EDITORIAL

Human Wound and Its Burden: Updated 2022 Compendium of Estimates

Chandan K. Sen[1,2,*]

[1]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[2]University of Pittsburgh Medical Center Health System Wound Care Service, Pittsburgh, Pennsylvania, USA.

Significance: Chronic wounds affect 10.5 million (up 2.3 million from the 2014 update) of U.S. Medicare beneficiaries. Chronic wounds impact the quality of life of nearly 2.5% of the total population of the United States. This fraction is larger in the elderly. These wounds can lead to a range of complications and health care costs. Given the aging population, the continued threat of diabetes and obesity worldwide, and the persistent problem of infection, it is expected that chronic wounds will continue to be a substantial clinical, social, and economic challenge. Disparities in the prevalence and management of chronic wounds exist, with underserved communities and marginalized populations often facing greater challenges in accessing quality wound care. These disparities exacerbate the public health burden.

Recent Advances: U.S. Centers for Medicare and Medicaid Services had proposed revision of its local coverage determination limiting the use of skin substitute grafts/cellular and/or tissue-based products for the treatment of diabetic foot ulcers and venous leg ulcers in the U.S. Medicare population. In response to the comment phase, this proposal has been put on hold. The U.S. Food and Drug Administration (FDA) has renewed its focus on addressing nonhealing chronic wounds and has outlined efforts to address identified barriers to product development for nonhealing chronic wounds. The new approach places emphasis on engaging key wound healing stakeholders, including academia, professional associations, patient groups, reimbursement organizations, and industry. Finally, recent advances demonstrating that wounds closed by current FDA definition of wound closure may remain functionally open because of deficiencies in restoration of barrier function warrant revisiting the wound closure endpoint. Such "closed" wounds that are functionally open, also known as invisible wounds, are likely to be associated with high wound recurrence.

Future Directions: Addressing the public health problem of chronic wounds will require a multifaceted approach that includes prevention, improved wound care management, and addressing the underlying risk factors.

Keywords: public health, wound care, community outreach

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Chandan K. Sen, PhD

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*Correspondence: McGowan Institute for Regenerative Medicine, University of Pittsburgh, 450 Technology Drive, Pittsburgh, PA 15261, USA (e-mail: c.k.sen@pitt.edu).

INTRODUCTION

Chronic wounds impact the health care system because of their increasing prevalence and cost, and affect policy and planning, monitoring trends in burden, and real-world cost-effectiveness of new therapies.[1] Järbrink and colleagues laid out a systematic process for collection of information to better understand the burden of such wounds.[1,2] The humanistic burden, presented

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as health-related quality of life (HRQoL), is a key component included in their systematic review of publications from a 15-year period. Low HRQoL in patients with chronic wounds together with the chronic wound itself contributed to the economic burden. Very few studies before this work and since address the HRQoL component as a key element in burden of chronic wounds in health care. In 2014, 14.5% of U.S. Medicare beneficiaries were impacted by chronic wounds. In 2019, that population increased to 16.3%.[3]

Based on the 2019 data, chronic nonhealing wounds impact 10.5 million (up 2.3 million from the 2014 update) of U.S. Medicare beneficiaries.[3] This included substantive increases in the prevalence of pressure ulcers (PUs), chronic ulcers, diabetic foot ulcers (DFUs), and DFUs and surgical infections in younger (<65 years) age groups. U.S. Medicare expenditures have shifted to the physician's office from the hospital-based outpatient department. Whether this is helping our hurting patient outcomes remains to be seen.[3] Suggested reasons accounting for the abovementioned shift in U.S. Medicare expenditure have been attributed mostly to the Centers for Medicare and Medicaid Services (CMS) and Medicare program/policy changes.

These include the following: (a) CMS-initiated prior authorization programs, (b) switch from ICD-9 to ICD-10 codes, (c) Medicare limiting hospital facility fees, and (d) use and reimbursement for cellular and tissue-based products (CTPs) for treatments. The authors caveat that these changes limit an accurate comparison of chronic wound-related expenditure between 2014 and 2019 because of the inability to clearly delineate cost contributions of chronic wounds.[3] There is a clear disconnect between increasing cases of chronic wounds and apparently decreasing costs that remains unresolved. The substantial net increase in chronic infected wounds is a cause for continued alarm and needs proportionate investment in research support, which is still not on par with the threat of these debilitating health issues.[4,5] Recent investment of the National Institutes of Health (NIH) in establishing a national diabetic foot consortium has established a first-of-its-kind research infrastructure for the rigorous conduct of clinical research.[6]

DFUs (30.5%), for example, have a comparable 5-year mortality rate to cancer (31%) that has remained unchanged since 2007, and yet, funding for studies related to these life-threatening complications remains significantly lower than that for cancer research.[7] The most common wounds are driven by metabolic disruptions (*e.g.*, diabetes), vascular deficits (*e.g.*, venous or arterial insufficiency), or mechanical impacts (*e.g.*, persistent/localized pressure), making chronic wound patients particularly vulnerable to coronavirus disease-19 (COVID-19) infection. The prepandemic wound care model typically required visits to an outpatient facility (*e.g.*, wound care center) that, in response to the pandemic, were misclassified as nonessential or limited access. The direct consequence of such changes in health care is the disruption of the continuity of wound care in several ways. However, such changes while negatively impacting wound outcomes have highlighted the need to develop telemedicine-based wound care.

