurunluoglu R (2015) The innervated gracilis muscle for microsurgical functional lip reconstruction: review of the literature. Ann Plast Surg 74(2):204–209
15. Sadove R, Luce EA, McGrath PC (1991) Reconstruction of the lower lip and chin with the composite radial forearm-palmaris longus free flap. Plast Reconstr Surg 88:209
16. Serletti JM, Tavin E, Moarn SL, Coniglio JU (1997) Total lower lip reconstruction with a sensate composite radial forearm-palmaris longus free flap and a tongue flap. Plast Reconstr Surg 99:559

17. Carroll CM, Pathak I, Irish J et al (2000) Reconstruction of total lower lip and chin defects using the composite radial forearm palmaris longus tendon free flap. Arch Facial Plast Surg 2:53
18. Jeng SF, Kuo YR, Wei FC, Su CY, Chien CY (2004) Total lower lip reconstruction with a composite radial forearm-palmaris longus tendon flap: a clinical series. Plast Reconstr Surg 113(1):19–23
19. Jeng SF, Kuo YR, Wei FC, Su CY, Chien CY (2005) Reconstruction of extensive composite mandibular defects with large lip involvement by using double free flaps and fascia lata grafts for oral sphincters. Plast Reconstr Surg 115(7):1830–1836
20. Mackinnon SE, Colbert SH (2014) Principles and techniques of peripheral nerve repair, grafts, and transfers. In: Thorne CH (ed) Grabb and Smith's plastic surgery, 7th edn. Lippincot Williams and Wilkins, Philadelphia, pp 77–86
21. Dai J, Shen SG, Zhang S, Wang X, Zhang W, Zhang L (2013) Rapid and accurate identification of cut ends of facial nerves using a nerve monitoring system during surgical exploration and anastomosis. J Oral Maxillofac Surg 71(10):1809.e1–1809.e5
22. Davis RE, Telischi FF (1995) Traumatic facial nerve injuries: review of diagnosis and treatment. J Craniomaxillofac Trauma 1(3):30–41
23. Terzis JK, Anesti K (2014) Facial paralysis. In: Thorne CH (ed) Grabb and Smith's plastic surgery, 7th edn. Lippincot Williams and Wilkins, Philadelphia, pp 399–409

The Role of Negative Pressure Wound Therapy for Salvaging Implant-Based Breast Reconstruction

David Goltsman, Ju Yong Cheong, Atara Posner, Earl Abraham, Farhad Azimi, and Sanjay Warrier

1 Introduction

A well-known consequence of implant-based breast reconstruction after nipple sparing, skin sparing or a combination of the two mastectomies is breast prosthesis infection, which often facilitates severe consequences to patients. Treatment of this postoperative complication involves removal of the infected implant, washout of the cavity and prolonged administration of intravenous antibiotics. In both subpectoral and prepectoral reconstruction, the space may be affected as a consequence. Typically, the space may contract or it can be lost due to the infection. Patients are subjected to further morbidity as a consequence of implant infection due to the delayed reconstruction until the space is cleared of bacteria. This chapter presents a novel technique employed for the management of breast implant infections in subpectoral plane-based breast reconstruction post mastectomy. The five cases presented identify how the use of negative pressure wound therapy with instillation using Veraflow™ (KCI USA, Inc., San Antonio, TX) can successfully treat such infections and maintain the subpectoral space.

Informed consent was obtained from all patients for use of this treatment.

D. Goltsman (✉) · J. Y. Cheong · A. Posner
E. Abraham · F. Azimi · S. Warrier
Chris O'Brien Lifehouse Centre, Camperdown, NSW, Australia

Prince of Wales Hospital, Sydney, NSW, Australia

Institute of Academic Surgery, RPA, Camperdown, NSW, Australia
e-mail: dgoltsman@optusnet.com.au

2 Cases with Complications

2.1 Case 1

The 47-year-old woman had a 28 mm grade 3 invasive ductal carcinoma. In 2012, the patient underwent breast-conserving wide local excision of the cancer, along with adjuvant chemotherapy and radiotherapy. In 2014, the patient developed left-sided lobular carcinoma for which she underwent a bilateral nipple-sparing mastectomy. During the operation, expanders were inserted, which were subsequently inflated percutaneously with saline solution. In 2015, the expanders were replaced with permanent breast implants. The patient subsequently developed septicaemia with abscesses around the implants 18 days postoperatively. There was a small wound dehiscence and leakage of seroma just prior to this event. Organism cultured from blood as well as breast cavity was methicillin-sensitive *Staphylococcus aureus*.

2.2 Case 2

The 39-year-old woman had history of 20 mm grade 3 invasive ductal carcinoma. In early 2015,

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_123, © Springer International Publishing AG
Published Online: 11 July 2018

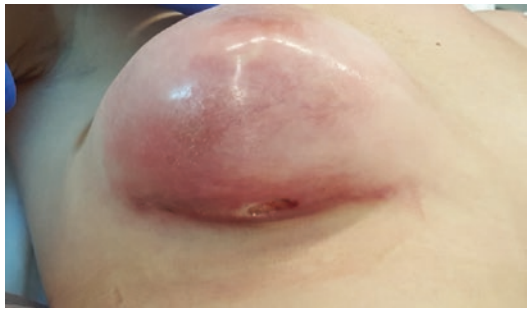


Fig. 1 Mastitis and wound edge necrosis with underlying abscess involving the breast implant

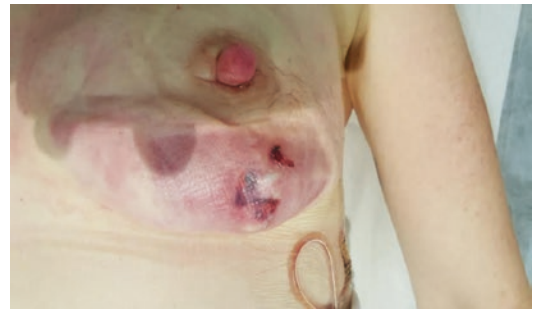


Fig. 2 Skin necrosis and exposure of the underlying expander

the patient underwent nipple-sacrificing, skin-sparing mastectomy with the insertion of an expander. The expander was subsequently inflated with saline solution. Six months afterwards, the expander was replaced with implant. The wound appeared to heal; however 3 months postoperatively, the patient presented with breast abscess around the implant. Organism cultured from breast cavity was methicillin-sensitive *Staphylococcus aureus*.

2.3 Case 3

The 36-year-old woman had 21 mm, grade 2 right breast invasive ductal cancer for which she had breast-conserving wide local excision and adjuvant chemotherapy. Rather than adjuvant radiotherapy, the patient decided to undergo bilateral nipple-sparing mastectomy and the insertion of expanders. Two months after their insertion, the inframammary incision wound developed a small area (2 × 0.5 cm) of dehiscence with exposure of the expander. Image 1 shows the dehiscence and surrounding cellulitis of the wound (Fig. 1). Operative breast cavity culture showed growth of *Staphylococcus epidermidis*.

2.4 Case 4

The 42-year-old woman had two synchronous right breast cancer. The patient had bilateral nipple-sparing mastectomy and subpectoral expander inserted. The expanders were not inflated at time of the operation and were secured superiorly and inferiorly. One month after the operation, the expanders had rotated subpectorally, creating a tenting effect and subsequent pressure necrosis of the overlying skin (Fig. 2). The expanders was removed, necrotic skin was excised and Veraflow™ was inserted for 1 week. There was no growth from breast cavity wound culture.

2.5 Case 5

This 57-year-old woman had left skin-sparing mastectomy and insertion of tissue expander for multifocal triple-negative breast cancer. She had adjuvant radiotherapy to the site. The wound was gradually expanded and 2 years later, she underwent exchange of tissue expander to implant. One year following this, there was a small wound dehiscence with exposure of the implant. The implant was removed and Veraflow™ was inserted for 1 week. Operative culture of the breast cavity showed growth of *Serratia marcescens* resistant to ampicillin and cefazolin.

3 Treatment

All five patients were taken to surgery for removal of the breast implants and for washout. We utilised a novel technique for the cavity irrigation and for the maintenance of the cavity. Using Veraflow™, the cavity was packed with rolls of

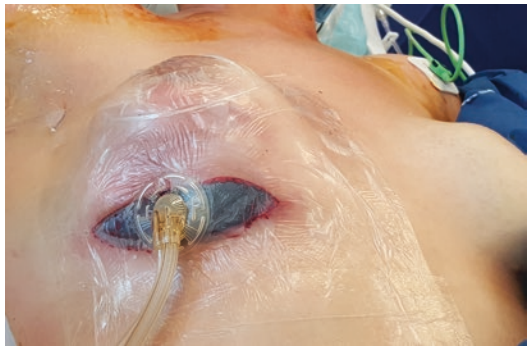


Fig. 3 In surgery the wound was cleaned and Veraflow™ attached, with a gauze used to protect the nipple

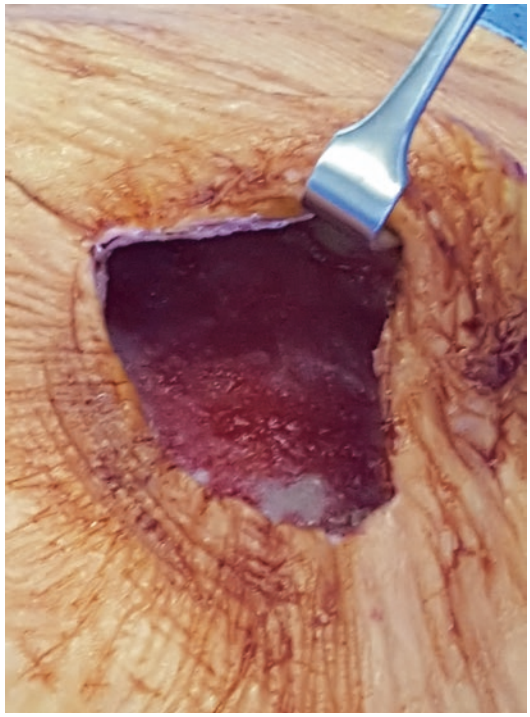


Fig. 4 Left breast cavity after the second application of Veraflow™. Note the healthy granulation tissue and, most importantly, the maintenance of the cavity

sterile foam. An airtight seal was then achieved and connected by suction/irrigation tubing to the Veraflow™ device. The Veraflow™ alternated between an interval of irrigation (15 min) of the wound with normal saline, followed by 45 min of a continuous vacuum suction (setting 75 mmHg) (Fig. 3). The sponge was changed every second day in the operating theatre (Fig. 4).

By the seventh day, the wound cavity was clean, with healthy granulation tissue. One week after admission with failed, infected prosthesis, all five patients had successful reinsertion of breast implants. The successful maintenance of the breast cavity volume allowed reinsertion of implants of the same size as previously (between 300 and 350 mL). Figure 5 shows the breast 2 weeks after implant reinsertion.

4 Discussion

Cosmesis is an important goal of oncoplastic breast surgery. Implant infection has severe consequences as the loss of prosthesis, and the ensuing inflammation may result in loss of the cavity and scarring. Negative pressure wound therapy has been indicated for a number of breast conditions, such as breast reconstruction dehiscence, chronic wound caused by chronic mastitis, granulomatous mastitis, radiation necrosis of the breast, necrotizing fasciitis of the breast and pyoderma gangrenosum [1–4]. The current mainstays of these conditions have been wound washout, intravenous antibiotics and negative pressure dressings with/without re-reconstruction. Simultaneous instillation therapy has not been utilised prior.

The Veraflow™ system delivers negative pressure wound therapy with intermittent instillation using an instillation-specific reticulated open-cell foam dressing. Negative pressure wound therapy has been found to facilitate wound healing by promoting tissue granulation, increasing angiogenesis and perfusion, decreasing oedema and removing the bacterial bioburden [5, 6]. Veraflow™ is used for intermittent instillation and irrigation with topical fluids, including saline, antibiotics and antimicrobials, to cleanse the wound and remove the biofilms. In our situation, we have used normal saline. Although its use is novel in breast surgery, negative pressure wound therapy with instillation has been used for a number of other conditions, such as chronic osteomyelitis or orthopaedic prosthesis infections [7–10], stoma site breakdowns [11], diabetic leg ulcers [12] and necrotizing fasciitis wounds [13].

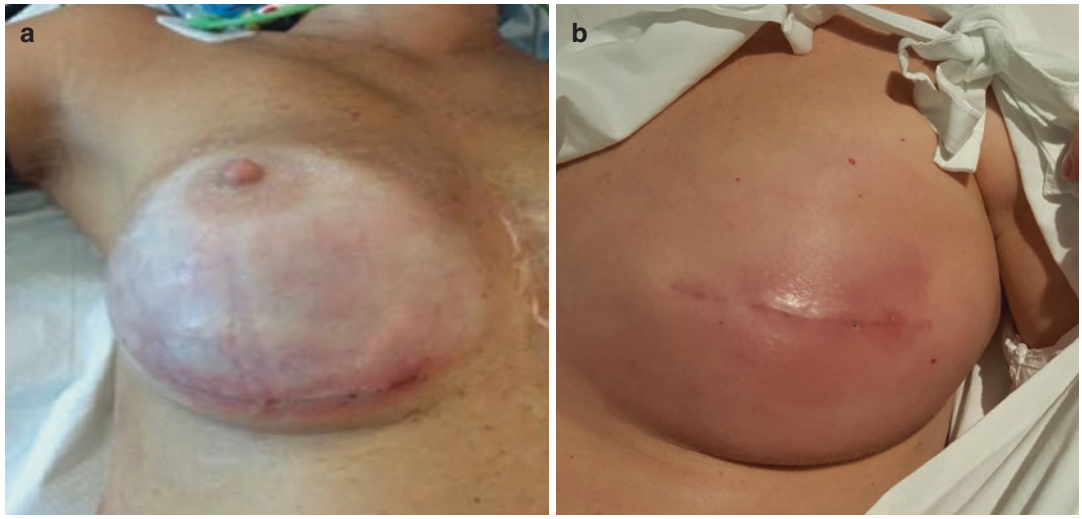


Fig. 5 After 1 week of negative pressure wound treatment with instillation, implant was reinserted. Wound 2 weeks after implant reinsertion. (**a**) Right breast. (**b**) Left breast

Conclusions

Negative pressure wound therapy with instillation has been an effective adjunctive tool in the management of complex breast wounds.

References

1. Giacalone PL, El Gareh N, Rihaoui S, Giovannini U (2006) Transverse rectus abdominis myocutaneous flap wound-healing complications in breast reconstruction: assisted closure using foam suction dressing. Breast J 12:481–484
2. Leak K, Spruce P, Johnson S (2009) Improving outcomes for patients following surgery for breast cancer. Wounds UK 5:47–55
3. Luedders DW, Bohlmann MK, Hornemann A, Dittmer C, Diedrich K, Thill M (2011) Successful application of vacuum-assisted closure therapy for treatment of mastitis-associated chronic breast wounds. Arch Gynecol Obstet 283:1357–1362
4. Schintler MV, Grohmann M, Donia C, Aberer E, Scharnagl E (2010) Management of an unfortunate triad after breast reconstruction: Pyoderma gangrenosum, full-thickness chest wall defect and Acinetobacter baumannii infection. J Plast Reconstr Aesthet Surg 63:e564–e5e7
5. Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA (2003) A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. Ann Vasc Surg 17(6):645–649
6. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 38(6):553–562
7. Timmers MS, Graafland N, Bernards AT, Nelissen RG, van Dissel JT, Jukema GN (2009) Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis. Wound Repair Regen 17(2):278–286
8. Koster G (2009) Management of early periprothetic infections in the knee using the vacuum-instillation therapy. Infection 37(Suppl 1):18–20
9. Lehner B, Weiss S, Suda J, Witte D (2009) Application of V.A.C. Instill® therapy in case of periprosthetic infection in hip arthroplasty. Infection 37(Suppl 1):13–17
10. Lehner B, Fleischmann W, Becker R, Jukema GN (2011) First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study. Int Orthop 35(9):1415–1420
11. Wolvos T (2004) Wound instillation--the next step in negative pressure wound therapy. Lessons learned from initial experiences. Ostomy Wound Manage 50(11):56–66
12. Bernstein BH, Tam H (2005) Combination of subatmospheric pressure dressing and gravity feed antibiotic instillation in the treatment of post-surgical diabetic foot wounds: a case series. Wounds 17(2):37–48
13. Schintler MV, Prandl EC, Kreuzwirt G, Spendel S, Grohmann M (2009) The impact of V.A.C. Instill® in severe soft tissue infections and necrotizing fasciitis. Infection 37(Suppl 1):31–36

Intraoperative Treatment with 5-FU

Guillermo Blugerman, Diego Schavelzon, Roberto Rodrigo Cáceres, Victoria Schavelzon, Miguel Mussi, and Guido Blugerman

1 Introduction

Hypertrophic scars and keloids are unintended consequences of surgical interventions, from the functional and aesthetic point of view for both patients and surgeons. Both entities are characterized by a pathologically excessive dermal fibrosis and an aberrant cicatrization of the wound, due to abnormal scarring in response to trauma, inflammation, surgery, or burns in predisposed individuals [1].

Inflammation causes cell proliferation or change in cellular behavior where cytokines, hormone-like proteins, modulate cellular behavior. These include interleukins, lymphokines, monocytes, interferons, tumor necrosis factors, and chemokines [2]. The prevention of the extension of inflammation through the inhibition of the extracellular matrix and the production of inflammatory proteins with anti-inflammatory agents is one of the best established approaches for the management of the scar. Corticosteroids are effective in the majority of uninfected scars that present symptoms such as pain and pruritus [3].

Villafuerte-Vélez et al. [4] performed a work where they infiltrated the dermis and the subcutaneous cellular tissue with dexamethasone acetate on the marking line, prior to the incision of the reduction mastoplasties. They demonstrated that pathological scarring can be prevented. Their study was based on the anti-chemotactic and anti-inflammatory properties of corticosteroids, which decrease the synthesis of collagen, glycosaminoglycans, and biochemical mediators. In this way it controls the inflammatory and fibroblastic response that is increased in these anomalous healing processes.

It has been shown that 5-FU inhibits the proliferation of fibroblasts in the body and reduces postoperative scarring by reducing fibroblastic proliferation. The efficacy and safety of the drug has been demonstrated in trabeculectomy surgery with long-term follow-up and in multicentric studies [5]. A study by Bulstrode et al. [6] revealed that 5-FU selectively inhibits collagen synthesis. 5-FU interrupts the synthesis of DNA and RNA at several levels, including the inhibition of thymidylate synthetase and the production of toxic metabolites. The interest in antineoplastic agents as a therapeutic modality is logical, since it has been demonstrated that keloids exist in a hypermetabolic state. Both in vitro and in vivo studies have confirmed that 5-FU inhibits collagen synthesis. There are a number of clinical reports in the literature on the efficacy of various antineoplastic drugs on the modification of healing [7].

There is a series of clinical studies on the efficacy of 5-FU in the keloid treatment that revealed promising results. Fitzpatrick was the first to publish an anecdotal report of extensive experience with 5-FU, although no quantitative

G. Blugerman (✉) · D. Schavelzon · R. R. Cáceres
V. Schavelzon · M. Mussi · G. Blugerman
Centro B & S Excelencia en Cirugía Plástica,
Buenos Aires, Argentina
e-mail: drblugerman@gmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_122, © Springer International Publishing AG
Published Online: 11 July 2018

data or control groups were presented. The Fitzpatrick regimen used a 9:1 ratio of 5-FU with steroids. The small concentration of triamcinolone has no additive therapeutic effect, but Fitzpatrick claimed that it reduces the side effect of the erythema that can occur with the injection of pure 5-FU. A recent prospective study revealed a statistically significant improvement in the efficacy of 5-FU compared to triamcinolone [8].

The possibility of altering the pathophysiology of keloid scars was investigated in patients using a single application of 5-fluorouracil solution for 5 min, after performing the excision of the scar. At the same time, excisions were made creating wounds to treat with a phosphate-buffered saline for 5 min and then serving as synchronous controls. An objective and subjective scoring system was used to evaluate the change in the quality of wound healing and scar tissue produced by this treatment. All the wounds treated with fluorouracil, compared to the control samples, had a significant reduction in all markers of recurrence; in addition the fibroblasts showed a reduced contractile capacity [9].

Fatemi et al. [10], on the hind leg of rabbits, on the index and annular fingers, cut the skin to open the flexor tendon sheath and cut it. Then a repair was made with 5/0 nylon suturing the tendon core, nylon 6/0 for the peripheral sutures. A 50 mg/mL 5-FU solution was applied with cotton for a period of 5 min. After 3 weeks, the severity of the peritendinous adhesion was measured. With a histopathological examination, subjective evaluations of the adhesion site regeneration criteria that included fibroplasia, fine vascular formation, and collagen precipitation were obtained, obtaining as a result that the local application of 5-FU significantly reduced the peritendinous adhesion.

The effects of 5-fluorouracil in a biodegradable slow-release gelatin system on the healing of chicken tendons were investigated. The third and fourth finger tendons were cut and then repaired with 5-0 atraumatic monofilament polypropylene sutures. The epitenon was repaired with 6-0 non-traumatic monofilament polypropylene sutures. A 20 × 10 × 1 mm gelatin mold block composed of 25% glycerin and 10 mg 5-FU was placed under the repaired area between the tendon and the fibrous aspect of the finger and then wrapped around it. In the third week, a histopathological examination was used, demonstrating that, through a slow-release 5-FU gelatin system, they reduced the formation of adhesions in the flexor tendon healing [11].

2 Patients and Methods

Through a prospective, longitudinal, analytical study, we included a total of 45 patients diagnosed with pathological scarring, of which 15 patients with a history of scarring hypertrophy in other previous surgeries, 10 patients with a history of keloid healing in another body area, 12 patients with recurrence of scarring hypertrophy that was amenable to secondary resection, and 8 patients with recurrent keloid scarring after primary surgical treatment. The duration of the study comprised the year 2012–2017, during which each patient was followed up with the evaluation of the state of healing through the Vancouver scale.

The surgical protocol practiced was the use of a sterile gauze measuring 10 cm × 10 cm in size (Fig. 1), embedded to its full saturation state, with 10 mg of 5-FU (Figs. 2 and 3), which rested on the total surgical surface area resulting from the resection of the previous scar or over the surgical incision of the surgery to which the patient was subjected (Fig. 4). The application time was 5 min in total, after which, surgical closure was made by planes using monofilament or absorbable multifilament sutures. In no case was postoperative topical medication administered, nor mechanical scarring plates.

Fig. 1 Sterile gauze measuring 10 cm × 10 cm in size

Fig. 3 Embedded to its full saturation state, with 10 mg of 5-FU

Fig. 2 Embedding sterile gauze with 5-FU

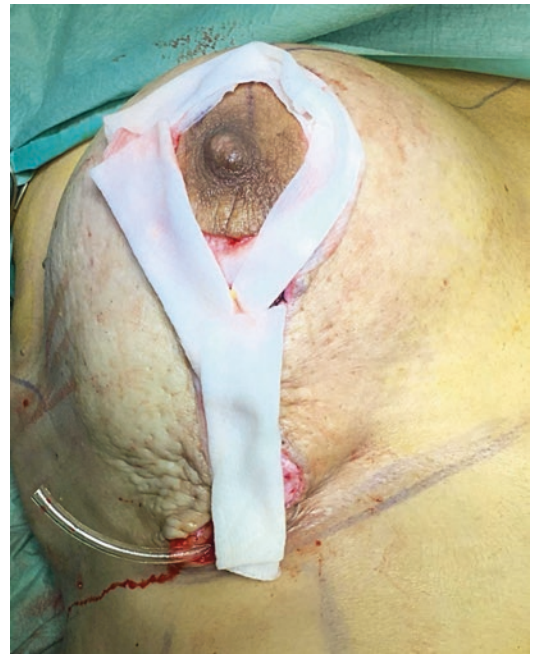


Fig. 4 Rested on the total surgical surface area

Once all the patients received the treatment, the warning signs were explained in the case of the presence of a vicious cicatrization, warning that the first one to appear is pruritus. In the presence of this symptom, they had to go to the clinic for infiltration with 5FU and intralesional triamcinolone.

3 Results

Of the 45 participating patients, those of the group with a history of hypertrophic scarring in other previous surgeries and of the group with keloid scarring in another body zone, only in three cases, the presence of vicious healing was observed in the new scar, representing 12%. In the rest of the cases of these two groups, in 88% of the patients, a notorious preventive activity of bad scarring was observed with this technique.

For the group of patients with recurrence of scarring hypertrophy that was amenable to secondary resection and the group of patients with recurrent keloid scarring after primary surgical treatment, in four cases the presence of vicious scarring was observed in the new scar, representing 20%, so that these patients were subsequently controlled with intralesional injections of 5FU and triamcinolone reducing the total percentage of poor healing to 5% of patients.

In this way, with this work protocol, hypertrophic and keloid healing was controlled in 91% of the patients, with 45 patients participating, of whom 41 patients had a successful outcome with no evidence of any alteration in healing (Figs. 5, 6, and 7).

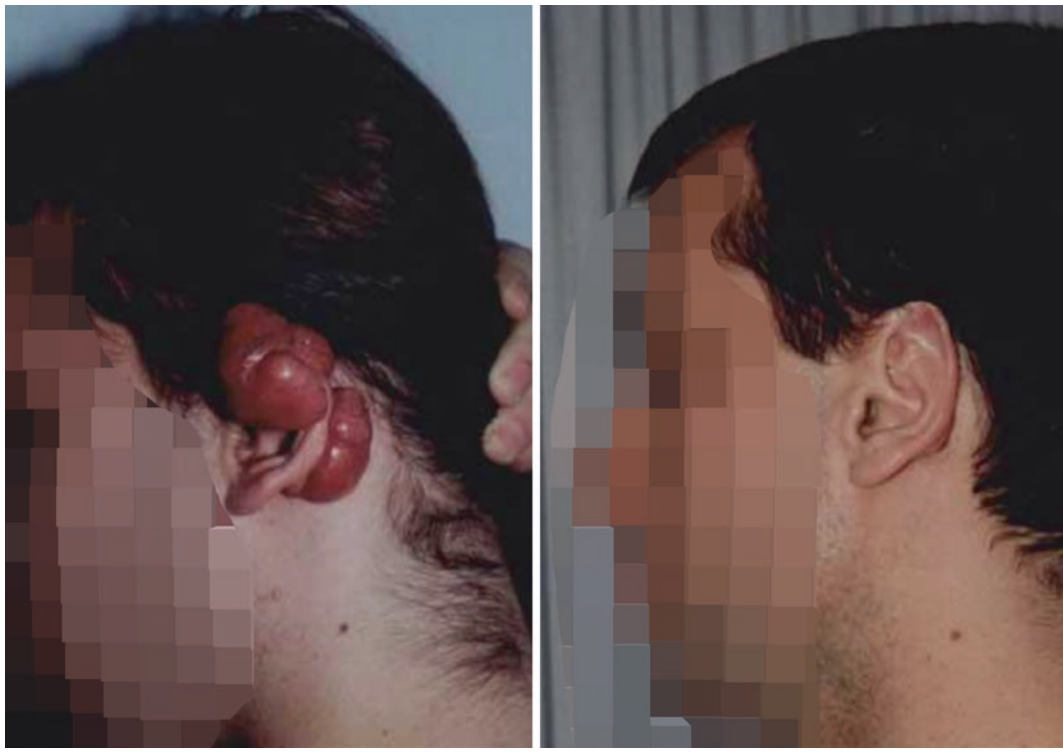


Fig. 5 (Left) Preoperative. (Right) 5 years after treatment

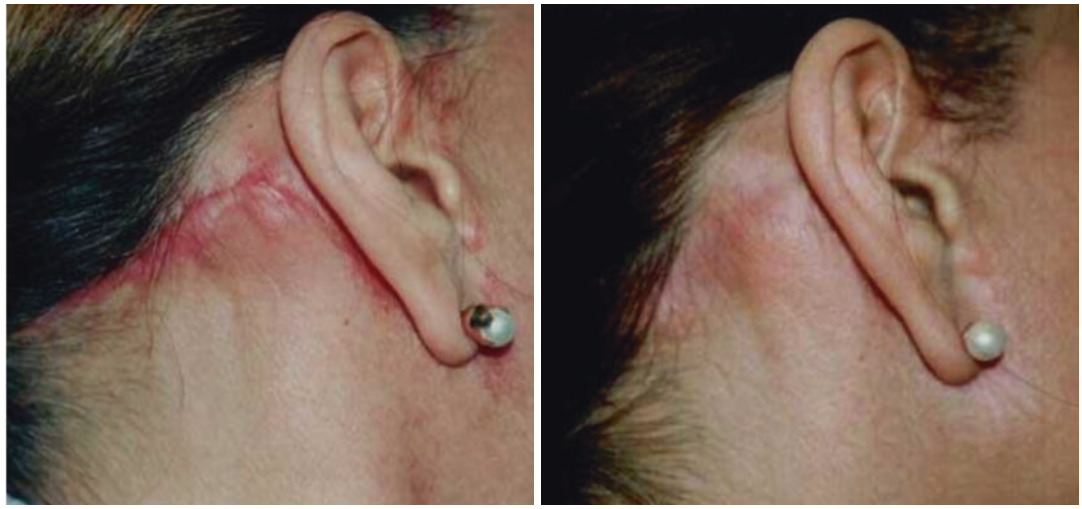


Fig. 6 (Left) Before treatment. (Right) After intraoperative treatment

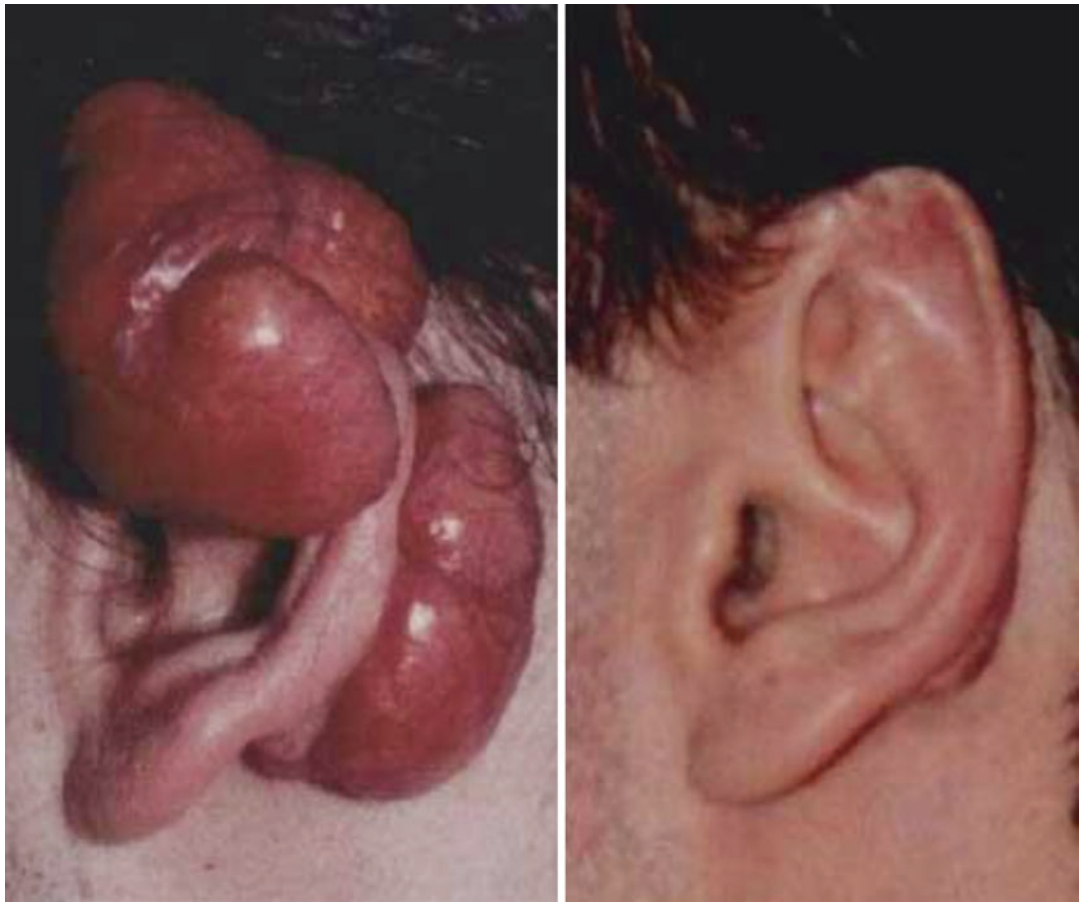


Fig. 7 (Left) Before resection. (Right) After treatment but recurred later

4 Discussion

The hypothesis of the use of intraoperative 5-FU that would prevent or diminish the development of pathological scarring is based on the fact that it would act in the initial stages of healing, that is, the inflammatory period selectively inhibiting collagen synthesis, interrupting the synthesis of DNA and RNA at several levels, including the inhibition of thymidylate synthetase and the production of toxic and fibroblastic metabolites, which occur within the first 15 days after the cutaneous wound has been produced.

In addition, there being important evidence in several studies that the prolonged contact of the 5-FU enhances its effects, an ideal carrier with low cost that can be used by the surgeon in any medium in which it is found is sought. With the application of 5-FU through a gauze, the substance is able to come into contact and stay longer in the area of the beginning of the inflammatory cascade, unlike traditional techniques, and without the need to find in complex presentations.

Conclusions

With the protocol implemented during the course of 5 years, the use of 5-FU in sterile gauze, applied for 5 min on the bloody sites either by resection of a previous scar or on a surgical incision, showed that this simple technique improves the results in the prevention of pathological scars, being able to be used especially in patients where vicious scarring could occur.

References

1. Kose O Waseem A (2008) Keloids and hypertrophic scars: are they two different sides of the same coin? Dermatol Surg 34:336–346
2. Tayal V, Kalra BS (2008) Cytokines and anticytokines as therapeutics an update. Eur J Pharmacol 579:1–12
3. Edriss AS, Mestak J (2005) Management of keloid and hypertrophy scars. Ann Burns Fire Disasters 18(4):202–210
4. Villafuerte-Vélez CK, Castro-Cabrera AC, Restrepo-Villafuerte C (2017) Corticoterapia profiláctica transquirurgica de la hiperplasia cicatrizal. Cir Plast Iberolatinoam 43(1):33–39
5. Five-year follow-up of the Fluorouracil Filtering Surgery Study. The Fluorouracil Filtering Surgery Study Group (1993) Am J Ophthalmol 115:82–92
6. Bulstrode NW, Mudera V, McGrouther DA, Grobbelaar AO, Cambrey AD (2005) 5-fluorouracil selectively inhibits collagen synthesis. Plast Reconstr Surg 116:209–221
7. Khaw PT, Sherwood MB, MacKay SL, Rossi MJ, Schultz G (1992) Five minute treatments with fluorouracil, floxuridine, and mitomycin have long term effects on human Tenon's capsule fibroblasts. Arch Ophthalmol 110:1150–1154
8. Fitzpatrick RE (1999) Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg 25:224–232
9. Uppal RS, Khan U, Kakar S, Talas G, Chapman P, McGrouther AD (2001) The effects of a single dose of 5-fluorouracil on keloid scars. A clinical trial of timed wound irrigation after extralesional excision. Plast Reconstr Surg 108:1218–1224
10. Fatemi MJ, Shirani S, Sobhani R, Lebaschi AH, Gharegozlou MJ, Bagheri T, Pedram M, Saberi M, Araghi S, Fatemi MA (2018) Prevention of peritendinous adhesion formation after the flexor tendon surgery in rabbits. A comparative study between use of local interferon-α, interferon-β, and 5-fluorouracil. Ann Plast Surg 80(2):171–175
11. Karaaltin MV, Ozalp B, Dadaci M, Kayıkcıoglu A, Kecik A, Oner F (2012) The effects of 5-fluorouracil on flexor tendon healing by using a biodegradable gelatin, slow releasing system. Experimental study in a hen model. J Hand Surg Eur Vol 38(6):651–657

Treatment of Subacute Traumatic Lower Limb Wounds by Assisted Healing and Delayed Selective Reconstruction

Zoran Marij Arnež, Giovanni Papa, Vittorio Ramella, Frasca Andrea, and Chiara Stocco

1 Introduction and Background

Traumatic soft tissue defects that cannot be closed by direct suture are usually covered by split/full-thickness skin grafts, dermal substitutes, or different kinds of flaps (local, regional, or free flap), but timing of coverage has been a matter of discussion over the years [1–5].

Godina's [1] experience with coverage of acute wounds by free flaps within 72 h after injury which resulted in less infection, less free flap failure, and shorter time to bone healing and full weight-bearing, compared to coverage of subacute and chronic wounds, has become a milestone directing surgeons dealing with lower extremity trauma toward early closure of both simple and complex traumatic soft tissue defects [1, 2].

Z. M. Arnež (✉) · G. Papa · F. Andrea · C. Stocco
Department of Plastic and Reconstructive Surgery, Ospedale di Cattinara, Azienda Ospedaliero—Universitaria Ospedali Riuniti di Trieste (ASUITS), Trieste, Italy
e-mail: zoran.arnez@asuits.sanita.fvg.it; zoran.arnez@aots.sanita.fvg.it

V. Ramella
Department of Medicine, Surgery and Health Sciences, Plastic and Reconstructive Surgery, Ospedale di Cattinara, Azienda Ospedaliero—Universitaria Ospedali Riuniti di Trieste (ASUITS), Trieste, Italy

The "fix and flap" principle has become widely accepted all over the world.

Such treatment, however, requires a clean wound before coverage, which can be achieved only by a radical (pseudotumor) wound debridement (with little space for "second-look" procedures), copious irrigation of the wound, and full (often non-specific) antibiotic coverage.

The purpose of early coverage of acute traumatic wounds is to provide well-vascularized soft tissue cover, in particular for open fractures, exposed growth plates, and bone fixation materials, before wound colonization, inevitably leading to invasive infection and additional tissue loss [6]. On the contrary, Byrd [2] suggested the management of subacute wounds (lesions that have occurred more than 7 days from wounding that are characterized by signs of inflammation such as erythema, swelling, and cellulitis and/or by seropurulent drainage and are colonized or infected) by open wound technique "until the parameters of a chronic localized wound are established, at which time flap coverage is again indicated." Indeed, flap closure of subacute wounds, compared to acute and chronic ones, in Godina's [1] experience, leads to the worst results.

Many things have changed since the 1980s: devices such as negative pressure wound therapy (NPWT) increase vascularity of the wound,

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_124, © Springer International Publishing AG
Published Online: 11 July 2018

promote growing of granulation tissue, decrease edema and thus the circumference of the limb, and serve as an effective barrier against nosocomial infection [1–10].

Hydrosurgery performed by water scalpel (Versajet®) permits allows more accurate debridement and irrigation of the wound while protecting noble structures [1–4]. Piezoelectric bone cutters excise bones without thermal damage to cutting surfaces and with no possibility of transection of underlying noble structures [1].

Strong cooperation has been built between trauma/orthopedic and plastic surgeons who, instead of looking at the patient only from the standpoint of fractures or soft tissue problems, causing considerable delay in treatment, at present, see the patient together at the same time, in the emergency room, planning the treatment from the beginning to the end. Standards for the management of lower limb open fractures have been produced by BAPRAS/BOA detailing optimal treatment for patients with these challenging injuries [1].

From the results of such treatment, it became clear that complex lower extremity wounds should not be treated as medical emergencies, in the middle of the night, but instead in a programmed way. Two "time windows" exist: during the first day after injury, the wound debridement and temporary bone fixation are necessarily performed, whereas definitive wound cover (by a flap) can be carried out within 7 days from the day of injury. In the meantime, one or more "second-look" procedures and additional debridements can take place, after which the wound is always "sealed" by a NPWT device. At the time of the definitive reconstruction, within 1 week after injury, which takes place in the programmed trauma/orthopedic operating room during the normal working hours with the dedicated nurses and expert surgeons, the temporary (external) bone fixation is changed for the definitive one (internal) and immediately covered by well-vascularized tissue provided by transposition or free transfer of different types of flaps (muscle, musculo-/fascio-cutaneous, or perforator flaps) [11].

Due to several reasons, such as long cardiocirculatory instability in intensive care units following poly-trauma, other diseases precluding general anesthesia, problems with transport, etc., patients are still being referred for coverage of complex lower extremity wounds in the subacute phase of wound healing.

After 1 week from the injury, the wound enters the subacute phase of healing in which treatment of complex wounds becomes more prone to complication because the wound changes from contaminated to infected one (involving both bone and soft tissue infection) and blood vessels become fragile and, after microvascular anastomoses, more prone to vascular complications (spasm, thrombosis) leading to free flap failure [2, 6].

Additional time is necessary also to correct severe hyperglycemia in diabetic patients as well as to define targeted antibiotic therapy to fight wound infection. During this time the wound has to be covered by special dressings or, better, sealed by the negative pressure wound therapy. In addition, elderly traumatized poly-morbid patients with generalized atherosclerosis often present with stenosis/occlusion of one or more lower leg main arteries with critical distal perfusion requiring careful assessment and perhaps endovascular dilatation and stenting before definitive soft tissue reconstruction. All such situations require a different type of approach compared to acute traumatic injuries [4, 5].

By embracing the concept of ADH-DSR, the subacute wounds are treated conservatively at first. During this time the wound is debrided by several conservative debridements, sealed by NPWT or covered by modern dressings, while the patient's comorbidities are treated. Better vascularity of the wound is achieved by intraluminal vessel dilatation (PTA) and stenting, hyperglycemia is corrected, and cardiac and pulmonary problems are solved. During the wound bed preparation when granulation tissue growth is enhanced by NPWT, delayed selective reconstruction (by a combination of two or more reconstructive techniques such as skin grafts (SG), dermal substitutes (DS), and flaps) is planned to be performed when the wound is clean and the patient is prepared for operation (comorbidities under control, operation under general anesthesia possible, etc.).

How should patients with subacute traumatic wounds to lower limbs be treated? Is it possible to achieve results comparable to the results of contemporaneous acute wound closure? [4, 5].

