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PERSPECTIVES

Opportunities and Challenges of the Management of Chronic Wounds: A Multidisciplinary Viewpoint

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Abstract: Chronic nonhealing wounds are debilitating with high morbidity and mortality in a highly vulnerable patient population. Despite extensive efforts to develop therapeutic strategies for effective treatment of chronic wounds, so far, limited clinical success has been achieved. The reasons for the limited clinical success include (i) the absence of validated centers of excellence, education, and standards in wound care management; (ii) limited numbers of funding agencies with the central focus on chronic wounds; (iii) lack of robust evidence for wound healing approaches in the current literature together with the lack of methodologic consistency in clinical trials; (iv) complexity of wound environment due to patients' comorbidity; (v) lack of transparency in politics including complexity of the reimbursement procedures; (vi) growing complexity with the increasing percentage of aging populations; and (vii) crowded market with overwhelming "me too" products with limited clinical efficacies. This perspective is intended to discuss these challenges in the field of wound care and introduce multidisciplinary opportunities for substantial improvement of wound healing management. To address the current challenges in the field, we suggest that stakeholders in wound care adopt a proactive integrated response that utilizes a broad network and takes full advantage of emerging technologies.

Keywords: chronic nonhealing wounds, infection, comorbidity, obesity, stakeholders

Introduction

Chronic wounds are generally referred to as wounds that fail to heal through the body's natural healing process (roughly less than 30% wound closure in four weeks after treatment).[1–4] Several critical parameters, including anatomical location of the wounds and complications caused by concurrent diseases that the patients may have, affects the complexity of chronic wounds.[5] Some of the causalities in creation of chronic wounds are, but not limited to: poor circulation, unusual local pressure to the wound site, existence of neuropathy which causes loss of protective sensation, risk of infection, unresolved inflammation, and other severe impaired healing processes such as lack of angiogenesis, epithelial migration, and cell proliferation.[5–10] The impact of these problems on chronic wounds is heightened by having complex diseases out of control, for example, by glucose accumulation in the wound site.[11]

All of these complex issues limit the success in wound management which, in turn, negatively affects the quality of life of the patients and induces huge costs to the global health-care systems.[12–15] The complexity of the wound care ecosystem may worsen in the near future due to (i) increasing costs of wound care; (ii) an aging population; (iii) increasing prevalence of comorbidities (eg, obesity); and (iv)

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bacterial resistance to antimicrobials.[5] Predictive approaches demonstrate that the prevalence of complex diseases (eg, diabetes, heart disease, and neurodegenerative disorders) will significantly increase over the next few decades. In addition, modern medicine has extended our life span which means that age, as another complex parameter, will play a critical role in worsening the complexity of chronic wounds. Therefore, it is crucial that we act now in a proactive and innovative approach to revolutionize the way wounds are treated. If we do not, we risk future generations judging us on how much we knew and what we could have done.

To revolutionize the current wound management practices, we first need to thoroughly identify and understand the problems from the perspectives of all key stakeholders including patients and caregivers, clinicians (with all related specialties), nurses, engineers (with all related expertise), decision-makers (eg, in hospitals, biotechnology companies, and insurance companies), influencers, and saboteurs. Once the problems are well established, we will be able to propose strategies to overcome the issues.

In this perspective, we identify and introduce the current issues/barriers with the chronic wound ecosystem (ie, interaction of all involved stakeholders and their entire efficiency) that are limiting clinical success. To do this, in addition to our own knowledge and experiences, we gathered viewpoints of experts from various stakeholders stated above. We also propose strategies for ways to use this knowledge as a unique opportunity to materially improve the quality and success rate of wound healing management.

The Core Problem

Almost all the current issues regarding chronic wounds stem from a core strategic problem: wounds are not considered as an actual disease. This means that patients with chronic wounds are being treated by a wide variety of clinicians and nurses, based on their experience and views on the treatment strategies, which can differ significantly from one setting and region to another.[16]

The fact that wounds are not viewed as a disease entity sets the stage for the major issues we face in the current wound care system including, but not limited to: (i) lack of robustness and reproducibility in both clinical and research outcomes which causes misinterpretation of the wound healing data and limits meta-analysis; (ii) a poor understanding of the wound environment and the corresponding biomolecular signals (eg, through exudates); (iii) reliance on outdated systems/tools to categorize/measure various types of wounds; (iv) limited integrated functioning between stakeholders; and (v) the crowded, inefficient market with an overwhelming number of similar products. Therefore, one of the central questions that needs to be properly answered is that of "who should treat chronic wounds"? The first step for addressing this question and the associated issues is to target the core problem by recognizing "chronic wound" as a disease. This will require involvement of key decision-makers and legislators to create a clear, comprehensive, and thoughtful strategic plan for the wound care ecosystem (similar to what has been done for other life-threatening conditions including cancer, cardiovascular and neurodegenerative diseases).