In the long term, further development of telemedicine is likely to access a much larger patient population and improve compliance with treatment.[8] The current review updates the previously published human wounds burden review from 2021.[9]

CHRONIC WOUNDS

Wounds that have not progressed through the normal process of healing and are open for more than a month are classified as chronic wounds.[10] There are varying etiologies of chronic wounds, all of which burden the health care system. Patients suffering from diabetes and obesity are at high risk of developing chronic wounds. A vast majority of the people who have a prolonged open wound usually also have other major health conditions. The simultaneous presence of a combination of chronic diseases is called comorbidity. Chronic wounds are often complicated by comorbidities, making it difficult to track chronic wounds as a disease in itself.[10] As such, research funding directly addressing the study of chronic wounds is disproportionately low compared to the overall impact of chronic wounds as a health care problem.[11,12]

Chronic wounds are mostly seen in the elderly population.[13,14] However, recent studies show a clear rise in the incidence of chronic wounds in the younger (<65 years) population.[3] Taken together, the public health problem of chronic wound needs urgent attention. In the United States, 3% of the population older than 65 years have open wounds[14] By the year 2060, the U.S. government estimates that the elderly population will be more than 94.7 million,[15] suggesting that chronic wounds will continue to be an increasingly persistent problem in this population. Overall, in the United States $\sim$2% of the total population are estimated to be affected by chronic wounds.[1]

The Global Wound Care Market is projected to grow at a compound annual growth rate of 4.61% from 2023 to 2030, according to a new report pub-

lished by Verified Market Research®. The report reveals that the market was valued at USD 20.18 billion in 2022 and is expected to reach USD 30.52 billion by the end of the forecast period.[16] Effective from October 1, 2023, the U.S. CMS had proposed revision of its local coverage determination (LCD; L36377) for skin substitute grafts/CTPs for the treatment of DFUs and venous leg ulcers in the Medicare population. Reportedly, this LCD has been revised to be consistent with current evidence. Later (when this article was in press), in response to the comment phase, this proposal was put on hold. An LCD is a decision made by a Medicare Administrative Contractor (MAC) on whether a particular service or item is reasonable and necessary, and therefore covered by Medicare within the specific jurisdiction that the MAC oversees.

If acted upon, the proposed revision announced in early August 2023 would have reduced the cost of wound care but also directly affects patient care across 15 states, Washington DC, and Puerto Rico in the following ways: (a) noncovered CTPs will roughly double limiting product choices. Importantly, the underlying scientific rationale remains unclear; (b) for the use of approved CTPs, the number of product applications is limited to four over a 12-week treatment period compared with nine allowed before this revision. This does not account for patients with wounds that are larger or more severe than those that were included in clinical trials, nor does it account for patients who are improving but not healed after four applications; (c) tight implementation deadline of just 8 weeks after the final revision policy was released is likely to disrupt ongoing patient care.

For example, if a wound care provider is adhering to a product label and plan of care requiring more than four applications over a 12-week period of time, they must stop a patient's care midtreatment after the fourth application of the CTP, regardless of the wound healing progress on October 1, 2023. These concerns highlight the need for policies developed in conjunction with appropriate stakeholders.[17]

In its renewed focus on chronic wounds, the U.S. Food and Drug Administration (FDA) recognizes the need to effectively engage a wide range of stakeholders in bringing innovative wound care products to the U.S. market.[18] A review of wound care products by the FDA will reveal that although >70 products, including wound dressings, are cleared by the FDA for the management of wounds so that the natural healing process can take place, they are not intended for the treatment of nonhealing chronic wounds. For the treatment of chronic wounds, only becaplermin gel (biologic) and two moderately effective cell-based therapies (Dermagraft and Apligraf; Organogenesis, MA) have been FDA approved for the indication of treating (*i.e.*, healing) a nonhealing chronic wound. No other treatments have received FDA approval for the treatment of nonhealing chronic wounds. FDA recognizes the need to be proactive in making progress on chronic wound care.

From 2020 to 2021, the Division of Dermatology and Dentistry, through a Science Strategies program, launched by the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER), collaborated with experts from the Center for Biologics and Evaluation Research (CBER), Center for Devices and Radiological Health (CDRH), and OND's Division of Clinical Outcome Assessment to assess areas of unmet need and activity in the product development pipeline for wound healing. At the FDA, activities to advance innovative product development for nonhealing chronic wounds begin with identifying and building collaborations with key wound healing stakeholders. These include but are not limited to patient groups, academia, professional associations, industry, and reimbursement organizations. Internally, the FDA's Inter-Center Wound Healing Working Group (ICWHWG) reportedly convenes CDER, CDRH, and CBER staff involved in wound care product regulation on a quarterly basis.