2 Patients and Methods

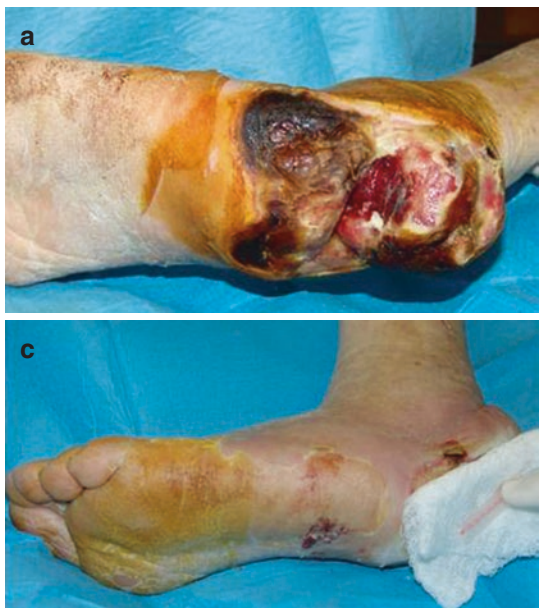
We first manage subacute wounds conservatively by "assisted healing" and only after that by "delayed selective reconstruction." "Assisted healing" stands for trying to assist and speed up the natural healing process by fighting infection, by supporting and enhancing wound bed preparation (granulation tissue growth), and by treating comorbidities.

During this time the subacute wound is cleaned (when possible without any blood loss) by multiple conservative/operative debridements using hydrosurgery or piezoelectric scalpels, thus selectively removing only definitively necrotic tissues until it is macroscopically clean [12–16]. Excised tissues, including bone fragments, are sent for microbial tissue culture and definition of susceptible antibiotics (antibiogram) in order to program targeted antibiotic therapy. This phase is combined with optimal dressing care and/or, when indicated, negative pressure wound therapy, which decreases edema and promotes formation of granulation tissue (Figs. 1 and 2) [8–10, 17–23].

The aim of "assisted healing" is to reduce the size of the soft tissue defect requiring flap coverage by growing granulation tissue which leads to an increase of the wound surface that can be closed by dermal substitutes and skin grafts only (Fig. 2). Each patient is carefully assessed for comorbidities, which can impair the healing process.

Respiratory and cardiac problems are treated first, followed by correction of hypoproteinemia by appropriate nutrition. The healing potential is increased by revascularization of stenotic/occluded arteries by PTA, by providing glycemic control, by targeted antibiotic therapy, by offloading, and by compression therapy (Fig. 3).

During the wound bed preparation phase, the reconstruction is being planned. All reconstructive techniques (skin grafts, dermal substitutes,



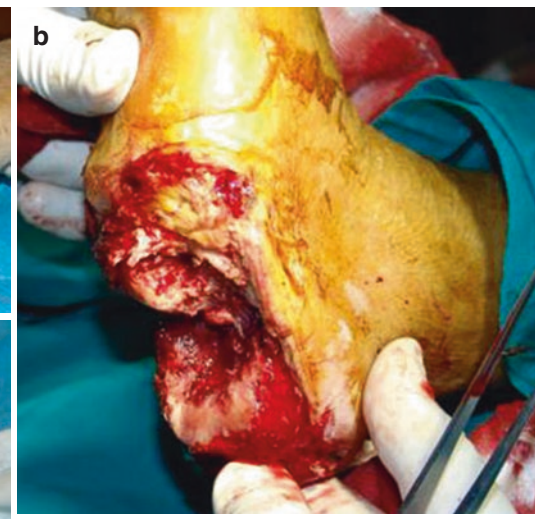


Fig. 1 (**a**) Open fracture of the calcaneus in a diabetic patient 3 weeks after injury. Note: extensive soft tissue defect on a weight-bearing zone, presence of necrosis and serous-purulent discharge. (**b**) First operation 3 days after admission: (conservative) debridement of soft tissues and bone. (**c**) First operation 3 days after admission: placement of NPWT (VAC®) after debridement

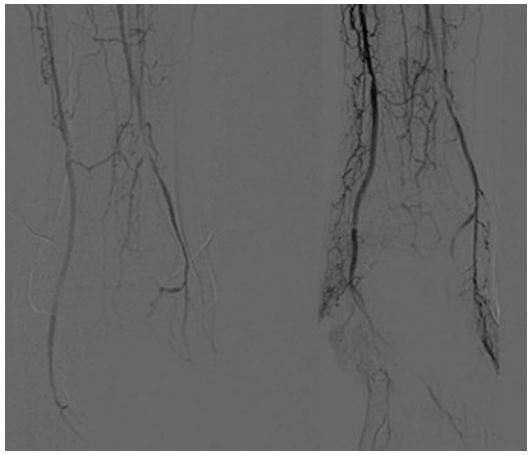


Fig. 2 (Left) Angiography of the lower leg after first debridement, performed on basis of partial tissue oxygen pressure level less than 20 mmHg measured the day before, showing poor perfusion of the foot. (Right) Angiogram after PTA performed during the same session showing improved perfusion of the foot

and all types of flap) are being considered alone or in combination to be used when necessary. Only when required, flaps are planned focusing on the requirements of the recipient site (size, thickness), tissue composition, but also the donor site (little/no functional deficit, hidden scar). For these reasons we are talking about delayed "selective reconstruction."

The goal of "selective reconstruction" is to use flaps only when truly necessary and cover areas that present granulation tissue, promoted during the assisted healing period, by dermal substitutes and skin grafts: in this way, the reconstruction requires flaps that are smaller in size, thus leading to better functional and esthetic results (Fig. 4)

The other available possibility would be a surgical conversion of the subacute wound into an acute one, by super radical debridement at the

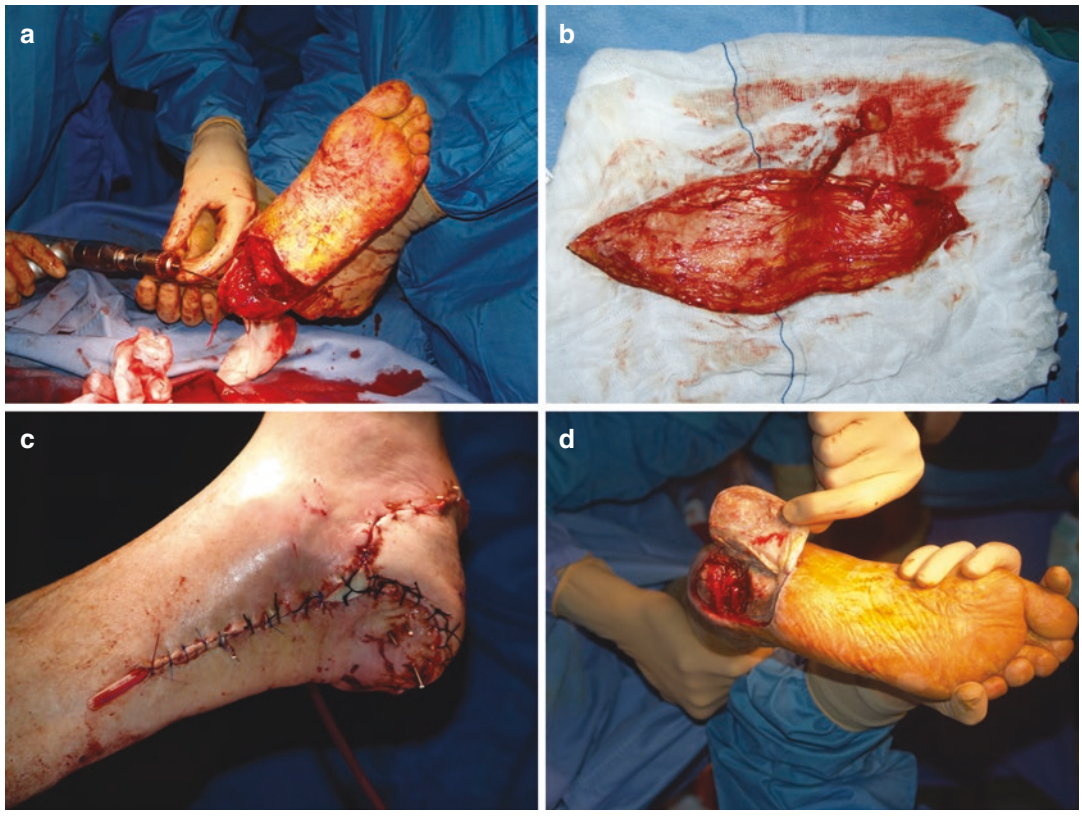


Fig. 3 (**a**) Second operation, 1 week after revascularization by PTA, consisted of radical wound debridement, bone fixation by two K wires, and wound closure by free ALT flap. (**b**) Free ALT fascio-cutaneous perforator flap. (**c**) Result after the second operation. Note: well-perfused flap, access to the posterior tibial vascular axis for end-to-side microvascular anastomosis, two percutaneous K wires for calcaneus fixation. (**d**) Third operation 5 weeks after radical debridement, bone fixation, and free flap transfer: cancellous bone grafting to the calcaneal bone defect

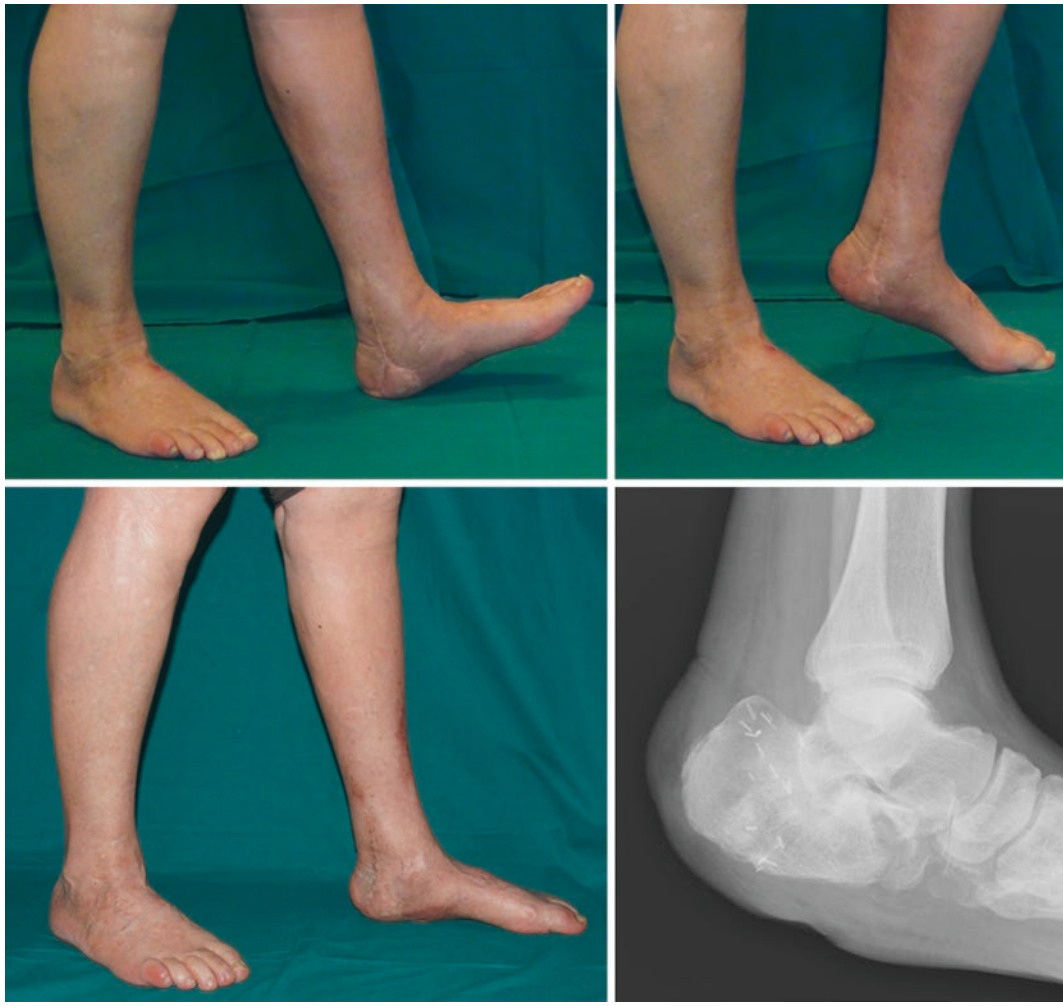


Fig. 4 Full weight-bearing and walking in normal shoes 6 months after last surgery showing good shape of calcaneus and healed fracture

cost of larger soft tissue defects and more chance of loss of function afterward. Further damage would be created at the flap donor site since larger flaps would be required for coverage; moreover, such operations, without managing comorbidities properly, can carry to increased risks of immediate systemic and local complications.

3 Results

During the period from 2007 to 2017, we treated subacute wounds on lower extremities by AH-DSR method in 34 patients (20 males [58.8%] and 14 women [41.2%]) with a mean age of 49.6 years (range, 16–88 years) (Table 1). Sixteen patients (47%) presented with a concomitant fracture: 1 (2.9%) had a Gustilo-Anderson (GA) type II fracture, 5 (14.7%) had GA IIIA fractures, and 18 (29.4%) had GA IIIB fractures [1, 2]. Eighteen patients (53%) had a lower limb injury with no fracture associated. All lower limbs sustained some degloving: 17 (50%) pattern 1, 13 (38.2%) pattern 2, and 4 (11.8%) pattern 4, according to Arnez et al. soft tissue degloving classification [24, 25].

The dimensions of soft tissue defect ranged from 28 to 880 cm^2 (mean 203.8 cm^2). The number of operations per patient ranged from one to five (mean 2.9) most of which were surgical debridements. Negative pressure wound therapy (NPWT)

Table 1 Patients' demographics, mechanism of injury, associated fractures, type of reconstruction, follow-up, and complications

Case	Sex	Age	Trauma	Poly-trauma	Fracture	Degloving	Operations	Hospitalization (days)	Follow-up (days)	Size (cm^2)	Debridements	Antibiotic therapy	NPWT	Reconstruction	Complications
1	M	16	Road traffic injury	Yes	IIIB	1	4	47	96	750	2	Yes	No	ALT + DS + SG	Osteomyelitis
2	M	28	Road traffic injury	No	IIIB	1	3	61	36	150	2	Yes	No	ALT	No
3	F	21	Road traffic injury	Yes	–	1	3	39	18	100	2	Prophylaxis	Yes	DS + SG	No
4	F	80	Road traffic injury	No	IIIA	1	3	74	90	300	2	Yes	Yes	SG	No
5	M	56	Crush	No	IIIA	2	3	49	80	200	3	Yes	Yes	SG	No
6	M	48	Road traffic injury	Yes	IIIA	2	4	30	76	100 + 30	3	Yes	No	SG	Pseudoarthrosis
7	F	76	Road traffic injury	No	IIIA	1	2	33	12	150	1	Prophylaxis	No	SG	No
8	F	22	Road traffic injury	Yes	–	1	4	9	16	80 + 8	3	Yes	No	DS + SG	No
9	M	22	Road traffic injury	No	IIIB	2	4	20	30	36	2	Prophylaxis	No	SG	No
10	M	39	Road traffic injury	No	–	2	2	15	30	250	2	Yes	Yes, instill	SG	No
11	M	16	Road traffic injury	Yes	IIIB	2	3	61	57	100	3	Yes	Yes, instill	ALT + nerve graft	No
12	F	64	Fall	Yes	II	2	3	161	34	40	3	Yes	Yes	SG	No
13	F	29	Road traffic injury	No	–	2	5	53	44	75	3	Yes	Yes	SCIP + DS + SG	Venous thrombosis
14	M	55	Road traffic injury	Yes	IIIA	1	2	31	90	72 + 8 + 8	2	Yes	No	SG	No
15	F	76	Road traffic injury	No	–	2	3	59	30	200	3	Yes	Yes	SG	No
16	F	37	Road traffic injury	No	IIIB	2	4	47	18	40	4	Prophylaxis	Yes	Ulnar flap + palmaris longus + DS + SG	No
17	F	87	Road traffic injury	No	I- > IIIB	1	4	41	30	28	2	Yes	Yes	Local fascio-cutaneous flap	No

18	M	25	Road traffic injury	No	IIIB	4	3	61	90	50	2	Yes	Yes	ALT	No
19	M	49	Road traffic injury	No	IIIB	1	4	45	24	35	2	Yes	Yes	DS + SG	No
20	M	85	Fall	No	–	2	3	20	180	280	2	Prophylaxis	Yes, instill	SG	No
21	M	58	Fall	No	–	2	2	34	90	375	1	Prophylaxis	Yes	SG	No
22	M	30	Road traffic injury	Yes	–	4	3	30	600	880	1	Yes	Yes, instill	DS + SG	No
23	M	35	Road traffic injury	No	–	1	2	28	180	56	1	Prophylaxis	Yes	SG	No
24	M	29	Road traffic injury	Yes	–	1	3	37	180	50	2	Prophylaxis	Yes	DS + SG	No
25	M	51	Road traffic injury	No	–	1	2	31	60	20	1	Prophylaxis	Yes, instill	DS + SG	No
26	M	53	Road traffic injury	Yes	IIIB	2	4	80	360	280	1	Yes	Yes	ALT + DS + SG	No
27	F	59	Fall	No	IIIB	1	3	34	90	96	1	Yes	No	MSAP + DS + SG + local flap	No
28	F	70	Fall	No	–	1	1	11	30	48	1	Prophylaxis	No	SG	No
29	F	84	Fall	No	–	1	1	12	60	28	1	Prophylaxis	No	SG	No
30	M	20	Road traffic injury	No	–	1	2	25	30	105	1	Prophylaxis	Yes	DS + SG	No
31	M	62	Work injury	No	–	2	1	26	180	175	1	Yes	Yes	Local perforator flap + SG	No
32	F	88	Fall	No	–	1	2	28	30	220	3	Yes	Yes	SG	No
3	M	54	Road traffic injury	Yes	IIIB	4	4	120	110	600	2	Yes	Yes	DS + SG + ALT	No
34	M	61	Fall	No	–	4	1	21	10	600	1	Yes	No	SG	No

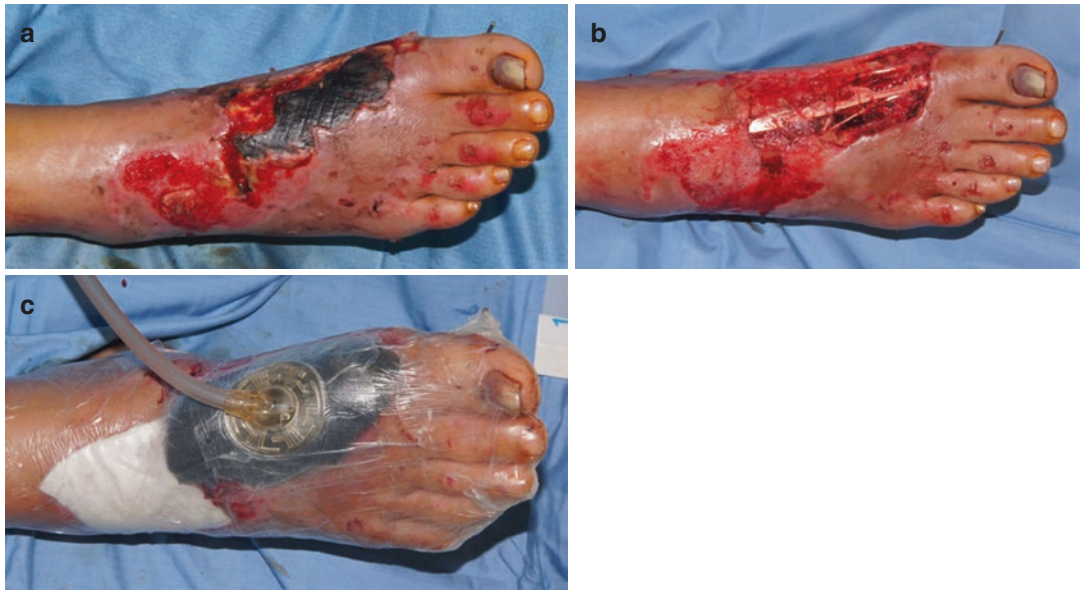


Fig. 5 (**a**) Open fracture of first metatarsal bone 2 weeks after injury. (**b**) After first debridement. Note: exposed extensor hallucis longus tendon requiring flap coverage and preserved dermis on the lateral dorsum of the foot which can be grafted by split-thickness skin grafts. (**c**) NPWT was started after the debridement

was used in 28 patients(82.3%), 23 times as VAC® and 5 times as VAC instill®. Antibiotics were given to all patients, in 12 (35.3%) as prophylaxis, as per our institution's guidelines, and in 22 (64.7%) as therapy, suggested by the infectious disease department consultants. The mean hospital stay was 34 days (range, 9–161 days).

The reconstruction was performed by split-thickness skin grafts (SG) in 16 patients (47%) (Fig. 5), by dermal substitutes (DS) in 8 patients (23.5%), by local fascio-cutaneous flaps in 2 patients (5.9%), and by free flaps in 8 patients (23.5%) (Fig. 6). All free flaps were planned in combination with DS and SG. In this case series, three (8.8%) complications were recorded: one osteomyelitis treated only with antibiotics, one intra-flap venous thrombosis in a free flap (complication that was solved through the revision of anastomosis), and one pseudoarthrosis that was treated by intramedullary nailing performed by

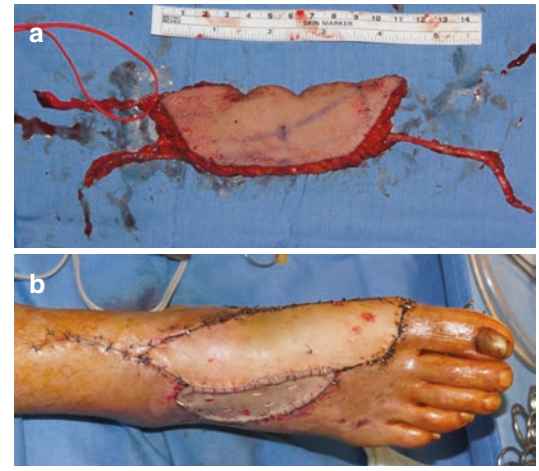


Fig. 6 (**a**) Ulnar artery perforator free flap (UAPF) after harvesting. (**b**) Result at the end of the second operation. Note: thin ulnar artery perforator free flap with anastomosis to the anterior tibial vessels covers the exposed tendon, whereas skin graft only is required for coverage of a partial thickness abrasion wound with preserved dermis

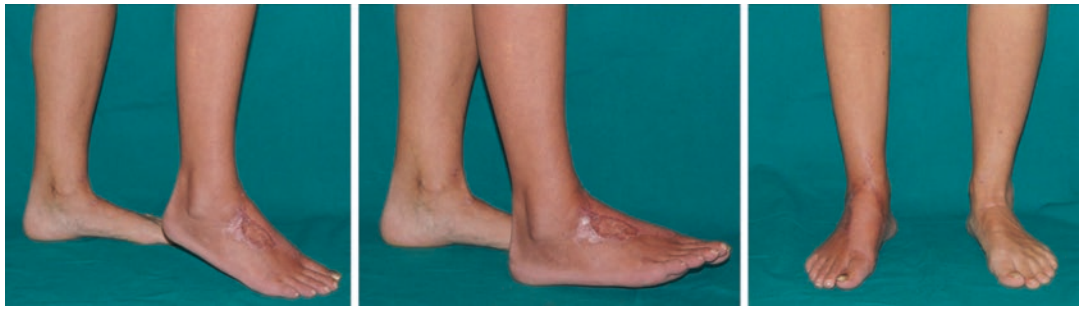


Fig. 7 (Left, middle, right) End result at 8 months after injury. Note: good functional and esthetic result. The patient is able to walk in normal shoes

our orthopedic surgeons. In addition, one free flap needed postoperative delayed debulking.

The mean follow-up was 90.9 days (range, 10–600 days)

Conclusions

Treatment of subacute traumatic wounds in the lower extremities by the AH-DSR approach in our case series is characterized by low infection rate (2.9%) and a low complication rate (8.8%), results comparable to other series [4, 5].

There was a single case of infection (an osteomyelitis treated without surgery, by antibiotics only). The complication rate was low in spite of the fact that we were dealing with complex wounds (47% were open fractures; 29% were GA IIIB open fractures [26, 27]). The three complications we recorded were the osteomyelitis described previously, a pseudoarthrosis of tibia resolved by intramedullary nailing in a wound covered by dermal substitute and SG, and an intra-flap venous thrombosis of a superficial circumflex iliac artery perforator flap which required operative revision resulting in a complete survival of the free flap. There was no free flap loss. Eight free flaps were used for coverage of open fractures and an exposed extensor hallucis longus tendon, and their average size was 192.6 cm^2 (range, 40–750 cm^2). Five anterolateral thigh (ALT) free flaps with a mean size of 266 cm^2 were used to provide coverage of larger defects, whereas smaller areas requiring thin flap coverage were treated by superficial circumflex iliac artery perforator free flap (SCIP) (75 cm^2), ulnar artery perforator free flap (UAPF) (40 cm^2) (Fig. 5), and medial sural artery perforator free flap (MSAP) (96 cm^2). Nine open fractures did not require free flap coverage and were managed by DS and SG only. Only one of them was complicated by the previously described pseudoarthrosis.

On the other hand, the wounds covered by dermal substitutes and SG averaged 202 cm^2.

The mean number of operations till final result was 2.9 (range, 1–5) per patient, while the average in-hospital stay was 34 days (range, 11–161).

These results are well comparable with the results of acute injuries treatment within 3 days of injury by the fix and flap principle [7].

By adhering to the AH-GSR approach and treatment of lower extremity subacute wounds, a surgeon can expect results which appear to be comparable to the ones obtained with the treatment of acute wounds during the first week after injury both in terms of function and esthetics (Figs. 4 and 7) [23].

References

1. Godina M (1986) Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg 78:285–292
2. Byrd HS, Spicer TE, Cierny GD 3rd. (1985) Management of open tibial fractures. Plast Reconstr Surg 76:719–730
3. Yaremchuk MJ, Brumback RJ, Manson PN, Burgess AR, Poka A, Weiland AJ (1987) Acute and definitive management of traumatic osteocutaneous defects of the lower extremity. Plast Reconstr Surg 80:1–14
4. Kumar AR, Grewal NS, Chung TL, Bradley JP (2009) Lessons from Operation Iraqi Freedom: successful subacute reconstruction of complex lower extremity battle injuries. Plast Reconstr Surg 123:218–229
5. Karanas YL, Nigriny J, Chang J (2008) The timing of microsurgical reconstruction in lower extremity trauma. Microsurgery 28:632–634
6. Arnez ZM (1991) Immediate reconstruction of the lower extremity—an update. Clin Plast Surg 18(3):449–457
7. Gopal S, Majumder S, Batchelor AG, Knight SL, De Boer P, Smith RM (2000) Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg (Br) 82(7):959–966
8. DeFranzo AJ, Argenta LC, Marks MW, Molnar JA, David LR, Webb LX, Ward WG, Teasdall RG (2001) The use of vacuum-assisted closure therapy for the treatment of lower-extremity wounds with exposed bone. Plast Reconstr Surg 108:1184–1191
9. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 38(6):553–562
10. Argenta LC, Morykwas MJ (1997) Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg 38(6):563–576
11. Nanchahal J, Nayagam S, Khan U, Moran C, Barrett S, Sanderson F, Pallister I (2009) Standards for the management of open fractures of the lower limb. Royal Society of Medicine Press, London
12. Oosthuizen B, Mole T, Martin R, Myburgh JG (2014) Comparison of standard surgical debridement versus the VERSAJET Plus™ Hydrosurgery system in the treatment of open tibia fractures: a prospective open label randomized controlled trial. Int J Burns Trauma 4(2):53
13. Hong CC, Nather A, Lee JK, Mao HT (2014) Hydrosurgery is effective for debridement of diabetic foot wounds. Ann Acad Med Singap 43(8):395–399
14. Mattera E, Iovene MR, Rispoli C, Falco G, Rocco N, Accurso A (2014) Assessment of bacterial infection in chronic wounds in the elderly: biopsy versus VERSAJET. Int J Surg 12(Suppl 2):S50–SS5
15. Sönnergren HH, Polesie S, Strömbeck L, Aldenborg F, Johansson BR, Faergemann J (2015) Bacteria aerosol spread and wound bacteria reduction with different methods for wound debridement in an animal model. Acta Derm Venereol 95(3):272–277
16. Arnez Z, Papa G, Renzi N, Ramella V, Panizzo N, Toffanetti F (2009) Use of piezoelectric bone scalpel in hand and reconstructive microsurgery. Acta Chir Plast 51(1):27–31
17. Banwell PE (1999) Topical negative pressure therapy in wound care. J Wound Care 8(2):79–84
18. Deva AK, Buckland GH, Fisher E, Liew SC, Merten S, McGlynn M, Gianoutsos MP, Baldwin MA, Lendvay PG (2000) Topical negative pressure in wound management. Med J Aust 173(3):128–131
19. Banwell PE, Téot L (2003) Topical negative pressure (TNP): the evolution of a novel wound therapy. J Wound Care 12(1):22–28
20. Avery C, Pereira J, Moody A, Whitworth I (2000) Clinical experience with the negative pressure wound dressing. Br J Oral Maxillofac Surg 38(4):343–345
21. Armstrong DG, Lavery LA, Abu-Rumman P, Espensen EH, Vazquez JR, Nixon BP, Boulton AJ (2002) Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. Ostomy Wound Manage 48(4):64–68
22. Fleischmann W, Becker U, Bischoff M, Hoekstra H (1995) Vacuum sealing: indication, technique, and results. Eur J Orthop Surg Traumatol 5(1):3740
23. Kloth LC (2002) 5 questions-and answers-about negative pressure wound therapy. Adv Skin Wound Care 15(5):226–229
24. Arnez ZM, Tyler MP, Khan U (1999) Describing severe limb trauma. Br J Plast Surg 52:280–285
25. Arnez ZM, Khan U, Tyler MP (2010) Classification of soft-tissue degloving in limb trauma. J Plast Reconstr Aesthet Surg 63:1865–1869
26. Gustilo RB, Anderson JT (1976) Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am 58:453–458
27. Gustilo RB, Mendoza RM, Williams DN (1984) Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma 24:742–746

Partial Chemical Capsulectomy and Closing of the Mammary Capsule with Anchoring Flaps

Guillermo S. Blugerman, Diego E. Schavelzon, Roberto Rodrigo Cáceres, Victoria E. Schavelzon, Miguel A. Mussi, and Guido A. Blugerman

1 Introduction

Silicone prostheses have been used in the reconstruction and aesthetic augmentation of the breast since the 1960s. Some patients who are long-term recipients of these devices are now reporting complications that require their removal. At the time of surgical explantation, the existing fibrous capsule related to the implant can be completely removed by capsulectomy. Alternatively, the capsule can be modified to receive a replacement implant or it can be left in place as a new implant cavity is created anterior or posterior to the intermediate pectoral muscle. The formation of a capsule around the breast implant is a common inflammatory process in the presence of a foreign body [1]. The periprosthetic capsule is usually well defined 3 or 4 weeks after surgery.

G. S. Blugerman (✉) · D. E. Schavelzon
Centro B & S Excelencia en Cirugía Plástica, Buenos Aires, Argentina
e-mail: drblugerman@gmail.com

R. R. Cáceres · M. A. Mussi
Rotante Centro B & S Excelencia en Cirugía Plástica, Buenos Aires, Argentina

V. E. Schavelzon
Residente 3er año Hospital Enrique Tornú, CABA, Buenos Aires, Argentina

G. A. Blugerman
Servicio de Cirugía Plástica, HIGA Pedro Fiorito, Buenos Aires, Argentina

The histology of the capsule is usually different when smooth or textured implants are used, and it is also different when it is formed in the retroglandular space or in the submuscular space.

When using a smooth surface implant, the capsule is usually thin, whitish or pink, attached to adjacent tissues and with a smooth, shiny internal surface that does not adhere to the implant [2]. In some capsules of many years of evolution has been observed the formation of calcified plaques by deposit of calcium on its internal surface.

The capsules of the rough prostheses are usually macroscopically thicker and vascularized; in these capsules, the deposition of collagen fibers is greater, so the capsule appears to be thicker. In addition, texturized surface implants allow tissue to be introduced into texture irregularities, which often results in a Velcro effect that adheres the implant to the tissues [3].

Capsular contracture is the most frequent complication after breast augmentation surgery, it appears when the capsule thickens and contracts, compressing the implant, deforming it and altering the cosmetic result of the surgery, creating a discomfort to the patient, physical and psychological discomfort [4]. The causes of the appearance of a capsular contracture are not completely known; they can be multifactorial and appear after several years of having the surgery, although the most important incidence occurs in the first year after surgery. However, there are known factors that in some way would increase

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_138, © Springer Nature Switzerland AG
Published Online: 06 December 2018

the possibility of a capsular contracture, such as the presence of clinical and subclinical infection (Biofilm), bruises, seromas, and radiotherapy administered before or after surgery, among other causes. It should be noted that some studies indicate the greater incidence of capsular contracture when the implant is placed in the subglandular plane.

According to the ASPS, nearly 400,000 women in the USA have inserted breast implants filled with saline or silicones, making it the most frequent surgery. Although no other biomaterial reveals comparable properties in terms of availability, adaptability, and immunogenicity, silicone remains a foreign body prone to a physiological and obligatory reaction of the foreign body. Therefore, the inserted silicone is encapsulated by the fibrotic tissue, which despite the intention to protect the organism against potentially harmful materials, can actually lead to a deleterious complication in itself, namely capsular contracture. Visible deformities, palpable hardness, and progressive pain make capsular contracture clinically relevant in up to 30% of cosmetic cases and even in 73% of reconstructive cases after radiotherapy; therefore, capsular contracture is the most common long-term complication after reconstruction and augmentation with silicones.

The proposed mechanisms include direct immunostimulation and subclinical infection, which are mainly responsible for the initiation and maintenance of capsule formation. Both mechanisms are able to induce a chronic inflammatory reaction that stimulates the proliferation and differentiation of fibroblasts and the subsequent synthesis of collagen and other proteins of the extracellular matrix. Considering that sterile working conditions and perioperative antibiotics to reduce the risk of infection, modifications of the silicone implant, especially its surface, were invented to increase biocompatibility and, therefore, decrease capsular fibrosis.

Nowadays, smooth, textured, and polyurethane covers are available. Although the latter revealed good results in some studies, the removal can be painful when necessary, and especially in the context of the ongoing discussion on cancer induction, implants covered with polyurethane are the least preferred therapeutic option for most of the surgeons. In contrast, smooth or textured implants are commonly used in clinical practice for breast augmentation. Interestingly, the incidence of capsular fibrosis varies significantly in the current literature and the choice of surface type is mainly based on the personal preference of the surgeon. However, in a meta-analysis recently published by Luke et al. [5] only the surface properties and in particular the smooth surfaces are more probably associated with capsular contracture. Reports like this demonstrate the impact of the implant surface on capsular fibrosis and the need for new studies that can explain these clinical findings. In addition, animal models lack noninvasive in vivo evaluations of capsule formation and, especially, of objective methods to evaluate contracture, which is mandatory for the investigation of therapeutic applications in future studies.

The histological analysis of the periprosthetic capsules showed a relatively uniform pattern during the postoperative period. Basically, three layers were observed around silicone breast implants: an outer layer composed of tissue rich in collagen, an inner layer corresponding to metaplasia similar to the synovium, and an intermediate layer, predominantly composed of loose connective tissue (Fig. 1). The outer and intermediate layers were present in all cases. The effectiveness of the texturing of breast prostheses in the prevention of capsular contracture has been reported for more than 20 years. It is believed that the characteristics of the surface of the prosthesis can cause changes in the healing process. A texture of less than 150 mm in height or depth usually leads to the formation of a full-type capsule, while a coarser, irregular texture (200 mm in height or depth) seems to cause an irregular and interrupted capsule with growth of tissue, which leads to a greater binding effect, which has been related to the reduction not only of inflammation but also of capsular contracture. On the

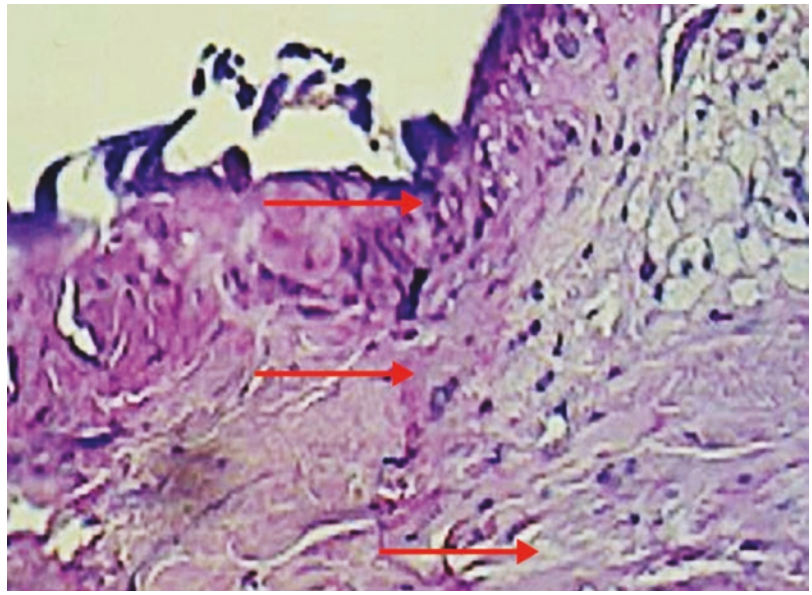


Fig. 1 Histological section with hematoxylin-eosin stain where the capsule is observed in a cross section of the mammary capsule showing the different layers. Top arrow: The outer layer is composed of tissue rich in collagen. Middle arrow: The intermediate layer, predominantly composed of loose connective tissue. Bottom arrow: The inner layer corresponding to synovial metaplasia

contrary, some researchers believe that the surface of textured breast implants and their capsules may not be directly related to the prevention of capsular contracture. According to Burkhardt et al. [6], a tissue 154 response involving a prosthesis and accompany- 155 ing its contours is an expected physiological 156 response of healing to foreign material; in addition, this response can result in capsular contracture with the consequent modification of the shape and consistency of the breast. These effects are undesirable events in plastic surgery procedures. Capsular contracture seems to have an idiosyncratic effect in humans. It can occur unilaterally and in different postoperative periods. In addition, it usually occurs within the first few years after breast augmentation.

Considering that the capsular contracture can be the result of a progressive response and of a repair tissue caused by the presence of a foreign body, we decided to evaluate the healing process for a period of up to 9 months. Therefore, in order to improve the understanding of the phenomenon of healing after breast augmentation, the intensity of the capsular contracture was controlled by the applanation tonometry method. The values found could be correlated with the histological analysis during the postoperative period considering the influence of smooth or textured implant covers.

In our study, synovial-type metaplasia occurred more often in textured implants, indicating that this factor may also be related to the decrease in the appearance of capsular contracture after breast augmentation. It is important to mention that the role of these non-collagenous layers in capsular contraction is still unknown and deserves a more extensive study for a better understanding of this event. In both groups, the thickness of the collagen layer did not show significant variations during the evaluated periods (all the factors showed descriptive values). Therefore, in both groups, there was a variation in the total thickness of the capsule due to the increase in the non-flaking, composed of connective tissue and, sometimes, of synovial metaplasia.

2 Materials

In situations that require the definitive removal of the implant, the transient extraction of the implant or the change of the position of the implant from the retroglandular plane to the retromuscular

plane and vice versa, citing evidence that the capsules related to breast implants are resolved without incident, the surgeons have chosen to leave the capsules in place when the implants are removed because the capsulectomy adds as much morbidity as the expense to the procedure. However, recent clinical and histopathological evidence suggests that resolution without complications is not always the case, and several potential problems may arise from retained capsules after implant removal. Implanted implant capsules can result in a spiculated mass suspicious for carcinoma, dense calcifications that obscure neighboring mammary tissue in subsequent imaging studies, and cystic masses due to persistent serous effusion, expansive hematoma, or encapsulated silicone-filled cysts. In addition, the retained capsules are a deposit of foreign material related to the implant in the case of implants filled with silicone gel and textured implants that promote tissue growth.

In these cases, total or partial capsulectomy may be resorted to or the empty capsule may be abandoned. In other situations, a partial treatment of the capsule may be required to rearrange a pathologically displaced implant that requires the performance of a capsulorrhaphy, capsulotomy, or capsulectomy.

2.1 In the Presence of a Residual Capsule, What Are the Options?

2.1.1 Total or Partial Surgical Capsulectomy

Disadvantages of capsulectomy at the time of implant removal include increased operative time and blood loss. The retroglandular implants (submammary) develop capsules that adhere strongly to the pectoral fascia and pectoral muscle well vascularized, while submuscular (subpectoral) can adhere to the ribs and intercostal muscles. To prevent bruising and decrease the risk of pneumothorax, some surgeons remove the anterior wall of the capsule, leaving the posterior capsule in place in the chest wall.

2.1.2 Capsulorrhaphy with Sutures

We use sutures that join the anterior capsule with the parietal. When this technique is performed, the pseudosinovia that covers the internal face of the capsules is left behind and the biofilm in the tissues is not inactivated. Few authors have addressed the consequences of retained capsules. Mammographic masses that are palpable or detected mammographically related to mammary implant capsules have been described. Such masses may be well circumscribed or bilaterally symmetrical, which indicates their benign nature and often have not been excised. Spiculated masses, on the other hand, are excised for histopathological examination to rule out adenocarcinoma.

2.1.3 Radiated Capsulotomy

This method seeks the destruction of the cavity leaving abandoned portions of capsule with their corresponding pseudosynovia in contact with the tissues. It has not been determined what happens with these tissues after their abandonment. The procedure is usually bleeding and can cause the formation of bruises of greater or lesser amounts. These hematomas present an increased risk of infection due to the presence of biofilm on the tissue and residual fibrosis.

2.1.4 Proposed Is a New Option of Total or Partial Chemical Capsulectomy and Closure of the Cavity with Anchoring Flaps

As it has been demonstrated histologically, the inner surface of the mammary capsules presents an epithelial metaplasia similar to the synovium of the joints that is usually of an exudative nature. In addition, in many of the cases, the presence of silicone residues that in a certain degree waterproof the capsule is observed. The other layers of the capsule are nothing more than

fibrocellular structures of tissue reacting to the foreign body.

If we wanted to achieve the collapse of this cavity we should destroy only the inner layer of it. To achieve this, physical, mechanical, or chemical methods can be used. Among the physical methods we could imagine the use of an ablative laser such as CO_2 or Erbium, or use some photodynamic therapy drug, but we believe that they would be more expensive and more complicated methods in their application. In the mechanical methods we could use a mechanical abrasion of the internal face of the capsule, but due to the characteristics of this tissue and its location it seems to be not viable with the elements that we have today.

Finally we have the possibility of using a chemical method. Among the elements most used in medicine are acids that are caustic liquids widely used in dermatology to remove the upper layers of the skin. Among the different acids, there is one that is very efficient, low cost, and that produces a frosting effect that facilitates the identification of the treated area (Fig. 2). Based on our experience in the use of Trichloroacetic Acid in acne lesions using the CROSS technique, and having observed the high efficiency of this acid to destroy the epithelial tissues, and its absence of local and systemic toxicity, we decided to use it for the purpose of performing a chemical Capsulectomy. To achieve a fast ablative action, effective and self-limiting effect was that we decided the concentration of 90% [7].

3 Surgical Technique

Once the implant is removed, the cavity is cleaned with gauze to remove any secretions and double capsules that may exist. Then the entire inner side of the cavity is topical using sterile cotton swabs, embedded with the 90% TCA solution (Fig. 3). Immediately upon contacting the tissues with the acid, an apoptosis and cell death of the pseudosynovial layers takes place, which is manifested by a pearly white coloration of the tissues. There would be the possibility of using a blue dye as in the Obagi peeling technique to make sure we have treated the entire internal capsular surface [8].

Wait two minutes for the acid to act completely and neutralize it with the instillation in the

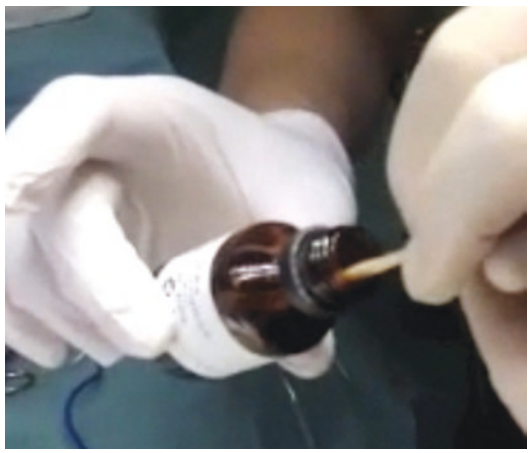


Fig. 2 Use of 90% trichloroacetic acid as a chemical element of capsulectomy

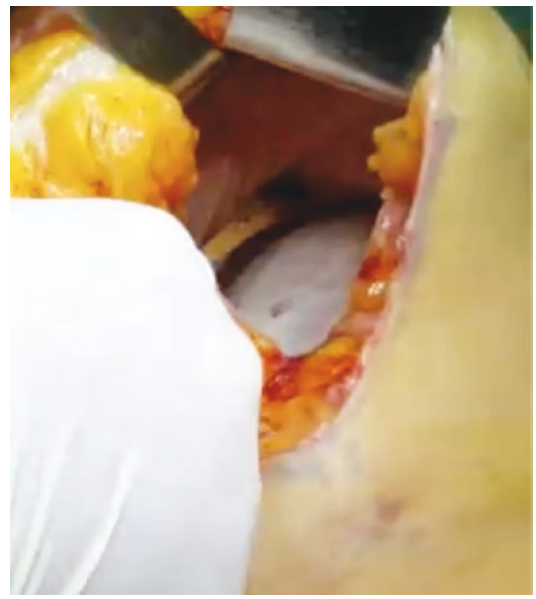


Fig. 3 Application of trichloroacetic acid through the swab, placed directly on the inner layer of the capsule

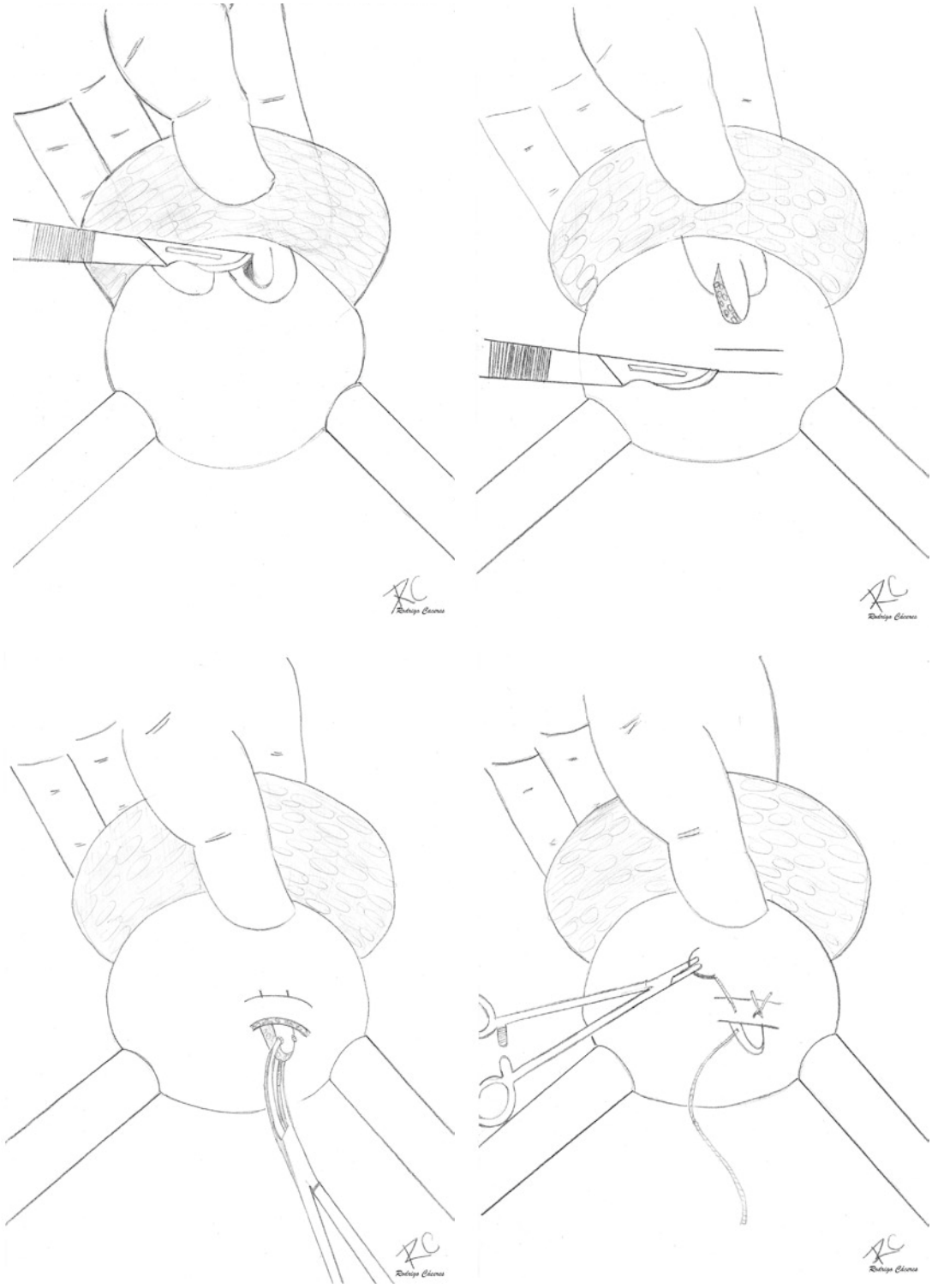


Fig. 4 Diagram of the stages for the realization of the anchoring flap in four steps: Incision on the anterior wall of the capsule, creating the anterior vertical flap; Incision on the posterior wall of the capsule, creating the posterior horizontal flap on the handle; Anchoring movement interacting both flaps. Fixation with suture of the flaps

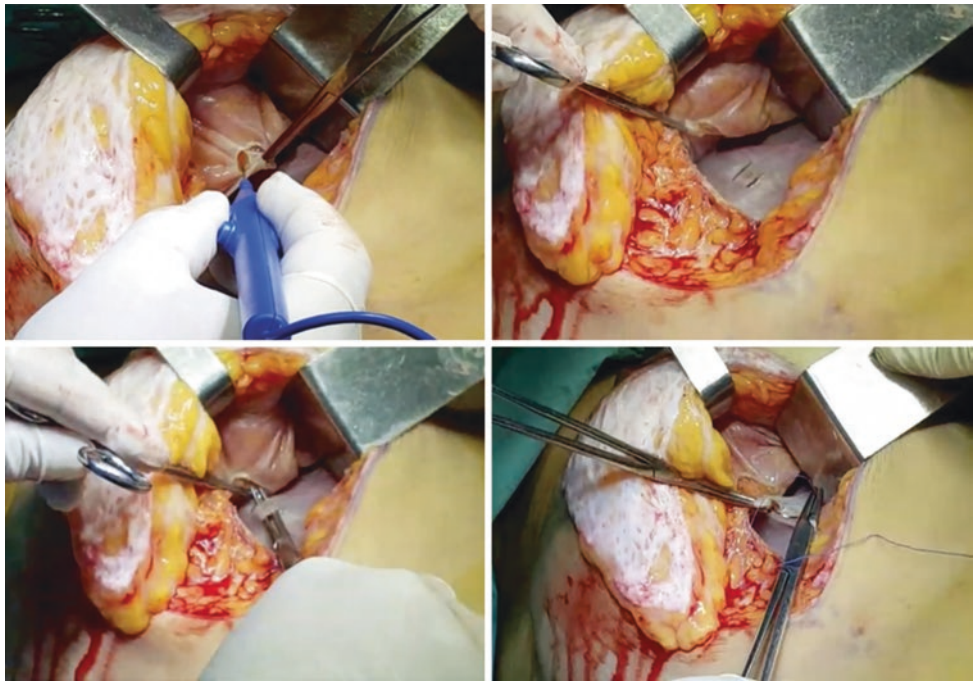


Fig. 5 Intraoperative images of the stages for the realization of the anchoring flap in four steps. Top left: Incision on the anterior wall of the capsule, creating the anterior vertical flap. Top right: Incision on the posterior wall of the capsule. Bottom left: Creating the posterior horizontal flap on the handle. Bottom right: Anchoring movement interacting both flaps and fixation with suture of the flaps

cavity of 30 or 40 mL of molar bicarbonate and abundant sterile saline solution. Once the chemical ablation process has been completed and in order to be able to predict the position of the remaining breast tissue, promoting adherence of the tissues in the desired position by the surgeon [9], we complement the ablation with the utilization of anchor capsular flaps. It is a flap, which as a key-lock allows a better coaptation of the two capsular walls, closing the dead space and also allowing the elevation and fixation of the mammary tissues, giving an effect of internal pexy (Figs. 4 and 5) [10].

In the cases of chemical capsulectomy for change of implant plane or definitive explantation we leave a non-aspirative drainage consisting of a modified Angiocath 14. In the case of chemical capsulectomy for the treatment of late or recurrent seroma, we leave an Jackson Pratt drainage due to a contracture.

4 Histology

Samples were sent for anatomicopathological study and the aspects of the pseudosinovia before and after the topicalization with TCA acid were compared [11]. In the untreated capsule, the sections show fibro-connective tissue in which a capsule with synovial metaplasia composed of fibrohistiocytic cells is recognized. In the sections treated with TCA, they show fibro-connective tissue in which capsule with synovial metaplasia is recognized; they present less thickness with respect to the control sample. A less number of cells is observed, acidophilia of the cytoplasm and presence of "finger-like" projections on the surface (toward the cavity). In some sectors loss of the layer of fibrohistiocytic cells that make up the synovial membrane is observed (Fig. 6).

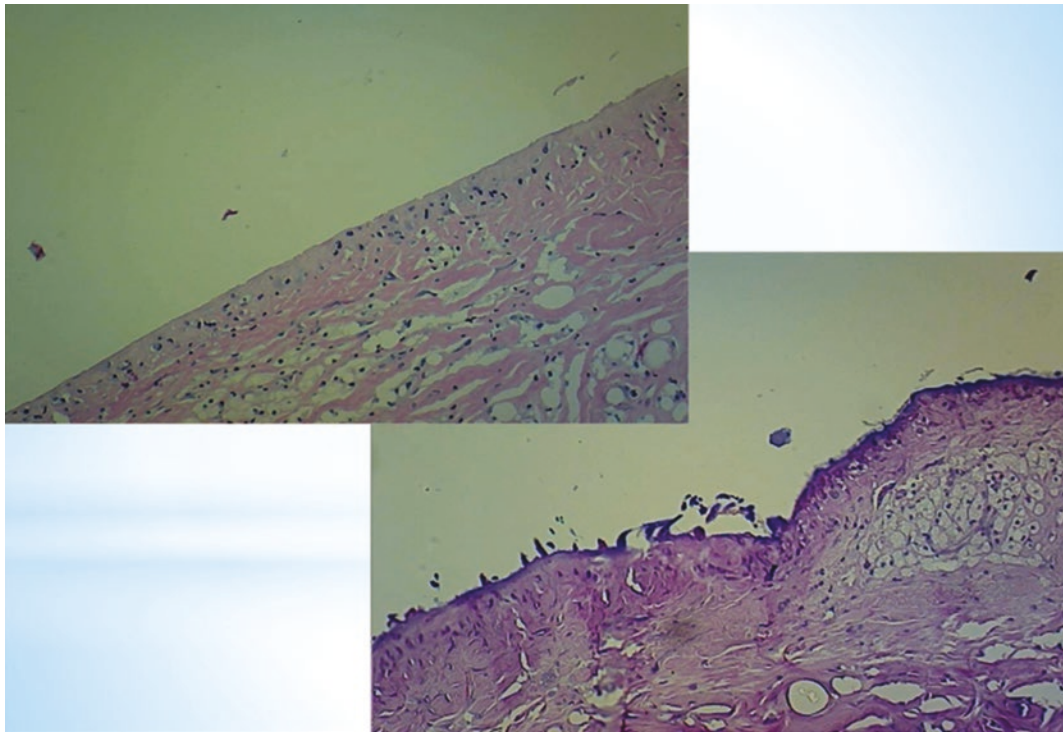


Fig. 6 Histological section with hematoxylin-eosin stain where it is observed in a cross section, Top: TCA treated breast capsule. Bottom: Without the acid

5 Indications for This Technique

1. Definitive explanation (Fig. 7).
2. Transient explantation.
3. Treatment of the peri-implant seroma (Fig. 8).
4. Partial remodeling of the capsule to correct sinomastia (Fig. 9).
5. Partial remodeling of the capsule to correct axillary displacement of the implant.
6. Partial remodeling of the capsule to correct bottoming up.
7. Change of implant plane from subpectoral to retroglandular.
8. Change of implant plane from the retroglandular to the subpectoral.

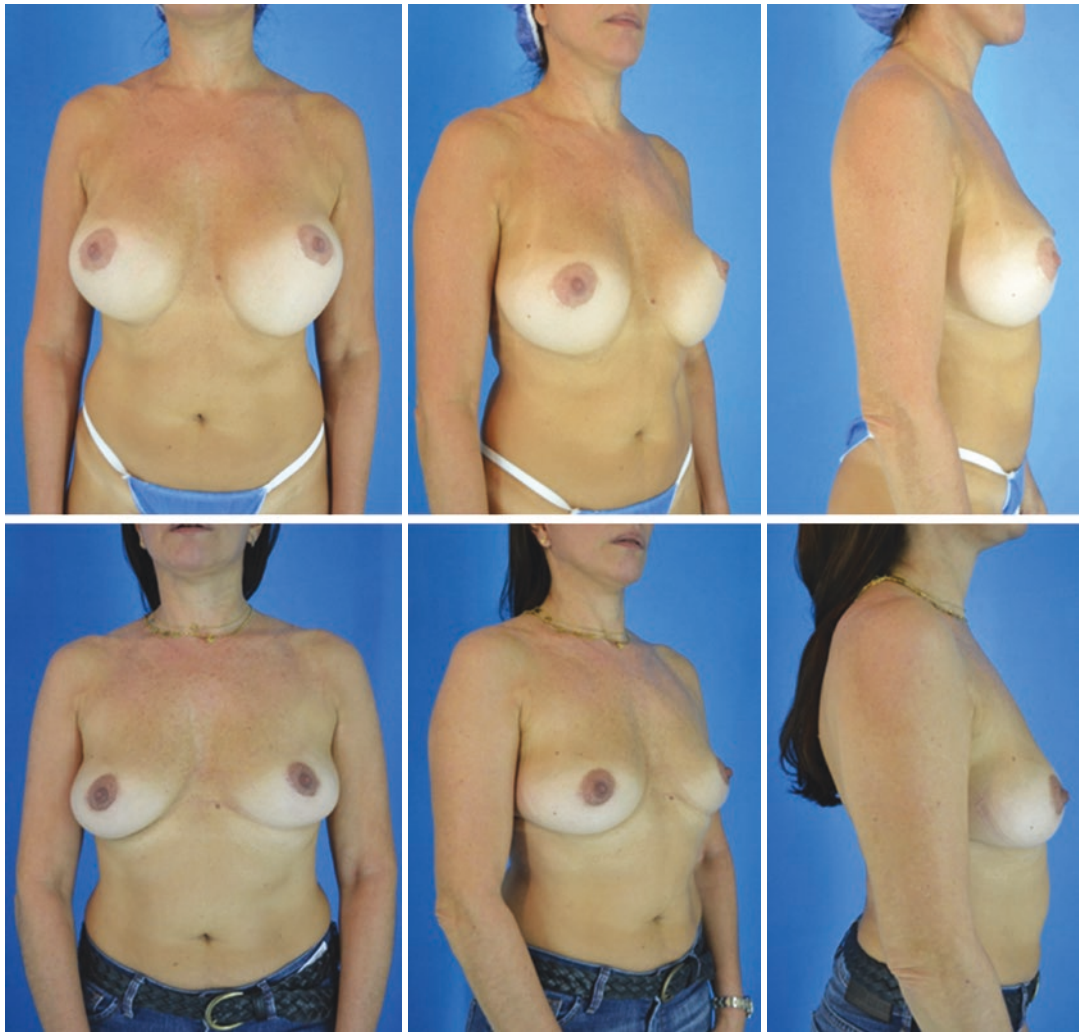


Fig. 7 Top: Preoperative patient. Bottom: 1 month postoperative after explantation

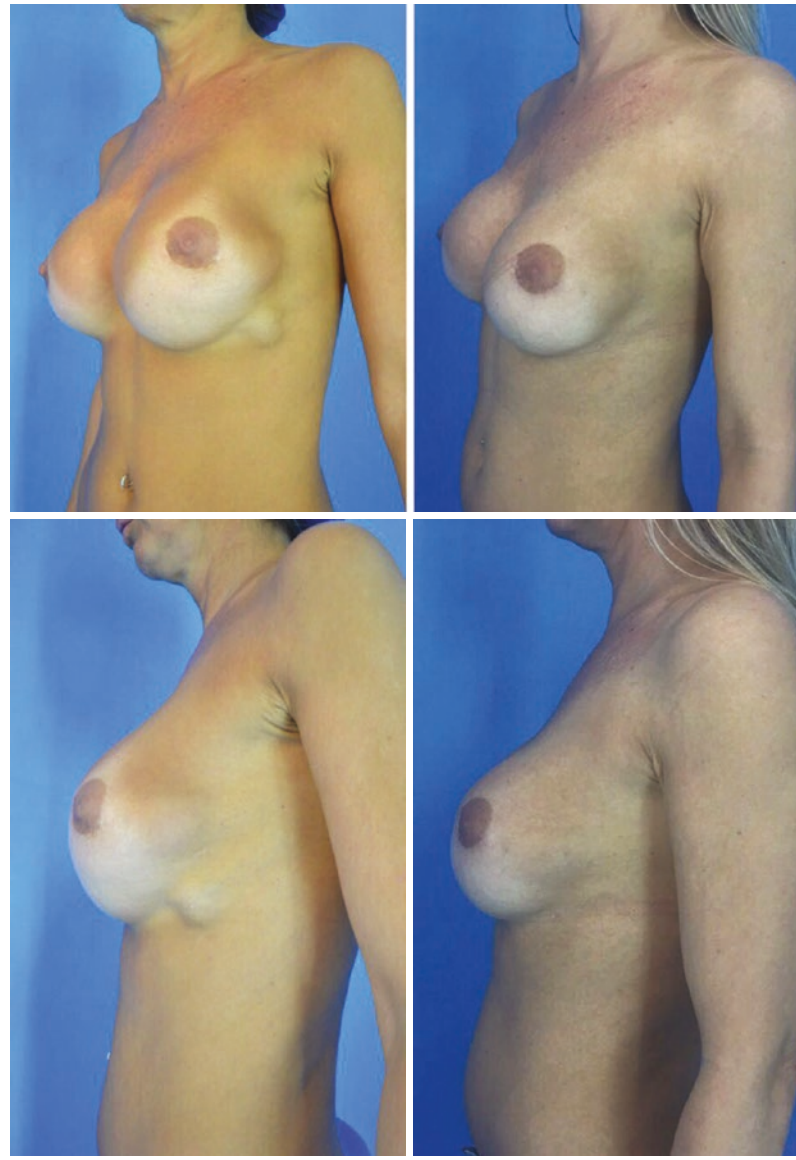


Fig. 8 Left: Preoperative patient. Right: 1 month postoperative after treatment of peri-implant seroma

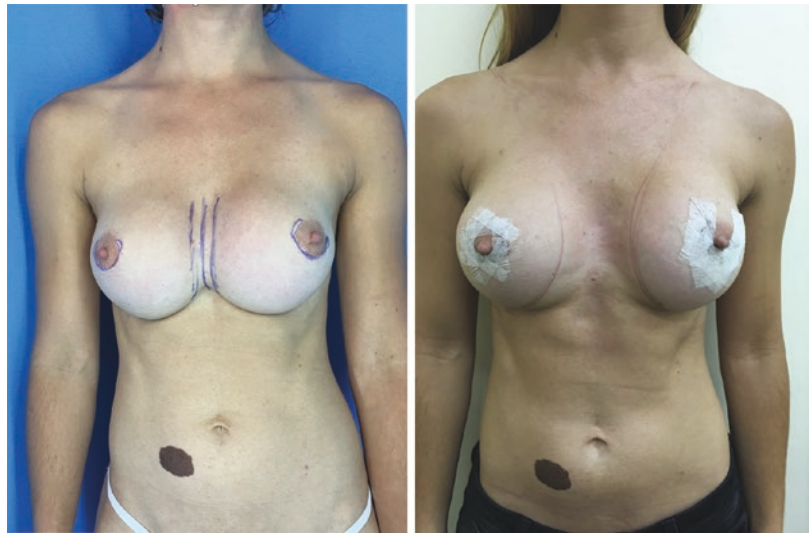


Fig. 9 Left: Preoperative patient. Right: 1 month postoperative after partial remodeling of the capsule to correct synmastia

6 Results

We have used this method in 61 patients to treat the different options in which it has been necessary to act on a residual capsule.

1. Definitive explanation in 10.
2. Transient explant by extrusion in 2 [12].
3. Treatment of the peri-implant seroma in 2.
4. Partial remodeling of the capsule to correct synmastia in 2.
5. Partial remodeling of the capsule to correct axillary displacement of the implant in 10.
6. Partial remodeling of the capsule to correct bottoming out in 4.
7. Change of implant plane from subpectoral to retroglandular in 1.
8. Change of implant plane from the retroglandular to the subpectoral in 30.

Conclusions

The results obtained with this method have been highly satisfactory to correct the problems that the patients presented and the prevention of the appearance of complications that could arise when leaving the capsules abandoned to their free evolution.

References

1. Fischer S, Hirche C, Reichenberger MA, Kiefer J, Diehm Y, Mukundan S Jr, Alhefzi M, Bueno EM, Kneser U, Pomahac B (2015) Silicone implants with smooth surfaces induce thinner but denser fibrotic capsules compared to those with textured surfaces in a rodent model. PLoS One 10(7):e0132131
2. Kasper CS (1994) Histologic features of breast capsules reflect surface configuration and composition of silicone bag implants. Am J Clin Pathol 102(5):655–659
3. Bucky LP, Ehrlich HP, Sohoni S, May JW Jr (1994) The capsule quality of saline-filled smooth silicone, textured silicone, and polyurethane implants in rabbits: a long-term study. Plast Reconstr Surg 93:1123–1131
4. Collis N, Coleman D, Foo IT, Sharpe DT (2000) Ten-year review of a prospective randomized controlled trial of textured versus smooth subglandular silicone gel breast implants. Plast Reconstr Surg 106:786–791
5. Luke JL, Kalasinsky VF, Turnicky RP, Centeno JA, Johnson FB, Mullick FG (1997) Pathological and biophysical findings associated with silicone breast implants: a study of capsular tissues from 86 cases. Plast Reconstr Surg 100:1558–1565
6. Burkhardt BR, Dempsey PD, Schnur PL, Tofield JJ (1986) Capsular contracture: a prospective study of the effect of local antibacterial agents. Plast Reconstr Surg 77:919–932
7. El-Domyati MB, Attia SK, Saleh FY, Ahmad HM, Uitto JJ (2004) Trichloroacetic acid peeling versus dermabrasion: a histometric, immunohistochemical,

and ultrastructural comparison. Dermatol Surg 30:179–188
8. Minami E, Koh IH, Ferreira JC, Waitzberg AF, Chifferi V, Rosewick TF, Pereira MD, Saldiva PH, de Figueiredo LF (2006) The composition and behavior of capsules around smooth and textured breast implants in pigs. Plast Reconstr Surg 118(4):874–884
9. Brodland DG, Roenigk RK, Cullimore KC, Gibson LE (1989) Depths of chemexfoliation induced by various concentrations and application techniques of trichloroacetic acid in a porcine model. J Dermatol Surg Oncol 15:967–971
10. Rockwell BW, Casey HD, Cheng CA (1998) Breast capsule persistence after breast implant removal. Plast Reconstr Surg 101(4):1085–1088
11. Marques M, Brown S, Correia-Sá I, D S Cordeiro MN, Rodrigues-Pereira P, Gonçalves-Rodrigues A, Amarante J (2012) The impact of triamcinolone acetonide in early breast capsule formation in a rabbit model. Aesthet Plast Surg 36(4):986–994
12. Rohrich RJ, Beran SJ, Restifo RJ, Copit SE (1998) Aesthetic management of the breast following explantation: evaluation and mastopexy options. Plast Reconstr Surg 101(3):827–837

An Approach to Keloid Reconstruction with Dermal Substitute and Epidermal Skin Grafting

Tommaso Agostini, Christian Pascone, Raffaella Perello, and Antonio Di Lonardo

1 Introduction

The ability of the sore skin to regenerate and restore its function is ensured by the presence of epidermal cells in the deeper layer of the wound and the integrity of the underlying dermis; scarring will occur from the margin of the wound and will be insufficient if the latter is larger than a few inches [1]. This is why the wound healing process needs a cover that has a barrier function and protection against infections, loss of fluid, and favors the growth and development of the granulation tissue [2]. These wound cover materials are very important in trauma, where they create and grow a suitable environment for the formation and development of the granulation tissue, providing a barrier against infection and blood loss [1–4]. Depending on all this, some physical and chemical characteristics, inherent to the dermal substitute, are essential, which must be kept present, respected, and maintained during the manufacturing process (Table 1). Among the physical properties, we must remember the following: loss of fluids and moisture, ability to shape and conform to wound, resistance to tangential forces, elasticity, resistance to exfoliation, waterproofness to infections, porosity and three-dimensional structure, its ability to be handled easily, and the possibility of suturing at the margins of the wound [1–3]. Chemical properties include biodegradation and integration into the body; the absence of toxic metabolites; an inactivity that is not or does not cause an inflammatory reaction or a foreign body reaction; the ability to be colonized by cells of the host organism, to allow the synthesis of a new dermis; the prevention of an infection and abnormal scar formation; and the formation of a scar [3–6].

It is possible to obtain protection against infection of the substance loss and loss of fluid from the wound by adding a waterproof cover to the dermal replacement. This opportunity was first obtained by adding to the matrix a thin layer of silicone, which is withdrawn at the time of complete plaque stripping and replaced by a partial-thickness cutaneous self-grafting. This procedure is known as two-step procedures. The vascularization of the dermal matrix occurs progressively and lasts for about 3 weeks, during which unfortunately there is a risk of

Table 1 General characteristics of dermal substitutes

1. Wound protection from infections and loss of liquids
2. Provide a stable and biodegradable matrix that allows the neosynthesis of a dermal tissue
3. Colonization and immunoassay capabilities to allow matrix integration to host tissues, producing a dermal tissue rather than a scar tissue
4. Ease in handling dermal substitute and resistance to mechanical forces

T. Agostini (✉) · C. Pascone · R. Perello
A. Di Lonardo
Department of Plastic and Reconstructive Surgery, Clinica San Paolo, Pistoia, Italy

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_125, © Springer International Publishing AG
Published Online: 05 July 2018

infection [3]. This is the biggest disadvantage of this technique. For this reason, a second strategy has been developed. This method is known as a one-step procedure: in the same operating session, it is possible, after practicing the surgical toilets, to position the dermal matrix on the substance loss and cover it with a partial-thickness cutaneous self-adhesion [6].

2 Classification of Dermal Substitute

In classifying the various dermic substitutes, we can distinguish two major categories with very different purposes:

1. Substitute dermis suitable for temporary loss of substance loss.
2. Substitute dermatitis suitable for healing the loss of substance. All these compounds can be differentiated according to their origin into three major groups: natural organic derivatives, synthetic biological derivatives, and synthesis derivatives [1–5].

2.1 Natural Organic Derivatives

This class of derivatives consists of materials derived from human and animal body tissues that have been treated to produce an acellular matrix to be used as a dermal matrix. The advantages of these materials are primarily due to the fact that they have a structure, perfectly or almost identical to the host's dermis [3]. This three-dimensional structure, despite the various steps of sterilization and cell elimination, remains intact. The major disadvantage is that, unfortunately, these allogenic derivatives can be the subject of a rejection reaction by the host and therefore, they are used as temporary biological dressing rather than as permanent dermal substitutes [4]. Natural biological derivatives derived from the corpse can be the cause of transmission of viral diseases. Accurate screening is done on human derivatives in order to minimize this risk, though unfortunately it is not possible to eliminate it altogether. The allogenic skin coming from the corpse remains on site as a biological dressing for about 12–21 days after application due to the host's immune response to donor cellular residues [5]. The various techniques for eliminating donor cells are extremely aggressive and can alter the structure and composition of the dermis. Ghosh et al. [7] has shown that sterilization processes by ethylene oxide or gamma rays can cause alterations to the dermal structure, while a glycerol process seems to have minor deleterious effects on the dermis structure. This is crucial in the healing process because it allows the migration of fibroblasts, which will form neoderma and inhibit uncontrolled and abnormal production of scar tissue. Another important feature of these materials is that they all generally contain the basal membrane of the papillary dermis. Various studies have shown that the presence of the basal membrane allows increased adhesion, growth, and differentiation of keratinocytes [5]. This action is characterized by the presence of laminin and type IV collagen in the basal membrane. Sahota et al. [8] published a study on the problematic percentage of biological dermal substitutes (from corpses). This study draws attention to the fact that endothelial cells penetrate less rapidly into dermal substitutes of natural origin and that this migration becomes faster if the dermis is damaged. The amount of collagen fibers in these dermal substitutes is high and has a problem of rapid in vivo colonization.

2.2 Synthetic Biological Derivatives

This class of dermal substitutes comes from purified, lyophilized biological molecules that are incorporated into matrices synthesized in the laboratory. Synthetic matrices of natural origin are generally made up of collagen as the main constituent. The three-dimensional structure of the collagen of the matrix is controlled by various dry-freezing processes to which it is subjected to be able to adjust the pore size and the connection between them during the matrix production processes [3]. The use of this matrix has certain

advantages but also some disadvantages. The main advantage in the production of a cell matrix in a laboratory is to be able to use molecules (generally collagen) and natural components recognized as "self" by the host organism, which do not stimulate rejection due to an immune response, kind of foreign body reaction.

The nature and degree of immunogenicity of collagen is still somewhat strange [9]. It has been demonstrated that telopeptides located on the terminal part of the tri-helical structure of collagen can cause an immune reaction and that removal of this structure produces an atelocollagen which is better tolerated by the organism. Cells attach to the extracellular membrane through specific receptors, integrins. Most integrins recognize this sequence of amino acids, such as fibronectin, vitronectin, and RGD sequences. Interaction with these RGD sequences allows cells to attach to these fibers [2, 3]. The fibroblasts and the keratinocytes secrete the metalloproteinase (MMPs), which are able to remodel and alter the structure of the extracellular matrix. The associated action of integrins and MMPs allows cells to migrate into these materials and to remodel them to finally be fully integrated by the host organism [6, 9].

To allow dermic matrices to stay in the implant area long enough to be effective in promoting the healing process, it is often necessary to cross-link the structural collagen to strengthen its stability. Cross-linking is a "coupling" process from one material to another, so that it can alter its structure and modify the body's action of the body's cells on it [10]. Generally, this process is used to increase the stability of the dermis matrix but may have deleterious effects on the healing process. If the matrix is able to withstand the body's remodeling action for a long time, it will lead to excessive reaction of a foreign body reaction with alteration of the cicatrization process. Rodrigues et al. [11] demonstrated on pig collagen matrices that cross-linking with glutaraldehyde caused a foreign body reaction on these matrices with respect to the same matrices not treated with glutaraldehyde.

Additionally, toxic metabolites that can be created at the time of catabolism of these matrices must be taken into account; these products can become nephritic for the cicatrization process and prevent their development. Yannas and Burke [12], during the development of their Integra® precursor, found that the addition of GAGs, such as chondroitin-6-sulfate, chondroitin-4-sulfate, dermatan sulfate, and heparan sulfate, to collagen matrices increased their resistance collagenase. GAGs can stabilize matrices according to different mechanisms. By checking the components used, it is possible to obtain a matrix with precise physical and chemical characteristics. It would be possible, at least at the theoretical level, to add growth factors and cells that would favor the cicatrization process. However, still today, there is no full potential of these matrices. An important defect of these substitutes is that they lack the basal membrane, and their three-dimensional structure is not comparable to that of the physiological human derma [12]. In this class of substitutes, the two most probable and most well-known matrices, Integra® and Matriderm®, are mainly used in the treatment of serious burns.

Each additive added to the dermic matrix plays an important and different role in the vascularization of the matrix and its integration. For example, collagen/chondroitin-6-sulfate matrices, such as Integra®, require a two-step procedure protocol to be properly integrated and finally grafted with partial carcinoma of the skin. This is due to the use by the body of 3 weeks to adequately colonize the dermis. Other matrices containing collagen/elastin such as Matriderm® have been shown to be more important and more advanced vascularization, only after 1 week, and therefore a one-step procedure can be performed [13]. These differences in the revascularization process can be explained by the different behavior of chondroitin-6-sulfate (chondroitin sulfate A) and elastin. Various studies, such as those conducted by Calamia et al. [14], have shown that chondroitin sulfate A possesses antiangiogenic capacity when tested on a coronal-alcoenide membrane matrix (CAM) [4]. The reverse happens if elastin is tested on the same membrane. The latter has an elevated angiogenic power and favors the migration of smooth

endothelial muscle cells. The size of the pores of the matrix does not seem to affect vascularization in this case. The test is because the pores of the Integra® matrix are larger than those of the Matriderm® and therefore more easily accessible (for physical reasons) to the cells.

2.3 Synthetic Derivatives

Structurally similar to biological matrices, these dermal substitutes are constructed with molecules of non-natural origin and with polymers not present in human tissues. For this feature, dermic substitutes belonging to this class present the greatest difficulty in choosing their constituents (molecules and polymers) that can be integrated and accepted by the host without developing an excessive immune reaction that can result in a foreign body reaction [15]. Using nonorganic products can be problematic when trying to develop a biocompatible material. Although there are many synthetic components that have been tested in vitro or on an animal, only someone is currently used on man [10]. The fibroblasts and the other cells involved in the construction of the dermis need chemoreceptive signals and receptors, which can attract and bind to the dermal membrane. The interaction of these cells with the synthetic membrane will substantially differ from the interaction between cells and ECM [6].

The architecture and molecular composition of these synthetic substitutes, as well as for biological dermatologic substitutes, are a major action and influence on migration, adhesion and cellular stability, intercellular signal, etc. To allow the recognition of these synthetic matrices as "self" by the cells of the host organism, it was thought to integrate them with biomimetic protein sequences. These sequences are integrated into the matrices, allowing cellular motion. In these years, RGD peptides have begun to be used. Incorporating these RGD peptides into some hydrogels facilitates migration and persistence of fibroblasts within these materials, determining and increasing the interaction between cells and matrix and consequently a contraction of the fibroblast matrix [13, 15].

3 Available Commercials Products

3.1 Alloderm® Natural Biologic Derivatives (KCI/Life Cell©)

Alloderm® is a human-derived acellular dermis (UAT) from the American Association of Tissue Banks. This matrix is subject to minimally invasive chemical-physical processes and therefore its natural structure is virtually unaltered. The FDA considers it as a bank tissue. During its production, Alloderm® is subjected to the separation of the epidermal layer from the dermal basal membrane, and subsequently all the cells and the components that exhibit histocompatibility antigens are removed to avoid a rejection process. Once implanted, this substitute is virtually replaced by host collagen. Alloderm® allows cellular migration from the wound edges and surrounding tissues. Its indications are many and can be used in all cases of reconstruction of the tegument, including the gum. The use of this dermal substitute is contraindicated in patients with autoimmune connective tissue pathologies. Conditions that could potentially inhibit the integration of this acellular matrix are nonvascular surrounding tissues, mechanical traumas, local or systemic infection, and poor performance status [5].

3.2 Glyaderm® (Euro Skin Bank)

Glyaderm® is an acellular matrix derived from human donor skin, treated with collagen-elastin. The skin is treated with glycerol in a low concentration of NaOH (sodium hydroxide). This dermal substitute was designed to reconstruct the dermis in the skin's full-thickness loss in combination with a partial-thickness self-adhesion to restore a double-layered skin similar to the natural one. It can be used in deep burns, in oncologic exerts, in giant melanocytic fluids, in necrosis post-fascic reconstructions and in traumas with major substance leakage. This matrix is revascularized in about a week and allows a self-adhesion of partial-thickness skin

to restore a double-layered skin. It is not indicated in infected wounds or without adequate surgical preparation. An adequate surgical wound should be done to eliminate all necrotic and infected tissues following trauma. Only later, Glyaderm® can be placed on the receiving site. A well-damaged wound and with a suitable granulation tissue allows the integration of the Glyaderm® dermal matrix [5].

Epiflex® is a human acellular dermal extract from healthy donors. The dermis, once taken, is treated with processes to eliminate the cells present, sterilized, and subsequently preserved. Before being applied it must be rehydrated. This natural dermal substitute is recommended for the treatment of severe burns and chronic ulcers, oncological resections (such as sarcomas), postmastoplasty mammary reconstructions at the lower part of the prosthesis leg, repair of the rotator cuff in the surgery shoulder, and in all areas where there has been a great loss of soft tissue substance [5].

3.3 GammaGraft™ (Promethean LifeSciences, Inc.)

GammaGraft™ is the first human skin irradiated with gamma rays and is used as temporary medication in trauma, burns, or chronic ulcers, with partial or total loss of the dermis. Its use is recommended in clean and granular wounds, is not intended as a dressing with decapatory power, but is a dressing that can provide an ideal environment for the healing process. It is recommended as dressing sites for caries of partially thick carnitines and eviscerations, to cover the viscera. In joint areas or areas at risk of slipping, some precautions should be taken to prevent GammaGraft™ from detaching from the scarring bed before the cicatricial process is consolidated [5].

3.4 EZ Derm™ Porcine Xenograft (Brennen Medical, LLC)

EZ Derm™ Porcine Xenograft is a pig skin, where collagen is cross-linked with an aldehyde. This xenografting of acute porcine can be used in burns, in traumas with partial or total loss of skin, in dermabrasion, and in cutaneous areas. EZ Derm™ is also recommended as a temporary cover in deeper burns to allow dermatological restoration. The EZ Derm™ receiving zones must be detached before the xenografting; after about 8–10 days, you can go to the next stage with EZ Derm™ surgical removal and self-grafting of the substance loss skin, restoring a double-layered skin [5].

3.5 Integra® Bilayer and Single-Layer (Integra Lifesciences) Biological Derivatives

Integra® is a biologically synthesized, acellular derivative made up of biodegradable bovine collagen polymerized with GAGs copolymers. The matrix is composed of type I collagen and chondroitin-6-sulfate. GAGs are coprecipitated, frozen, and cross-linked. It is a three-dimensional, porous matrix, whose diameter is between 20 and 125 μm and is available in two thicknesses: A 2 mm "double-layer" specimen is covered with a thin layer of silicone elastomer, which requires a two-stroke procedure. First, wound cleansing and deposition of the matrix. Following three weeks the matrix is covered with a split thickness skin graft. This interval is necessary to allow cellular colonization of the host matrix and its integration with the organism resulting in vascularization. A 1 mm "single-layer" specimen is not covered by silicone and can be used in procedures in one time, i.e., during the same surgical intervention, wound cleansing, matrix deposition, and autografting of partial-thickness skin carcinoma on the matrix. Integra® is the most used dermal substitute, especially for burners, along with Matriderm®, described below. It is indicated in the post-exeresis treatment of partial or total loss of substance in the dermis, in the burns, in the loss of substance with structures such as bones and tendons, and in all cases where a simple skin graft does not take root. Integra® is very effective, but quite sensitive to infections, so a special attention must be paid when dressing between first and second surgical time [5, 13, 15–19].

3.6 Matriderm® Bilayer and Single-Layer (Dr. Suwelack Skin & Health Care AG)

Matriderm® is a dermal matrix consisting of type I, III, and V bovine collagen fibrils, derived from the nuclease and elastin ligaments, which are structurally intact and facilitate and support dermal regeneration. This matrix is a porous matrix with pores of a diameter of about 75 μm. Matriderm® is used to reconstruct the dermis in all-thickness skin leaks together with a partial-thickness self-adhesion. It is recommended in the treatment of intermediate, deep, and third-degree burns, major trauma, and scarring burn outcomes. This dermal substitute, as well as the Integra®, is available in two different thicknesses of 1 mm and 2 mm, respectively, used with self-adhesion of partial-thickness skin at the same time as the operative of the pose and subsequently after about 3 weeks to allow the colonization and vascularization of the matrix. Its contraindications are given by the patient's hypersensitivity to the cattle constituents of collagen and elastin, the use on infected areas. This matrix, too, does not tolerate the use of iodine (Betadine®) disinfectants and caustic substances because they would cause alteration of collagen proteins [5, 10, 15].