Externally, FDA stakeholders have engaged with the Wound-care Experts/FDA-Clinical Endpoints Project through a Critical Path Innovation Meeting on clinically meaningful endpoints for wound healing clinical trials and have begun collaborating with the recently formed Wound Care Collaborative Community. The Medical Device Development Tools program and Drug Development Tool program allow the FDA to qualify clinical outcome assessments (including patient-reported outcomes), biomarker tests, and nonclinical assessment models for use in the development and review of medical devices, drugs, and biologics. Finally, the Critical Path Innovation Meeting, while not a substitute for formal pre-IND or other regulatory meetings, is a means by which CDER and investigators from industry, academia, scientific consortia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development.[18]

PRESSURE ULCERS

Pressure or pressure in combination with shear and/or friction promotes the development of localized ulcers called PUs. PU care is expensive and

costs more than $26.8 billion annually according to a study that used a Markov simulation to estimate cost for hospital-acquired staged PU.[19,20] The cost of individual patient care ranges from $20,900 to $151,700 per PU. Apart from hospital costs, additional charges for food, transportation, and maintenance are approximately $43,180 per year.[21] Globally, the number of incident and death cases, the PU burden measured in disability-adjusted life years, steadily increased from 1990 to 2019.

In addition, from the estimated annual percentage change of PU in incidence, disability-adjusted life years, and deaths, it is found that the burden of PU was considered to be increasing in most of the regions, and from the relationship of estimated annual percentage change with sociodemographic index levels, universal health coverage, and gross domestic product, the age-standardized rate of PU decreased as the economy developed and a country's health care system performance improved. These phenomena suggest that national health care systems need to increase funding for PU prevention and intervention strategies.[22]

The COVID-19 pandemic increased vulnerabilities to PU prompting the National Pressure Injury Advisory Panel (NPIAP) to release resources to assist with responses.[23] In keeping with this, the European Pressure Ulcer Advisory Panel (EPUAP) virtual meeting held in September 2020 highlighted the link between the pathophysiology of COVID-19 and development of Pus, including the impact of treatment modalities (proning, ventilator use) and the role of inflammation in this process.[24] The incidence of PU increases with age and is promoted by a lack of skin perfusion, moisture, and nutrition, all of which are factors in the COVID-19-driven increase in the incidence of PUs.[25–27] They are usually preventable, but they can be lethal if proper timely care is not received.[23,25,26] The global market for PU care products is expected to reach $11.1 billion by 2032.[28]

A recent Swedish study showed that the implementation of a national patient safety program has had an impact on the nationwide prevalence of PUs in hospital care and the occurrence of prevention strategies.[29]

DIABETES

The National Diabetes Statistics Report provides up-to-date information on the prevalence and incidence of diabetes and prediabetes, risk factors for complications, acute and long-term complications, deaths, and costs. At present, it is listed that in the United States, a total of 37.3 million people have diabetes (11.3% of the U.S. population). Of these, diagnosed are 28.7 million people, including 28.5 million adults. Undiagnosed are 8.5 million people (23.0% of adults are undiagnosed). In addition, 6 million people aged 18 years or older have prediabetes (38.0% of the adult U.S. population). According to the Diabetes Report Card of the Centers for Disease Control (CDC), the prevalence of prediabetes among U.S. adults remained steady from 2005–2008 to 2017–2020. However, notification of prediabetes status nearly tripled (from 6.5% to 17.4%).

American Indian or Alaska Native, non-Hispanic black, Hispanic, and non-Hispanic Asian people are more likely to be diagnosed with diabetes than non-Hispanic white people (14.5%, 12.1%, 11.8%, 9.5%, and 7.4%, respectively).[30]

Globally there is an interesting observation of an intertwining of preexisting silent pandemics (diabetes, obesity, etc.) with the raging COVID-19 pandemic, bringing to light the broad disparities within our society particularly related to human health. A Lancet study from the United Kingdom identified that 30% of COVID-19 deaths were in diabetics.[31] Type 1 diabetes (T1D) patients were at three times the risk for dying, and type 2 diabetes (T2D) patients were twice as likely to die compared with nondiabetics. A recent article in the *New England Journal of Medicine* highlighted a unique bidirectional relationship between diabetes and COVID-19.[32] On the one hand, there was a correlation between preexisting diabetes and severe COVID-19 symptoms in keeping with the CDC's shortlist of risks for severe disease.[33] On the other hand, some patients infected with SARS-CoV2 develop diabetes with severe sequelae, suggesting a complex pathophysiology of COVID-19 in the context of diabetes.