Renoskin® is a double-layer dermal substitute consisting of a layer of bovine collagen and a silicone layer that protects during the grafting period before engaging it. It is a product similar to the Matriderm® and Integra®, which we have already talked about. Its indications are similar to those of the Matriderm® and Integra®: deep and second-degree burns, exerted by congenital giant melanocytes, and loss of substance with tendon or bone exposure, where the simple grafting of the skin would not come up. It is also necessary for Renoskin® to cleanse the wound and to practice the exeresis of the necrotic or traumatized tissue prior to its application; after about 3 weeks, the time it takes for its grafting and vascularization, it is possible to practice partial carcinoma of the skin [5].

Pelnac® is an artificial dermatitis of pig origin, consisting of a three-dimensional atelocollagen matrix with low antigenicity and a silicone layer. For the time being, it is used only in Japan, Korea, China, and Brazil. It is indicated in third-degree burns, traumas with significant loss of soft tissues and oncologic resections. To be used with caution in allergic subjects, with asthma and urticaria history; it is not a product with bactericidal or bacteriostatic properties, so it should be used with caution on wounds that present a possible infection [5].

3.7 Hyalomatrix® PA (Fidia Advanced Biopolymers S.R.L.)

Hyalomatrix® PA is a dermal remedy of avian biological origin, used as temporary medication. This matrix consists of a double layer: a layer that promotes dermal restoration consisting of Hyaff 11, an esterified ester of hyaluronic acid, and a more superficial layer given by a semipermeable silicone membrane. Hyaff 11, biodegradable, in contact with the wound, acts as a three-dimensional scaffold for cell invasion and neoangiogenesis. The silicone monitors the water leakage and increases the strength of the Hyaff 11 matrix to the traction forces which may occur once positioned. It is indicated as immediate dressing in important skin loss and where immediate area coverage is required, but a graft is temporarily not indicated. It can be used as a dermal substitute in oncologic resections and then covered with a split-thickness skin graft. Even this dermal substitute, like the ones so far listed, does not possess bacteriostatic or bactericidal activity [5].

Apligraf® is the only biological dermal substitute, created from neonatal fibroblasts integrated into a type I bovine collagen matrix associated with neonatal keratinocytes sown on the upper part. It is especially indicated in the use of noninfected wounds with partial or total loss of dermis, such as venous ulcers and diabetic foot. Some studies also recommend it for burns of grades II and III. It is contraindicated in infected wounds, as it does not possess bactericidal and bacteriostatic powers [5].

3.8 Oasis Wound Matrix: Oasis® Burn Matrix (HealthPoint)

These matrices are pure acellular biological matrices. They contain a matrix extracellular intact and allow an optimum environment for insertion of the matrix into host tissues and cicatrization. They favor the restoration of dermal collagen and its three-dimensional structure and contain the subtracting layer of the small pork intestine. They are indicated in burns, trauma, chronic lower limbs, diabetic foot and post-oncological resections. They are contraindicated in third-degree burns. Veloderm® (BTC SRL) is the only biological plant matrix and contains a polymer of Crystacell 77™, a particular type of microcrystalline cellulose obtained with particular patented biotechnology processes, characterized by a low polymerization rate and a high level of crystallinity. After being hydrated with a physiological solution, the Veloderm® matrix acquires a translucent, dense, thick, and flexible appearance similar to human skin with similar permeability properties. It is particularly permeable to gases while remaining waterproof to bacteria and water. Its permeability varies from 1.100 g/m^2/24 h when the wound is non-exudative at 15,000 g/m^2/24 h when the wound is exudative. Veloderm® is a temporary epidermis replacement in deep and deep grade II burns, but not for third-degree burns. It is used in all dermatitis and superficial dermatitis in Lyell's skin lesions in chronic ulcers. It can be applied to all wounds made cleaned by a surgical toilette and without any local infection signs [5].

3.9 Dermagraft® (Advanced BioHealing)

Dermagraft® is a synthetic dermal substitute made up of a biodegradable synthetic polygon (Vicryl™) matrix, extracellular matrix, and cryopreserved human fibroblasts, added to the matrix together with TGF- and decorin. The fibroblasts are derived from the baby's foreskin. It is indicated in all ulcers of the diabetic foot, which last for more than 6 weeks, affecting the skin and the dermis, but not the tendons, the joint capsules and the bones. It is contraindicated in infected ulcers or in ulcers with fistulas.

3.10 Dermagen® (Genevrier)

This synthetic matrix consists of collagen, GAGs, and a chitosan matrix (PRODERM®), colonized by allogeneic fibroblasts. Chitosan is a natural polysaccharide, which has structural characteristics similar to GAGs; it is not toxic to the body and is absorbable. It is indicated for the treatment of severe grade III burns, chronic ulcers, and diabetic foot [5].

3.11 Biobrane® (Smith & Nephew)

It is a biosynthetic dressing, consisting of a silicon film with nylon fabric (polyamides) partially bonded to the silicone film. The tissue remains in contact with the wound, and this complex three-dimensional structure exhibits chemically attached collagen. Its mechanism of action acts on the imposition of blood clot in its nylon mesh, which will adhere Biobrane® to the scarring bed until it is reepitelized. It is indicated in the surface burns and the areas of picking up of a carcinogen of skin. It does not adhere to the necrotic tissue, while remaining under this membrane can cause local infections; a proper surgical toilet must be made before putting Biobrane®, as well as a careful hemostasis. An allergic reaction has been noted on certain subjects after applying Biobrane®; this will have to be removed. Suprathel® (PolyMedics Innovations GmgH (PMI)) is a temporary dermal substitute in the form of a resorbable membrane, consisting of D, L-polylactide (PLA), with a structure having micropoles of 2–50 μm. It is very much used for the temporary coverage of noninfected superficial wounds, partial-thickness self-adhesive donor sites, and second-degree burns associated with areas with grade III burns. It has been proven that it reduces the total time of treatment, reduces pain to its removal, and does not require a frequent change. It is not usable on

infected wounds nor on deep chronic ulcers. If there is a bleeding, you will need to associate the Suprathel® with a hemostatic [5].

4 One-Step Procedure

Most templates are relatively thick (bilaminar) and thus involve a two-step procedure with an interval of several weeks between dermal matrix implantation and skin grafting. Consequently, valuable time is lost and cost increases. Several years ago, a company producing Matriderm introduced a thin dermal template 1 mm thick. It has been successfully used in one-step procedures in combination with split-thickness skin grafts (STSG). More recently, Integra Life Sciences also developed a thin version, namely, Integra Single Layer, lending itself ideally to also be used in one-stage procedures in combination with STSG, just like Matriderm. Two weeks after the procedure, we observed a complete take of both templates, Matriderm and Integra Single Layer; cell density has been proved to be higher in Matriderm-derived neodermis than in Integra Single Layer-derived neodermis. There was also a certain difference in thickness between the two template-derived neodermis. The most tenable explanation for this phenomenon is a more rapid degradation of Matriderm because its collagen components are (as opposed to Integra Single Layer) not cross-linked. It is well known that cross-linking reinforces matrix stability and makes it less susceptible to degradation (increased resistance against enzymatic digestion). Yet, a potentially adverse effect of cross-linking is that degradation products can decrease cell survival, proliferation, and adhesion, which could explain the lower cell density observed in the Integra Single Layer-derived neodermis [5, 6, 13, 15].

5 Clinical Application

The one-step approach can be safely used to repair acute trauma or scar contracture following deep burns due to hypertrophic or keloid scars. In particular, pathologic scarring occurs in peculiar anatomic site (hands, elbow, knee) following improper medical management as showed in Fig. 1, where intermediate burn healed by

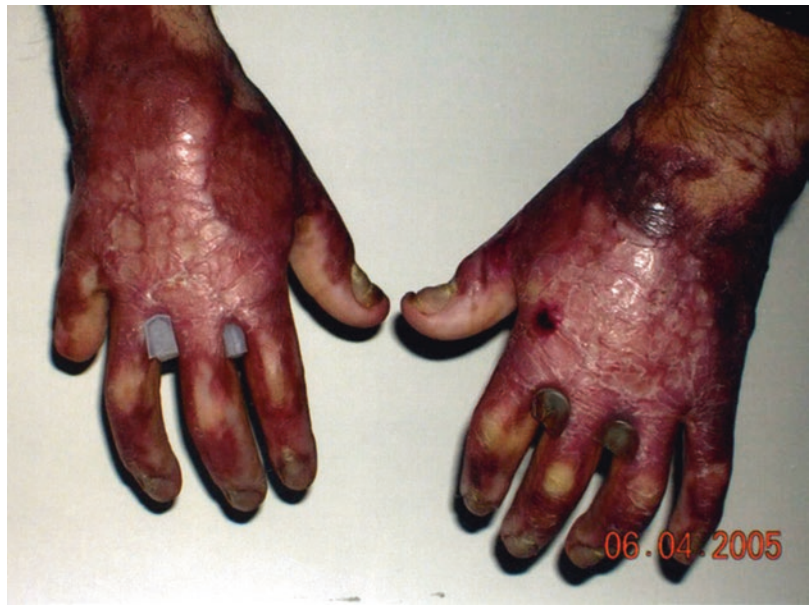


Fig. 1 Keloid scar involving the dorsum of the hands following deep burn. A 25-year-old patient lamented limited movements in the ordinary activities

secondary intention; this patient underwent scar resection till the deep fascia (Figs. 2 and 3) and immediate reconstruction using Integra single-layer and split-thickness skin graft harvested from the thigh (Fig. 4) which lead to a successful reconstruction of the dorsum of the hand with a complete range of motion following 2 years (Figs. 5, 6, and 7). Beyond extensive reconstruction of extreme case of scar contracture, the one-step reconstruction with dermal substitute can be performed for limited area of scar contracture as

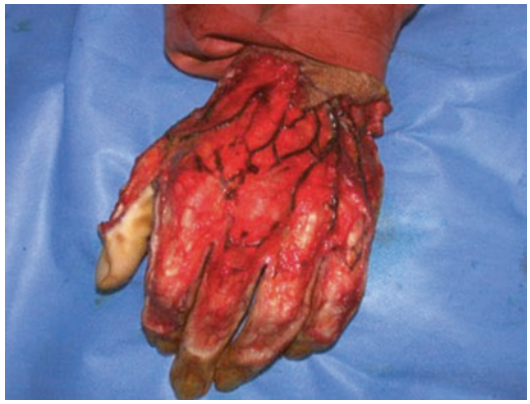


Fig. 2 Intraoperative view of the right hand following degloving of the pathologic scar tissue down to the superficial fascia and superficial venous system

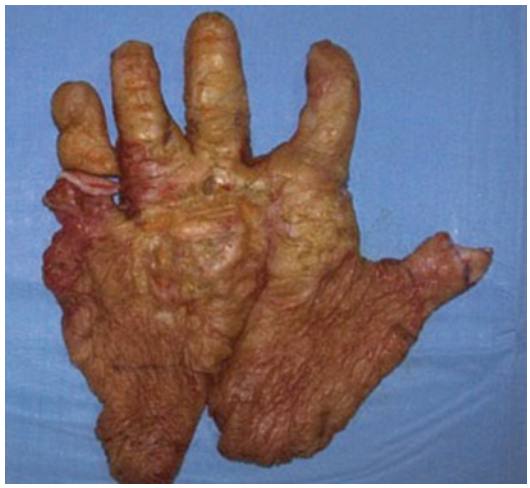


Fig. 3 Intraoperative view of the degloved scar tissue from both hands

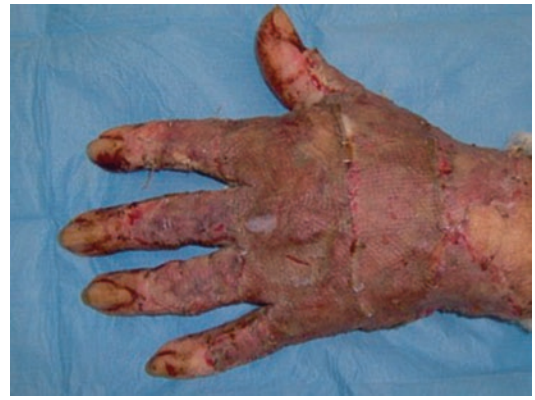


Fig. 4 Epidermal grafts harvested from the thighs were applied to the dorsum following 21 days form the reconstruction with dermal substitute (Matriderm)

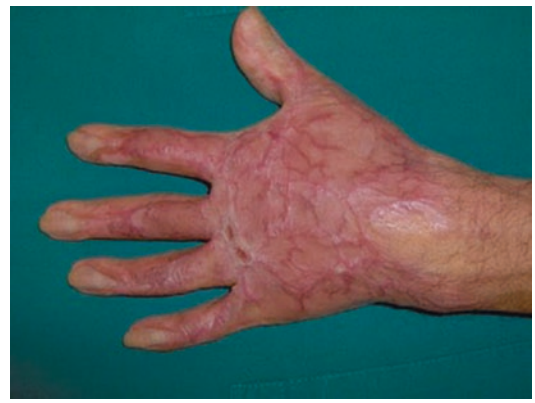


Fig. 5 Postoperative outcome following 12 months showing a full range of motion on the hand during extension

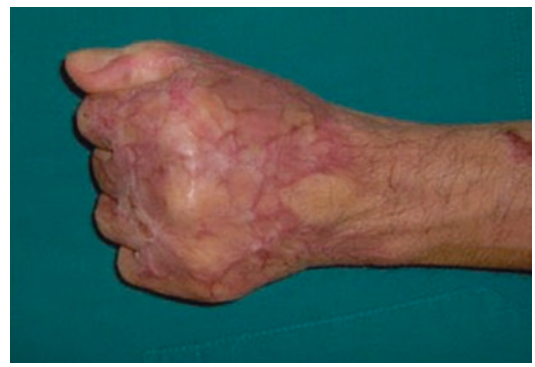


Fig. 6 Postoperative outcome following 12 months showing a full range of motion on the hand during flexion

shown in Fig. 8, where we performed a scar resection till the deep fascia (Fig. 9) and an immediate reconstruction with Matriderm single-layer and split-thickness skin graft form the thigh (Fig. 10) with a complete wound healing and full range of motion after 1 year (Figs. 11 and 12). Although pathologic scarring involves more frequently the hands for obvious reasons, the same principle of reconstruction can be safely applied to other anatomic area as the elbow (Fig. 13) scar contracture was successfully treated with Integra single-layer and immediate skin grafting (Figs. 14 and 15) with excellent outcome (Fig. 16).

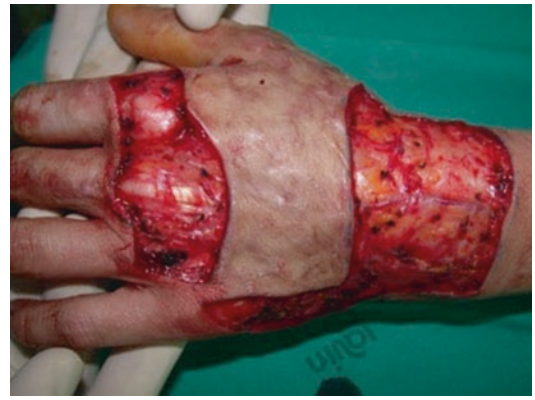


Fig. 9 Intraoperative view of the same patients following degloving of the scar tissue

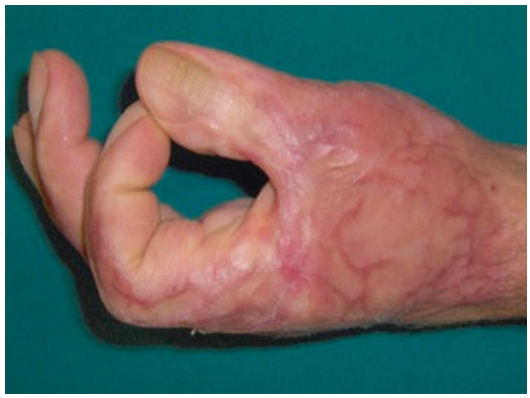


Fig. 7 Postoperative outcome following 12 months showing a full range of motion of the fingers

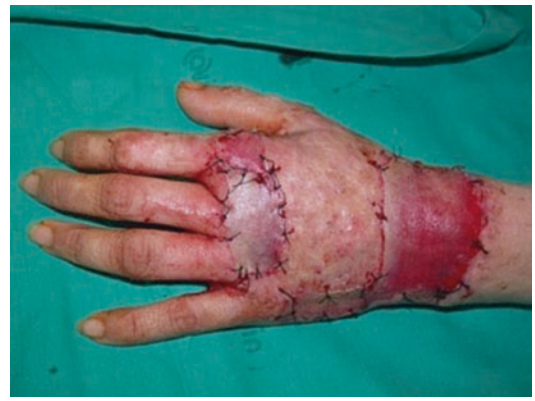


Fig. 10 Epidermal grafts harvested from the thigh were applied to the dorsum following 21 days form the reconstruction with dermal substitute (Integra)

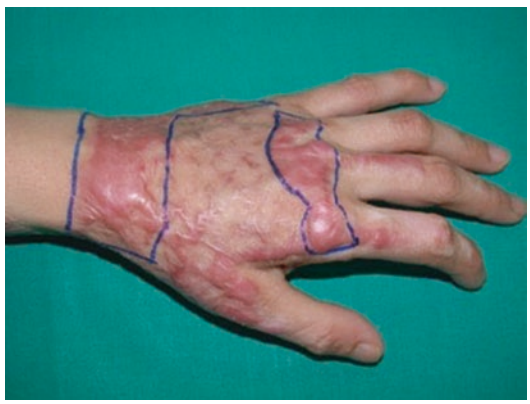


Fig. 8 Keloid scars involving partially the dorsum of the left hand of a 18-year-old man

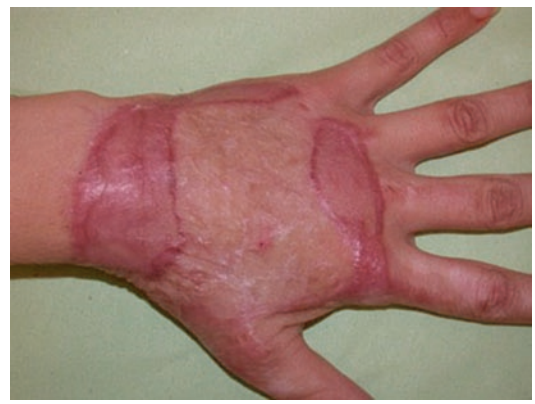


Fig. 11 Postoperative outcome following 24 months showing a full range of motion on the hand during extension

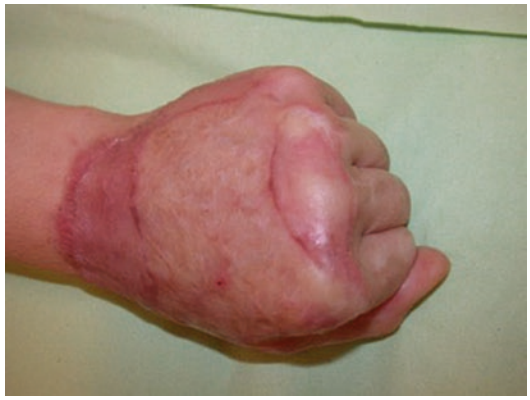


Fig. 12 Postoperative outcome following 24 months showing a full range of motion on the hand during flexion

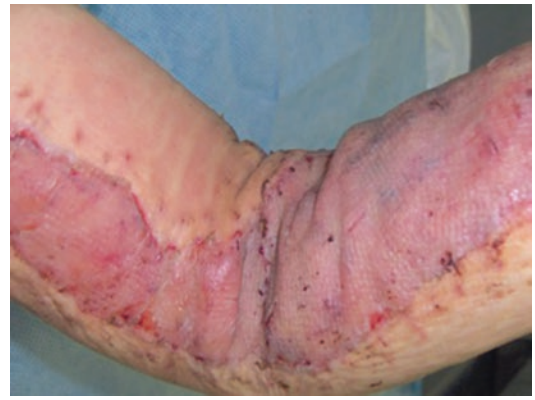


Fig. 15 Postoperative outcome following 21 days showing a full range of motion of the upper limb

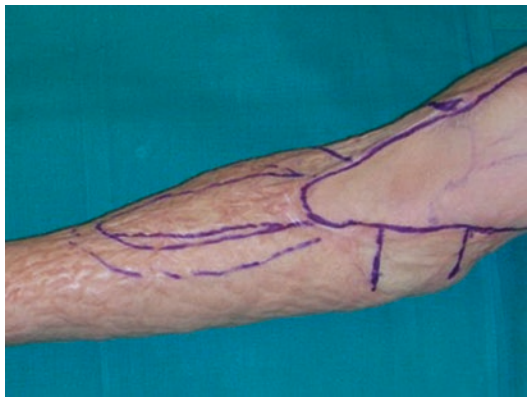


Fig. 13 Keloids involving the right elbow of a 37-year-old woman following reconstruction after intermediate burn

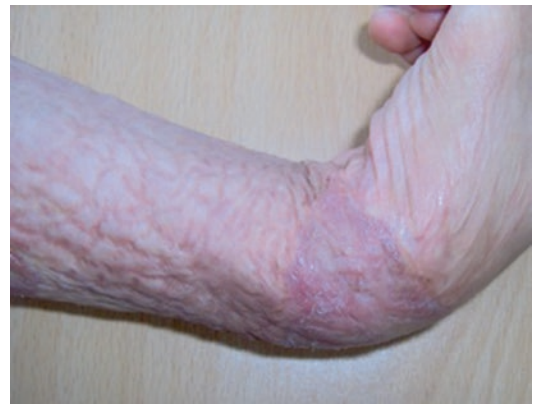


Fig. 16 Postoperative outcome following 36 months showing a full range of motion of the upper limb

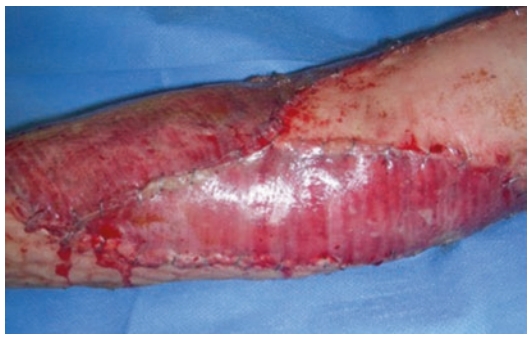


Fig. 14 Epidermal grafts harvested from the thigh were applied following 21 days form the reconstruction with dermal substitute (Matriderm)

References

1. Nguyen DQ, Dickson WA (2006) A review of the use of a dermal skin substitute in burns care. J Wound Care 15(8):373–376
2. van der Veen VC, Boekema BK, Ulrich MM, Middelkoop E (2011) New dermal substitutes. Wound Repair Regen 19(Suppl 1):s59–s65
3. Kolokythas P, Aust MC, Vogt PM, Paulsen F (2008) Dermal subsitute with the collagen-elastin matrix Matriderm in burn injuries: a comprehensive review. Handchir Mikrochir Plast Chir 40(6):367–371
4. Min JH, Yun IS, Lew DH, Roh TS, Lee WJ (2014) The use of matriderm and autologous skin graft in the treatment of full thickness skin defects. Arch Plast Surg 41(4):330–336

5. Debels H, Hamdi M, Abberton K, Morrison W (2015) Dermal matrices and bioengineered skin substitutes: a critical review of current options. Plast Reconstr Surg Glob Open 3(1):e284
6. Haslik W, Kamolz LP, Manna F, Hladik M, Rath T, Frey M (2010) Management of full-thickness skin defects in the hand and wrist region: first long-term experiences with the dermal matrix Matriderm. J Plast Reconstr Aesthet Surg 63(2):360–364
7. Ghosh MM, Boyce S, Layton C, Freedlander E, Mac Neil S (1997) A comparison of methodologies for the preparation of human epidermal-dermal composites. Ann Plast Surg 39(4):390–404
8. Sahota PS, Burn JL, Brown NJ, MacNeil S (2004) Approaches to improve angiogenesis in tissue-engineered skin. Wound Repair Regen 12(6):635–642
9. Lumenta DB, Kamolz LP, Frey M (2009) Adult burn patients with more than 60% TBSA involved-meek and other techniques to overcome restricted skin harvest availability--the Viennese concept. J Burn Care Res 30(2):231–242
10. Böttcher-Haberzeth S, Biedermann T, Schiestl C, Hartmann-Fritsch F, Schneider J, Reichmann E, Meuli M (2012) Matriderm® 1 mm versus Integra® single layer 1.3 mm for one-step closure of full thickness skin defects: a comparative experimental study in rats. Pediatr Surg Int 28(2):171–177
11. Rodrigues FT, Martins VCA, Plepis AMG (2010) Porcine skin as a source of biodegradable matrices: alkaline treatment and glutaraldehyde crosslinking. Polímeros 20(2):92–97
12. Yannas IV, Burke JF (1980) Design of an artificial skin. I. Basic design principles. J Biomed Mater Res 14(1):65–81
13. Dini M, Quercioli F, Mori A, Romano GF, Lee AQ, Agostini T (2012) Vacuum-assisted closure, dermal regeneration template and degloved cryopreserved skin as useful tools in subtotal degloving of the lower limb. Injury 43(6):957–959
14. Calamia V, Lourido L, Fernández-Puente P, Mateos J, Rocha B, Montell E, Vergés J, Ruiz-Romero C, Blanco FJ (2012) Secretome analysis of chondroitin sulfate-treated chondrocytes reveals anti-angiogenic, anti-inflammatory and anti-catabolic properties. Arthritis Res Ther 14(5):R202
15. Chu CS, McManus AT, Matylevich NP, Goodwin CW, Pruitt BA Jr (2002) Integra as a dermal replacement in a meshed composite skin graft in a rat model: a one-step operative procedure. J Trauma 52(1):122–129
16. Nguyen DQ, Potokar TS, Price P (2010) An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. Burns 36(1):23–28
17. Capo JT, Kokko KP, Rizzo M, Adams JE, Shamian B, Abernathie B, Melamed E (2014) The use of skin substitutes in the treatment of the hand and upper extremity. Hand (NY) 9(2):156–165
18. Vithlani G, Santos Jorge P, Brizman E, Mitsimponas K (2017) Integra(®) as a single-stage dermal regeneration template in reconstruction of large defects of the scalp. Br J Oral Maxillofac Surg 55(8):844–846
19. Zajíček R, Grossová I, Šuca H, Kubok R, Pafčuga I (2017) Experience with Integra® at the Prague Burns Centre 2002-2016. Acta Chir Plast 59(1):18–26

Part IV

Thoracic Surgery

Sternotomy Techniques

Jacob Zeitani

1 Midline Sternotomy and Alternative Access to the Mediastinum

> If it be established that median thoracic incision is a fairly safe procedure, I have no doubt that it will constitute the most generally useful route to the thoracic organs. And if once a safe route is established, a grate field for surgical interference lies open
>
> —H. Milton (1897)

In 1897, Milton [1, 2] was the first to describe median sternotomy. The first median sternotomy was performed to remove massive tuberculous lymph nodes and some years later. The second operation was performed to gain access to the trachea but only in 1953 Shumacker [3] became the first surgeon to recommend median sternotomy as the preferred approach for heart operations. The same year that Gibbon [4] described the first successful open-heart surgery using extracorporeal circulation. However, midline sternotomy remained a seldom used procedure until 1957 when Julian [5] reported the superiority of this access over thoracotomy, a surgical procedure characterized by time-consuming, complication-prone, and painful procedure. Indeed, only 4 years after the first successful open-heart surgery procedure performed via midline sternotomy bilateral anterior thoracotomy procedure was abandoned in favor of the latter.

To access the mediastinum through the median sternotomy, a skin incision is made, approximately 2 cm under the sternal notch and extended below the xiphoid. The exact midline over the sternum is marked with electrocautery to avoid faulty sternotomy. Shafir et al. [6] found paramedian sternotomy as a determinant factor for sternal wound complication, while our recent study confirms this finding [7]. Before the sternum incision is made, a pathway is created above the suprasternal ligament and then continued beneath the manubrium and finally performed as well under the xiphoid to guarantee the separation of the mediastinum structures from the posterior sternum bone. The continuing persistence of sternal wound complications has led surgeons to improve postoperative sternum stability, including alternative sternum incisions, though without compromising surgical field and results. Of those, an interlocking sternotomy with a lazy S-shaped incision is performed, reducing cranial-caudal sternum displacement [8]. Alternative means of surgical accesses to the mediastinum have also been proposed. These include the use of small incisions in J or T form leaving the manubrium or part of the sternum intact. In 1996 Cosgrove and Sabik [9] reported a surgical technique for aortic valve replacement, consisting of a 10 cm right parasternal incision, extending from the lower edge of the second costal cartilage to the superior edge of the fifth costal cartilage.

J. Zeitani
Department of Cardiac Surgery,
Tor Vergata University of Rome, Rome, Italy
e-mail: zeitani@hotmail.com

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_72, © Springer International Publishing AG
Published Online: 07 June 2018

Recently, small right anterolateral thoracotomy for mitral and aortic valve procedures has gained popularity [10–12]. Smaller incisions have a number of potential advantages. One of these is decreased pain reported by patients, which is probably related to the absence of the retraction and stress placed on the ribs, especially when surgery is performed via port access. Such procedures allow faster extubation and possibility of earlier discharge from the hospital. In addition the smaller size of the wound can reduce the risk of wound infection and blood loss, as well as being cosmetically more acceptable to patients.

However, there are some disadvantages in this access which make it questionable as a limited surgical field and increase the risk for intraoperative complications, such as air embolism and aorta dissection. Appropriate, new surgical instruments, technological improvement, and introduction of the heart port and robotic surgery helped to make these surgical procedures more practical and decreased related procedure complications [13].

Special attention should be given to resternotomy in patients who already underwent surgery. New and/or progression of treated cardiovascular diseases might require redo surgery. Reentry to the mediastinum poses additional risks and is considered between the surgical risk factors of all scores including the STS score and Euroscore. The pericardiectomy in the first surgery and the procedure itself including the use of foreign materials promote adhesion formation. If the pericardium was left open, the heart and grate vessels will be in direct contact with the sternum. Ascending aorta aneurysm or dilated heart chambers, in particular the right atrium or ventricle, might be damaged by the saw. In these cases going on extracorporeal circulation before sawing the sternum should be considered. Indeed, low blood pressure and empty heart chambers will reduce the risk of catastrophic uncontrolled bleeding while dividing the bone. In first-time midline sternotomy oscillating or striker saws can be used, but in case of resternotomy only the oscillating saw is recommended. The stainless steel wires are removed and the hemisterna should be lifted vertically, with the use of Backhaus clamps that are placed temporarily on either side of the sternum, in order to reduce the risk of the internal organ injury while sawing. During the first surgery the pleura space might have been opened; therefore, to avoid damage to the lungs, the patient should be also disconnected temporarily from the ventilator. It can be useful to saw the bone longitudinally for all its length but not complete thickness first. Once the sternum is divided completely, adhesions should be dissected carefully gaining space bellow the sternum required to place retractors. It is recommended to use the small one first. To avoid rupture of the heart or vessels and in particular the innominate vein, hemisternum separation should be done gradually following careful adhesion dissection.

Because redo surgery is considered a risk factor, transcatheter solutions gained popularity for myocardial revascularization and/or valve replacement. Indeed, patent grafts pose particular surgical challenges. However, once the patient is scheduled for surgery, previous procedure should be considered and alternative approach to the classic midline sternotomy is required. For example, Zeitani et al. reported a partial sternotomy in patients who required aortic valve replacement after myocardial revascularization with both arterial mammary arteries. A manubrium-sparing sternotomy can in such instances avoid injury to the right internal thoracic artery graft during both resternotomy and adhesion dissection, thus reducing surgical risk and operative time [14].

2 Midline Sternotomy Closure Techniques and Materials

Throughout the years, a variety of sternal closure techniques and materials have been described where stainless steel wires remain the most commonly used both because they are inexpensive and easy to perform guaranteeing satisfactory results [15–17].

2.1 Stainless Steel Wires

The standard method for sternum reapproximation is achieved by mean of stainless steel wires passed through the sternum bone or at the parasternal intercostal spaces. The steel

sutures are pulled and twisted until complete approximation of the hemisternums [18].

2.1.1 Transsternal Wires

Single-cerclage stainless steel wires are passed through the sternum approximately 1 cm on each side. The suture wires are then crossed, pulled, twisted, and bent to lie flat over the sternum. This approach avoids potential risk of damage to vessel structures but, especially if the sternum is unusually narrow or osteoporotic, the wires may easily cut through the bone causing transverse fractures. To prevent these complications, various modifications of the single transsternal suture have been used such as employing wires in combination of mattress and single cerclage or in a figure of eight. Other techniques are including the combined use of single and double cross to gain equaled distribution of forces within the two crosses of the suture or interlocking multi-twisted wires to reduce lateral compression of the sternum [19, 20].

2.1.2 Peristernal Wires

Peristernal sutures are passed laterally to the free margin including the complete width of the sternum so that no damage to the bone occurs, and should be considered especially when the sternum is narrow or osteoporotic. However there is some additional risk of damage to the mammary artery and to adjunctive veins as well as to the intercostal branches. As an alternative to simple interrupted suture, a figure-eight interlocking closure can be performed [21].

2.1.3 Pericostal Wires

Pericostal wire closure techniques rely upon the costal cartilages outside the operative area to avoid disruption of the sternum bone [22, 23].

2.2 Stainless Steel Bands

The stainless steel band guarantees major contact with the sternum bone so that the load spreads over a larger surface area, but as the bands are rigid they do not conform to the shape of the sternum, while there is no locking mechanism other than the tightening of the device, making quick removal difficult if emergency reoperation is required [24–26].

2.3 Other Techniques

Sternum closure by means of rigid titanium plates has been proposed in an “H” shape to offer better rigidity and reduce lateral displacement when compared with standard techniques of sternum re-approximation while blood supply to the sternum will not be compromised. An electromechanical study confirmed that the use of rigid plate fixation can reduce lateral motion when compared to the use of wire, providing better sternum stability. However, damage to the underlying structures by the use of a drill and also the high cost of the plates were among the major concerns identified with this technique. Stainless steel bone plates screwed longitudinally along the sternotomy, with both peri- and transsternal circumferential wires attached around the plates also being proposed [27–32].

2.4 Absorbable Sutures

The incidence of foreign body-induced wound infection has prompted surgeons to use absorbable sutures even in median sternotomies where the need for rigid and stable closure is well known. Most commonly, absorbable materials are used especially during operation on children, where chest dimensions and respiratory related forces are minor compared with adults. The mechanical performance of synthetic absorbable sutures is similar to stainless steel wires and can be used also on adults, though it should be remembered that their use has not yet been widely reported and slow wound-healing process should be considered [33].

3 Sternal Reinforcement Techniques

> The prevention or treatment of sternum separation is a problem inevitably encountered by those who frequently perform open heart operations
>
> —F. Robicsek (1977)

A large number of clinical conditions and surgical related risk factors have been identified, including diabetes, obesity, and chronic obstructive pulmonary disease, where only some of these factors such as faulty sternotomy and severe obesity were found to be an independent risk factor for wound dehiscence, making sternal reinforcement essential. Sternal reinforcement should be considered when several risk factors are presented concomitantly. The growing number of patients at risk of sternum instability has led to the development of a number of techniques for the reinforcement of fragile sternum after median sternotomy. In 1977 Robiscek [34] was the first to describe a simple and valid technique, where bilateral parasternal running wires were passed anteriorly and posteriorly to the costal cartilages from the manubrium down to the xiphoid process, with alternating sutures. After lateral reinforcement of the sternum, steel wires are passed and tied in the usual manner. In later publications, several authors suggested modified variation of the Robicsek technique though they kept to the same principle [35–38]. They include the use of continuous wire on either side of the sternum and tied both lines cranially and caudally. Another reinforcement technique consists of applying staples on the sternum parallel to the free lateral margin of the sternum in order to avoid the stainless steel wires cutting into the anterior cortical layers, especially during sternum reapproximation. A solution with a reinforcement device has been suggested by Zeitani. The proposed device, DSS: Sternal Synthesis Device, consists of separate clips made of titanium sheet, sliding into each other to form two braces placed at either side of the sternum. In particular, a large vertical grooved arm of the clip is constructed to be placed into the intercostal space in a way that there is no direct contact between the stainless steel wire and side of the sternum [39].

4 Sternal Wound Complications

4.1 Introduction

Sternal wound complications vary from persistent chest pain and sternum instability to partial or complete wound dehiscence and mediastinitis. Of all sternal wound complications, mediastinitis is considered the most serious; it requires surgical treatment, prolonged antibiotic therapy, and continues to have a dramatic impact on patient survival, with a reported hospital mortality rate of between 10 and 20%. Gram-positive bacteria are the most commonly isolated bacteria in mediastinitis; *Staphylococcus aureus* or *S. epidermidis* is identified in 70–80% of cases. Gram-negative bacteria and fungal infections are less common [40–44]. Mixed infections may account for up to 40% of cases. Special attention should be given to bacteria which have become resistant to antibiotics that are in common use as prophylaxis, in particular, the methicillin-resistant *Staphylococcus aureus* (MRSA) or those resistant to vancomycin (VISA) [45].

In addition, mediastinitis has been found to affect long-term survival and to be an independent risk factor for late mortality in patients who have undergone CABG surgery.

The exact mechanism by which mediastinitis develops is controversial and multifactorial. There are several opinions regarding the chain of events; some surgeons believe that sternal separation occurs within a few days as an effect rather than a cause of wound infection. Others believe that sterna instability, followed by skin breakdown with seepage of bacteria into the deeper layers, is the key element in the development of mediastinal wound infection [46, 47]. Another hypothesis for the pathogenesis of mediastinitis is inadequate mediastinal drainage, leading to a large retrosternal collection, which acts as a culture medium for bacterial growth. In the early stages of deep wound infection, the mediastinum is separated by fibrin and adhesion formation; however, the mediastinal structures are soft and still relatively mobile. Osteomyelitis is usually confined to the sternal edges [48, 49]. Chronic mediastinitis evolves over a few weeks and is characterized by the formation of sinus tracts extending into the middle and posterior mediastinum, and in particular by the presence of foreign materials [49]. In recent reports, the average incidence has approached 1–2% [41–43]. In one of the largest studies, Loop et al. [42] reported an incidence of 1.1% in 6504 patients, but in other

studies the reported incidence of mediastinitis reached 2%. Distinguishing mediastinitis from deep wound infections can be difficult. In an attempt to achieve consistency of diagnosis the Centers for Disease Control and Prevention (CDC) defined criteria for surgical site infections (SSI) [50]. Briefly, superficial SSI involves only the skin or subcutaneous tissue of the incision, and superficial SSI must include at least one of the following:

1. Presence of purulent drainage
2. Isolation of an organism from the incision
3. Presence of at least one of the following symptoms: tenderness, swelling, redness, or heat

Deep SSI must meet the following criteria: Infection occurs within 30 days after surgical procedure, infection involves deep soft tissue of the incision, and at least one of the following is present:

1. Purulent drainage from the deep incision
2. Deep incision that spontaneously dehisces or when body temperature is over 38 °C or the surgeon has made the diagnosis

In 1996 El Oakly [48] suggested another classification as follows:

1. Mediastinal Dehiscence
   Median sternotomy wound breakdown in the absence of clinical or microbiologic evidence of infection
2. Mediastinal Wound Infection
   Clinical or microbiologic evidence of infected presternal tissue and sternal osteomyelitis, with or without mediastinal sepsis and with or without unstable sternum
   Subtypes for the above classification include:

1. Superficial wound infection
   Wound infection confined to the subcutaneous tissue

Deep wound infection (mediastinitis) is associated with sternal osteomyelitis with or without infected retrosternal space and based on the time of first presentation.

The presence or absence of risk factors is classified into four subtypes. In the absence of infection, sternal wound complications include sternal nonunion manifesting as persisting chest pain and/or instability detected on physical examination or detected by CT scan. Hendrickson et al. suggested a classification with regard to sternal nonunion [17]:

Type I: midline nonunion without transverse fractures

Type II: nonunion with unilateral transverse fractures

Type III: single or multiple bilateral transverse fractures

Type IV: nonunions which are characterized by multiple fractures with a missing bone segment and subsequent free-floating bone fragments

However, a simple classification of the sternal wound complications which most concern the surgeon includes:

1. Superficial wound dehiscence with or without presence of infection involving skin and subcutaneous layers with stable sternum
2. Unstable sternum with or without sterile wound drainage
3. Sternum dehiscence with evidence of infection but without evidence of mediastinitis
4. Mediastinitis

4.2 Risk Factors

> … Through the identification of the things which in toto determine the success or failure of our operations, things which we call incremental risk factors … we can approach decision- making for individual patients more precisely.
>
> —J. W. Kirklin Birmingham (Feb. 1979)

The National Nosocomial Infection Surveillance (NNIS) system of the Centers for Disease Control and Prevention uses a composite index for predicting risk of surgical site infection based on three risk factors: duration of surgery, wound class, and American Society of Anesthesiology score. However, a review of the literature reveals the existence of numerous risk factors affecting wound healing in cardiac surgery through a

midline sternotomy, risk factors which vary with different studies. This lack of consistency could be related to the different studies' objectives. In addition the low incidence of sternal wound infection means that a very large number of patients are required for analysis to reach statistical significance, while this number is not achieved in all studies. Risk factors affecting wound healing can be divided into those related to the patient and those relating to surgical procedures. In general, though, it is a combination of both the patients' risk factors and the surgical strategy that determines the outcome.

4.2.1 Patient's Related Risk Factors

A variety of patient characteristics have been associated with an increased incidence of wound dehiscence and mediastinitis, suggesting that certain factors may predispose patients to the development of this complication.