This was further supported in a meta-analysis from the Smidt Heart Institute (Cedars Sinai Medical Center, LA), which also showed that vaccination lowered the risk for diabetes.[34]

The tenth edition of the International Diabetes Federation (IDF) Diabetes Atlas reports that 10.5% (537 million) of the adult population (20–79 years) have diabetes, with almost half unaware that they are living with the condition.[35] In addition, 541 million adults have impaired glucose tolerance, which places them at high risk of T2D. By 2045, IDF projections show that one in eight adults, ~783 million, will be living with diabetes, an increase of 46%. More than three in four adults with diabetes live in low- and middle-income countries. Diabetes was responsible for 6.7 million deaths in 2021—one every 5 s. Diabetes caused at least USD 966 billion in health expenditure—a 316% increase over the last

15 years. Around 15–25% of patients with diabetes mellitus will develop a DFU during their lifetime.[36]

Overall, about 5% of patients with diabetes mellitus develop foot ulcers (FUs) and 1% end up with an amputation.

FOOT ULCERS

An open sore on the foot is called an FU. It may be shallow, confined only to the surface of the skin. Deep FUs can involve full thickness of the skin, muscle, tendons, and bones.[37–41] FUs are common in people with diabetes and individuals with compromised blood circulation.[40] Despite advanced health care and pharmacotherapy techniques that are widely available, prevalence of FUs has not changed in the past two decades.[42] A total of 14–24% suffer from amputation.[43] Neuroischemic ulcers were particularly associated with limb amputations.[44]

A systematic review and meta-analysis of the global epidemiology of FUs performed using PubMed, EMBASE, ISI Web of science, and Cochrane database searches remain the largest and most comprehensive analysis of its kind including more than 800,000 subjects from 33 countries. Annually, the incidence of FUs globally is between 9.1 and 26.1 million. A recent report increases that estimate to 40–60 million people[45] and attributes the disparity to factors, including approach to surveillance, definition of DFU, and wound care access. FU is more prevalent in North America (13%) compared with Europe (5.1%), with a global average of 6.4%. Recently, higher DFU rates (15%) are being reported from Africa and South America.[45] Males are generally more prone to FUs compared with females (3.5%). T2D patients were more likely to develop FUs (6.4% compared with 5.5% in T1D).[46,47]

In the United States, populations such as Latinos, African Americans, and Native Americans are more likely to develop FUs compared with other ethnicities.[36]

Allied market research reports in Bloomberg that the DFU treatment market is expected to reach $7.4 billion from the current $4.4 billion, globally, by 2032. The global DFU treatment market is experiencing growth due to several factors, including an increase in the prevalence of DFU cases, technological advancements in wound care management, and a rise in new product launches for DFU treatment. However, stringent regulations for the manufacturing of wound care dressings and devices are hampering the growth of the DFU treatment market. On the contrary, the growth opportunities in emerging countries are expected to offer remunerative opportunities for the expansion of the DFU treatment market in the upcoming years.[48]

VENOUS ULCERS

Venous ulcers (VUs), also known as venous stasis ulcers or varicose ulcers, are a type of chronic wound that typically occurs on the lower legs, particularly around the ankle and calf region.[49,50] These ulcers are a consequence of chronic venous insufficiency, a condition in which the veins in the legs have difficulty returning blood to the heart, leading to blood pooling in the lower extremities. VUs are the most common type of leg ulcers, accounting for the majority of chronic lower extremity wounds. They are one of the most common types of chronic wounds, affecting 3–5% of those 65 years and older.

In the United States, an estimated 500,000–600,000 people have venous leg ulcers creating a nearly $1 billion burden on health care.[51] Wound recurrence is a major problem in VU. Approximately 50–76% of VUs open again after healing, tending to increase with following years. Recurrent venous leg ulcers were identified primarily in women >60 years, obese, hypertensive, and diabetic. Obesity increases by 8.7 times the chances for patients with healed ulcers to have an ulcer recurrence.[52]

The nonoperative approach to patients with chronic venous insufficiency includes lifestyle modification, compression, and pharmacologic therapies.[53] In a recently reported meta-review, it was learnt that there is a statistically significant difference in healing rates when compression is used compared with no compression, with moderate-certainty evidence. Otherwise, there is no statistically different difference in healing rates using elastic compression versus inelastic compression, four-layer versus less than four-layer bandage systems, different four-layer bandage systems, or compression bandages versus compression stockings.[54] Endovenous ablation, adequate varicectomy, compression therapy, moist wound healing, and skin care are effective in treating and preventing recurrence of VU.[55] In a recently reported double-blind randomized controlled trial (RCT), it was observed that adding topical hyaluronic acid to a protocol of care that included standardized elastic compression improved healing outcomes of VLUs and mixed venous–arterial ulcers.[56,57]

Venous leg ulcers result in significant health care expenditure. The annual direct health care expenditure of $10.73 billion is associated with disease-related venous leg ulcer care in seven countries analyzed. The authors report this is an underestimation of the actual costs.[58]

OVERWEIGHT AND OBESITY

The World Health Organization defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health. A body mass index over 25 is considered overweight, and over 30 is obese. Worldwide obesity has nearly tripled since 1975. The issue has grown to epidemic proportions, with more than 4 million people dying each year as a result of being overweight or obese in 2017 according to the global burden of disease. More people are obese than underweight in every region except sub-Saharan Africa and Asia. Once considered a problem only in high-income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings. The vast majority of overweight or obese children live in developing countries, where the rate of increase has been more than 30% higher than that of developed countries.[59]

High-risk factors for the obese patients include infection, seromas, anastomotic leaks, and incision dehiscence. Tissue perfusion is of great concern and is a key factor in most assessments. Obesity adds another dimension to the needs of the patient and presents challenges to nurses.[60] Skin wound problems that are common, yet more difficult to manage for obese patients, include PUs, tracheostomy care (potentially resulting from ventilatory insufficiency), candidiasis, tape-related skin tears, incontinence, and lymphedema.[61] The increase in visceral adipose tissue observed in obese subjects, and the related perturbations in endocrine and immunological functions, partially explains most associated comorbidities.