Obesity

Obesity is measured in terms of the body mass index (BMI), which is calculated from weight (kg)/height squared (m^2). According to the National Institutes of Health guidelines [51, 52] normal BMIs range from 18.5 to 24.9, mild obesity BMIs 25 to 34.9, moderate obesity BMIs 35 to 39.9, and extreme obesity BMIs 40 and over. However, in most studies, obesity is considered to be present when the body mass index is >30. The exact mechanisms by which obese patients are predisposed to wound infection are not clear. Large amounts of adipose tissue with low resistance to suture line tension pose technical difficulties with regard to dead-space obliteration, which facilitates seroma formation, interferes with normal wound healing, and probably also serves as a better substrata for bacteria growth, thus exacerbating wound infection. Poor blood perfusion, delayed wound healing, and antibiotics prophylaxis cover. In a large study of over 11,000 patients from the Northern New England Cardiovascular Disease Study Group, obesity was not found significantly to increase the risk of postoperative complications with the exception of sternal wound infections. In most other studies, sternal wound complications have been higher in obese patients who underwent midline sternotomy [53–58]. This higher incidence of wound complications in obese patients included both superficial and deep sternal wounds dehiscence.

Prasad et al. compared 250 obese patients with 250 control patients: an incidence of 9.2% of deep sternal infections was observed in the obese group versus 2.8% observed in the non-obese patients [55]. The incidence of such complication increases in patients in advanced age, and with comorbidities as renal failure, diabetes, and chronic obstructive pulmonary disease, or when bilateral internal mammary artery is used for myocardial revascularization with incidence of 14%. Based on the Society of Thoracic Surgeons National Cardiac Database, moderate (body mass index 35–39.9) patients are slightly at higher risk when compared with patients with MBI <35, but extremely obese patients are markedly at higher risk for mediastinitis. Other studies strongly support this finding. For example, in a recent publication including 1253 obese patients, 81 (6.46%) suffered sternal dehiscence, of whom 96% experienced mediastinitis and sepsis [53]. Also in this paper, the higher the degree of obesity, the higher the incidence of dehiscence, with up to 43% when the BMI was greater than 49.

Diabetes Mellitus

Diabetes mellitus is the most common endocrine disease, affecting almost every system in the body. The way in which diabetes interferes with the wound-healing process is not completely clear and is multifactorial. One potential pathogenic mechanism is that glycation of proteins alters the correct function. Moreover, in diabetic patients, glucose is reduced to sorbitol by the enzyme aldose reductase, which appears to function as a tissue toxin. With regard to bone structure, individuals with diabetes have a decreased bone mass and so are at a higher risk of bone fracture. Gooch et al. [59] investigated alterations in the expression of mRNA for type II and type X collagen in fracture callus of experimentally induced diabetic animals when compared with a control group. Radiographs showed a more intense periosteal reaction and a more rapid

reconstitution of cortices in the control group versus diabetic animals. Histologically there was a delay in chondrocyte maturation and hypertrophy seen in diabetics. Immunolocalization of type X collagen demonstrated a delay in type X collagen expression around the hypertrophic chondrocytes, where biomechanical analysis showed a decrease in the strength of healing fractures in diabetic animals. Bone fracture healing in diabetic patients is compromised and therefore may lead to delays in bone union. Nevertheless the exact mechanisms are unknown, while evidence of decreased mechanical strength of the fracture suggests that associated changes in collagen expression and chondrocyte maturation are mechanisms which lead to delayed healing in untreated and poorly controlled diabetes. Diabetic patients are more prone to wound infection when wound dehiscence has occurred. This may be due to impaired leukocyte function. In recent studies, postoperative glucose control has been shown to be effective in improving wound healing, leading to a lower incidence of wound infection [60, 61].

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a condition associated with excessive tracheobronchial mucus production, sufficient to cause cough with expectoration. Mostly it is associated with patients suffering from bronchitis and emphysema. Hyperplasia and hypertrophy changes in the large cartilaginous airways and abnormalities and alteration in the small airways such as inflammatory cell infiltration, peribronchial fibrosis, and increased smooth muscle cell mass result in airways narrowing. In addition, loss of elastic recoil of the lungs of in patients suffering from emphysema leads to respiratory insufficiency Such preoperative respiratory conditions may require prolonged postoperative ventilation. Indeed, reduced lung volumes following open-heart surgery are well documented [62–65]. The incidence of postoperative pulmonary complications has been reported to range from 20 to 90%, depending on the criteria for pulmonary complications and the methods of evaluation and analysis [45]. Performing sternotomy might lead to impaired respiratory muscles, decreased pulmonary function, and atelectasis for up to 8 weeks postoperatively. Hemisternums retraction and eventually mammary artery harvesting might also cause changes in respiratory motion and pulmonary function. Patients who received LITA grafts showed a greater reduction in total mean postoperative respiratory motion. Probably the elevation of the left side of the chest wall during LITA harvesting causes greater trauma to the costovertebral joints with a greater reduction in left-sided thoracic motion. Oxygen blood saturation is likely to be low in patients affected by chronic obstructive pulmonary disease. Reduced availability of oxygen and blood supply to the sternum in patients undergoing coronary artery bypass with the use of internal thoracic arteries may affect the healing process [66, 67]. Forces applied to the re-approximated hemisternums during coughing that are very common during the postoperative period and are more frequent in patients with chronic obstructive pulmonary disease should also be considered. Theoretic forces applied on the sternum during coughing might reach 1500 Newtons with high bone solicitation. With such high mechanical solicitation the material used for hemisternum fixation and in particular the stainless steel wires can cut through the bone, resulting in multiple fractures and consequently sternum instability [68].

4.2.2 Other Risk Factors

Osteoporosis is a common disorder of the older adult skeleton that predisposes an individual to an increased risk of fracture. As the population ages, a growing number of older patients are now undergoing cardiac surgery procedures through median sternotomy. Indeed, advanced age is a most important factor and is associated with not only reduced bone mass but also reduced quality of the bone. Thus, for any given bone mass, the risk of fracture increases with age. Parathyroid hormone is primarily thought of as a catabolic protein involved in the physiologic release of calcium from bone. During recent years a number of animal studies and clinical trials have demonstrated that intermittent administration of parathyroid hormone induces anabolic effects on both cancellous and cortical bone, enhancing the bone

mass and increasing the mechanical strength of the bones. Many studies, both animal and human, have addressed the treatment of osteoporosis, and parathyroid hormone represents an important new advance in the therapy of osteoporosis.

Parathyroid hormone (PTH) which is naturally secreted by the parathyroid glands is a potent anabolic agent for bone, being a major regulator of calcium and phosphate homeostasis. The main function of PTH is to maintain the calcium–ion concentration of the extracellular fluids within physiological limits. The overall effect of parathyroid hormone action is to increase and conserve serum calcium by enhancing gastrointestinal absorption of calcium, increasing renal calcium reabsorption, and liberating calcium from the skeleton through a process of enhanced bone reabsorption. Whereas continuous exposure to PTH results in bone reabsorption, administration of intermittent doses results in bone formation by increasing osteoblast number and activity [69, 70].

4.3 Antibiotic Therapy

Antibiotics therapy is widely used in cardiac surgery as a prophylaxis or as a prolonged treatment when site or systemic infection is detected. However, several antibiotics are known to have side effects, especially if the therapy is prolonged. Of these, for instance, ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic used in the treatment of a wide range of gram-positive and gram-negative infections. Although worldwide data from clinical trials with oral ciprofloxacin clearly demonstrate that the drug is relatively safe for adults, and that side effects are usually mild or moderate in intensity and are reversible, in children it has an adverse effect on growing cartilage and endochondral ossification and so could adversely affect healing process. Hauddleston et al. [71] conducted a study on rats to determine whether ciprofloxacin has an adverse effect on the healing of experimental fractures. In this study radiographic, histological, and biomechanical studies were used to evaluate fracture healing. Radiographs revealed significantly better healing of the control group fractures when compared with the fractures in the ciprofloxacin-treated group, which showed decreased strength in torsional strength testing and stiffness of the fracture callus. Also, fracture calluses in the animals treated with ciprofloxacin showed abnormalities in cartilage morphology and endochondral bone formation and a significant decrease in the number of chondrocytes compared with the control group.

4.4 Risk Factors Related to Surgical Procedure

4.4.1 Faulty Sternotomy

Following skin incision, the exact midline over the sternum should be marked with electrocautery before sternum separation to avoid off-center incision. With some clinical conditions, such as obesity or when the sternum is especially narrow, the midline can be difficult to find. Faulty sternotomy is an obvious risk for the development of wound complications. Shafir et al. [6] identified paramedian sternotomy as the main factor causing wound complications after a median sternotomy. In this study, in 11 of 55 patients with complications of median sternotomy, a paramedian sternotomy has been detected by computed tomography at the time of reoperation for wound dehiscence and fractures were visualized. In their conclusion, the authors suggest that, if a paramedian sternotomy is diagnosed during the initial operation, special closure techniques should be undertaken. In a prospective study, paramedian sternotomy, detected intraoperatively, was found to be an independent risk factor. Briefly, data of 171 patients undergoing cardiac surgery through a midline sternotomy were collected. Intraoperative measurements of sterna dimensions included both the thickness and the width at the manubrium, the third and fifth intercostal spaces. Paramedian sternotomy was defined as the width of one side of the sternum 75% of entire width, at any of the three levels. Chest instability was detected in 12 (7%) patients and wound infection in 2 (1.2%). Patient

weight, depressed left ventricular function, use of inotropic drugs, sternum thickness (indexed to body weight), and paramedian sternotomy ($p = 0.0001$) were risk factors of postoperative instability. Paramedian sternotomy was the only independent predictor [7].

4.4.2 Excessive Use of Electrocautery and Bone Wax

Excessive use of diathermy or bone wax reduces tissue resistance to infection because of tissue damage and reduced blood supply to the involved region. In addition, diathermy can also cause seroma formation in the subcutaneous tissue, so interfering with physiologic wound healing and low antibiotic concentration. Bone wax is a non-biodegradable material that inhibits bone healing and facilitates bacterial growth. In a study on rats affected with chronic osteomyelitis, addition of bone wax significantly reduced the dose of bacterial inoculum required to cause chronic osteomyelitis [72].

4.4.3 Iatrogenic Partial or Complete Sternum Fractures

Intraoperative hemisternum fractures can occur during oblique retraction required for mammary artery harvesting or transversal retraction to reach the mediastinum organs, while this is of particular concern to patients with osteoporotic bone. Such fractures weaken the bone structure and the closure wires cannot be placed at the segments concerned. Not only macro- but also microfractures may affect negatively bone strength and resistance to solicitations or other abnormal loads that cause shear stress in trabecular bone. Microdamage can also increase the likelihood of further damage during subsequent normal loading conditions, resulting in atraumatic or "spontaneous" fractures.

4.4.4 Prolonged Surgical Time

Patients undergoing a cardiopulmonary bypass (CPB) procedure are at a substantial risk of acquiring infections because of secondary impairment of their immune responses and because of the increased number of potential ports of entry of bacterial pathogens [55].

4.4.5 Use of Bilateral Internal Thoracic Artery

Use of bilateral internal thoracic arteries (ITAs) has recently been reported to improve survival and freedom from recurrent angina [73]; however, the use of ITAs causes extensive devascularization of the sternum [74]. In a study, using radioactive isotopes to measure sternal blood flow before and after median sternotomy and ITA procedures showed that blood flow to the sternal is significantly reduced from 4.5 to 0.8 mL/g/min, which represents a 90% decrease in the mean rate of flow within the ITA-harvested sterna versus a stable flow rate for the unharvested sides [75, 76]. Sternum devascularization increases the risk of wound infection and dehiscence, especially in patients with additional known risk factors, such as diabetes mellitus or chronic obstructive pulmonary disease. The risk increases seriously when both mammary arteries are harvested. To maintain the benefit of receiving two ITAs in high-risk patients, a method of partial right BITA harvesting and composite arterial graft fashioning has been proposed, which seems to offer substantial residual blood flow to the middle and distal portions of the right hemisternum [77, 78]. However, skeletonization of bilateral ITAs significantly decreases the incidence of both superficial and deep sterna infection independently from most commonly known risk factors [79].

4.4.6 Early Postoperative Blood Transfusion

The correlation between the number of blood units transfused and the incidence of wound infection has been described in early publications. Zacharias et al. [80] analyzed factors that enhance the risk of median sternotomy complications. In a retrospective study that examined 2317 consecutive patients undergoing cardiac surgery, 41 sternal infections were documented. Of these, 21 (0.91%) were deep infections with mediastinal involvement and 20 (0.86%) were superficial. Ten variables were associated with infection by univariate analysis, and of these five were independent predictors by multivariate logistic regression. These predictors were obesity,

insulin-dependent diabetes, use of internal mammary artery grafts, surgical reexploration of the mediastinum, and postoperative transfusions.

Olsen et al. [81] conducted a retrospective study examining 1980 consecutive patients undergoing coronary artery bypass surgery, in which independent risk factors for surgical site infection were identified with multivariate logistic regression. The study included 37 (1.9%) cases of deep chest and 46 (2.3%) cases of superficial chest surgical site infections. Obese diabetic patients had a 7.7-fold increased risk of deep-chest infections and postoperative transfusion (odds ratio, 2.3). In particular, the higher the number of blood transfusion units, the higher the occurrence of septicemia/bacteremia superficial and deep sternal wound infection. The correlation between the number of blood units transfused and the incidence of wound infection is also reported in other publications [82, 83].

4.4.7 Reoperation for Bleeding

Reoperation for hemostasis requires reopening of the chest which leads to soft-tissue damage. Reentry to the chest through previous and still unhealed incisions can increase the risk of infection because of the presence of bacteria at the incision site. Blood transfusions, necessary because of excessive blood loss, are reported to be a risk factor in their own right. In addition, excessive postoperative bleeding can lead to hemodynamic instability with peripheral low blood perfusion, which requires the use of positive inotropic drugs with its vasal constructive effects. The increased risk added to the tissue injury and ischemia at a time when sterna blood flow is most critical for early healing and consequent sterna stabilization. In fact, exploration for excessive postoperative bleeding (200 mL/h for 4 h) more than 6–7 h after chest closure has been shown to carry a significantly higher incidence of wound dehiscence and infection [84, 85].

4.4.8 Unappropriate Sternal Closure

While it is not pertinent to discuss at length inappropriate surgical techniques here, technical errors cannot be excluded as a reason for wound dehiscence and the non-recovery of patients. Too tight or too lose closure can cause—respectively—fracture of the sternum (especially if the bone is fragile) or excessive movement of the hemisternum during respiratory motion and coughing, with continuous bone solicitation.

5 Surgical Treatment

Successful management of the dehisced sternum requires an appreciation of the underlying causes. When sterile dehisced sternum has occurred, simple rewiring may be sufficient. For complicated sternal wound dehiscence, or if infection has occurred, the optimal method of wound treatment remains controversial and a variety of techniques have been reported. These generally can be divided into three groups:

5.1 Topical Treatment and Delayed Surgical Closure

Primary closure with irrigation-suction system

Muscle or omentum flap and primary wound closure

Primary closure with irrigation-suction system

The high incidence of wound dehiscence and ensuing high mortality rates following topic treatment have led to a search for other surgical solutions. Debridement and mediastinum irrigation were first described by Schumaker and Mendelbaum in 1963 [86]. Since then, this method has become the preferred initial therapy for mediastinitis in most cardiothoracic centers. Indeed, this technique has been found to be a rapid and effective procedure. As for the irrigation solution, several authors reported the use of saline solution or antibiotics. In alternative a low-concentration povidone-iodine solution was also proposed. The sole suction was also proposed using redon catheter. In a comparison study between the two methods, the vacuum drainage system was found to be a more effective therapy, because it is associated with significantly less treatment failure and shorter hospital stays [87, 88].

5.2 Topical Treatment with Secondary Wound Healing

The surgical debridement is mandatory to eradicate infected tissue and to remove necrotic and devascularized tissue in all surgical procedures for wound dehiscence. Broad-spectrum antibiotic coverage should be instituted initially until the specific bacteria have been identified. Delayed surgical closure consists of topic medication with disinfection solutions. However, this technique is associated with prolonged treatment, with considerable discomfort to patients and with high mortality rate. In the 1990s negative-pressure treatment for dehisced wound was introduced [89, 90]. It has been claimed that the negative-pressure system has several advantages over conventional wound dressing. It reduces tissue edema and improves blood supply, while sealing of the wound provides an optimal physiologic environment for tissue repair. Continuous negative pressure provides active suction and bacterium removal reducing the bacterium flora. The vacuum device should be programmed to create a continuous negative pressure in the wound of 125 mmHg. As soon as bacteria can be presented constantly in the cultural tests, plasma C-reactive protein has been proposed as indication for wound closure. When levels are getting into the range of 30–70 mgh, secondary surgical closure might be performed. Considering the above as arbitrary indicator, general aspect and presence of secretion should also be considered. They reported that mean duration of treatment was 27 days (range 8–66 days), with wound dressings being changed every 48 h.

5.3 Muscle and Omentum Flap Reconstruction

Reconstruction of the sternum wound dehiscence might be achieved by pectoralis major muscular and musculocutaneous flaps. Surgical strategies for muscle mobilization should take into consideration the eventual use of the internal mammary artery for myocardial revascularization. Indeed, the flaps constructed from the pectoralis major are dependent on its primary and secondary blood supplies. The primary blood supply to the muscle comes from the thoracoacromial artery and the secondary blood supply is provided by the collateral branches of the internal mammary artery. One or both of the pectoralis major muscles may be used to close the wound. The muscle flap might also be split along its midline to allow part of the muscle to cover, respectively, the upper and lower parts of the sternum. The rectus abdominis muscular and musculocutaneous flap has also been used successfully in reconstructing the dehisced median sternotomy wound. The primary blood supply for this muscular/musculocutaneous flap when used in chest wall reconstruction is the superior epigastric artery and vein. A continuous arterial/venous arcade exists in the muscle connecting the inferior and superior epigastric vessels. Obviously, the integrity of this arcade has to be preserved or the distal portion of the muscle will suffer necrosis when the pedicle is rotated. The vertical rectus flap can be rotated as either a muscular or a musculocutaneous flap. When the flap is transferred as a musculocutaneous flap, the anterior leaf of the rectus sheath as well as the subcutaneous tissues and skin are transferred with the flap. As such the flap can be used to fill a substantial midline defect as well as supply a skin island for the dermal closure. The use of the omental flap in reconstructing the dehisced median sternotomy can be highly advantageous, because of its resistance to infection and its ability to fill large spaces, especially in cases where mediastinitis has occurred in patients who underwent surgery with implantation of synthetic materials. The blood supply for the omentum is the epiploic arteries and veins coursing along the greater curvature of the stomach. The omentum may be pedicled on both sets of vessels or either one alone [89–96]. Latissimus dorsi muscle can also be used having an excellent blood supply and can be used to cover large defects or when other flaps are not available. However, mobilization is more demanding surgically and therefore this flap is being used less frequently than other flaps [97].

6 Clinical and Economical Consequences

Sternal wound complications are significant in terms of morbidity, mortality, and also economic cost, especially when mediastinitis occurs, as this usually requires prolonged hospital stays, reoperation for the purpose of sternal debridement, application of one of the techniques of chest closure, and prolonged treatment with antibiotics. Chronic infection and sinus tract formation can also occur, requiring reoperation, prolonging healing time, and greatly adding to the patient's discomfort. Deep-chest infections also carry a high risk for mortality; in recent publications reported mortality rate ranged from 10 to 20%. In addition, mediastinitis has been found to affect long-term survival rates. After adjustment for common risk factors for late mortality among CABG patients, mediastinitis remains a significant independent predictor of late mortality. Furthermore, the impact of sternal wound infection on the health-care system is significant, where the average stay of patients with wound complications is 43 days while the hospitalization cost of these patients is three times greater than that of those patients who did not experience postoperative complications. This higher cost is primarily due to the associated high morbidity and the need for repeated surgical procedures [98].

Conclusions

Deep wound dehiscence and the consequent instability of the chest closure undoubtedly represent the most feared complications following sternotomy procedures, facilitating tissue infection and mediastinitis. The latter is associated with prolonged hospital stay, and high morbidity and high mortality rates. Long-term survival rates are also reduced, probably because of damage to the systemic organs during sepsis, and prolonged antibiotic therapy. When mediastinitis occurs, patient isolation is mandatory to avoid bacterial contamination spreading to other patients. However, the patients' clinical conditions do not always allow complete isolation, especially when intensive care treatment is required. Therefore, prevention of sternum wound infection complications remains a major challenge for cardiothoracic surgeons and hospital staff. Wound complications can be reduced by effective identification of risk factors, and by tailoring surgical strategies to the patient's clinical conditions, rather than adhering too closely to strict cardiac pathology.

Continuous insulin infusion to diabetic patients during the postoperative period helps keeping glucose levels within the normal range, reducing the incidence of wound infection. Likewise for high-risk patients, ensuring short operating time and accurate hemostasis can improve survival rates. In the face of the changing characteristics of patients who undergo cardiac surgery procedures, and also improvements in surgical procedures, it is essential to evaluate and update risk factors affecting wound healing, as well as monitor the incidence of wound complications and their implications for patient survival.

References

1. Milton H (1897) Mediastinal surgery. Lancet 1:872–875
2. Milton H (1901) Removal of a foreign body from the bronchus by intrathoracic tracheotomy. Lancet 1:242–244
3. Shumacker HB Jr, Lurie PR (1953) Pulmonary valvulotomy: description of a new approach about diagnostic characteristics of a pulmonic valvular stenosis. J Thorac Surg 25:173–186
4. Gibbon JH Jr (1954) Application of a mechanical heart and lung apparatus to cardiac surgery. Minn Med 37:171–180
5. Julian OC, Lopez-Belio M, Dye WS, Javid H, Grove WJ (1957) The median sternal incision in intracardiac surgery with extracorporeal circulation: a general evolution of its use in heart surgery. Surgery 42:753–761
6. Shafir R, Weiss J, Herman O, Cohen N, Stern D, Igra Y (1988) Faulty sternotomy and complications after median sternotomy. J Thorac Cardiovasc Surg 96:310–313
7. Zeitani J, Penta de Peppo A, Moscarelli M, Gurrieri L, Scafuri A, Nardi P, Nanni F, Di Marzio E, Chiariello L (2006) Influence of sternal size and inadvertent paramedian sternotomy on stability of the closure site: a clinical and mechanical study. J Thorac Cardiovac Surg 132:38–42

8. Joshi R, Abraham S, Sampath Kumar A (2004) Interlocking sternotomy: initial experience. Asian Cardiovasc Thorac Ann 12(1):16–18
9. Cosgrove DM, Sabik JF (1996) Minimally invasive approach for aortic valve operations. Ann Thorac Surg 62:596–597
10. Arom KV, Emery RW (1997) Minimally invasive mitral operations. Ann Thorac Surg 63:1219–1220
11. Konertz W, Waldenberger F, Schmutzler M et al (1996) Minimal access valve surgery through superior partial sternotomy: a preliminary study. J Heart Valve Dis 5:638–640
12. Izzat MB, Yim AP (1998) Minimally invasive intracardiac surgery. Hosp Med 59(2):100–103
13. Dogan S, Aybek T, Risteski PS, Deltho F, Rappo A, Wimmer Greinecke G, Moritz A (2005) Minimally invasive port access versus conventional mitral valve surgery: prospective randomized study. Ann Thorac Surg 79(2):492–498
14. Zeitani J, Pugliese M, Mve Mvondo C, Chiariello AG, Bellos K, Simonetti G, Chiariello L (2013) Surgical approach to aortic valve replacement after previous bilateral internal thoracic artery grafting. Tex Heart Inst J 40(2):170–172
15. Timmes JJ, Wolvek S, Fernando M, Bas M, Rocko J (1973) A new method of sternal approximation. Ann Thorac Surg 15(5):544
16. Goodman G, Palatianos GM, Bolooki H (1986) Technique of closure of median sternotomy with trans-sternal figure-of-eight wires. J Cardiovasc Surg 27:512–513
17. Mariani MA, Vaccari G, Marullo A et al (1998) Combined use of single and double-cross steel wires for closure of midline sternotomy. J Cardiovasc Surg 39: 833–837
18. Casha AR, Ashraf SS, Kay PH, Cooper GJ (1999) Routine sternal closure using interlocking multitwisted wires. Eur J Cardiothorac Surg 16:353–355
19. Actis Dato G, Deorsola L (1998) Interlocking sternal closure. Ann Thorac Surg 66:1860–1861
20. Murray KD, Pasque MK (1997) Routine sternal closure using six overlapping figure-of-eight wires. Ann Thorac Surg 64:1852–1854
21. Di Marco RF, Lee MW, Bekoe S, Grant KJ, Woelfel GF, Pellegrini RV (1989) Interlocking figure-of-eight closure of the sternum. Ann Thorac Surg 47:927–929
22. Taber RE, Madaras J (1969) Prevention of sternotomy wound disruptions by use of figure-of-eight pericostal sutures. Ann Thorac Surg 8:367–369
23. Katz N (1997) Pericostal sutures to reinforce sternal closure after cardiac surgery. J Card Surg 12:277–281
24. Kalush SL, Bonchek LI (1976) Peristernal closure of median sternotomy using stainless steel bands. Ann Thorac Surg 21:172–173
25. Badellino M, Cavarocchi NC, Kolff J, Alpern JB, McClurken JB (1988) Sternotomy closure with Parham bands. J Card Surg 3:235–236
26. Soroff HS, Hartman AR, Pak E, Sasvary DH, Pollak SB (1996) Improved sternal closure using steel bands: early experience with three-year follow-up. Ann Thorac Surg 61:1172–1176
27. Sanfelippo PM, Danielson GK (1972) Nylon bands for closure of median sternotomy incisions: an unacceptable method. Ann Thorac Surg 13:404–406
28. Sirivella S, Zikria EA, Ford WB et al (1987) Improved technique for closure of median sternotomy incision: mersilene tapes versus standard wire closure. J Thorac Cardiovasc Surg 94(4):591–595
29. Ozaki W, Buchman SR, Iannettoni MD et al (1998) Biomechanical study of sternal closure using rigid fixation technique in human cadavers. Ann Thorac Surg 65:1160–1165
30. Pai S, Gunja NJ, Dupak EL et al (2005) In vitro comparison of wire and plate fixation for midline sternotomies. Ann Thorac Surg 80:962–968
31. Smoot EC, Weiman D (1998) Paramedian sternal bone plate reinforcement and wiring for difficult sternotomy wounds. Ann Plast Surg 41:464–467
32. Song DH, Lohman RF, Renucci DJ, Jeevanandam V, Raman J (2004) Primary sternal plating in high-risk patients prevents mediastinitis. Eur J Cardiothorac Surg 26:367–372
33. Schwab RJ, Hahnel JC, Paek S et al (1994) Sternal closure with resorbable synthetic suture material in children. Thorac Cardiovasc Surg 42:185–186
34. Robiscek F, Daugherty HK, Cook JW (1977) The prevention and treatment of sternal separation following open heart surgery. J Thorac Cardiovasc Surg 73:267–268
35. Totaro P, Lorusso R, Zogno M (2001) Reinforced sternal closures for prevention of sternal dehiscence in high risk patients. J Cardiovasc Surg 42:601–603
36. Chlosta WF, Elefteriades JA (1995) Simplified method of reinforced sternal closure. Ann Thorac Surg 60:1428–1429
37. Triggiani M, Donatelli F, D'Ancona G et al (1997) Reinforced closure of precarious sternum after median sternotomy. Ann Thorac Surg 63:1221–1222
38. Zeitani J, Penta de Peppo A, Bianco A, Nanni F, Scafuri A, Bertoldo F, Salvati A, Nardella S, Chiariello L (2008) Performance of a novel sternal synthesis device after median and faulty sternotomy: mechanical test and early clinical experience. Ann Thorac Surg 85:287–293
39. Tavilla G, van Son JAM, Veehagen AF, Lacquet LK (1991) Modified Robiscek technique for complicated sternal closure. Ann Thorac Surg 52:1179–1180
40. Tang GH, Maganti M, Weisel RD, Borger MA (2004) Prevention and management of deep sternal wound infection. Semin Thorac Cardiovasc Surg 16: 62–69
41. Braxton JH, Marrin CA, McGrath PD et al (2004) 10-year follow-up of patients with and without mediastinitis. Semin Thorac Cardiovasc Surg 16:70–76
42. Loop FD, Lytle BW, Cosgrove DM, Mahfood S, McHenry MC, Goormastic M, Stewart RW, Golding LA, Taylor PC (1990) J. Maxwell chamberlain memorial paper. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. Ann Thorac Surg 49:179–187

43. Zeitani J, Bertoldo F, Bassano C, Penta de Peppo A, Pellegrino A, El Fakhri FM, Chiariello L (2004) Superficial wound dehiscence after median sternotomy: surgical treatment versus secondary wound healing. Ann Thorac Surg 77:672–675
44. Zacharias A, Habib R (1996) Delayed primary closure of deep sternal wound infections. Tex Heart Inst J 23:211–216
45. Dancer SJ, Coyne M, Speekenbrink A, Samavedam S, Kennedy J, Wallace PG (2006) MRSA acquisition in an intensive care unit. Am J Infect Control 34: 10–17
46. The Parisian Mediastinitis Study Group (1996) Risk factors for deep sternal wound infection after sternotomy: a prospective multicenter study. J Thorac Cardiovasc Surg 111:1200–1207
47. Jacob HG, Borneff-Lipp M, Bach A, von Pückler S, Windeler J, Sonntag H, Hagl S (2000) The endogenous pathway is a major route for deep sternal wound infection. Eur J Cardiothorac Surg 17:154–160
48. El Oakley RM, Wright JE (1996) Postoperative mediastinitis: classification and management. Ann Thorac Surg 61:1030–1036
49. Bitkover CY, Gardlund B (1998) Mediastinitis after cardiovascular operations: a case-control study of risk factors. Ann Thorac Surg 65:36–40
50. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections 1988. Am J Infect Control 16:128–140
51. Culver DH, Horan TC, Gaynes RP et al (1991) Surgical wound infection by wound class, operative procedures, and patient risk index. Am J Med 91(Suppl 3B):152S–157S
52. National Institutes of Health (1998) Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. National Heart, Lung and Blood Institute, Bethesda, MD
53. O'Connor GT, Plume SK, Olmstead EM et al (1992) Multivariate prediction of in-hospital mortality associated with coronary artery bypass graft surgery. Northern New England cardiovascular disease study group. Circulation 85:2110–2118
54. Molina JE, Lew RS, Hyland KJ (2004) Postoperative sternal dehiscence in obese patients: incidence and prevention. Ann Thorac Surg 78:912–917
55. Milano CA, Kesler K, Archibald N et al (1995) Mediastinitis and long-term survival after coronary artery bypass graft surgery. Circulation 92:2245–2251
56. Prasad US, Walker WS, Sang CT, Campanella C, Cameron EW (1991) Influence of obesity on the early and long term results of surgery for coronary artery disease. Eur J Cardiothorac Surg 5:67–73
57. Birkmeyer NJ, Charlesworth DC, Hernandez F et al (1998) Obesity and risk of adverse outcomes associated with coronary artery bypass surgery. Circulation 97:1689–1694
58. Prabhakar G, Haan CK, Peterson ED et al (2002) The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. Ann Thorac Surg 74(4):1125–1130
59. Gooch HL, Hale JE, Fujioka H, Balian G, Hurwitz SR (2000) Alterations of cartilage and collagen expression during fracture healing in experimental diabetes. Connect Tissue Res 41:81–91
60. Cohen O, Dankner R, Chetrit A et al (2003) Multidisciplinary intervention for control of diabetes in patients undergoing coronary artery bypass graft (CABG). Cardiovasc Surg 11:195–200
61. Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP (1999) Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 88:1011–1016
62. Cohen AJ, Moore P, Jones C et al (1993) Effect of internal mammary harvest on postoperative pain and pulmonary function. Ann Thorac Surg 56:1107–1109
63. Shenkman S, Shir Y, Weiss YG et al (1997) The effect of cardiac surgery on early and late pulmonary functions. Acta Anaesthesiol Scand 41:1193–1199
64. Wahl GW, Swinburne AJ, Fedullo AJ et al (1993) Effect of age and preoperative airway obstruction on lung function after coronary art e ry bypass grafting. Ann Thorac Surg 56:104–107
65. Hulzebos EH, Van Meeteren NL, De Bie RA, Dagnelie PC, Helders PJ (2003) Prediction of postoperative pulmonary complications on the basis of preoperative risk factors in patients who had undergone coronary artery bypass graft surgery. Phys Ther 83:8–16
66. Sofer D, Gurevitch J, Shapira I, Paz Y, Matsa M, Kramer A, Mohr R (1999) Sternal wound infections in patients after coronary artery bypass grafting using bilateral skeletonized internal mammary arteries. Ann Surg 229:585–590
67. Greif R, Akça O, Horn EP, Kurz A, Sessler DI (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes research group. N Engl J Med 342:161–167
68. Casha AR, Yang L, Cooper GJ (1999) Measurement of chest wall forces on coughing with the use of human cadavers. J Thorac Cardiovasc Surg 118:1157–1158
69. Arnaud CD, Tenenhouse AM, Rasmussen H (1967) Parathyroid hormone. Annu Rev Physiol 29:349–372
70. Holzer G, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA (1999) Parathyroid hormone enhances fracture healing. A preliminary report. Clin Orthop 366:258–263
71. Huddleston PM, Steckelberg JM, Hanssen AD, Rouse MS, Bolander ME, Patel R (2000) Ciprofloxacin inhibition of experimental fracture healing. J Bone Joint Surg Am 82:161–173
72. Nishida H, Grooters RK, Soltanzadeh H et al (1993) Discriminate use of electrocautery on the median sternotomy incision. A 0.16% infection rate. J Thorac Cardiovasc Surg 101:488–494
73. Endo M, Nishida H, Tomizawa Y, Kasanuki H (2001) Benefit of bilateral IMA grafts over single IMA graft for multiple coronary artery bypass grafting. Circulation 104:2164–2170

74. Arnold M (1972) The surgical anatomy of sternal blood supply. J Thorac Cardiovasc Surg 64:596–610
75. Carrier M, Gregoire J, Tronc F, Cartier R, Leclerc Y, Pelletier LC (1993) Effect of internal mammary artery dissection on sternal vascularization: 1993 update. Ann Thorac Surg 55:803–804
76. Carrier M, Gregoire J, Tronc F, Cartier R, Leclerc Y, Pelletier LC (1992) Effect of internal mammary artery dissection on sternal vascularization. Ann Thorac Surg 53:115–1196
77. Zeitani J, Penta de Peppo A, De Paulis R et al (2005) Partial right internal thoracic artery harvesting is sufficient for obtuse marginal branch bypass grafting. Ann Thorac Surg 79:361–362
78. Zeitani J, Penta de Peppo A, De Paulis R, Nardi P, Scafuri A, Nardella S, Chiariello L (2006) Benefit of partial right-bilateral internal thoracic artery harvesting in patients at risk of sternal wound complications. Ann Thorac Surg 81:139–143
79. De Paulis R, de Notaris S, Scaffa R, Nardella S, Zeitani J, Del Giudice C, De Peppo AP, Tomai F, Chiariello L (2005) The effect of bilateral internal thoracic artery harvesting on superficial and deep sternal infection: the role of skeletonization. J Thorac Cardiovasc Surg 129:536–543
80. Zacharias A, Habib RH (1996) Factors predisposing to median sternotomy complications. Deep vs superficial infection. Chest 110:1173–1178
81. Olsen MA, Locl-Bukley P, Hopkins D et al (2002) The risk factors for deep and superficial chest surgical-site infections after coronary artery bypass graft surgery are different. J Thorac Cardiovasc Surg 124:136–145
82. El Oakley R, Paul E, Wong PS et al (1997) Mediastinitis in patients undergoing cardiopulmonary bypass: risk analysis and midterm results. J Cardiovasc Surg 38:595–600
83. Murphy PJ, Connery C, Hicks GL et al (2001) Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. J Thorac Cardiovasc Surg 104:1092–1099
84. Talamonti MS, LoCicero J III, Hoyne WP, Sanders JH, Michaelis LL (1987) Early reexploration for excessive postoperative bleeding lowers wound complication rates in open heart surgery. Am Surg 53:102–104
85. Boeken U, Eisner J, Feindt P, Petzold TH, Schulte HD, Gams E (2001) Does the time of resternotomy for bleeding have any influence on the incidence of sternal infections, septic courses or further complications? Thorac Cardiovasc Surg 49:45–48
86. Shumacker HB Jr, Mandelbaum I (1963) Continuous antibiotic irrigation in the treatment of infection. Arch Surg 86:384–387
87. Bryant LR, Spencer FC, Trinkle JK (1969) Treatment of median sternotomy infection by mediastinal irrigation with an antibiotic solution. Ann Surg 169:914–920
88. Durandy Y, Batisse A, Bourel P, Dibie A (1989) Mediastinal infection after cardiac operation; a simple closed technique. J Thorac Cardiovasc Surg 97:282–285
89. Gustafsson RI, Sjogren J, Ingemansson R (2003) Deep sternal- sparing technique with vacuum-assisted closure therapy. Ann Thorac Surg 76:2048–2053
90. Tang AT, Ohri SK, Haw MP (2000) Novel application of vacuum assisted closure technique to the treatment of sternotomy wound infection. Eur J Cadio-thorac Surg 17:482–484
91. Graeber GM, Langenfeld J (1998) Chest wall resection and reconstruction. In: Franco H, Putman JB (eds) Advanced therapy in thoracic surgery. BC Decker, Inc, London, pp 175–185
92. Seyfer AE, Graeber GM, Akind FF (1986) The pectoris major muscle and musculocutaneous flaps. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of Chest Wall reconstruction. Aspen Publishers, Rockville, MD
93. Tofin GR (1989) Pectoralis major muscle-musculocutaneous flap for chest wall reconstruction. Surg Clin North Am 69:991–1006
94. Zeitani J, Pompeo E, Nardi P, Sergiacomi G, Scognamiglio M, Chiariello G, Del Giudice C, Arganini C, Simonetti G, Chiariello L (2013) Early and long-term results of pectoralis muscle flap reconstruction versus sternal rewiring following failed sternal closure. Eur J Cardiothorac Surg 43(6):e144–e150
95. Zeitani J, Russo M, Pompeo E, Sergiacomi GL, Chiariello L (2016) Pectoralis muscle flap repair reduces paradoxical motion of the chest wall in complex sternal wound dehiscence. Korean J Thorac Cardiovasc Surg 49(5):366–373
96. Seyfer AE, Graeber GM, Akind FF (1986) The omentum. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of chest wall reconstruction. Aspen Publishers, Rockville, MD
97. Seyfer AE, Graeber GM, Akind FF (1986) The latissimus dorsi muscle and musculocutaneous flaps. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of chest wall reconstruction. Aspen Publishers, Rockville, MD
98. Hollenbeak CS, Murphy DM, Koenig S, Woodward RS, Dunagan WC (2000) The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft. Chest 118:397–402

Sternal Wound Complications

Jacob Zeitani

1 Introduction

Sternal wound complications vary from persistent chest pain and sternal instability to partial or complete wound dehiscence and mediastinitis. Of all sternal wound complications, mediastinitis is considered the most serious; it requires surgical treatment and prolonged antibiotic therapy and continues to have a dramatic impact on patient survival, with a reported hospital mortality rate of between 10% and 20%. Gram-positive bacteria are the most commonly isolated bacteria in mediastinitis; *Staphylococcus aureus* or *S. epidermidis* are identified in 70–80% of cases. Gram-negative bacteria and fungal infections are less common [1–10]. Mixed infections may account for up to 40% of cases. Special attention should be given to bacteria which have become resistant to antibiotics that are in common use as prophylaxis, in particular the methicillin-resistant *Staphylococcus aureus* (MRSA), or those resistant to vancomycin, vancomycin intermediate-resistant S. aureus (VISA) [11, 12]. In addition, mediastinitis has been found to affect long-term survival and to be an independent risk factor for late mortality in patients who have undergone CABG surgery.

J. Zeitani, M.D.
Department of Cardiac Surgery, Tor Vergata University of Rome, Rome, Italy
e-mail: zeitani@hotmail.com

The exact mechanism by which mediastinitis develops is controversial and multifactor. There are several opinions regarding the chain of events; some surgeons believe that sternal separation occurs within a few days as an effect rather than a cause of wound infection. Others believe that sternal instability, followed by skin breakdown with seepage of bacteria into the deeper layers, is the key element in the development of mediastinal wound infection [13–16]. Another hypothesis for the pathogenesis of mediastinitis is inadequate mediastinal drainage, leading to a large retrosternal collection, which acts as a culture medium for bacterial growth. In the early stages of deep wound infection, the mediastinum is separated by fibrin and adhesion formation; however, the mediastinal structures are soft and still relatively mobile. Osteomyelitis is usually confined to the sternal edges [17–20]. Chronic mediastinitis evolves over a few weeks and is characterized by the formation of sinus tracts extending into the middle and posterior mediastinum, and in particular by the presence of foreign materials [18, 20]. In recent reports, the average incidence has approached 1–2% [2–4, 7–9]. In one of the largest studies, Loop et al. [3, 8] reported an incidence of 1.1% in 6504 patients, but in other studies, the reported incidence of mediastinitis reached 2%. Distinguishing mediastinitis from deep wound infections can be difficult. In an attempt to achieve consistency of diagnosis, the Centers for Disease Control and Prevention (CDC) defined the criteria for surgical

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_73, © Springer International Publishing AG
Published Online: 03 May 2018

site infections (SSI) [21, 22]. Briefly, superficial SSI involves only the skin or subcutaneous tissue of the incision, and superficial SSI must include at least one of the following:

1. Presence of purulent drainage
2. Isolation of an organism from the incision
3. Presence of at least one of the following symptoms: tenderness, swelling, redness, or heat

Deep SSI must meet the following criteria:

Infection occurs within 30 days after surgical procedure.
Infection involves deep soft tissue of the incision.
At least one of the following is present:

1. Purulent drainage from the deep incision
2. Deep incision that spontaneously dehisces or when body temperature is over 38 °C or the surgeon has made the diagnosis

In 1996 El Oakley [17] suggested another classification as follows:

1. Mediastinal dehiscence
   Median sternotomy wound breakdown in the absence of clinical or microbiologic evidence of infection
2. Mediastinal wound infection
   Clinical or microbiologic evidence of infected presternal tissue and sternal osteomyelitis, with or without mediastinal sepsis and with or without unstable sternum

Subtypes for the above classification include:

1. Superficial wound infection
2. Wound infection confined to the subcutaneous tissue
3. Deep wound infection (mediastinitis)
4. Wound infection associated with sternal osteomyelitis with or without infected retrosternal space and based on the time of first presentation

The presence or absence of risk factors is classified into four subtypes. In the absence of infection, sternal wound complications include sternal nonunion manifesting as persisting chest pain and/or instability detected on physical examination or detected by CT scan. Hendrickson et al. [23] suggested a classification with regard to sternal nonunion.