An interesting emerging twist is that white adipose tissue is recognized as being implicated in many different physiological processes beyond fat storage, including wound healing. Adipose tissue represents a strategic source for mesenchymal stromal cells, known for their beneficial role in managing both inflammation and tissue repair. How the power of adipose-derived stem cells may be harnessed to improve wound healing in obese subjects remains an open challenge.[62]

SOCIAL DETERMINANTS IN CHRONIC WOUND HEALING

The strongest predictor of health outcomes in the United States is not medical care but rather the broader social context in which people live and work. These social determinants of health (SDOH), such as economic conditions, housing, nutrition, the environment, transportation, and education, are estimated to account for half of the county-level variation in health outcomes and are a major driver of health disparities. Advancing racial equity and supporting underserved communities are a central priority of the Biden-Harris administration. The HHS has developed a three-pronged strategy to address social determinants: (a) better data, (b) improving health and social services connections, and (c) whole-of-government collaborations.[63]

The conditions in which people are born, grow, live, work, and age have a recognized impact on their health.[64] Characteristics such as socioeconomic status (SES) (*e.g.*, income, education, employment status), physical environment, psychosocial factors (stress, depression, etc.), and social support networks (collectively packaged under the umbrella term SDOH) interact with the biology of the individual, determining health outcomes such as disease development, wound healing, and life expectancy.[9] SES restricts the freedom of choice. For instance, a person without a job or steady income or low education (high school degree or lower) is less likely to have access to health insurance, adequate housing, gym memberships (or other physical activity outlets), and healthy food options.

Food insecurity, defined as the *lack of consistent access to enough food to sustain a healthy lifestyle*, is a key SDOH factor that affects 11% of U.S. households and correlates with chronic diseases such as obesity, diabetes, and by association wound healing.[65,66] Several lines of evidence have addressed the impact of supporting wound healing with proper nutritional support. Recently, the impact of nutrition in overall health was recognized by the NIH in their effort to promote the concept of precision nutrition. This effort, detailed in the 2020–2030 Strategic Plan for NIH Nutrition Research, aims to catalyze nutrition research cross-cutting research areas, including minority health, women's health, rigor, and reproducibility, data science, systems science, and artificial intelligence.[67]

The social impact of diabetic foot is the most important factor for management and prevention, in terms of aggravation and more, of the diabetic foot.[68] A patient's SDOH history has a significant and considerably stronger correlation with pressure injury progression than predictors that are traditionally studied such as sex, race, or body mass index.[69] What is becoming clearer as we delve deeper into a more holistic approach to improving health is that these factors influence functionality at the level of the gene (social genomics) resulting in changes that can be global (epigenetic) or specific to cellular subsets and in some cases, heritable. From the perspective of wound healing, several

independent studies have shown how the SES, environment, and psychosocial stress impair wound healing by increasing pain response, decreasing inflammatory responses, increasing risk for infection, and affecting hormonal responses among others.[9,70]

BIOFILM INFECTION AND THE "INVISIBLE WOUND"

Bacteria rapidly colonize in open skin wounds after burn injury[71–74] or surgical incisions.[37,75–78] Microorganisms colonizing these wounds are typically the patient's normal flora or may be transferred via contact with contaminated external contact such as water, fomites, or the soiled hands of health care workers.[76,77] Gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus* spp, gram-negative organisms such as *Pseudomonas aeruginosa* and *Acinetobacter* spp, and fungi such as *Candida* spp and *Aspergillus* spp, are all among a list of common pathogens that can cause acute wound infections and several of them are resistant to antibiotics.[79–82] The 2019 health care-associated infections data (CDC-National Healthcare Safety Network)[75] indicated a 7% decrease in the standardized infection ratio. Surgical-site infections are costly and account for an annual cost of $3.3 billion and associated with 1 million additional inpatient days annually.