Type I: midline nonunion without transverse fractures
Type II: nonunion with unilateral transverse fractures
Type III: single or multiple bilateral transverse fractures
Type IV: nonunions which are characterized by multiple fractures with a missing bone segment and subsequent free-floating bone fragments

However, a simple classification of the sternal wound complications which most concern the surgeon includes:

1. Superficial wound dehiscence with or without the presence of infection involving the skin and subcutaneous layers with stable sternum
2. Unstable sternum with or without sterile wound drainage
3. Sternal dehiscence with evidence of infection but without evidence of mediastinitis
4. Mediastinitis

2 Risk Factors

> … Through the identification of the things which in toto determine
> the success or failure of our operations, things which we call
> incremental risk factors … we can approach decision-making for
> individual patients more precisely.
> J. W. Kirklin Birmingham Feb. 1979

The National Nosocomial Infection Surveillance (NNIS) system of the Centers for Disease Control and Prevention uses a composite index for predicting risk of surgical site infection based on three risk factors: duration of surgery, wound

class, and American Society of Anesthesiology score. However, a review of the literature reveals the existence of numerous risk factors affecting wound healing in cardiac surgery through a midline sternotomy, risk factors which vary with different studies. This lack of consistency could be related to the different studies' objectives. In addition the low incidence of sternal wound infection means that a very large number of patients are required for analysis to reach statistical significance, while this number is not achieved in all studies. Risk factors affecting wound healing can be divided into those related to the patient and those relating to surgical procedures. In general, though, it is a combination of both the patients' risk factors and the surgical strategy that determines the outcome.

2.1 Patient's Related Risk Factors

A variety of patient characteristics have been associated with an increased incidence of wound dehiscence and mediastinitis, suggesting certain factors may predispose patients to the development of this complication.

2.1.1 Obesity

Obesity is measured in terms of the body mass index (BMI), which is calculated from weight (kg)/height squared (m^2). According to the National Institutes of Health guidelines [24, 25], normal BMIs range from 18.5 to 24.9, mild obesity BMIs 25 to 34.9, moderate obesity BMIs 35 to 39.9, and extreme obesity BMIs 40 and over. However, in most studies, obesity is considered to be present when the body mass index >30. The exact mechanisms by which obese patients are predisposed to wound infection are not clear. Large amounts of adipose tissue with low resistance to suture line tension pose technical difficulties with regard to dead space obliteration, which facilitates seroma formation, interferes with normal wound healing, and probably also serves as a better substrate for bacterial growth, thus exacerbating wound infection. Poor blood perfusion delays wound healing and antibiotic prophylaxis cover. In a large study of over 11,000 patients from the Northern New England Cardiovascular Disease Study Group, obesity was not found significantly to increase the risk of postoperative complications with the exception of sternal wound infections. In most other studies, sternal wound complications have been higher in obese patients who underwent midline sternotomy [26–31]. This higher incidence of wound complications in obese patients included both superficial and deep sternal wound dehiscence.

Prasad et al. [28] compared 250 obese patients with 250 control patients: an incidence of 9.2% of deep sternal infections was observed in the obese group versus 2.8% observed in the non-obese patients. The incidence of such complication increases in patients in advanced age and with comorbidities as renal failure, diabetes, and chronic obstructive pulmonary disease or when bilateral internal mammary artery is used for myocardial revascularization with incidence of 14%. Based on the Society of Thoracic Surgeons National Cardiac Database, moderate (body mass index 35 to 39.9) patients are slightly at higher risk when compared with patients with MBI < 35, but extremely obese patients are marked at higher risk for mediastinitis. Other studies strongly support this finding. For example, in a recent publication [26] including 1253 obese patients, 81 (6.46%) suffered sternal dehiscence, of whom 96% experienced mediastinitis and sepsis. Also in this paper, the higher the degree of obesity, the higher the incidence of dehiscence, with up to 43% when the BMI was greater than 49.

2.2 Diabetes Mellitus

Diabetes mellitus is the most common endocrine disease, affecting almost every system in the body. The way in which diabetes interferes with the wound healing process is not completely clear and is multifactorial. One potential pathogenic mechanism is that glycation of proteins alters the correct function. Moreover, in diabetic patients, glucose is reduced to sorbitol by the enzyme aldose reductase, which appears to function as a tissue toxin. With regard to bone

structure, individuals with diabetes have a decreased bone mass and so are at a higher risk of bone fracture. Gooch et al. [32] investigated alterations in the expression of mRNA for type II and type X collagen in fracture callus of experimentally induced diabetic animals when compared with a control group. Radiographs showed a more intense periosteal reaction and a more rapid reconstitution of cortices in the control group versus diabetic animals. Histologically there was a delay in chondrocyte maturation and hypertrophy seen in diabetics. Immunolocalization of type X collagen demonstrated a delay in type X collagen expression around the hypertrophic chondrocytes, where biomechanical analysis showed a decrease in the strength of healing fractures in diabetic animals. Bone fracture healing in diabetic patients is compromised and therefore may lead to delays in bone union. Nevertheless the exact mechanisms are unknown, while evidence of decreased mechanical strength of the fracture suggests that associated changes in collagen expression and chondrocyte maturation are mechanisms which lead to delayed healing in untreated and poorly controlled diabetes. Diabetic patients are more prone to wound infection when wound dehiscence has occurred. This may be due to impaired leukocyte function. In recent studies, postoperative glucose control has been shown to be effective in improving wound healing, leading to a lower incidence of wound infection [33, 34].

2.3 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a condition associated with excessive tracheobronchial mucus production, sufficient to cause cough with expectoration. Mostly it is associated with patients suffering from bronchitis and emphysema. Hyperplasia and hypertrophy changes in the large cartilaginous airways and abnormality alteration in the small airways, such as inflammatory cell infiltration, peribronchial fibrosis, and increased in smooth muscle cells mass, result in airway narrowing. In addition, loss of elastic recoil of the lungs in patients suffering from emphysema leads to respiratory insufficiency. Such preoperative respiratory conditions may require prolonged postoperative ventilation. Indeed, reduced lung volumes following open-heart surgery are well documented [35–38]. The incidence of postoperative pulmonary complications has been reported to range from 20% to 90%, depending on the criteria for pulmonary complications and the methods of evaluation and analysis [11]. Performing sternotomy might lead to impair respiratory muscles, decrease pulmonary function, and produce atelectasis for up to 8 weeks postoperatively. Hemisternum retraction and eventually mammary artery harvesting might also cause changes in respiratory motion and pulmonary function. Patients who received LITA grafts showed a greater reduction in total mean postoperative respiratory motion. Probably the elevation of the left side of the chest wall during LITA harvesting causes greater trauma to the costovertebral joints with a greater reduction in left-sided thoracic motion. Oxygen blood saturation is likely to be low in patients affected by chronic obstructive pulmonary disease. Reduced availability of oxygen and blood supply to the sternum in patients undergoing coronary artery bypass with the use of internal thoracic arteries may affect the healing process [39, 40]. Forces applied to the re-approximated hemisternums during coughing, very common during the postoperative period and are more frequent in patients with chronic obstructive pulmonary disease, should also be considered. Theoretic forces applied on the sternum during coughing might reach 1500 newtons with high bone solicitation. With such high mechanical solicitation, the material used to hemisternum fixation and in particular the stainless steel wires can cut through the bone, resulting in multiple fractures and consequently sternal instability [41].

2.4 Other Risk Factors

Osteoporosis is a common disorder of the older adult skeleton that predisposes an individual to an increased risk of fracture. As the population ages, a growing number of older patients are

now undergoing cardiac surgery procedures through median sternotomy. Indeed, advanced age is a most important factor and is associated with not only reduced bone mass but also reduced quality of the bone. Thus, for any given bone mass, the risk of fracture increases with age. Parathyroid hormone is primarily thought of as a catabolic protein involved in the physiologic release of calcium from bone. During recent years a number of animal studies and clinical trials have demonstrated that intermittent administration of parathyroid hormone induces anabolic effects on both cancellous and cortical bone, enhancing the bone mass and increasing the mechanical strength of the bones. Many studies, both animal and human, have addressed the treatment of osteoporosis, and parathyroid hormone represents an important new advance in the therapy of osteoporosis.

Parathyroid hormone (PTH) which is naturally secreted by the parathyroid glands is a potent anabolic agent for bone, being a major regulator of calcium and phosphate homeostasis. The main function of PTH is to maintain the calcium ion concentration of the extracellular fluids within physiological limits. The overall effect of parathyroid hormone action is to increase and conserve serum calcium by enhancing gastrointestinal absorption of calcium, increasing renal calcium reabsorption and liberating calcium from the skeleton through a process of enhanced bone reabsorption. Whereas continuous exposure to PTH results in bone reabsorption, administration of intermittent doses results in bone formation by increasing osteoblast number and activity [42, 43].

2.5 Antibiotic Therapy

Antibiotic therapy is widely used in cardiac surgery as a prophylaxis or as a prolonged treatment when site or systemic infection is detected. However, several antibiotics are known to have side effects, especially if the therapy is prolonged. Of these, for instance, ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic used in the treatment of a wide range of gram-positive and gram-negative infections. Although worldwide data from clinical trials with oral ciprofloxacin clearly demonstrate that the drug is relatively safe for adults, and that side effects are usually mild or moderate in intensity and are reversible, in children it has adverse effect on growing cartilage and endochondral ossification and so could adversely affect healing process. Huddleston et al. [44] conducted a study on rats to determine whether ciprofloxacin has an adverse effect on the healing of experimental fractures. In this study radiographic, histological, and biomechanical studies were used to evaluate fracture healing. Radiographs revealed significantly better healing of the control group's fractures when compared with the fractures in the ciprofloxacin-treated group, which showed decreased strength in torsional strength testing and stiffness of the fracture callus. Also, fracture calluses in the animals treated with ciprofloxacin showed abnormalities in cartilage morphology and endochondral bone formation and a significant decrease in the number of chondrocytes compared with the control group.

2.6 Risk Factors Related to Surgical Procedure

2.6.1 Faulty Sternotomy

Following skin incision, the exact midline over the sternum should be marked with electrocautery before sternal separation to avoid off-center incision. With some clinical conditions, such as obesity or when the sternum is especially narrow, the midline can be difficult to find. Faulty sternotomy is an obvious risk for the development of wound complications. Shafir et al. [45] identified paramedian sternotomy as the main factor causing wound complications after a median sternotomy. In this study, in 11 of 55 patients with complications of median sternotomy, a paramedian sternotomy has been detected by computed tomography at time of reoperation for wound dehiscence and fractures were visualized. In their conclusion, the authors suggest that, if a paramedian sternotomy is diagnosed during the initial operation, special closure techniques should be

undertaken. In a prospective study, paramedian sternotomy, detected intraoperatively, was found to be an independent risk factor. Briefly, data of 171 patients undergoing cardiac surgery through a midline sternotomy were collected. Intraoperative measurements of sternal dimensions included both the thickness and the width at the manubrium and the third and fifth intercostal spaces. Paramedian sternotomy was defined as the width of one side of the sternum and 75% of entire width, at any of the three levels. Chest instability was detected in 12 (7%) patients and wound infection in 2 (1.2%). Patient weight, depressed left ventricular function, use of inotropic drugs, sternum thickness (indexed to body weight), and paramedian sternotomy ($p = 0.0001$) were risk factors of postoperative instability. Paramedian sternotomy was the only independent predictor [46].

2.6.2 Excessive Use of Electrocautery and Bone Wax

Excessive use of diathermy or bone wax reduces tissue resistance to infection because of tissue damage and reduced blood supply to the involved region. In addition, diathermy can also cause seroma formation in the subcutaneous tissue, interfering with physiologic wound healing and low antibiotic concentration. Bone wax is a nonbiodegradable material that inhibits bone healing and facilitates bacterial growth. In a study on rats affected with chronic osteomyelitis, addition of bone wax significantly reduced the dose of bacterial inoculum required to cause chronic osteomyelitis [47].

2.6.3 Iatrogenic Partial or Complete Sternal Fractures

Intraoperative hemisternum fractures can occur during oblique retraction required for mammary artery harvesting or transversal retraction to reach the mediastinum organs, while this is of particular concern to patients with osteoporotic bone. Such fractures weaken the bone structure, and the closure wires cannot be placed at the segments concerned. Not only macro but also micro fractures may affect negatively bone strength and resistance to solicitations or other abnormal loads that cause shear stress in trabecular bone. Microdamage can also increase the likelihood of further damage during subsequent normal loading conditions, resulting in atraumatic or "spontaneous" fractures.

2.6.4 Prolonged Surgical Time

Patients undergoing a cardiopulmonary bypass (CPB) procedure are at a substantial risk of acquiring infections because of secondary impairment of their immune responses and because of the increased number of potential ports of entry of bacterial pathogens [28].

2.6.5 Use of Bilateral Internal Thoracic Artery (ITA)

Use of bilateral ITAs has recently been reported to improve survival and freedom from recurrent angina [48]; however, the use of ITAs causes extensive devascularization of the sternum [49]. In a study, using radioactive isotopes to measure sternal blood flow before and after median sternotomy and ITA procedures showed that blood flow to the sternum is significantly reduced from 4.5 to 0.8 mL/g/min, which represents a 90% decrease in the mean rate of flow within the ITA-harvested sterna versus a stable flow rate for the unharvested sides [50, 51]. Sternal devascularization increases the risk of wound infection and dehiscence, especially in patients with additional known risk factors, such as diabetes mellitus or chronic obstructive pulmonary disease. The risk increases seriously when both mammary arteries are harvested. However, skeletonization of bilateral ITAs significantly decreases the incidence of both superficial and deep sternal infection independently from the most commonly known risk factors [6].

2.6.6 Early Postoperative Blood Transfusion

The correlation between the number of blood units transfused and the incidence of wound infection has been described in early publications. Zacharias et al. [7] analyzed factors that enhance the risk of median sternotomy complications. In a retrospective study that examined 2317 consecutive patients undergoing cardiac surgery, 41 sternal infections were documented. Of these,

21 (0.91%) were deep infections with mediastinal involvement and 20 (0.86%) were superficial. Ten variables were associated with infection by univariate analysis, and of these, five were independent predictors by multivariate logistic regression. These predictors were obesity, insulin-dependent diabetes, use of internal mammary artery grafts, surgical re-exploration of the mediastinum, and postoperative transfusions.

Olsen et al. [8] conducted a retrospective study examining 1980 consecutive patients undergoing coronary artery bypass surgery, in which independent risk factors for surgical site infection were identified with multivariate logistic regression. The study included 37 (1.9%) cases of deep chest and 46 (2.3%) cases of superficial chest surgical site infections. Obese diabetic patients had a 7.7-fold increased risk of deep chest infections and postoperative transfusion (odds ratio, 2.3). In particular, the higher the number of blood transfusion units, the higher was the occurrence of septicemia/bacteremia superficial and deep sternal wound infection. The correlation between the number of blood units transfused and the incidence of wound infection is also reported in other publications [9, 10].

2.6.7 Reoperation for Bleeding

Reoperation for hemostasis requires reopening of the chest which leads to soft tissue damage. Reentry to the chest through previous and still unhealed incisions can increase the risk of infection because of the presence of bacteria at the incision site. Blood transfusions, necessary because of excessive blood loss, are reported to be a risk factor in their own right. In addition, excessive postoperative bleeding can lead to hemodynamic instability with peripheral low blood perfusion, which requires the use of positive inotropic drugs with its vasal constructive effects. The increased risk is added to the tissue injury and ischemia at a time when sternal blood flow is most critical for early healing and consequent sternal stabilization. In fact, exploration for excessive postoperative bleeding (200 mL/h for 4 h) more than 6–7 h after chest closure has been shown to carry a significantly higher incidence of wound dehiscence and infection [12, 15].

2.6.8 Inappropriate Sternal Closure

While it is not pertinent to discuss at length the inappropriate surgical techniques here, technical errors cannot be excluded as a reason for wound dehiscence and the non-recovery of patients. Too tight or too loose closure can cause—respectively—fracture of the sternum (especially if the bone is fragile) or excessive movement of the hemisternum during respiratory motion and coughing, with continuous bone solicitation.

3 Surgical Treatment

Successful management of the dehisced sternum requires an appreciation of the underlying causes. When sterile dehisced sternum has occurred, simple rewiring may be sufficient. For complicated sternal wound dehiscence, or if infection has occurred, the optimal method of wound treatment remains controversial, and a variety of techniques have been reported. These generally can be divided into three groups.

3.1 Topical Treatment and Delayed Surgical Closure

1. Primary closure with irrigation-suction system
2. Muscle or omentum flap and primary wound closure
3. Primary closure with irrigation-suction system

The high incidence of wound dehiscence and ensuing high mortality rates following topic treatment have led to a search for other surgical solutions. Debridement and mediastinal irrigation was first described by Schumaker and Mendelbaum in 1963 [16]. Since then, this method has become the preferred initial therapy for mediastinitis in most cardiothoracic centers. Indeed, this technique has been found to be a rapid and effective procedure. As for the irrigation solution, several authors reported the use of saline solution or antibiotics. In alternative a low concentration povidone-iodine solution was also proposed. The solely suction was also proposed using Redon

catheter. In a comparative study between the two methods, the vacuum drainage system was found to be a more effective therapy, because it is associated with significantly less treatment failure and shorter hospital stays [19, 20].

3.2 Topical Treatment with Secondary Wound Healing

The surgical debridement is mandatory to eradicate infected tissue and to remove necrotic and devascularized tissue in all surgical procedures for wound dehiscence. Broad-spectrum antibiotic coverage should be instituted initially until the specific bacteria have been identified. Delayed surgical closure consists of topic medication with disinfection solutions. However, this technique is associated with prolonged treatment, with considerable discomfort to patients and with high mortality rate. In the 1990s, negative-pressure treatment for dehisced wound was introduced [22, 52]. It has been claimed that the negative-pressure system has several advantages over conventional wound dressing. It reduces tissue edema and improves blood supply, while sealing of the wound provides an optimal physiologic environment for tissue repair. Continuous negative pressure provides active suction and bacteria removal reducing the bacteria flora. The vacuum device should be programmed to create a continuous negative pressure in the wound of 125 mmHg. As soon as bacteria can be presented constantly in the cultural tests, plasma C-reactive protein has been proposed as indication for wound closure. When levels are getting into the range of 30–70 mgh, secondary surgical closure might be performed. Considering the above as arbitrary indicator, general aspect and the presence of secretion should also be considered. The reported mean duration of treatment was 27 days (range, 8–66 days), with wound dressings being changed every 48 h.

3.3 Muscle and Omentum Flap Reconstruction

Reconstruction of the sternal wound dehiscence might be achieved by pectoralis major muscular and musculocutaneous flaps [54]. Surgical strategies for muscle mobilization should take into consideration the eventual use of the internal mammary artery for myocardial revascularization. Indeed, the flaps constructed from the pectoralis major are dependent on its primary and secondary blood supplies. The primary blood supply to the muscle comes from the thoracoacromial artery, and the secondary blood supply is provided by the collateral branches of the internal mammary artery. One or both of the pectoralis major muscles may be used to close the wound. The muscle flap might be also split along its midline to allow part of the muscle to cover, respectively, the upper and lower part of the sternum. The rectus abdominis muscular and musculocutaneous flap has also been used successfully in reconstructing the dehisced median sternotomy wound. The primary blood supply for this muscular/musculocutaneous flap when used in chest wall reconstruction is the superior epigastric artery and vein. A continuous arterial/venous arcade exists in the muscle connecting the inferior and superior epigastric vessels. Obviously, the integrity of this arcade has to be preserved or the distal portion of the muscle will suffer necrosis when the pedicle is rotated. The vertical rectus flap can be rotated as either a muscular or a musculocutaneous flap. When the flap is transferred as a musculocutaneous flap, the anterior leaf of the rectus sheath and the subcutaneous tissues and skin are transferred with the flap. As such the flap can be used to fill a substantial midline defect as well as supplying a skin island for the dermal closure. The use of the omental flap in reconstructing the dehisced median sternotomy can be highly advantageous, because of its resistance to infection and its ability to fill large spaces, especially in cases where mediastinitis has occurred in patients who underwent surgery with implantation of synthetic materials. The blood supply for the omentum is through the epiploic arteries coursing along the greater curvature of the stomach. The omentum may be pedicled keeping either both sets of vessels or one alone to guarantee blood supply [22, 52–58]. Latissimus dorsi muscle can also be used having an excellent blood supply and can be used to cover large defects or when other flaps are not available. However, mobilization is more demanding surgically, and therefore this flap is being used less frequently than other flaps [59].

4 Clinical and Economical Consequences

Sternal wound complications are significant in terms of morbidity, mortality, and also economic cost, especially when mediastinitis occurs, as this usually requires prolonged hospital stays, reoperation for the purpose of sternal debridement, application of one of the techniques of chest closure, and prolonged treatment with antibiotics. Chronic infection and sinus tract formation can also occur, requiring reoperation, prolonging healing time, and greatly adding to the patient's discomfort. Deep chest infections also carry a high risk for mortality; in recent publications reported mortality rate ranged from 10% to −20%. In addition, mediastinitis has been found to affect long-term survival rates. After adjustment for common risk factors for late mortality among CABG patients, mediastinitis remains a significant independent predictor of late mortality. Furthermore, the impact of sternal wound infection on the healthcare system is significant, where the average stay of patients with wound complications is 43 days, while the hospitalization costs of these patients are three times greater than that of those patients who did not experience postoperative complications. This higher cost is primarily due to the associated high morbidity and the need for repeated surgical procedures [60].

Conclusions

Deep wound dehiscence and the consequent instability of the chest closure undoubtedly represent the most feared complication following sternotomy procedures, facilitating tissue infection and mediastinitis. The latter is associated with prolonged hospital stay, high morbidity, and high mortality rates. Long-term survival rates are also reduced, probably because of the damage to the systemic organs during sepsis and prolonged antibiotic therapy. When mediastinitis occurs, patient isolation is mandatory to avoid bacterial contamination spreading to other patients. However, the patients' clinical conditions do not always allow complete isolation, especially when intensive care treatment is required. Therefore, prevention of sternal wound infection complications remains a major challenge for cardiothoracic surgeons and hospital staff. Wound complications can be reduced by effective identification of risk factors and by tailoring surgical strategies to the patient's clinical conditions, rather than adhering too closely to strict cardiac pathology.

Continuous insulin infusion to diabetic patients during the postoperative period helps in keeping glucose levels within the normal range, reducing the incidence of wound infection. Likewise for high-risk patients, ensuring short operating time and accurate hemostasis can improve survival rates. In the face of the changing characteristics of patients who undergo cardiac surgery procedures, and also improvements in surgical procedures, it is essential to evaluate and update risk factors affecting wound healing, as well as monitoring the incidence of wound complications and their implications for patient survival.

References

1. Tang GH, Maganti M, Weisel RD, Borger MA (2004) Prevention and management of deep sternal wound infection. Semin Thorac Cardiovasc Surg 16: 62–69
2. Braxton JH, Marrin CA, McGrath PD, Morton JR, Norotsky M, Charlesworth DC, Lahey SJ, Clough R, Ross CS, Olmstead EM, O'Connor GT (2004) 10-year follow-up of patients with and without mediastinitis. Semin Thorac Cardiovasc Surg 16:70–76
3. Loop FD, Lytle BW, Cosgrove DM, Mahfood S, McHenry MC, Goormastic M, Stewart RW, Golding LA, Taylor PC (1990) J. Maxwell chamberlain memorial paper. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. Ann Thorac Surg 49:179–187
4. Zeitani J, Bertoldo F, Bassano C, Penta de Peppo A, Pellegrino A, El Fakhri FM, Chiariello L (2004) Superficial wound dehiscence after median sternotomy: surgical treatment versus secondary wound healing. Ann Thorac Surg 77:672–675
5. Zacharias A, Habib R (1996) Delayed primary closure of deep sternal wound infections. Tex Heart Inst J 23:211–216
6. De Paulis R, de Notaris S, Scaffa R, Nardella S, Zeitani J, Del Giudice C, De Peppo AP, Tomai F, Chiariello L (2005) The effect of bilateral internal thoracic artery harvesting on superficial and deep sternal infection: the role of skeletonization. J Thorac Cardiovasc Surg 129:536–543

7. Zacharias A, Habib RH (1996) Factors predisposing to median sternotomy complications. Deep vs. superficial infection. Chest 110:1173–1178
8. Olsen MA, Locl-Bukley P, Hopkins D, Polish LB, Sundt TM, Fraser VJ (2002) The risk factors for deep and superficial chest surgical-site infections after coronary artery bypass graft surgery are different. J Thorac Cardiovasc Surg 124:136–145
9. El Oakley R, Paul E, Wong PS, Yohana A, Magee P, Walesby R, Wright J (1997) Mediastinitis in patients undergoing cardiopulmonary bypass: risk analysis and midterm results. J Cardiovasc Surg 38:595–600
10. Murphy PJ, Connery C, Hicks GL Jr, Blumberg N (1992) Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. J Thorac Cardiovasc Surg 104:1092–1099
11. Dancer SJ, Coyne M, Speekenbrink A, Samavedam S, Kennedy J, Wallace PG (2006) MRSA acquisition in an intensive care unit. Am J Infect Control 34:10–17
12. Talamonti MS, LoCicero JIII, Hoyne WP, Sanders JH, Michaelis LL (1987) Early reexploration for excessive postoperative bleeding lowers wound complication rates in open heart surgery. Am Surg 53:102–104
13. The Parisian Mediastinitis Study Group (1996) Risk factors for deep sternal wound infection after sternotomy: a prospective multicenter study. J Thorac Cardiovasc Surg 111:1200–1207
14. Jacob HG, Borneff-Lipp M, Bach A, von Pückler S, Windeler J, Sonntag H, Hagl S (2000) The endogenous pathway is a major route for deep sternal wound infection. Eur J Cardiothorac Surg 17:154–160
15. Boeken U, Eisner J, Feindt P, Petzold TH, Schulte HD, Gams E (2001) Does the time of resternotomy for bleeding have any influence on the incidence of sternal infections, septic courses or further complications? Thorac Cardiovasc Surg 49:45–48
16. Shumacker HB Jr, Mandelbaum I (1963) Continuous antibiotic irrigation in the treatment of infection. Arch Surg 86:384–387
17. El Oakley RM, Wright JE (1996) Postoperative mediastinitis: classification and management. Ann Thorac Surg 61:1030–1036
18. Bitkover CY, Gardlund B (1998) Mediastinitis after cardiovascular operations: a case-control study of risk factors. Ann Thorac Surg 65:36–40
19. Bryant LR, Spencer FC, Trinkle JK (1969) Treatment of median sternotomy infection by mediastinal irrigation with an antibiotic solution. Ann Surg 169:914–920
20. Durandy Y, Batisse A, Bourel P, Dibie A (1989) Mediastinal infection after cardiac operation; a simple closed technique. J Thorac Cardiovasc Surg 97:282–285
21. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16:128–140
22. Gustafsson RI, Sjogren J, Ingemansson R (2003) Deep sternal- sparing technique with vacuum-assisted closure therapy. Ann Thorac Surg 76:2048–2053
23. Hendrickson SC, Koger KE, Morea CJ, Aponte RL, Smith PK, Levin LS (1996) Sternal plating for the treatment of sternal nonunion. Ann Thorac Surg 62:512–518
24. Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, Banerjee SN, Edwards JR, Tolson JS, Henderson TS et al (1991) Surgical wound infection by wound class, operative procedures, and patient risk index. Am J Med 91(Suppl 3B): 152S–157S
25. NHLBI (1998) Obesity education initiative expert panel on the identification, evaluation, and treatment of obesity in adults (US). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. National Heart, Lung and Blood Institute, Bethhesda, MD
26. O'Connor GT, Plume SK, Olmstead EM, Coffin LH, Morton JR, Maloney CT, Nowicki ER, Levy DG, Tryzelaar JF, Hernandez F et al (1992) Multivariate prediction of in-hospital mortality associated with coronary artery bypass graft surgery. Northern New England cardiovascular disease study group. Circulation 85:2110–2118
27. Molina JE, Lew RS, Hyland KJ (2004) Postoperative sternal dehiscence in obese patients: incidence and prevention. Ann Thorac Surg 78:912–917
28. Milano CA, Kesler K, Archibald N, Sexton DJ, Jones RH (1995) Mediastinitis and long-term survival after coronary artery bypass graft surgery. Circulation 92:2245–2251
29. Prasad US, Walker WS, Sang CT, Campanella C, Cameron EW (1991) Influence of obesity on the early and long term results of surgery for coronary artery disease. Eur J Cardiothorac Surg 5:67–73
30. Birkmeyer NJ, Charlesworth DC, Hernandez F, Leavitt BJ, Marrin CA, Morton JR, Olmstead EM, O'Connor GT (1998) Obesity and risk of adverse outcomes associated with coronary artery bypass surgery. Circulation 97:1689–1694
31. Prabhakar G, Haan CK, Peterson ED, Coombs LP, Cruzzavala JL, Murray GF (2002) The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. Ann Thorac Surg 74(4):1125–1130
32. Gooch HL, Hale JE, Fujioka H, Balian G, Hurwitz SR (2000) Alterations of cartilage and collagen expression during fracture healing in experimental diabetes. Connect Tissue Res 41:81–91
33. Cohen O, Dankner R, Chetrit A, Luxenburg O, Langenauer C, Shinfeld A, Smolinsky AK (2003) Multidisciplinary intervention for control of diabetes in patients undergoing coronary artery bypass graft (CABG). Cardiovasc Surg 11:195–200

34. Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP (1999) Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 88:1011–1016
35. Cohen AJ, Moore P, Jones C, Miner TJ, Carter WR, Zurcher RP, Lupkas R, Edwards FH (1993) Effect of internal mammary harvest on postoperative pain and pulmonary function. Ann Thorac Surg 56:1107–1109
36. Shenkman Z, Shir Y, Weiss YG, Bleiberg B, Gross D (1997) The effect of cardiac surgery on early and late pulmonary functions. Acta Anaesthesiol Scand 41(9):1193
37. Wahl GW, Swinburne AJ, Fedullo AJ, Lee DK, Shayne D (1993) Effect of age and preoperative airway obstruction on lung function after coronary artery bypass grafting. Ann Thorac Surg 56:104–107
38. Hulzebos EH, Van Meeteren NL, De Bie RA, Dagnelie PC, Helders PJ (2003) Prediction of postoperative pulmonary complications on the basis of preoperative risk factors in patients who had undergone coronary artery bypass graft surgery. Phys Ther 83:8–16
39. Sofer D, Gurevitch J, Shapira I, Paz Y, Matsa M, Kramer A, Mohr R (1999) Sternal wound infections in patients after coronary artery bypass grafting using bilateral skeletonized internal mammary arteries. Ann Surg 229:585–590
40. Greif R, Akça O, Horn EP, Kurz A, Sessler DI (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes research group. N Engl J Med 342:161–167
41. Casha AR, Yang L, Cooper GJ (1999) Measurement of chest wall forces on coughing with the use of human cadavers. J Thorac Cardiovasc Surg 118:1157–1158
42. Arnaud CD, Tenenhouse AM, Rasmussen H (1967) Parathyroid hormone. Annu Rev Physiol 29:349–372
43. Holzer G, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA (1999) Parathyroid hormone enhances fracture healing. A preliminary report. Clin Orthop 366:258–263
44. Huddleston PM, Steckelberg JM, Hanssen AD, Rouse MS, Bolander ME, Patel R (2000) Ciprofloxacin inhibition of experimental fracture healing. J Bone Joint Surg Am 82:161–173
45. Shafir R, Weiss J, Herman O, Cohen N, Stern D, Igra Y (1988) Faulty sternotomy and complications after median sternotomy. J Thorac Cardiovasc Surg 96:310–313
46. Zeitani J, Penta de Peppo A, Moscarelli M, Gurrieri L, Scafuri A, Nardi P, Nanni F, Di Marzio E, Chiariello L (2006) Influence of sternal size and inadvertent paramediansternotomy on stability of the closure site: A clinical and mechanical study. J. Thorac Cardiovac Surg 132:38–42
47. Nishida H, Grooters RK, Soltanzadeh H, Thieman KC, Schneider RF, Kim WP (1991) Discriminate use of electrocautery on the median sternotomy incision. A 0.16% infection rate. J Thorac Cardiovasc Surg 101:488–494
48. Endo M, Nishida H, Tomizawa Y, Kasanuki H (2001) Benefit of bilateral IMA grafts over single IMA graft for multiple coronary artery bypass grafting. Circulation 104:2164–2170
49. Arnold M (1972) The surgical anatomy of sternal blood supply. J Thorac Cardiovasc Surg 64:596–610
50. Carrier M, Gregoire J, Tronc F, Cartier R, Leclerc Y, Pelletier LC (1993) Effect of internal mammary artery dissection on sternal vascularization: 1993 update. Ann Thorac Surg 55:803–804
51. Carrier M, Gregoire J, Tronc F, Cartier R, Leclerc Y, Pelletier LC (1992) Effect of internal mammary artery dissection on sternal vascularization. Ann Thorac Surg 53:115–119
52. Tang AT, Ohri SK, Haw MP (2000) Novel application of vacuum assisted closure technique to the treatment of sternotomy wound infection. Eur J Cadiothorac Surg 17:482–484
53. Graeber GM, Langenfeld J (1998) Chest wall resection and reconstruction. In: Franco H, Putman JB (eds) Advanced therapy in thoracic surgery. BC Decker, Inc, London, pp 175–185
54. Zeitani J, Russo M, Pompeo E, Sergiacomi GL, Chiariello L (2016) Pectoralis Muscle Flap Repair Reduces Paradoxical Motion of the Chest Wall in Complex Sternal Wound Dehiscence. Korean J ThoracCardiovasc Surg. 49(5):366–373
55. Seyfer AE, Graeber GM, Akind FF (1986) The pectoris major muscle and musculocutaneous flaps. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of chest wall reconstruction. Aspen Publishers, Rockville, MD
56. Tofin GR (1989) Pectoralis major musclemusculocutaneous flap for chest wall reconstruction. Surg Clin North Am 69:991–1006
57. Zeitani J, Pompeo E, Nardi P, Sergiacomi G, Scognamiglio M, Chiariello G, Del Giudice C, Arganini C, Simonetti G, Chiariello L (2013) Early and long-term results of pectoralis muscle flap reconstruction versus sternal rewiring following failed sternal closure. Eur J Cardiothorac Surg 43(6):e144–e150
58. Seyfer AE, Graeber GM, Akind FF (1986) The omentum. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of chest wall reconstruction. Aspen Publishers, Rockville, MD
59. Seyfer AE, Graeber GM, Akind FF (1986) The latissimus dorsi muscle and musculocutaneous flaps. In: Seyfer AE, Graeber GM, Wind GG (eds) Atlas of chest wall reconstruction. Aspen Publishers, Rockville, MD
60. Hollenbeak CS, Murphy DM, Koenig S, Woodward RS, Dunagan WC (2000) The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft. Chest 118:397–402

Negative-Pressure Wound Therapy as Prevention Measure After Cardiac Surgery: Principles and Techniques

Richard van Valen, Carina T. Domingues, and Ad J. J. C. Bogers

1 Introduction

About 250 million major surgical procedures are performed worldwide each year [1]. The surgical wound, however, can be at risk for complications. These include infection, seroma, haematoma, local skin ischaemia, necrosis and dehiscence as well as delayed healing in the short term and poor healing or abnormal scarring in the long term. Surgical site infections (SSIs) have been the focus of surveillance programmes and prevention initiatives worldwide, not only to reduce the incidence of wound infection and improve the outcomes for individual patients but also to reduce the associated costs for healthcare systems.

An emerging trend in preventive therapies is to reduce surgical site complications. Negative-pressure wound therapy (NPWT) is one of the interventions that can be used in patients at risk for a wound infection after surgery. In this chapter NPWT as a prevention measure is discussed by summarising the principles, current techniques, most used devices, clinical application, findings from recent studies and cost-effectiveness.

2 Normal Wound Healing

To understand the mechanism through which NPWT works on a clean, closed, surgical wound, understanding normal wound healing is important. Briefly summarised, the phases of wound healing consist of haemostasis, inflammation, proliferation and remodelling [2]. For surgical wounds, the basic principles are the same. Haemostasis is characterised by vascular constriction, combined with platelet aggregation and fibrin formation. During inflammation period the wound is infiltrated with neutrophils, monocytes (which differentiate into macrophages) and lymphocytes. This is essentially the body's response to injury. During proliferation, new blood vessels are formed, collagen is synthesised, and the extracellular matrix takes shape. The final phase involves remodelling of the structures, both by remodelling of the collagen and maturation of the blood vessels and later regression. These phases can be disrupted by patient factors as well as environmental factors.

3 Factors Affecting Wound Healing

The factors that impact wound healing can be placed into two categories: local and systemic factors [3]. The local factors that influence wound healing are multifactorial but can be divided into either a perfusion deficit or accumulation of

R. van Valen (✉) · C. T. Domingues · Ad J. J. C. Bogers
Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, The Netherlands
e-mail: r.vanvalen@erasmusmc.nl

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_74, © Springer International Publishing AG
Published Online: 29 April 2018

fluids. Perfusion is defined as blood flow in the affected area. Poor blood flow leads to low oxygen tension which can result in ischaemia and even necrosis in wounds. The other important negative factor is accumulation of fluid in or near the wound. This can be oedema but also blood or other fluids, which also leads to impaired perfusion of the inflicted area. Fluid in the wound area can also facilitate growth of microorganisms, leading to infections.

Systemic factors have been well established in research. The more important factors are diabetes, obesity, age, use of specific types of medication and malnutrition.

Diabetes can have a detrimental effect on wound healing [4]. On a molecular level, the decreased angiogenic response, collagen accumulation and the quantity of granulation tissue are the most important factors that cause this detrimental effect.

Obesity is a precursor for several important inhibitors in wound healing. The risk of surgery in obese patients is higher, not only for wound infections but also for cardiovascular complications. This applies mostly to patients with morbid obesity (body mass index of 40 kg/m^2 or greater). Three factors contribute to this increased risk. The first is the avascularity of the adipose tissue, which leads to poorer oxygenation and limited infiltration of leucocytes, neutrophils and macrocytes. The second is related to the habitus of these patients, which leads to higher demands on personal hygiene [5]. The third is the effect of lateral forces on wound edges. Large amounts of tissue can increase lateral tension, leading to decreased perfusion and thus decreased oxygen saturation of the wound and contributing to wound dehiscence and infections. Obesity and wound healing risk is discussed in more detail later on in this chapter.

Age and the associated frailty that is often seen with increasing age can contribute to higher rates of wound complications. Wound healing is negatively affected by age. The stages of normal wound healing, as described earlier, are less efficient or slower. The inflammatory response is delayed and can also be decreased compared to younger adults. Remodelling is still present but is less effective. The important phase of collagen formation is qualitatively different (and has a poorer quality) and also leads to poorer wound healing. Diseases that affect wound healing are more prevalent in the elderly and have a greater adverse effect on healing than in young adults. Elderly patients have comorbidities and often use medication that can impair wound healing [6].

3.1 Medication Use and Nicotine Usage

Medications that are strongly associated with an increased risk for surgical site infections (SSIs) usually have a negative effect on the immune. For example, bleomycin (chemotherapeutic agent) decreases blood vessel formation in a wound [7]. In daily practice patients using steroids require more attention. Steroid medication has several negative effects, for example, on the tensile strength of tissues and the resulting impaired wound contraction. Most importantly, steroid medication leads to delayed healing due to its anti-inflammatory and immunosuppressant effects [5].

For smokers, the dangers of nicotine have been well established. In cardiac surgery smokers have been shown to have higher rates of SSI [8]. The mechanism is based on the vasoconstrictive quality of nicotine leading to poorer circulation (and microcirculation) and healing.

3.2 Malnutrition

Malnutrition is primarily seen in patient groups who are already at risk for impaired wound healing: elderly patients, patients with chronic health problems and patients with a very limited (one-sided) diet (this can also apply to morbidly obese patients).

The most important factor is the lack of protein in the diet of these patients. Decreased protein intake leads to impaired wound healing due to decreased production of collagen, fibroblast proliferation and poorer angiogenesis [9].

3.3 Radiation Therapy

Radiation therapy can impair wound healing, even many decades after treatment. Immediately after radiotherapy, the inflammatory and proliferative phases are disrupted the most. More importantly, especially after a prolonged period, fibrosis and poor tissue quality can cause wound problems. For this reason, radiation of the surgical area is a major risk factor for SSI [10].

4 Wound Healing and Cardiac Surgery

SSIs remain a problem after cardiac surgery. Research shows a rate of 1–3% of deep sternal wound infections (DSWI) and a rate of 2–6% for superficial wound infections [11]. These complications can be very serious, and they contribute significantly to postoperative morbidity, mortality and healthcare costs [12]. The wounds from cardiac surgery occur at three locations: the sternotomy, the lateral thoracotomy and donor sites for graft material (e.g. the venectomy wound after harvesting of the vena saphena magna). Each location offers its own challenges in wound healing.

Host factors contributing to the risk of SSI after cardiac surgery have been well described in the literature and include previously discussed topics such as obesity, diabetes mellitus, advanced age, sex, smoking and steroid use, along with length of hospitalisation before surgery (more than 5 days) [13, 14]. Surgical risk factors include the use of one or two internal mammary artery (IMA) grafts (especially bilaterally), duration of surgery and perfusion time, prolonged mechanical ventilation, use of an intra-aortic balloon pump, postoperative bleeding, reoperation, sternal rewiring, extensive electrocautery, shaving with razors and use of bone wax [14, 15].