From the military perspective, a high priority of the Military Health System research enterprise is the prevention and management of military-relevant wound infections. Some key focus areas reported include the following: (a) focus on invasive fungal infections and morbidity in blast injuries, (b) skin and soft-tissue infections (SSTI) particularly *S. aureus* and completion of a phase 2 trial of a vaccine candidate, (c) host microbiome studies in SSTI, and (d) multidrug resistance in wound pathogens.[83]

An important factor in the failure of a sore to heal is the presence of polymicrobial consortia, living cooperatively in highly organized polymicrobial biofilm aggregates. The biofilm shields the pathogenic microbes from antimicrobial therapy and the patient's immune response. A recent review analyzing the hotspots of wound research over the last decade highlighted biofilm infections as one of three main hotspots.[84] A key focus in biofilm research is the development of suitable prevention and treatment options that would clear infection. Some newer forays into this avenue include nanotheranostics (using nanoparticles and fibers as a combination diagnostic and therapeutic tool against drug-resistant and biofilm-forming bacteria),[85] bacteriophages,[86–88] and electroceuticals[89–91] as some nonconventional approaches to targeting wound biofilm infections. Biofilm infections have been linked to wound chronicity.[73,74,92–97]

Furthermore, these infections cause defective wound closure, where the wound-site appears closed, but the repaired skin lacks barrier function, by triggering microRNAs that destabilize junctional proteins that are necessary for establishment of the barrier following closure.[73,74,91,94] Therefore, the covering of a wound and a lack of discharge may need to include the criterion that the repaired skin must have physiological functionality to be called "closed." Thus, covering of the wound, a lack of discharge, and restoration of barrier function should be considered as criteria for wound closure in patients. These studies have led to the notion of the "invisible wound." "Invisible wounds" are those that appear closed, in accordance with the current FDA definition of wound closure, but remain functionally open because of deficiencies in the restoration of the barrier function of the skin.[98–100]

Based on the current state of evidence, it is likely that such clinically closed wounds suffering from deficient barrier function are likely to recur as reported by the NIDDK Diabetic Foot Consortium at the 2023 national meeting of the American Diabetes Association. Thus, the "invisible wound" represents a paradigm shift in clinical wound care.

SCAR AND FIBROSIS

Scars and the associated functional as well as aesthetic concerns represent a huge burden on health care.[101] Burn wounds usually leave hypertrophic scars after they have healed. In particular, the face is highly susceptible to excessive scarring causing functional deficits and psychosocial burdens.[102] Burn-related contractures can significantly reduce quality of life and create a high economic burden for the individual and health system. The scale of the problem in low- and middle-income countries is large. Our current understanding of the underlying scientific mechanisms is weak warranting additional attention.[103]

Keloid disorder, a group of fibroproliferative skin disorders, clinically comprised keloids, hypertrophic scars, keloidalis nuchae, and acne keloidalis. The prototype of these disorders is keloids, which manifest as cutaneous lesions with excessive deposition of collagen following an initiating trauma of varying degrees. The principal cell type responsible for collagen accumulation is the myofibroblast, and its gene expression is modulated by a network of regulatory factors, including cytokines, growth factors, and noncoding RNA

species. In addition, keloids harbor a number of inflammatory cells, including macrophages and mast cells that interact with fibroblastic cells by direct contact or by paracrine actions.[104]

The global scar treatment market was valued at $13 billion in 2021 and is projected to reach $32 billion by 2031 according to Allied Market Research. Depending on the product, the market is classified into topical, laser-based treatment, and others. The topical segment dominated the market in 2021, and is expected to dominate during the forecast period, owing to easy availability of topical products and rise in consciousness regarding aesthetic appearance. On the basis of scar type, the market is divided into atrophic scar, hypertrophic and keloid scar, contractures, and stretch marks. The atrophic scar segment dominated the scar treatment market share in 2021, and is expected to dominate during the forecast period, owing to the increase in prevalence of acne and chicken pox.

A new study reviewed promising new strategies such as antiangiogenesis therapy, fat grafting, stem cell therapy, and molecular targets such as cytokines to prevent scarring following wounding.[105] Recent works have highlighted the important role of mechanical forces in the process of skin tissue repair and scar formation, in addition to related cell signaling. Skin biomechanics and mechanobiology play key roles in scar outcomes. Thus, efforts to develop novel mechanomodulatory wound dressings with the capacity to offload mechanical tension in the wound environment are of high significance.[106] Emerging studies show encouraging results with exosomal therapies.[107–110]

PHYSICIAN EDUCATION

With the development of wound care practices, there is an associated need for rigorous training, research, evidence development, and advocacy to improve patient wound outcomes. Evidence-based practice is the conscientious, explicit, judicious, and reasonable use of current best evidence in making decisions about the care of individual patients. Evidence-based practice integrates clinical experience and patient values with the best available research information. It is a movement that aims to increase the use of high-quality research in clinical decision-making. Evidence-based practice requires new skills of the clinician, including efficient literature-searching, and the application of formal rules of evidence in critically evaluating the research literature. The practice of evidence-based medicine is a process of lifelong, self-directed, problem-based learning in which caring for one's own patients creates the need for clinically important information about diagnosis, prognosis, therapy, and other clinical and health care issues.

Staying updated with the latest research and evidence-based guidelines is essential. Physicians should be aware of the most effective wound care treatments, dressings, and interventions to optimize patient outcomes.

Currently formal education for providers is limited to a few courses during pre- or postgraduate medical education. Although some training is provided if a physician chooses to work at a wound care center, it is typically not as rigorous as a typical residency or fellowship-based medical education. The American College of Wound Healing and Tissue Repair (ACWHTR) is a primary advocate for specialization in wound care with a patient-centered outcome approach and is working to create a board-certified specialty in wound management.[111] Comprehensive education is critical for the development of wound care management as a discipline in mainstream medicine particularly given the increasing geriatric population.[112] The American Board of Wound Management provides a Certified Wound Specialist (CWS®) board certification that formally recognizes masters-level knowledge and specialty practice in wound management.[113]

In Europe, wound care education is similarly lacking, but the European Wound Management Association is working toward establishing a core standard for acceptable wound management education.[114]

Training physicians to critically study research literature is essential to ensure evidence-based practice and the delivery of high-quality patient care. This can be achieved by providing formal training on research literacy and critical appraisal. Continuing medical education (CME) activities play a key role in this process. In addition, utilizing ratified online resources and platforms that offer training modules and interactive exercises on critical appraisal is recommended. Wound care providers must be trained to differentiate between various types of research studies, such as RCTs, observational studies, case–control studies, cohort studies, and systematic reviews/meta-analyses.

The strengths and limitations of each study design must be considered during data interpretation. Understanding the PICO(T) framework, which stands for patient/population, intervention, comparison, outcome, and time frame, is essential[115] This framework helps physicians formulate focused research questions and evaluate studies effectively. Physicians must be familiar with critical appraisal tools and checklists specific to differ-

ent study designs, such as the CONSORT statement for RCTs or the STROBE checklist for observational studies. Finally, in an environment dominated by aggressive marketing by vendors, physicians must recognize and assess potential sources of bias and confounding in research studies. They must be enabled to discuss strategies to minimize bias, such as randomization and blinding in RCTs. This will require adequate statistical literacy and critical reading practice. CME activities must foster group discussions where physicians can share their insights and learn from each other's perspectives. Pairing less experienced physicians with research mentors is effective.

NURSING EDUCATION, PHYSICAL THERAPY, AND OSTOMY

Traditionally, wound healing has been under the aegis of basic nursing practices,[116] such as wound covering management, therapeutic nutrition, mobility, and psychosocial support. Nurses play a crucial role in handling and managing acute wounds and chronic wounds such as PUs, bedsores, FUs and VUs. The Wound Ostomy and Continence Nurses Society is the oldest wound care society that has more than 6,000 board-certified nurses worldwide.[116] In 2010, the Organization of Wound Care Nurses (OWCN) was established.[117] OWCN offers the foundation and training for all the licensed nurses who are practicing in different care settings free of cost. Wound care and ostomy education programs for nurses are increasingly becoming available in an effort to improve nursing service quality.[51]

Appropriate professional use of multiple wound care disciplines may markedly impact wound care.[118–120] Physical therapy represents one such major discipline. Trained physical therapists may use numerous treatment regimens such as wound debridement, modalities, edema management, positioning, orthotic use, and mobility improvement. Occupational therapists may provide edema management, wound debridement, positioning, toileting programs, self-feeding, and wheelchair management as relevant to the need of the patient. Addressing supportive interventions such as physical and occupational therapy and nutrition management is likely to promote the rate of wound healing, thereby lowering the overall costs of wound care. After all, the longer a patient's healing time, the higher the cost to the facility.

Wound, ostomy, and continence nurses, in addition to being educated and trained to provide acute and rehabilitative care, represent an important component of the wound care ecosystem.[121–123] Ostomies, stomas, acute and chronic wounds, and urinary and fecal incontinence often present severe physical challenges for wound patients. These lead to emotional and social issues that may be addressed by properly trained and educated allied medical professionals. Limitations in the well-structured wound care education of providers may be viewed as a significant barrier to uniform evidence-based wound care throughout the country.

An important current gap is well-structured research training to critically evaluate research data presented by vendors during the marketing of wound care products. In addition to preparing well to practice evidence-based wound care as discussed above, the following approach may be followed. While it is necessary to be open to all research data available, wound care professionals must recognize that vendors have a vested interest in promoting their products. Their primary goal is sales, and so, it is important to maintain a healthy skepticism. Where applicable, it is advisable to seek help from those who have undergone research training to critically evaluate the design of the research study provided by the vendor. Look for information regarding the study's methodology, including whether it was an independent and registered study or conducted by the vendor themselves. Assess the study's duration, sample size, and inclusion/exclusion criteria.

A well-designed study should be robust and free from bias. Independent research conducted by reputable unbiased institutions is generally more reliable. Determine whether the research has undergone peer review and has been published in reputable, peer-reviewed journals. During data analysis, look for both quantitative and qualitative data, including statistical significance and clinical significance. Assess whether the study's outcomes are relevant to your patient population and clinical practice. Determine if the study included a control group and whether it was appropriately matched to the treatment group. The control group is essential for assessing the product's efficacy. Verify that data analysis was conducted independently and without bias. If the vendor performed the analysis, it may be prudent to seek additional independent analyses. Investigate whether any conflicts of interest are appropriately declared. Transparency is crucial for trustworthiness. Seek independent reviews and meta-analyses of the product if available.