The median sternotomy wound is traditionally closed with surgical steel wires. Thereafter the suprasternal tissues are closed. The skin can be closed by either intracutaneous sutures or skin staples. After this a wound dressing is applied. Depending on the surgeon's preference, the dressing is removed after 24 or 48 h. Note that the wounds discussed in this chapter are "clean wounds". The definition for a clean wound is a non-infective operative wound in which no inflammation is encountered and no colonised cavity is entered during the surgical procedure. In addition, these cases are elective or semi-elective, primarily closed and drained with a closed drainage system (if required).

5 History of Preventive Measures

In recent decades enormous progress has been made in the absolute reduction of SSI after cardiac surgery. However, high-risk patients still have an SSI rate of up to 15% after cardiac surgery [16]. Further reduction of these rates has been difficult, primarily due to the increasing number of comorbidities in cardiothoracic surgery patients and secondly due to the improvement in peri- and postoperative care, which enables sicker patients to survive but with more postoperative complications such as SSI.

Research into prevention of complications ranges from the best way to harvest internal mammary arteries (pedicled of skeletonised) to the usage and duration of antibiotic prophylaxis. Previous studies have proposed many interventions to lower the risk of wound infection after surgery. However, the evidence is not always sufficient. Another important aspect is the continuing need to identify patients who are at risk for wound infections.

Negative-pressure wound therapy (NPWT) is one of the interventions that can be used in patients at risk for a wound infection after surgery. NPWT is a wound care system consisting of a foam or dressing that is covered with an airtight adhesive film. Tubing connects the foam to an electronic pump that regulates and delivers an adjustable negative pressure [17]. Initially, the treatment was used for acute and chronic open wounds.

Research into the mechanism of this therapy has shown that NPWT helps to enhance the development of granulation tissue, stimulate perfusion, reduce colonisation by bacteria, reduce lateral tension and oedema and protect the wound from external sources of infection [18].

In the preventative domain, it has been used to improve outcomes after skin and biomatrix grafts, where it stabilises the graft to prevent shearing and removal [19]. It also aids in removal of exudate, which leads to less seroma formation.

6 Prevention and NPWT

The currently used terminology for technique is closed incision NPWT (ciNPWT). The most important mechanisms of NPWT in acute or chronic wounds that can be applied to clean surgical wounds are the following:

6.1 Reduction of Lateral Forces

The function of sutures or other surgical closure methods is to bring the wound edges together and to reduce lateral tension. Lateral wound tension may result in dehiscence of the wound, resulting in local granulation tissue formation and hypertrophic scarring in the healed incision. It also puts the wound at risk for poorer perfusion, with lower oxygenation status of tissue and increased risk of impaired wound healing. Figure 1 shows the difference in perfusion of the area (by reduction of lateral tension). The greener section in the figure shows improved perfusion, which reduces the chance of wound complications.

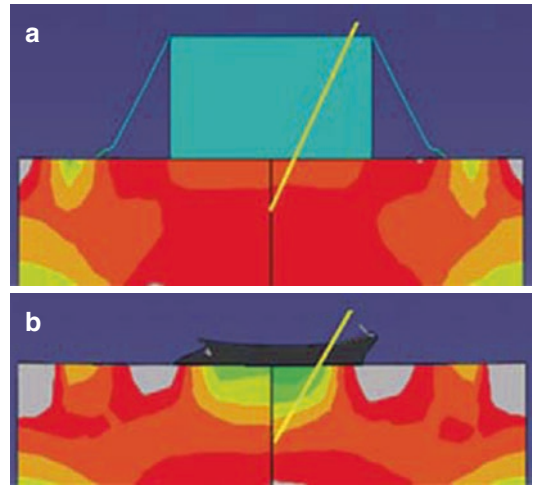


Fig. 1 Change in tissue perfusion (green is better perfusion in (**a**) Incision without ciNPWT. (**b**) Incision with ciNPWT

6.2 Reduction of Oedema, Haematoma and Seroma

Proponents of NPWT claim that it increases the activity of lymphatic drainage in the deep tissue. A second important precursor of infection is the collection of blood and serum. These fluids in subincisional tissues create dead spaces. This also increases the risk of infection [20].

6.3 Infection Prevention from Exogenous Sources

The wound is covered by the foam during the last phase of the surgery in a sterile environment. This coverage by the foam and device is continued during 5–7 days, making exposure to and infection from exogenous sources less likely. One of the products (the Prevena®) contains a small percentage of ionic silver (0.019%). According to the manufacturer, the ionic silver in the fabric reduces colonisation by bacteria such as *Staphylococcus epidermidis* and *Staphylococcus aureus* and by fungi.

These mechanisms affect the various risk factors differently (Table 1). This table is a summary of various studies and guidelines [20–24].

Table 1 Effect of NPWT on risk factors for wound complications

	Reduction lateral forces	Increase perfusion pressure	Reduction oedema	Protection exogenous sources	Enhance granulation tissue
Obesity	++	++	++	++	+
Diabetes mellitus	–	++	–	++	+
Steroid usage	–	++	–	++	+
Malnutrition	–	+	++	+	+
Post-radiation therapy	–	++	+	+	++

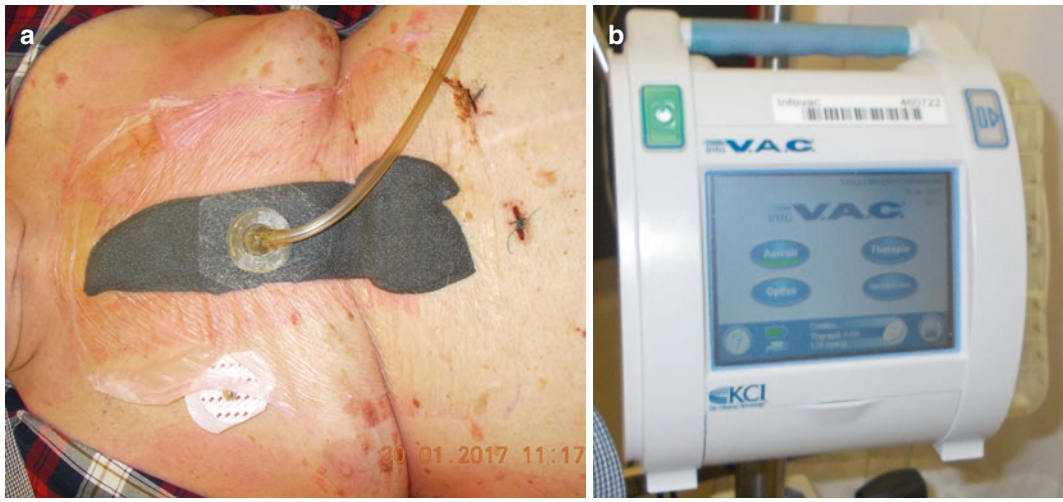


Fig. 2 Self-constructed NPWT prevention system, consisting of VAC INFO® by KCI

7 NPWT on Closed Wounds

7.1 Device Options

A vacuum-assisted closure system, which can be used for open as well as closed incisions (VAC® KCI, San Antonio, Texas), has been used the longest. This system consists of separate elements which have to be brought together by the operator. A single layer of nonadhesive gauze should be placed over the closed incision to avoid skin maceration, followed by a thin strip (1.0–1.5 cm) of foam (VAC GranuFoam® Dressing, KCI, San Antonio, TX, USA). The foam is a hydrophobic material with large pores that help to drain fluids and reach the negative pressure. An occlusive transparent dressing is placed over the foam, and negative pressure is applied to the foam through an incision in the drape via a pressure-sensing pad with tubing connected to the therapy unit, thereby creating the environment for NPWT. This device delivers a negative pressure of −125 mmHg (adjustable 50–125 mmHg). Silver-impregnated foam is also commercially available. An advantage of this device is that the foam can be cut and shaped to fit the wound edges exactly, for example, for non-linear incisions (Fig. 2).

ciNPWT systems have evolved substantially in recent years and are now available as single-use devices designed specifically for the management of closed incisions. Two simplified NPWT devices became commercially available in 2010 (Prevena® KCI, San Antonio, USA) and 2011 (PICO®; Smith & Nephew, Hull, UK). These NPWT devices consist of a single-use battery-powered negative-pressure therapy device, an easy-to-place dressing (simple peel-and-place

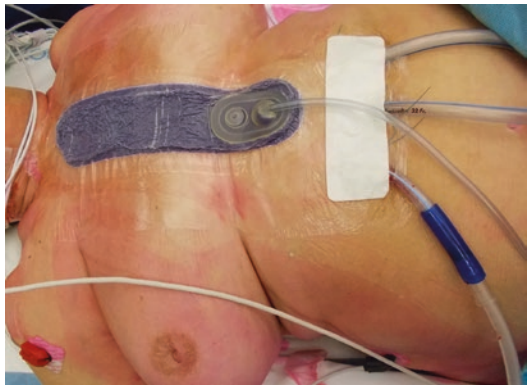


Fig. 3 Placement of Prevena® in theatre following closure of the sternotomy wound

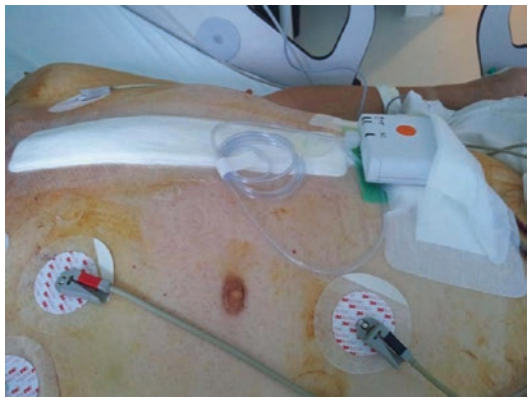


Fig. 4 PICO(r) device

process) and either a very small or easily portable system, facilitating its use in the outpatient setting. The Prevena® system has a skin interface layer containing 0.019% ionic silver and a canister for collecting incision exudate. It delivers negative pressure of −125 mmHg (Fig. 3). The PICO® system has no canister at all; the liquid is removed by evaporation through a semipermeable dressing. It delivers a negative pressure of −80 mmHg (Fig. 4). Both systems incorporate all the functional elements of standard incisional NPWT but in a simplified manner. The major difference between the products is the effect on lateral tension. Ex vivo experiments have shown a significantly higher reduction of incision width in favour of the Prevena® system.

The three devices discussed above are currently the most frequently used systems on the market. No clinical studies of self-fabricated NPWT devices or studies comparing the efficiency of two different NPWT devices were found in the literature.

7.2 Technical Application

Chlorhexidine, should be used for skin preparation, with careful drying to prevent foil blistering. NPWT must be applied immediately after surgery to clean, surgically closed incisions in a sterile field (while the patient is still in the operating room and before the sterile drapes have been removed).

When a conventional or self-fabricated NPWT (i.e. VAC GranuFoam® or a reticulated open-cell foam) dressing is used, a non-adherent layer should be placed between the foam dressing and the skin; placing the foam dressing directly against the skin can lead to maceration. The dressings designed specifically for closed incisions (i.e. the Prevena® or PICO® systems) can be applied directly to the skin due to their skin-friendly surface.

The optimum area of tissue that should be subjected to NPWT is still a point of contention. Ideally, the NPWT should cover all incision edges to ensure reduction of lateral forces and suction of fluids. In any case, the wound should be covered entirely. Incomplete coverage of the wound leads to a higher risk of exogenous contamination and fluid accumulation in the untreated area.

To ensure an adequate seal, chest tubes should be placed lower. Placing drains and pacing wires away from wound edges help in achieving an airtight seal. Before transferring a patient to ICU or the ward, checking of the airtight seal is essential. Areas that demand special are below the breasts and the most distal part of the wound. After applying the dressing, the therapy should be started by following the instructions on the product label.

7.3 Level of Negative Pressure

Despite the relatively good understanding of the mechanisms through which incisional NPWT might have an effect, surprisingly little information is available on the optimum negative pressure for clinical use. A major review of 33 recent studies on this topic, including study reports from orthopaedic surgery, cardiothoracic surgery and abdominal, plastic and vascular disciplines, showed that a range of pressure levels have been used with NPWT devices (with −75 and −125 mmHg being the most frequently used) without any obvious benefits or detriments in clinical efficacy [25]. No clinical studies have been published on the effects of various levels of negative pressure on desirable endpoints such as reduced haematoma or seroma, reduced oedema, increased wound strength or fewer complications. The emergence of single-use devices with a fixed pressure setting could reduce the likelihood that such studies are being performed [4, 5]. A study in pigs used gauze pads at −125 mmHg and showed reduction in haematoma, improved wound strength and improved visual appearance [6]. Negative pressure between −50 and −150 mmHg applied to the zone of tissue surrounding the incision appears to be the principal cause of the effect, although much scope remains for investigation. Higher levels of negative-pressure therapy (surpassing −150 mmHg) can damage cardiac structures.

7.4 Treatment Duration

Discontinuation criteria of NPWT for closed incisions have not been clearly defined. Variability in treatment duration may depend on procedure, type and localisation of incision and patient factors.

Opinions differ on the optimal timing for discontinuation of NPWT for closed incisions. Some advocate continuing therapy until no oedema fluid is evident in the canister for 12 h, usually 24–72 h after surgery [21]. The expert consensus is that minimal drainage is important [22]. However, that study was initiated prior to the availability of home NPWT and small portable units. Participants only used the NPWT for an average of 2–5 days because they were ready for discharge.

Later studies have reported slightly longer duration of incisional NPWT, likely due to increasing use of home NPWT devices. A study of the current literature reported a large variation in duration of treatment before first change of dressing, ranging from 2 days to 7 days (median 5) in the group treated with NPWT [23].

7.5 Complications

NPWT should be removed immediately if the skin is exposed to the foam (i.e. if the nonadhesive layer between the skin and the foam of a conventional NPWT is incomplete or forgotten). Otherwise, the skin can be seriously damaged. If the operated area is no longer sterile, the NPWT should not be applied again.

If patients present clear signs of wound infection, the NPWT should be discontinued immediately.

7.6 Contraindications

There are no specific contraindications to NPWT use on closed incisions. NPWT dressings containing silver should not be used in patients with sensitivity to silver. Use caution if patients have blistering around the wound or inflammation, cellulitis or erysipelas surrounding the incision. The therapy should only be applied on clean surgical wounds.

7.7 Removal

After switching off the negative pressure, the NPWT dressing should be carefully removed. The absence of signs of inflammation such as oedema and erythema and adequate closure of the wound edges suggest that the wound has healed adequately.

8 Discussion

NPWT has become a frequently used modality in the treatment of a large variety of dehiscent wounds and infected wounds. The capabilities of this modality to reduce wound dimensions, to enhance angiogenesis in the wound and to reduce oedema are important factors contributing to the success of NPWT.

Another important factor is reducing lateral tension on the wound. Excessive lateral tension diminishes perfusion and can contribute to poor wound healing. This is not only a problem in infected wounds; excessive lateral tension can also increase the risk of wound complications after cardiac surgery, especially in the morbidly obese or females with large mammae.

Three options are currently available for practitioners to use NPWT on a closed wound after "clean" surgery. Two are commercially available: (1) a wound incision management system which delivers a negative pressure of −125 mmHg and has a canister for collecting drained fluids and (2) a system that delivers lower negative-pressure levels (−80 mmHg). It has no canister and uses an evaporation-based method to prevent maceration of the skin or build-up of fluids. The third option is to custom-build the GranuFoam.

NPWT should be applied only under sterile conditions, if possible immediately following skin closure. Ideally, the system should be left undisturbed for at least 5 days, unless the patient develops clear signs of wound infection, such as pain. If re-exploration is needed, anew sterile set should be applied. Re-exploration is an important risk factor for developing wound complications after surgery.

Regarding cost-effectiveness, the current systems should only be used for patients with a high likelihood of wound complications after surgery. No validated models are currently available for identifying patients at risk for wound infections. However, morbidly obese patients and those with a poorly regulated diabetes mellitus are clearly at high risk. Furthermore, patients with large mammae and the previously discussed risk factors should be considered for this therapy.

Conclusive scientific evidence on the efficacy of NPWT is not yet available. Although this therapy has been used successfully in large case series, large randomised clinical trials with convincing results are lacking. According to current guidelines, NPWT can be considered for patients at risk [24].

Increasing evidence indicates that NPWT can be used in various types of surgery. Recent studies on NPWT in plastic surgery, orthopaedics and trauma surgery have shown promising results. However, randomised clinical trials to further build the evidence for this treatment modality are lacking.

In the future, risk models should be developed to identify patients at risk. Recent studies have shown that obesity, large mammae, poorly managed diabetes mellitus and immune suppressive medication are the most important risk factors for SSI. The risk model should take these factors into account. The clinician should use these models to make a decision on which patient to apply NPWT. The costs of these devices (both commercially available and self-built) demand that clinicians balance the costs of the device and the benefits for individual patient. The costs of these devices will remain a discussion point as long as these devices are used in patients with only a slightly elevated change for wound complications.

Equally important is that clinicians not only use NPWT as preventative measure but also strive to optimise the condition of the patient. While it may be advisable to use NPWT for a malnourished patient, it is even more important for a dietician to be involved to improve the condition of the patient.

9 Tips for Use

9.1 Preoperative Phase

Select patients that are at risk, for example, the morbidly obese, poorly regulated diabetics and patients after radiotherapy. Discuss NPWT with patient as a preventative measure.

9.2 Operative Phase

9.2.1 Intraoperative Phase

Consider type of incision and approach (if possible). Consider placement of the incision to accommodate the NPWT dressing. Consider placement of the port, tubing or wires, by leaving sufficient distance between them and the wound edges to secure the seal. Consider the size and the shape of the incision wedges, and select an appropriate NPWT dressing. Try to cover the wound completely.

Prepare the patient's skin with an antiseptic solution (chlorhexidine). The skin must be hair-free and dry to ensure dressing adhesion and formation of a seal. Take extra care in areas within which an airtight seal can be difficult (e.g. below the breasts). Gel strips may be useful to aid adhesion in areas that are difficult to seal.

Apply the dressing only under aseptic conditions (immediately after surgery, in the operating theatre and before the sterile drapes have been removed) and according to the manufacturer's instructions. After applying the dressing, start therapy by following the instructions on the product label. It is easily seen if the vacuum has been successfully achieved.

When using a conventional or home-made NPWT, always place a non-adherent layer between the foam dressing and the skin to avoid skin maceration of the healthy skin.

9.3 Postoperative Phase

Inspect the dressing, canister (if present) and power unit regularly. If the dressing needs to be changed, use an aseptic technique. We do not recommend changing of dressing after cardiothoracic surgery to avoid the risk of contamination, which could lead to mediastinitis.

In the case of reoperation, we strongly suggest placing a new NPWT unit, as reoperation is a risk factor on its own for wound infections. Leave the dressing in place for up to 5–7 days, according to manufacturer's instructions and availability of outpatient clinic access for removal, unless there are concerns about the incision or dressing change is required.

When the dressing is removed, if the incision is closed, dry and without signs of infection, the NPWT may be discontinued, and there is no need to reapply NPWT or a conventional dressing.

Provide patients who are discharged from hospital with written information about how to care for the NPWT system and when and how to contact a healthcare professional.

If signs of SSI occur, discontinue NPWT immediately and treat the patient according to standards of care.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA (2008) An estimation of the global volume of surgery: a modeling strategy based on available data. Lancet 372(9633):139–144
2. Gosain A, DiPietro LA (2004) Aging and wound healing. World J Surg 28:321–326
3. Rieger S, Zhao H, Martin P, Abe K, Lisse TS (2015) The role of nuclear hormone receptors in cutaneous wound repair. Cell Biochem Funct 33:1–13
4. Brem H, Tomic-Canic M (2007) Cellular and molecular basis of wound healing in diabetes. J Clin Invest 117:1219–1222
5. Anderson K, Hamm RL (2012) Factors that impair wound healing. J Am Coll Clin Wound Spec 4:84–91
6. Gerstein AD, Phillips TJ, Rogers GS, Gilchrest BA (1993) Wound healing and aging. Dermatol Clin 11:749–757
7. Maeda T, Yamamoto T, Imamura T, Tsuboi R (2016) Impaired wound healing in bleomycin-induced murine scleroderma: a new model of wound retardation. Arch Dermatol Res 308:87–94
8. Nagachinta T, Stephens M, Reitz B, Polk BF (1987) Risk factors for surgical-wound infection following cardiac surgery. J Infect Dis 156:967–973
9. Legendre C, Debure C, Meaume S, Lok C, Golmard JL, Senet P (2008) Impact of protein deficiency on venous ulcer healing. J Vasc Surg 48:688–693
10. Haubner F, Ohmann E, Pohl F, Strutz J, Gassner HG (2012) Wound healing after radiation therapy: review of the literature. Radiat Oncol 7:162
11. Gudbjartsson T, Jeppsson A, Sjogren J, Steingrimsson S, Geirsson A, Friberg O, Dunning J (2016) Sternal wound infections following open heart surgery—a review. Scand Cardiovasc J 50:341–348
12. Karra R, McDermott L, Connelly S, Smith P, Sexton DJ, Kaye KS (2006) Risk factors for 1-year mortality

after postoperative mediastinitis. J Thorac Cardiovasc Surg 132:537–543
13. Olsen MA, Lock-Buckley P, Hopkins D, Polish LB, Sundt TM, Fraser VJ (2002) The risk factors for deep and superficial chest surgical-site infections after coronary artery bypass graft surgery are different. J Thorac Cardiovasc Surg 124:136–145
14. Zacharias A, Habib RH (1996) Factors predisposing to median sternotomy complications. Deep vs superficial infection. Chest 110:1173–1178
15. Hollenbeak CS, Murphy DM, Koenig S, Woodward RS, Dunagan WC, Fraser VJ (2000) The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. Chest 118:397–402
16. Haley VB, Van Antwerpen C, Tsivitis M, Doughty D, Gase KA, Hazamy P, Tserenpuntsag B, Racz M, Yucel MR, McNutt LA, Stricof RL (2012) Risk factors for coronary artery bypass graft chest surgical site infections in new york state, 2008. Am J Infect Control 40:22–28
17. Argenta LC, Morykwas MJ (1997) Vacuum-assisted closure: a new method for wound control and treatment. Clin Exper Ann Plast Surg 38:563–576
18. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 38:553–562
19. Li RG, Ren GH, Tan XJ, Yu B, Hu JJ (2013) Free flap transplantation combined with skin grafting and vacuum sealing drainage for repair of circumferential or sub-circumferential soft-tissue wounds of the lower leg. Med Sci Monit 19:510–517
20. Meeker J, Weinhold P, Dahners L (2011) Negative pressure therapy on primarily closed wounds improves wound healing parameters at 3 days in a porcine model. J Orthop Trauma 25:756–761
21. Reddix RN Jr, Tyler HK, Kulp B, Webb LX (2009) Incisional vacuum-assisted wound closure in morbidly obese patients undergoing acetabular fracture surgery. Am J Orthop (Belle Mead NJ) 38: 446–449
22. Stannard JP, Volgas DA, McGwin G 3rd, Stewart RL, Obremskey W, Moore T, Anglen JO (2012) Incisional negative pressure wound therapy after high-risk lower extremity fractures. J Orthop Trauma 26:37–42
23. Hyldig N, Birke-Sorensen H, Kruse M, Vinter C, Joergensen JS, Sorensen JA, Mogensen O, Lamont RF, Bille C (2016) Meta-analysis of negative-pressure wound therapy for closed surgical incisions. Br J Surg 103:477–486
24. Leaper DJ, Edmiston CE (2017) World health organization: global guidelines for the prevention of surgical site infection. J Hosp Infect 95:135–136
25. Karlakki S, Brem M, Giannini S, Khanduja V, Stannard J, Martin R (2013) Negative pressure wound therapy for management of the surgical incision in orthopaedic surgery: a review of evidence and mechanisms for an emerging indication. Bone Joint Res 2:276–284

Surgical Management of Sternal Wound Dehiscence

Maria Pia Tocco, Eugenio Pompeo, and Giovanni Ruvolo

1 Introduction

Median sternotomy is the most common surgical approach in cardiac surgery and is also quite frequently employed in thoracic surgery.

The most frequent complication of this surgical access is wound infection eventually resulting in sternal wound dehiscence (SWD), which can be associated or not with sternal instability. Especially in open-heart surgery, it is responsible for significant morbidity, high mortality, additional multiple surgical procedures, prolonged hospitalization and increased cost of care.

Sternal wound dehiscence is a wound breakdown with or without clinical or microbiologic evidence of infection (Fig. 1) [1]. It can occur in the early postoperative days or after weeks or months.

In open-heart surgery, the incidence of SWD is about 0.9–20%, and the incidence of mediastinitis is 1–2% or somewhat higher. The variability in incidence can be addressed at least in part to the finding that a large number of wound complications occur after discharge, quite often in the rehabilitation centre, therefore, being sometimes missed by single-centre statistical analysis. Furthermore, there is a lack of a common comprehensive definition of postoperative SWD [1]. In fact, wound dehiscence, sternal wound

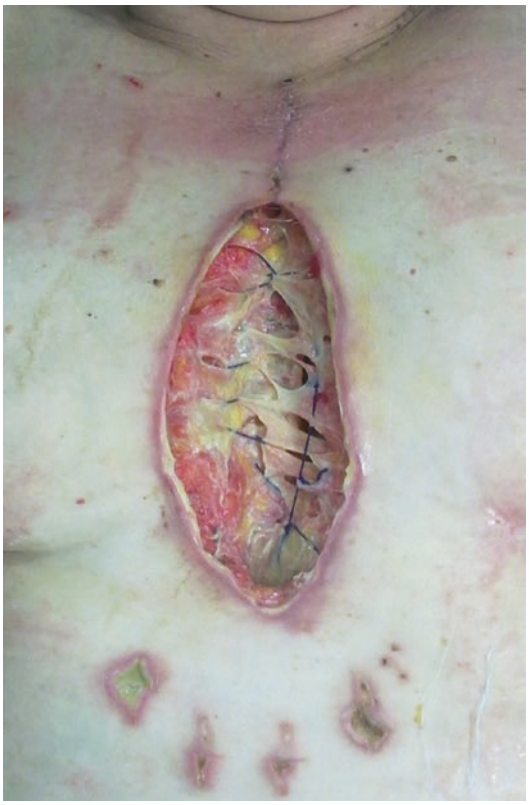


Fig. 1 A typical initial presentation of SWD in which skin dehiscence is evident whereas the status of the sternum is more difficult to be assessed

M.P. Tocco
Division of Thoracic Surgery, San Filippo Neri Hospital, Rome, Italy

E. Pompeo, M.D. (✉)
Division of Thoracic Surgery, Policlinico Tor Vergata University, Rome, Italy
e-mail: pompeo@med.uniroma2.it

G. Ruvolo
Division of Cardiac Surgery, Policlinico Tor Vergata University, Rome, Italy

Recent Clinical Techniques, Results, and Research in Wounds (2018)
DOI 10.1007/15695_2017_75, © Springer International Publishing AG
Published Online: 10 May 2018

infection, deep sternal wound infection, sternitis and mediastinitis are often used indifferently [1].

In the presence of a single or multiple skin breakdown along the sternal wound, sometimes it can be very difficult to understand whether the infection is superficial involving the subcutaneous tissue only or rather, constitutes the epiphenomena of a deeper underlying infection. The choice of the optimal treatment depends on the onset time, clinical presentation and radiologic features.

The aim of this chapter is to describe the preferred surgical methods which we selectively employed in this setting.

2 Pathogenesis

Median sternotomy presents several peculiar characteristics, which must be taken into account when considering pathogenetic factors of SWD:

1. The skin incision matches exactly to the sternal incision and hence allows the access to the mediastinum directly from the skin. For this reason all skin breakdowns should be considered potential door of access to the mediastinum. Sometimes, a limited wound dehiscence can be the "tip of an iceberg" of an underlying mediastinitis (Fig. 2).
2. The particular anatomy of the sternum, with the presence of the spongiosa bone characterized by wide inter-trabecular spaces containing red bone marrow, predisposes to the nesting of bacteria.
3. Anatomic variability of the internal mammary artery (IMA), in the absence of collateral blood flow, can be responsible for the loss of blood supply and hence of an impairment of the bone structure which can be more easily damaged by the sternal wires.
4. The presence of the ischaemia (or minor blood supply) of the bone due to the IMA harvesting can be responsible for a devastating sternum infection.
5. The immune deficiency due to compromising effects of cardiopulmonary bypass (CPB) on the immune system [2] can be responsible for the development of multidrug-resistant bacteria infections.

Whenever bacteria colonize the sternum, their eradication can prove extremely difficult for a number of reasons:

1. The trabecular bone structure of the sternum including the presence of the bone marrow.
2. A reduced blood supply due to previous harvesting of the IMA for bypass grafting.
3. The minor penetration of antibiotics in the bone due to sternal ischaemia, diabetes, obesity, etc.

The SWD can be expression of superficial or deep infection, and it can also be expression of

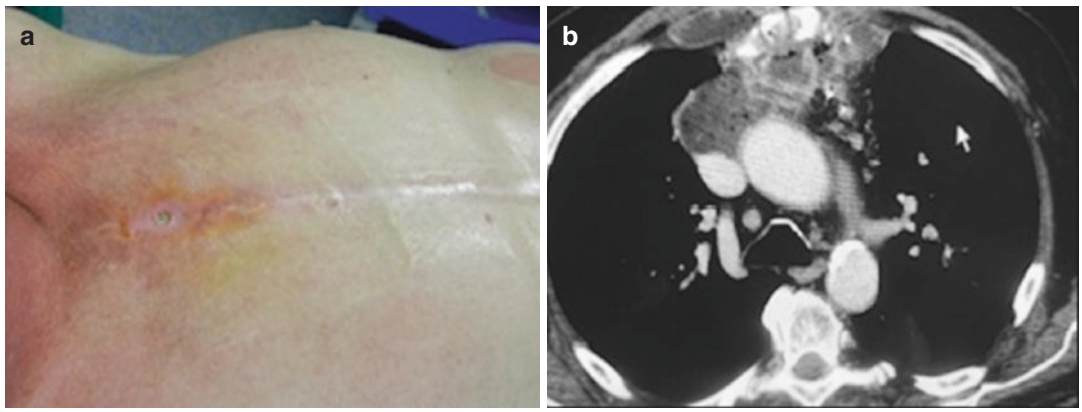


Fig. 2 Another case of SWD entailing minimal dehiscence of the skin wound and advanced mediastinitis with sternal dehiscence revealed by the CT scan

chronic osteomyelitis. The time of onset can orient the diagnosis. The mediastinitis occurs in the postoperative days, while chronic osteomyelitis presenting as sterno-cutaneous fistulas occurs after weeks, month or even years. However, in the presence of prosthetic material, mediastinitis as well may occur in a late stage even several years after surgery.

The sterno-cutaneous fistula presents as a draining sinus tract, in patient with a closed sternal wound [3]. It is often due to an incomplete eradication of the infection in the trabecular bone tissue. We have reported that CT imaging with 3D reconstruction algorithms of the bone can detect an area of osteomyelitis in correspondence of the fistula along the line of the sternotomy incision (Fig. 3) [4]. Sometimes, sternal osteomyelitis can be a result of a previous unrecognized or underestimated sternal wound infection. It can be also due to coagulase-negative staphylococci (CoNS) infection following postoperative SWD, which becomes the entrance door for bacteria colonizing the skin. In fact, in general the presence of CoNS in cultural samples is wrongly underestimated, and a treatment should be considered in some cases [3, 4].

For these reasons, it is very important not to underestimate any wound dehiscence. Rather, accurate monitoring of the inflammation parameters, clinical signs, radiologic features and the microbiological investigations can guide in obtaining a precise diagnosis, independent by the external appearance and extent of the wound dehiscence.

3 Risk Factors

Several studies have tried to assess the real incidence of this complication and have investigated the correlation with a large number of potential risk factors, which can be grouped into:

1. General factors such as age, gender, obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and smoking.

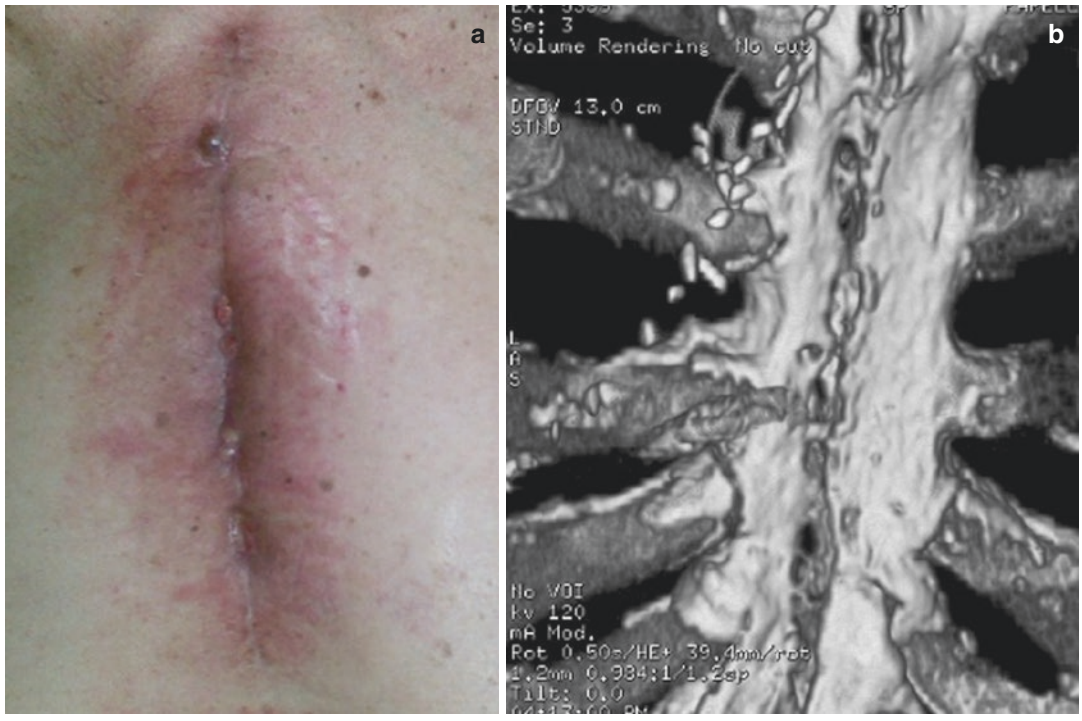


Fig. 3 Sternum-cutaneous fistula outlined by 3D chest CT

2. Procedure-related factors such as bilateral mammary graft, emergency operation, reoperation for bleeding, repeated blood transfusion, prolonged preoperative stay, duration of surgery, prolonged intensive care stay, prolonged postoperative mechanical ventilation, unilateral or bilateral pleurotomy, postoperative hyperglycaemia, off-midline sternotomy, use of bone wax and many others.

Overall, obesity and diabetes mellitus are recognized as the most important factors in the development of sternal wound infections [5].

COPD and smoking can facilitate the development of sternal instability due to excessive coughing and the consequent increased local fluid drainage, which in turn can become a broth for bacterial growth. In patients who are smokers, there is an increase of postoperative pulmonary complications and an impaired immune response.

Early tracheostomy can have an impact on the development of SWD although there are controversial opinions in this respect. Nonetheless, it is clearly evident that the mortality is higher when the infection occurs in patients who underwent tracheostomy postoperatively [6].

Nasal carriage of *Staphylococcus aureus* is considered another important risk factor in the pathogenesis of *Staphylococcus aureus*-related SWD [7].

Sternal ischaemia due to the IMA harvesting can play an important role in the pathogenesis of SWD. In fact, each hemisternum loses more than 90% of its blood supply after mobilization of the corresponding IMA [1]. This feature becomes particularly relevant, especially when both the IMAs are used for grafting and above all in the presence of risk other factors such as obesity, diabetes or COPD.

In this regard, a better preservation in the blood supply of the sternum has been reported to occur following harvest of the IMA according to the skeletonized technique as compared to the pedunculated one [8]. Moreover, the anatomical type of the arterial supply and in particular the presence or not of collateral branches have been considered an important issue. In fact, the arterial branches to the sternum originate either directly from the IMA or from the trunks that also give rise to the perforating branches and to the intercostal artery. Anatomical studies have shown that the common trunks can be of four main types:

1. Sternal/perforating
2. Sternal/intercostal
3. Perforating/intercostal
4. Sternal/perforating/intercostal

This variability of the anatomy as well as the presence of collateral flow to the sternum is considered important in the pathogenesis of sternal ischaemia, which facilitates the subsequent development of SWD [9].

An inadequate mediastinal drainage is another important factor [1]. In fact, the amount of liquid collected in the retrosternal space can spontaneously flow through the skin breakdown (Fig. 4).

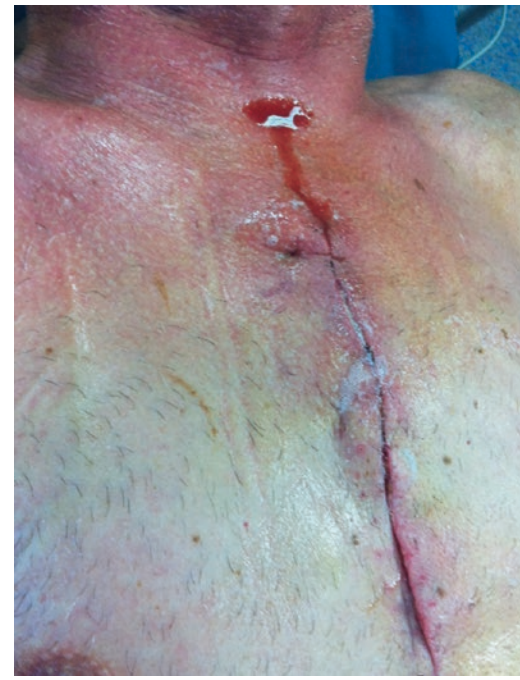


Fig. 4 Outflow of fluid from an infected SWD

The fluid is a broth for bacterial growth and can cause infection and sternal instability.

Many authors have tried to classify SWD or mediastinitis on the basis of the risk factors and the clinical aspects. Gardlund et al. [10] reported a classification of mediastinitis based on the correlation between the microbiological aspects and the risk factors. These authors underlined the following points:

1. Mediastinitis due to coagulase-negative staphylococci, often associated with some risk factors such as obesity and COPD, usually presents sternal instability.
2. Mediastinitis due to *Staphylococcus aureus*, often caused by perioperative contamination, is often associated with stable sternum.
3. Mediastinitis due to gram-negative rods, often caused by spread from concomitant infection in other sites, is associated with stable and instable sternum in similar frequencies.

Another useful classification has been provided by El Oakley and Wright in 1996 [1] who classified the mediastinitis into four types based on the time of first presentation, the presence or absence of risk factors and the presence or absence of one or more failed therapeutic attempts (Table 1). Overall, classifications prove useful tools for the prevention of this complication and contribute to the challenging task of providing standardized criteria for choosing an optimal surgical approach.

Table 1 Classification of mediastinitis according to El Oakley and Wright [1]

Type I	Mediastinitis presenting within 2 weeks after operation in the absence of risk factors
Type II	Mediastinitis presenting at 2–6 weeks after operation in the absence of risk factors
Type IIIA	Mediastinitis type I in the presence of one or more risk factors
Type IIIB	Mediastinitis type II in the presence of one or more risk factors
Type IVA	Mediastinitis type I, II or III after one failed therapeutic trial
Type IVB	Mediastinitis type I, II or III after more than one failed therapeutic trial
Type V	Mediastinitis presenting for the first time more than 6 weeks after operation

4 Surgical Management

The management of SWD involves a spectrum of different procedures. The choice of the optimal method must be based on the clinical and radiological features, on the time of onset as well as on the experience of the centre.

The clinical presentation is very important and is associated with the following main aspects:

1. Presence of purulent or serous drainage from the wound breakdown, fever and the presence or not of swelling and redness, chest pain, sternal instability and high serum levels of the reactive protein C and of other inflammatory parameters.
2. Contrast computed tomography features showing an involvement of the mediastinum and eventually of the sternum.

The fundamental aim of any treatment modality is to clean the wound and then, once the infection has been eradicated, to proceed with the wound closure.

In the last decades, many procedures including surgical revision, closed suction catheters with or without a continuous mediastinal irrigation, wound debridement and open dressing with delayed closure and aggressive early debridement followed by reconstructing plastic procedures using omental or muscle flaps have been described.

In recent years, the use of vacuum-assisted closure (VAC) has been increasingly adopted [11–13]. We also employ it as first choice method in the treatment of superficial and deep wound infections, as a bridge to would closure [14]. Use of VAC for treatment of SWD was first described in 1997 by Morikwas and Argenta [15, 16] and is based on prolonged application of a continuous negative pressure within the wound region [11]. This is usually achieved following accurate surgical debridement by using a polyurethane foam dressed into the entire wound (Fig. 5), which is sealed with a transparent adhesive film (Fig. 6) and then connected by a tube to a pump that gen-

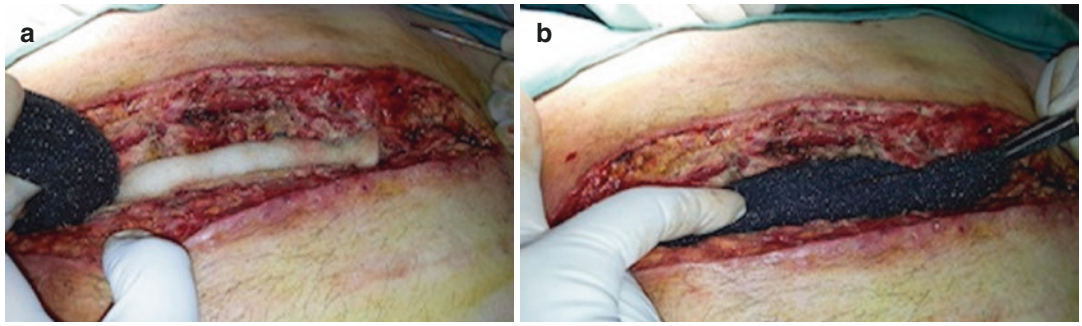


Fig. 5 Polyurethane foam dressed into the sternal wound

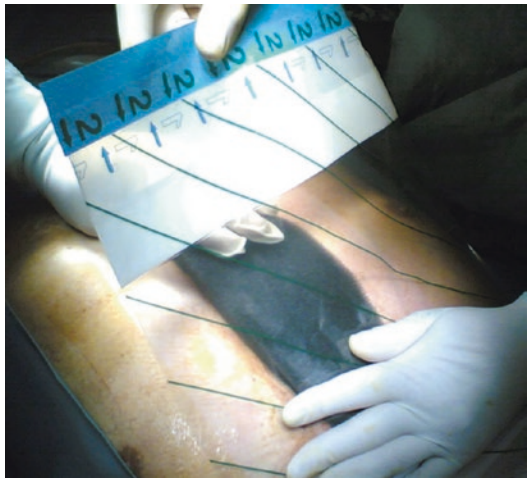


Fig. 6 Sealing of the dressed wound by a transparent adhesive film

erates a continuous negative pressure (usually −125 mmHg) (Fig. 7). A canister is placed in a portable pump to collect the fluid draining from the wound.