These reviews can provide a balanced assessment of the product's effectiveness. Discuss the vendor's research data with colleagues specializing in research. They may offer valuable insights and opinions.

PATIENT EDUCATION

Effective patient education starts with clear communication. Be patient and use clear, jargon-free language to explain the wound, its cause, and the treatment plan. Avoid medical terminology that might confuse the patient. Be culturally sensitive and respectful of patients' beliefs and practices. Tailor education to align with their cultural preferences and traditions. Using visual aids and demonstrations can be effective. Encourage patients to ask questions and practice under your supervision. Provide written instructions or handouts summarizing the wound care regimen, including dressing changes, medication instructions, and signs of infection. This allows patients to reference the information at home. Reiterate key points during each visit to reinforce patient understanding. Encourage patients to ask questions and voice any concerns. Tailor the education to the individual patient's needs and abilities. Consider their literacy level, language proficiency, and any cognitive or sensory impairments.

As appropriate, educate patients about managing wound-related pain, including the appropriate use of pain medications and nonpharmacological techniques such as positioning or relaxation exercises. Explain the importance of a balanced diet rich in protein, vitamins, and minerals for wound healing. Offer dietary recommendations and referral to a dietitian if necessary. Discuss the role of mobility and regular physical activity in promoting circulation and healing. Provide guidance on safe levels of activity and any restrictions. Emphasize the importance of infection prevention. Teach patients how to recognize signs of infection (*e.g.*, redness, swelling, pus) and when to seek medical attention. Teach patients how to assess their wound's status regularly, including checking for signs of complications, such as changes in drainage or odor. Encourage seeking help from family and friends to do so. Explain the purpose of medications prescribed for wound care, including antibiotics or pain relievers.

Provide clear dosing instructions and discuss potential side effects. Stress the importance of attending scheduled follow-up appointments and provide patients with reminders. These appointments allow for wound assessment, progress evaluation, and necessary adjustments to the care plan. Address any emotional or psychological challenges patients may face, such as anxiety or depression, related to their wound. Offer resources or referrals for counseling or support groups if needed. Encourage family members or caregivers to be actively involved in the patient's wound care education. Ensure they understand their role and responsibilities. Provide patients with contact information for health care professionals or wound care specialists, in case they have questions or concerns between appointments. Look proactively for telehealth and digital tools when appropriate to conduct remote wound assessments, answer questions, and provide ongoing education.

Continually assess the patient's comprehension and adherence to the wound care plan. Make adjustments as necessary and address any barriers to compliance. Patient education is an ongoing process. Patients may need reinforcement and additional guidance as they progress through their wound healing journey.[124–126]

CLOSING REMARKS

Addressing the growing public health burden of chronic wound care requires collaboration and coordination among multiple stakeholders, including health care providers, researchers, policymakers, and patients. It is prudent to collaborate with policymakers and advocacy groups to raise awareness about the importance of chronic wound care. We must also collaborate on the development of evidence-based clinical guidelines for the prevention and management of chronic wounds. These guidelines should be widely disseminated and updated regularly. Such efforts must be free of bias. It is advisable to advocate for policies that support wound care access, reimbursement, and quality improvement. We must foster research collaborations to advance wound care science, technology, and treatment modalities. Such efforts depend on funding initiatives and grants for wound care research, especially patient-based, encouraging innovation in wound care products and practices.

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ABOUT THE AUTHOR

Chandan K. Sen, PhD, is Director, McGowan Institute for Regenerative Medicine, and Chief Scientific Officer of the University of Pittsburgh Medical Central wound care services.

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Abbreviations and Acronyms

ACWHTR = American College of Wound Healing and Tissue Repair
CBER = Center for Biologics and Evaluation Research
CDC = Centers for Disease Control
CDER = Center for Drug Evaluation and Research
CDRH = Center for Devices and Radiological Health
CME = continuing medical education
CMS = Centers for Medicare and Medicaid Services
COVID-19 = coronavirus disease-19
CTP = cellular and/or tissue-based product
CWS = Certified Wound Specialist
DFU = diabetic foot ulcer
EPUAP = European Pressure Ulcer Advisory Panel
FDA = Food and Drug Administration
FU = foot ulcer
HRQoL = health-related quality of life
IDF = International Diabetes Federation
LCD = local coverage determination
MAC = Medicare Administrative Contractor
NIH = National Institutes of Health
NPIAP = National Pressure Injury Advisory Panel
OND = Office of New Drugs
OWCN = Organization of Wound Care Nurses
PICO(T) = patient/population, intervention, comparison, outcome, and time frame
PU = pressure ulcer
RCT = randomized controlled trial
SARS-CoV2 = severe acute respiratory syndrome coronavirus-2
SDOH = social determinants of health
SES = socioeconomic status
SSTI = skin and soft-tissue infections
T1D = type 1 diabetes
T2D = type 2 diabetes
VU = venous ulcer