The physiologic mechanism of action underlying this method is that the negative pressure created at the wound site increases the local blood flow allowing:

1. Better local penetration of the antibiotics
2. Reduction in bacterial colonization rates
3. Decrease of the local oedema
4. Optimal drainage of the wound

As a result, the production of the granulation tissue is stimulated, and progressive healing of the wound can be facilitated eventually allowing the definitive surgical closure.

Fig. 7 Negative-pressure generating pump

4.1 Closed Redon Catheter Drainage

In case of mediastinal inadequate drainage, sometimes, in the presence of an early SWD from which serous or corpuscolated fluid comes out, it is possible to place a closed Redon drainage in the subcutaneous tissue of the wound to drain all the liquid and close the wound breakdown with a suture. In fact, the Redon drainage makes it possible to keep dry the wound, whereas wound suturing can avoid the entrance of bacteria from the skin breakdown.

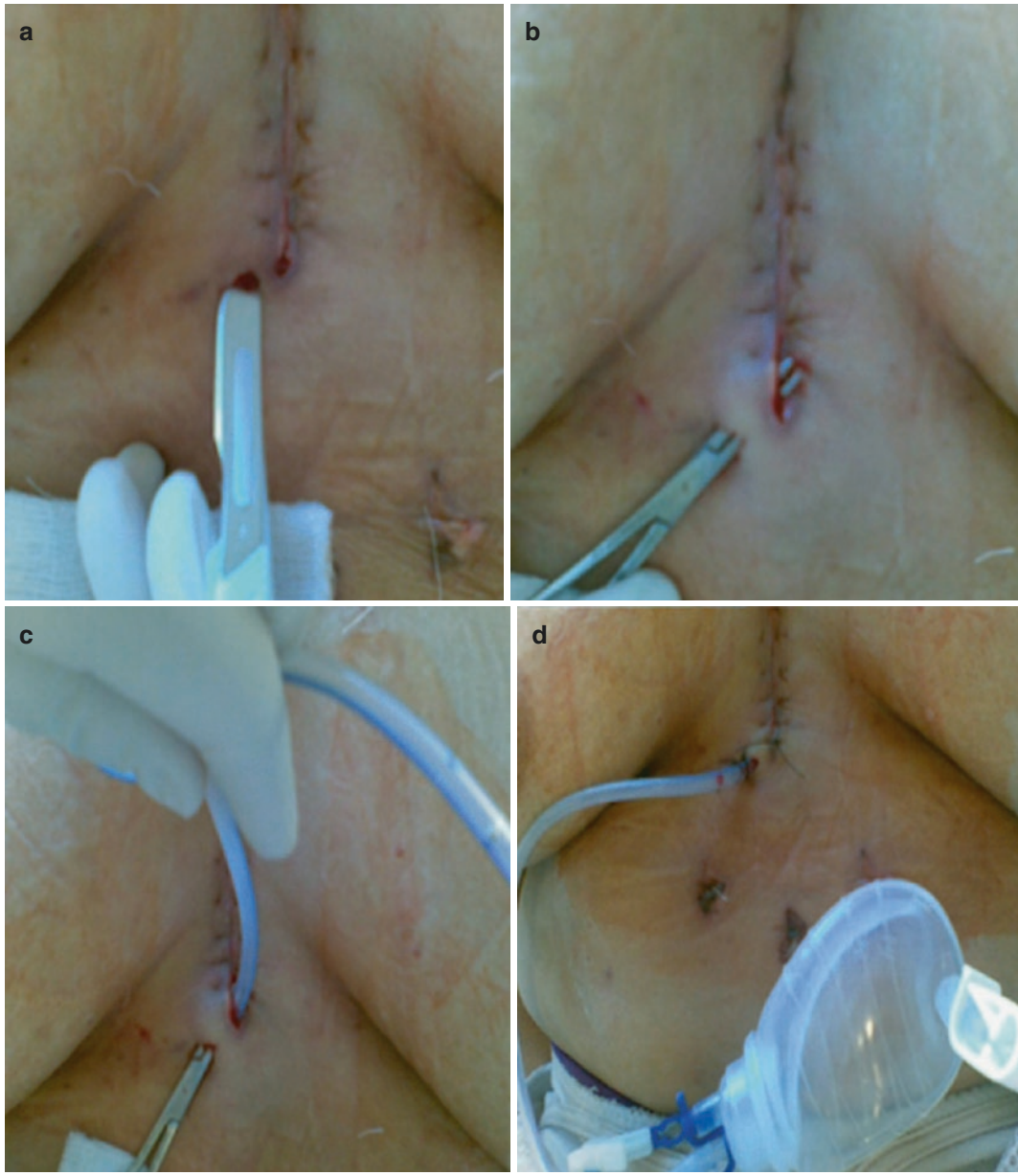


Fig. 8 Placement of multiple subcutaneous Redon drainages

The technique is very easy. We commonly perform a small opening in the lower part of the wound to insert the drainage, which it then pushed as far as possible (Fig. 8). The drainage is left in situ for several days until when the daily amount of drained fluid decreases significantly. Culture examinations of the liquid should be performed periodically during this type of treatment.

4.2 VAC therapy

In case of mediastinal involvement, the surgical approach must be more aggressive. In our experience, all patients are treated by VAC in order to eradicate the infection before performing the sternal closure.

All the patients undergo initial surgical debridement with the removal of all sternal wires,

all necrotic or devitalized tissue, the exposed cartilages and, whenever present, of the bone fragments. Any sharp sternal edges are also eliminated to avoid the risk of heart injury. After collecting tissue samples for microbiological investigation, the wound is washed with H_2O_2 and with 1% diluted povidone-iodine solution.

In the presence of sternal instability, we first protect the heart from mechanical injury with a special nonadhesive white sponge, which is positioned under the sternal edges. Afterwards, a black sponge, which can be cut in different shapes, is positioned between the sternal edges to keep clean the bone and the deep tissues. This measure aids also to give stability to the sternum. Finally we insert another layer of sponge to cover the entire wound (Fig. 5), and we seal all the wound area by applying a transparent film (Fig. 6). The sponges are changed twice a week in the operating room under mild sedation. Microbiology culture samples are periodically collected to evaluate changes in bacteria colonies and antibiotic susceptibility to verify the adequacy of the antibiotic therapy [16]. When the cultures become negative, the wound looks viable and serum levels of inflammatory parameters have lowered, surgical wound closure can be performed [17].

The technique employed for the wound closure can vary, depending on the status of the sternum.

If the bone is deemed in good condition, it is possible to re-suture the sternum directly using steel wire, Nitinol clips or titanium-made sternal devices.

When the sternum is found in a bad condition due to the extensive debridement or to the presence of multiple transversal fractures, the use of muscle flaps is considered more appropriate for closing the chest.

4.3 Thermo-reactive Nitinol clips

The Nitinol clips (Flexigrip, Praesidia srl, Bologna, Italy) are made of nickel and titanium alloy (Nitinol). They have thermo-reactive properties since cooling allows the transformation of Nitinol from austenite into martensite, which is a soft material, whereas heating allows the reverse of the cycle transforming martensite to austenite, which is a hard material.

Fig. 9 Nitinol clip

Before being implanted, these clips are thus cooled in order to allow a deformation which facilitates their insertion in the sternum sides. Once the clips are positioned, a warm gauze is placed above the clips, allowing them to contract and to return to the initial shape due to a preformed shape memory, eventually pulling together the sternal edges (Fig. 9).

The clips have different sizes and can be inserted through a hole made by the electrocautery in the intercostal space close to the sternal rim. Three clips are generally sufficient to achieve good sternal stability. If the sternum presents some fractures, some screwed plates are inserted in association with the clips.

The main advantage of Nitinol clips is that their application is rapid and noninvasive because there is no need to free the posterior face of the sternum from the mediastinal structures (Fig. 10) and the clips can be inserted in the parasternal space without any dissection of the substernal tissue [17–20]. As a result we consider this method particularly useful following the use of VAC, when rewiring can be difficult because the mediastinal structures are likely to become firmly adherent to the posterior aspects of the sternum and surgical dissection might be associated with a high risk of major bleeding.

4.4 Flap Reconstruction

When the sternum is in bad condition due to extensive debridement or to the presence of several bone crushes, muscle or omental flaps can be

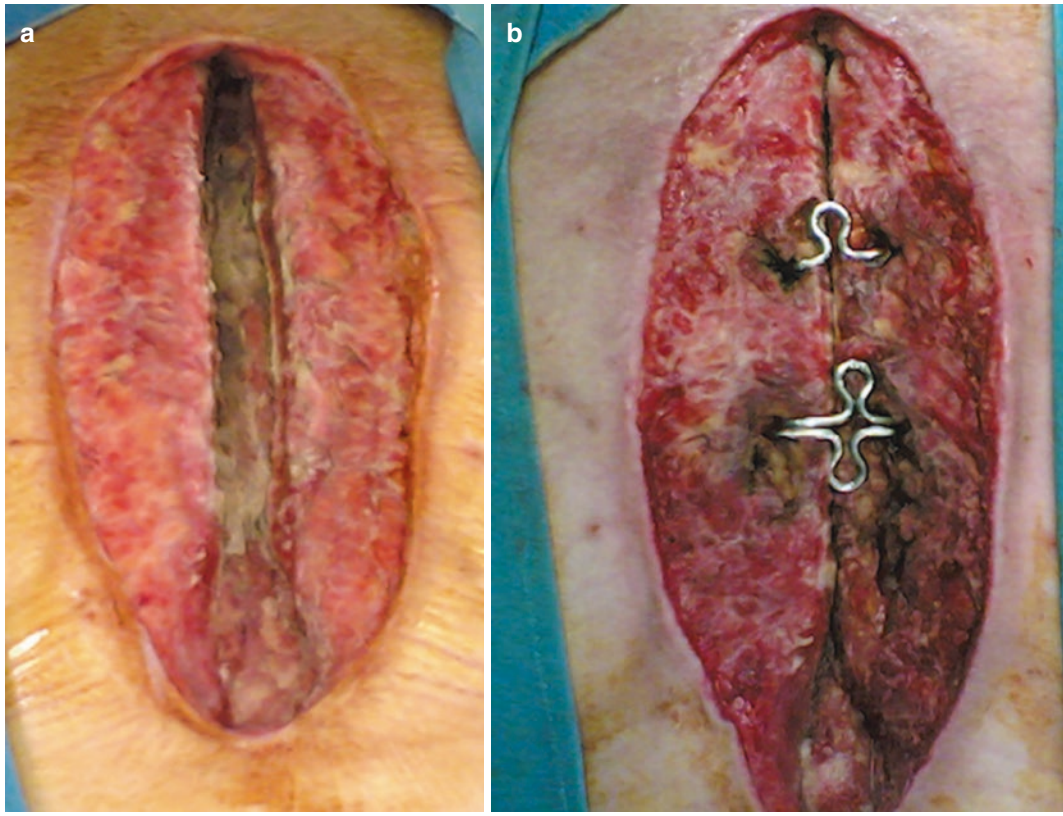


Fig. 10 Complete sternal dehiscence closure by Nitinol clips

used to close the chest. In recent years, the use of VAC has reduced the use of the great omentum or the rectus abdominis muscle flap because of a progressive reduction of the wound width and in depth by these less invasive methods. Furthermore, the use of the rectus muscle has a high risk of failure when the IMA has been already employed for the grafting. In our experience, in most of instances, the use of pectoralis muscle flap is adequate to close the gap between the sternal edges and to ensure a good chest closure. Moreover, Zeitani and coworkers [21, 22] have found that in patients with chronic complex SWD, the use of pectoralis muscle flap repair minimizes the occurrence of paradoxical motion of the chest wall when compared to sternal rewiring, eventually leading to better respiratory function and clinical outcomes including less pain and lower dyspnoea grade during the follow-up.

The surgical technique is easy and safely feasible without the need of any further skin incision. The dissection is performed on one side using the diathermy, starting from the sternal edges and proceeding by exposing the cartilages and the ribs. Laterally, the dissection is carried to the anterior axillary line. Superiorly, dissection manoeuvres are interrupted at the level of the clavicle taking care not to cut the pectoralis branch of the thoraco-acromial artery that supplies the pectoralis flap. Inferiorly, the attachment of the muscle fibres on the cartilages of the sixth and seventh rib is divided, and the aponeurosis of the abdominis external muscle is exposed. At this point the flap is freed laterally, inferiorly and medially, and it can be elevated off the chest wall (Fig. 11). Then, it can be advanced to the midline avoiding any tension, and it can be transposed into the mediastinum to fill in the space between the sternal edges. Equivalent manoeuvres are performed on the contralateral side. Absorbable and non-absorbable sutures can be alternatively placed to approximate the flap to the sternum and then the muscle flaps together (Fig. 12). Six Redon drainages are positioned

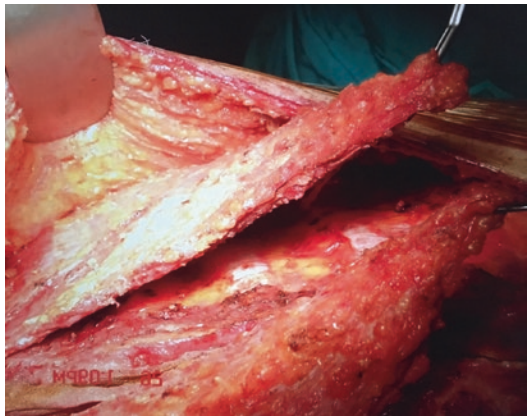


Fig. 11 Pectoralis muscle flap which is freed and elevated off the chest wall

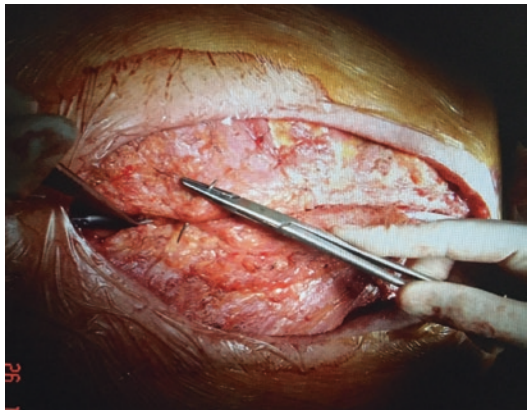


Fig. 12 Transposition of the flap into the mediastinum to fill in the space between the sternal edges

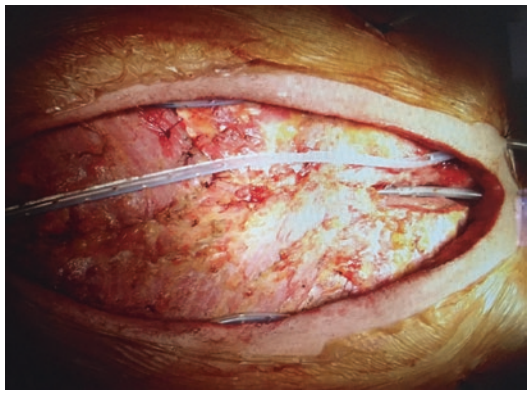


Fig. 13 Multiple Redon drainages are placed both below and above each flap

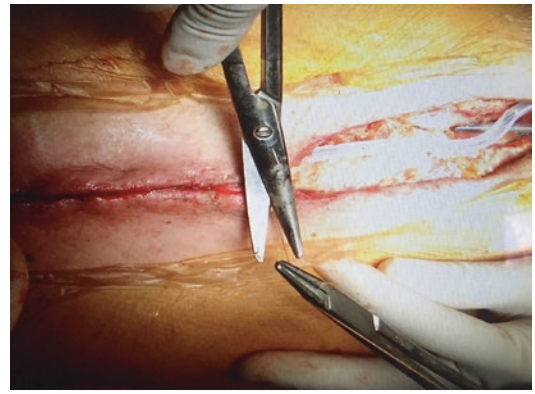


Fig. 14 Final suturing of the skin and subcutaneous tissue by absorbable sutures

either under or above each flap, in the mediastinum and above the flaps along the midline (Fig. 13). The skin and subcutaneous tissue are closed with absorbable sutures (Fig. 14).

Conclusions

Surgical management of SWD is not univocal and entails different options, which can be employed according to a tailored stepwise strategy of treatment following accurate assessment of clinical, radiological and microbiological features. As a rule an early aggressive treatment seems to offer the best chance of cure to any type of SWD.

The use of a closed Redon drainage and/or early debridement followed by the VAC therapy can guarantee, according to our experience, the best results in achieving a complete eradication of bacterial infection and constitute a mainstay of treatment since it helps prevent infection relapses and failures of muscle flaps repair. Before starting the VAC therapy, we consider important to remove all the steel wires to prevent the development of sternocutaneous fistula.

In the presence of clinically evident mediastinitis, an early debridement followed by the use of VAC is the optimal treatment option in terms of final outcome and overall survival.

The closure of the sternum must be delayed until when the cultural samples become negative.

In our experience, following VAC therapy, a direct closure of the sternum can be performed using Nitinol clips and/or screwed plates, to minimize risks of damaging the mediastinal structures. On the other hand, if the sternum is severely damaged and multi-fractured, use of pectoralis muscle flaps is a preferable option to assure an optimal repair and a satisfactory stability of the sternum with minimized risks of paradoxical motion of the chest during ventilation.

References

1. El Oakley RM, Wright JE (1996) Postoperative mediastinitis: classification and management. Ann Thorac Surg 61:1030–1036
2. Hornick P, Taylor KM (2000) Immune and inflammatory response after cardiopulmonary bypass. In: Gravlee GP, Davis RF, Kurusz M, Utley JR (eds) Cardiopulmonary bypass: principles and practice, 2nd edition, chapter 15. Lippincott Williams & Wilkins, Philadelphia
3. Steingrimsson S, Gustafsson R, Gudbjartsson T, Mokhtari A, Ingemansson R, Sjogren J (2009) Sternocutaneous fistulas after cardiac surgery: incidence and late outcome during a ten-year follow-up. Ann Thorac Surg 88:1910–1915
4. Tocco MP, Ballardini M, Masala M, Perozzi M (2013) Post-sternotomy chronic osteomyelitis: is sternal resection always necessary? Eur J Cardiothorac Surg 43:715–721
5. Borger MA, Rao V, Weisel RD, Ivanov J, Cohen G, Scully HE, David TE (1998) Deep sternal wound infection: risk factors and outcomes. Ann Thorac Surg 65:1050–1056
6. Force SD, Miller DL, Petersen R, Mansour KA, Craver J, Guyton RA, Miller JI Jr (2005) Incidence of deep sternal wound infections after tracheostomy in cardiac surgery patients. Ann Thorac Surg 80: 618–621
7. Jakob HG, Borneff-Lipp M, Bach A, von Pückler S, Windeler J, Sonntag H, Hagl S (2000) The endogenous pathway is a major route for deep sternal wound infection. Eur J Cardiothorac Surg 17:154–160
8. Dmitry Pevni MD, Rephael Mohr MD, Oren Lev-Run MD, Chaim Locer MD, Yosef Paz MD, Amir Kramer MD, Itzhak Shapira MD (2003) Influence of bilateral skeletonized harvesting on occurrence of deep sternal wound infection in 1,000 consecutive patients undergoing bilateral internal thoracic artery grafting. Ann Surg 237:277–280
9. Neuhuber W, Lyer S, Alexiou C, Buder T (2016) Anatomy and blood supply of the sternum. Deep sternal wound infection. In: Horch RE, Willy C, Kutuschka I (eds) Deep sternal wounds. Springer, Berlin
10. Gardlund B, Bitkover CY, Vaage J (2002) Postoperative mediastinitis in cardiac surgery-microbiology and pathogenesis. Eur J Cardiothorac Surg 21:825–830
11. Sjogren J, Malmsjo M, Gustafsson R, Ingemansson R (2006) Poststernotomy mediastinitis: a review of conventional surgical treatments, vacuum assisted closure therapy and presentation of the Lund University Hospital mediastinitis algorithm. Eur J Cardiothorac Surg 30:898–905
12. Sjogren J, Gustafsson R, Nilsson J, Malmsjo M, Ingemansson R (2005) Clinical outcome after poststernotomy mediastinitis: vacuum assisted closure versus conventional treatment. Ann Thorac Surg 79:2049–2055
13. Fleck TM, Fleck M, Moidl R, Czerny M, Koller R, Giovanoli P, Hiesmayer MJ, Zimpfer D, Wolner E, Grabenwoger M (2002) The vacuum-assisted closure system for the treatment of deep sternal wound infections after cardiac surgery. Ann Thorac Surg 74:1596–1600
14. Hersh RE, Jack JM, Dahrman MI, Morgan RF, Drake DB (2001) The vacuum assisted closure device as a bridge to sternal wound closure. Ann Plast Surg 46:250–254
15. Argenta LC, Morykwas MJ (1997) Vacuum assisted closure. A new method for wound control and treatment: clinical experience. Ann Plast Surg 38:563–577
16. Morykwas MJ, Argenta LC, Shelton Brown E, McGuirt W (1997) Vacuum assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 38:553–562
17. Tocco MP, Costantino A, Ballardini M, D'Andrea C, Masala M, Merico E, Mosillo L, Sordini P (2009) Improved results of the vacuum assisted closure and Nitinol clips sternal closure after postoperative deep sternal wound infection. Eur J Cardiothorac Surg 35:833–838
18. Reiss N, Schvett U, Kemper M, Bairaktaris A, Koerfer R (2007) New method for sternal closure after vacuum assisted closure therapy in deep sternal infection after cardiac surgery. Ann Thorac Surg 6:2246–2247
19. Centofanti P, La Torre M, Barbato L, Verzini A, Patanè F, Di Summa M (2002) Sternal closure using semi-rigid fixation with thermo-reactive clips. Ann Thorac Surg 74:943–945
20. Negri A, Manfredi J, Terrini A, Rodella G, Bisleri G, El Quarra S, Muneretto C (2002) Prospective evaluation of a new sternal closure method with thermoreactive clips. J Thorac Cardiovasc Surg 22:571–575
21. Zeitani J, Pompeo E, Nardi P, Sergiacomi G, Scognamiglio M, Chiariello G, Del Giudice C, Arganini C, Simonetti G, Chiariello L (2013) Early and long-term results of pectoralis muscle flap reconstruction versus sternal rewiring following failed sternal closure. Eur J Cardiothorac Surg 43:e144–e150
22. Zeitani J, Russo M, Pompeo E, Sergiacomi GL, Chiariello L (2016) Pectoralis muscle flap repair reduces paradoxical motion of the chest wall in complex sternal wound dehiscence. Korean J Thorac Cardiovasc Surg 49:366–373

Sternal Wound Reconstruction Using Internal Mammary Artery Perforator Flaps

Kashyap Komarraju Tadisina, Ahmed Abouzaid, and Raffi Gurunluoglu

1 Introduction

Sternal wound reconstruction to prevent deep sternal wound infections continues to be a mainstay of the plastic and reconstructive surgeon's practice. Patients with sternal defects are often cardiothoracic patients with multiple comorbidities including obesity, diabetes, smoking, macromastia, and poor wound healing that make reconstruction of particularly challenging. Traditionally, local muscle flaps such as the pectoralis major, latissimus dorsi, and omentum have been the standard of care for coverage of these wounds. However, recently, local reconstruction with fasciocutaneous flaps has gained popularity. Among these flaps, the internal mammary artery perforator (IMAP)-based fasciocutaneous flap has been increasingly described due to decreased donor site morbidity and sparing of accessory respiratory muscles [1–7]. These flaps have been found to be reliable in an often medically complex patient population [6–16] and present the reconstructive surgeon with another option when encountering sternal wounds. The authors describe the IMAP flap technique and review the literature regarding its use in sternal reconstruction.

K. K. Tadisina · A. Abouzaid · R. Gurunluoglu (✉)
Department of Plastic Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: gurunlr@ccf.org

2 Technique

Preoperatively, in addition to a thorough history, physical, and medical workup, attention must be paid specifically to the patient's surgical and medical history with respect to determining patency/viability of the internal mammary artery or prior radiation to the chest. Further, assessment of the patient's body mass index, breast size, and ptosis will assist in preoperative planning. A computed tomography angiogram (CTA) may be obtained if the surgeon wishes to further visualize the internal mammary artery, its patency, and/or the viability of perforators [10, 16].

Reliable perforators are identified using a handheld Doppler instrument and marked as such. Perforators are generally identified 1–2 cm lateral to the sternal edge. Variation among patients' chest side has been noted, with perforators generally being larger on the patient's right side [10]. Typically, the second IMA perforator is the largest and most reliable. The perforating vessels travel through the intercostal and pectoralis major muscle fibers.

Next, an island skin flap is designed and raised in a lateral to medial fashion, ensuring to leave the perforator intact and minimizing shear forces. The lateral extent of dissection has been described as far as the mid-axillary line if needed, with a maximum length of 25 cm being described. A 6–7 cm width has been reported as the maximum size that may be taken for primary closure of the

Recent Clinical Techniques, Results, and Research in Wounds (2018)
https://doi.org/10.1007/15695_2018_126, © Springer International Publishing AG
Published Online: 30 June 2018

donor site [15, 17]. This width can be confirmed preoperatively with a pinch test. Larger areas may be covered with multiple flaps that are taken simultaneously. Deeper wounds may be covered with a musculocutaneous variation of the IMAP flap, with the pectoralis major muscle being harvested along with the fasciocutaneous component. If performing this variation of the flap, a 1 cm cuff of pectoralis muscle around the fasciocutaneous component is recommended [15].

Once the flap has been raised, the IMAP flap is transposed/rotated into the wound defect and inset with minimal torsion and shear force to the flap and pedicle. The flap donor site is typically closed primarily. Drains are not typically used with these flaps.

2.1 Case Using IMAP Flap

A 40-year-old diabetic female patient with a history of left mastectomy and previous radiation for lymphoma and left breast cancer had received heart valve surgery which was complicated with sternal wound dehiscence secondary to osteoradionecrosis and infection. Initial sternal wound reconstruction was performed using a contralateral pedicled TRAM flap. Early postoperative course was complicated with partial flap necrosis requiring debridement and reconstruction of the residual chest defect (Fig. 1). An island skin flap of the fifth intercostal internal mammary artery perforator branch was planned. The patient was fully aware of the technique being used and was consented after discussion of procedure, risks, benefits, and alternatives to the surgery. The technique was practiced on multiple cadaveric bodies prior to being performed. Preoperatively, the perforator was identified by handheld Doppler on the right fifth intercostal space. The island skin flap was raised, incorporating the perfusion territory of the medial and inferior aspect of the right breast (Fig. 2). The IMAP flap was transposed to the defect and flap donor site was closed in the form of simultaneous unilateral breast reduction using a superior pedicle (Fig. 3). Postoperative course was unremarkable, and follow-up at 12 months had no complications (Fig. 4).

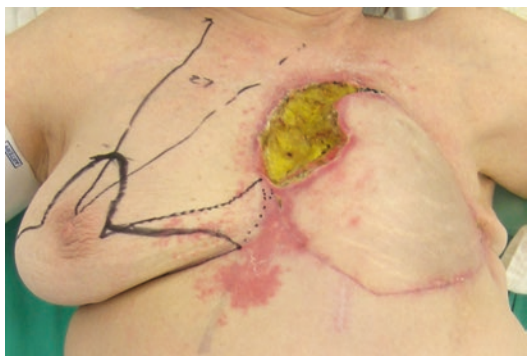


Fig. 1 Early postoperative course complicated with partial flap necrosis requiring debridement and reconstruction of the residual chest defect

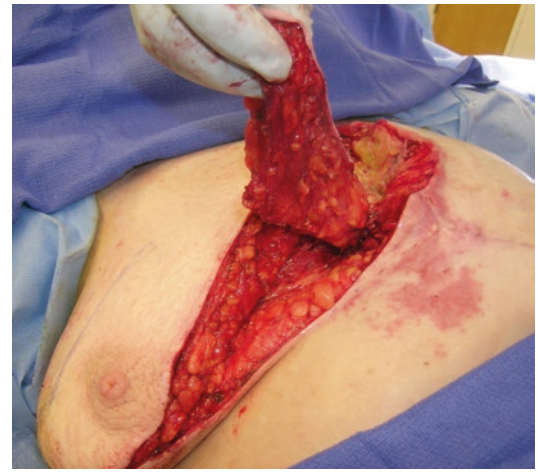


Fig. 2 Preoperatively, the perforator was identified by handheld Doppler on the right fifth intercostal space. The island skin flap was raised, incorporating the perfusion territory of the medial and inferior aspect of the right breast

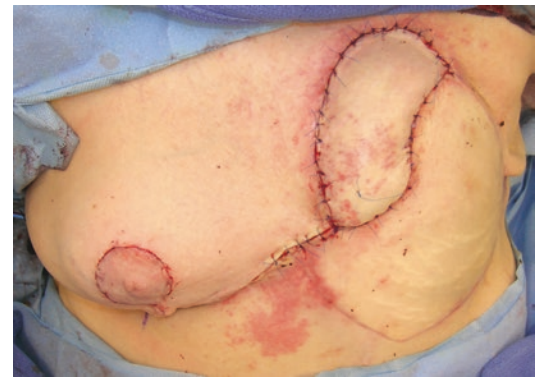


Fig. 3 The IMAP flap was transposed to the defect and flap donor site was closed in the form of simultaneous unilateral breast reduction using a superior pedicle

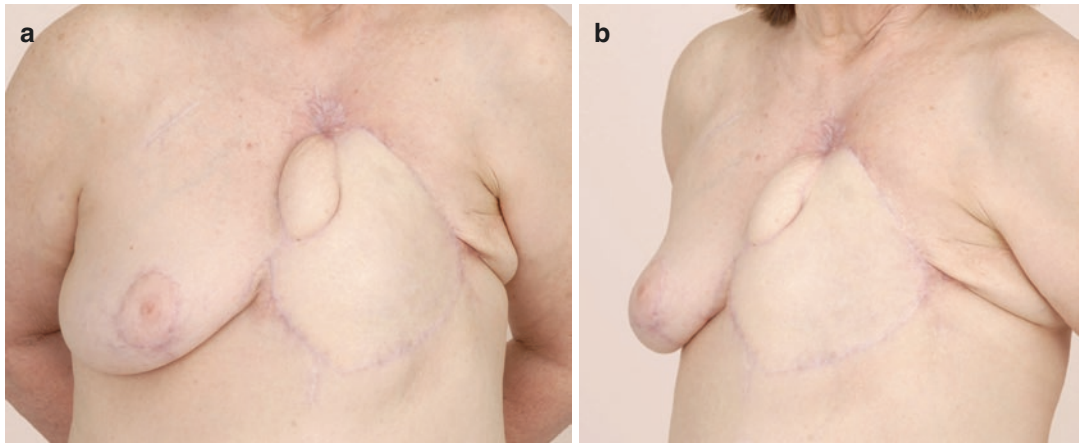


Fig. 4 (**a**, **b**) Postoperative course was unremarkable and follow up at 12 months had no complications, although some wound contracture and scarring at the superior portion of the wound was noted. This was determined to be due to the prior radiation at the recipient site

3 Discussion

While IMAP flaps are well described for head and neck reconstruction [2–5, 10], only fairly recently have studies shown the use of these flaps for sternal wounds. Within the clinical literature, IMAP flaps are reported to be reliable, versatile in size, large enough to cover the entirety of the sternum, and flexible in location of use. Compared to its predecessors (the deltopectoral, pectoralis major, latissimus dorsi, or omental flaps), the IMAP flap offers minimal dissection and donor site morbidity [13]. As an island flap, it offers the advantages of increased axis of rotation, size versatility, and primary donor site closure [3]. Further, use of the IMAP flap spares the use of accessory respiratory muscles and does not affect respiratory mechanics. Disadvantages are mainly from an aesthetic standpoint, particularly in the female population, as it can cause breast and nipple asymmetry or a prominent scar [1]. Although often sacrificed for coronary artery bypass graft surgery, if available, the IMAP flap can be an excellent tool for the reconstructive surgeon.

Within the last decade, the IMAP flap has been rigorously studied both through cadaveric and clinical studies. The authors have studied this technique, performed anatomic cadaveric studies, successfully employed this technique in clinical care [14], and reviewed relevant literature.

4 Cadaver Studies

Past and recent cadaveric studies have revealed characteristic anatomic features of the IMAP flap. Perfusion studies by Schmidt et al. [17], Gillis et al. [18], Paes et al. [19], and Vesely et al. [3] showed that IMAPs supplied skin from the clavicle to the superior abdominal wall and from the sternum to the mid-axillary line. These studies also revealed that the second IMAP was the largest in caliber, which was confirmed by other subsequent studies by Gillis et al. [18]. This same group reported that the dominant IMA perforator had anastomoses with the lateral thoracic artery. The second IMAP diameter has been reported to be 1–1.5 cm, with a length of ~7 cm from the sternal margin and ~5.2 cm superficial length [10, 18]. Variations of IMAP flap design have also been described in cadaver studies. Schmidt et al. [17] proposed that the fourth IMAP taken from the inframammary fold could be used for breast or contralateral thoracic defects and could be closed using a breast reduction technique. This theory was later employed clinically by the authors [14].

5 Clinical Studies

An updated review of the literature revealed a total of ten studies describing 42 cases utilizing IMAP flaps in sternal wound reconstruction. The most

commonly used perforators are the second and sixth IMAPs. The largest flap size reported was a 20 × 12 cm. One author advocates a largest length of an IMAP flap of up to 25 cm, with distal extent at the mid-axillary line. Donor sites of up to 7 cm were reported to be closed primarily. Overall complication rate was reported to be 12.5% (5/40), with two cases reporting dehiscence and three with partial flap necrosis treated conservatively. A summary of study findings are presented in Table 1.

Published reports show the use of IMAP flap in a variety of sternal reconstruction scenarios. IMAP flaps have been used for reconstruction of more common uses such as chronic sternal defects [1, 15] and sternal osteomyelitis [12], closure of keloid scar excision sites [10], burn contracture reconstruction [11], congenital chest wall reconstruction, and breast reconstruction [8, 9]. Multiple authors have described the IMAP flap in the setting of breast asymmetry correction. Ruegg et al. [8]

Table 1 Summary of published cases of sternal reconstruction with IMAP flaps

Author	Number of cases	Intercostal perforator used	Size of largest flap	Use	Findings	Complications
Kalendar et al.	7	6th and 7th	NR	Post-burn contracture		None
Kannan et al.	7	1st, 2nd, 3rd	25 × 7 cm	Coronary bypass surgical wound, cardiac transplantation wound, sternal osteomyelitis	Mean perforator diameter 1.5 mm Torsion angle of 80° Translational pedicle movement 1–2 cm Outcomes better in ASA classification <3	Partial flap necrosis (2) managed conservatively
Kim et al.	1	4th, 6th simultaneous	12 × 14 cm	Chronic sternal wound from prior cardiothoracic surgery	Bilateral flaps for midline wound	None
Koulaxouzidis et al.	9	2nd	122 cm^2 (average)	Deep sternal wound infections	Mean BMI of 32.8 Two cases of macromastia	Dehiscence (2) in patients with macromastia
Lima-Sanchez et al.	1	2nd	NR	Sternal osteomyelitis		None
Ruegg et al.	1	2nd, 4th simultaneous	20 × 12 cm	Contralateral sternoclavicular wound, severe breast ptosis	Ptosis improved	None
Schwabegger et al.	1	NR	NR	Pectus excavatum and breast asymmetry	Unilateral macromastia improved	None
Tadisina et al.	1	5th	NR	Sternal wound from prior surgery and radiation	Simultaneous wise pattern breast reduction	None
Takeuchi et al.	2	NR	6 × 15 cm	Post-mastectomy midline wounds		None
Wang et al.	10	6th	17 × 6 cm	Sternal keloid excision sites	Preoperative computed tomography angiography reliable	Tip necrosis (1)
Total	**40**					**5**

NR not reported

used a second and fourth IMAP-based flap to cover a contralateral sternoclavicular defect while also improving breast ptosis by elevating a flap from the superomedial portion of the ptotic breast. Schwabegger et al. [9] successfully used an inframammary IMAP flap from an asymmetrically larger breast to cover a silicone implant used to correct the same patient's pectus excavatum. The authors built upon these principles and used a fifth IMAP-based flap to cover a chronic sternal wound while performing a simultaneous breast reduction to reduce tension on the wound and utilizing the tissue that would have been removed during the breast reduction within the flap [14].

The wide spectrum of use of the IMAP flap has also resulted in several variations of prototypical flap design. Published variations of the typical IMAP flap include the use of multiple simultaneous IMAP flaps for reconstruction, musculocutaneous flaps with pectoralis major incorporation in deeper wound reconstruction [15], pre-expansion for additional area coverage [16], and simultaneous breast reduction at the time of IMAP flap reconstruction [14].

Conclusions

The IMAP flap is a reliable, versatile local reconstructive option for sternal wounds with minimal donor dissection or morbidity. It provides a large area of coverage with multiple variations that provide further flexibility. Current clinical studies show successful use in a wide variety of patients with sternal defects with a relatively low complication rate. The sternal IMAP flap is a useful tool for the armamentarium of any reconstructive surgeon and, in certain patients, can be used as the first-line coverage of sternal defects.

References

1. Koulaxouzidis G, Orhun A, Stavrakis T, Witzel C (2015) Second intercostal internal mammary artery perforator (IMAP) fasciocutaneous flap as an alternative choice for the treatment of deep sternal wound infections (DSWI). J Plast Reconstr Aesthet Surg 68(9):1262–1267
2. Mirghani H, Leymarie N, Amen F, Qassenmyar Q, Leclere FM, Kolb F (2014) Pharyngotracheal fistula closure using the internal mammary artery perforator island flap. Laryngoscope 124:1106–1111
3. Vesely MJ, Murray DJ, Novak CB, Gullane PJ, Neligan PC (2007) The internal mammary artery perforator flap: an anatomical study and a case report. Ann Plast Surg 58(2):156–161
4. Zan T, Li H, Du Z, Gu B, Liu K, Xie F, Xie Y, Li Q (2013) Reconstruction of the face and neck with different types of pre-expanded anterior chest flaps: a comprehensive strategy for multiple techniques. J Plast Reconstr Aesthet Surg 66(8):1074–1081
5. Schellekens PP, Paes EC, Hage JJ, van der Wal MB, Bleys RL, Kon M (2011) Anatomy of the vascular pedicle of the internal mammary artery perforator (IMAP) flap as applied for head and neck reconstruction. J Plast Reconstr Aesthet Surg 64(1):53–57
6. Kim KS, Kim ES, Hwang JH, Lee SY (2013) Internal mammary artery perforator-based V-Y advancement flap for the reconstruction of soft tissue defects in the sternal region. J Plast Surg Hand Surg 47(6):543–544
7. Takeuchi M, Sakurai H (2013) Internal mammary artery perforator flap for reconstruction of the chest wall. J Plast Surg Hand Surg 47:328–330
8. Rüegg EM, Lantieri L, Marchac A (2012) Dual perforator propeller internal mammary artery perforator (IMAP) flap for soft-tissue defect of the contralateral clavicular area. J Plast Reconstr Aesthet Surg 65(10):1414–1417
9. Schwabegger AH, Piza-Katzer H, Pauzenberger R, Del Frari B (2011) The internal mammary artery perforator (IMAP) breast-flap harvested from an asymmetric hyperplastic breast for correction of a mild funnel chest deformity. Aesthet Plast Surg 35(5):928–932
10. Wang J, Min P, Grassetti L, Lazzeri D, Zhang YX, Nicoli F, Innocenti M, Torresetti M, Levin LS, Persichetti P (2015) Preliminary outcomes of distal imap and seap flaps for the treatment of unstable keloids subject to recurrent inflammation and infections in the lower sternal and upper abdominal areas. J Reconstr Microsurg 31(9):621–630
11. Kalender V, Aydm H, Karabulut AB, Ozcan M, Amiraslanov A (2000) Breast reconstruction with the internal mammary artery pedicled fasciocutaneous island flap: description of a new flap. Plast Reconstr Surg 106(7):1494–1498
12. Lima Sánchez J, Sánchez Medina MT, García Duque O, Fernández-Palacios J (2015) Chronic sternoclavicular osteomyelitis: salvage surgery with internal mammary artery perforator flap. Cir Esp 93(2):129–131
13. Neligan PC, Gullane PJ, Vesely M, Murray D (2007) The internal mammary artery perforator flap: new variation on an old theme. Plast Reconstr Surg 119(3):891–893
14. Tadisina KK, Drake RL, Zins JE, Gurunluoglu R (2017) The simultaneous use of breast reduction and internal mammary artery perforator flap in sternal wound reconstruction. Ann Plast Surg 78(2): 236–239

15. Kannan RY (2016) The internal mammary artery perforator flap and its subtypes in the reconstruction of median sternotomy wounds. J Thorac Cardiovasc Surg 152(1):264–268
16. Wong S, Goggin JD, Webster ND, Saint-Cyr MH (2017) Pre-expanded internal mammary artery perforator flap. Clin Plast Surg 44(1):65–72
17. Schmidt M, Aszmann OC, Beck H, Frey M (2010) The anatomic basis of the internal mammary artery perforator flap: a cadaver study. J Plast Reconstr Aesthet Surg 63(2):191–196
18. Gillis JA, Prasad V, Morris SF (2011) Three-dimensional analysis of the internal mammary artery perforator flap. Plast Reconstr Surg 128(5):419e–426e
19. Paes EC, Schellekens PP, Hage JJ, van der Wal MB, Bleys RL, Kon M (2011) A cadaver study of the vascular territories of dominant and nondominant internal mammary artery perforators. Ann Plast Surg 67(1):68–72