The Absence of a Center of Excellence in Chronic Wounds

Another central issue of the wound care ecosystem is the absence of a center of excellence. It is noteworthy that chronic wounds are more life-threatening than generally realized. For example, the five-year mortality rate for patients dealing with a wide range of chronic wounds (eg, 70% for diabetic chronic ulcers)[5,17] is significantly higher than for patients with colorectal, breast, and prostate cancers.[9,18,19] However, unlike cancers (eg, National Cancer Institute) and other life-threatening conditions (eg, cardiovascular diseases; Cardiovascular Center of Excellence launched by American Heart Association), the wound care community is highly fragmented and lacks a core center of excellence to promote and orchestrate a multidisciplinary networking approach that includes surgeons, internal medicine, infectious disease, specialty nursing, engineers, basic scientists, social workers, and health economists. Similar to cancer and cardiac centers, such an entity in wound care is essential, mainly due to the complexity of the patients.

A center of excellence in wound care may also help our community to address the main question of "Who should treat chronic wounds?" In other words, such a center may provide accreditation at various levels (to define their roles and level of expertise) to the nurses and clinicians involved in wound healing management. A unified accreditation would signify to the public that their clinicians are well trained in wound care and following recognized guidelines established by a central governing body. A

good example for such an approach is the national bariatric surgery accreditation provided by The American College of Surgeons (ACS) and the American Society for Metabolic and Bariatric Surgery (ASMBS).

Establishment of a center of excellence in wound care would be an essential building block for modification of the current wound care ecosystem. For example, the field of chronic wounds suffers from the absence of standard protocols in reporting the wound healing success. Currently, the definition and measurement of the healing progress is conducted and reported by internal protocols/criteria of wound healing centers. Measurement is inaccurate and variable. The establishment of a center of excellence in chronic wounds can address, at least in large part, the lack of systematic care protocols in the field of wound care and provide, (i) standard protocols on identification and treatment of a wide range of chronic wounds, and (ii) well-defined criteria for measuring and reporting the success rate of the centers. The critical role of a center of excellence is to enable medical providers to benefit from provision of well-organized protocols and coordination that has been validated in many life-threatening diseases including cancers and cardiovascular disease.

The other importance of the center of excellence in wound care could be development of global standards for clinical trials. Despite guidance from the FDA, a number of deficiencies in wound care trials have been noted, particularly inadequate sample size and the tendency towards bias.[20–22] In addition to the CONSORT statement that applies to all RCTs, Bolton; and Brolmann et al published recommendations for study design and reporting standards specific to RCTs in wound care.[21,23,24] However, without having a recognized and agreed upon gold standard for chronic wound clinical trials, we cannot compare the outcomes of new treatments with the currently available approaches/techniques in the already saturated market. Standardization will include patient selection, control arm treatment and inclusion/exclusion criteria. The current methodological approach in population selection for RCTs in wound care is not standardized.[25–27] The population in the trial should exactly mirror the complexity of the patients with chronic wounds (eg, out of control diabetes and poor circulation). The Center of Excellence will also set the gold standard for the control population with consistent inclusion and exclusion criteria for clinical trials as well as agreed upon standards for control treatment. Current wound care clinical trial control treatments range from "local standard of care", saline moistened gauze, absorbent dressings, and topical, often at the discretion of the involved clinicians. Establishing these gold standards for wound research will make outcomes more robust and allow comparison between trials, which will subsequently allow for meta-analysis.

Another critical role of the center of excellence would be modification of the inaccurate and variable measurements of wound size and the corresponding closure rate. It is of critical importance to use a simple but reproducible technique for wound measurements that can be performed at the bedside. The conventional and highly subjective method of measuring wounds ie, L × W × D: measure the longest length (L), greatest width (W), and greatest depth (D) of the wound is not accurate and creates substantial errors.[28] Therefore, the center of excellence can facilitate development of new gold standard techniques for robust and reliable measurement of wound size. We propose that using digital technology, which has been shown to produce fast, accurate, and reliable/reproducible wound measurements, will become the new standard.[29–31] The cloud data storage of the digital imaging system allows for enhancements based on modeling and enables linking of outcomes to the patients' Electronic Health Records (EHRs). It is noteworthy that there are some shortcomings with the current digital technologies for wound measurements (eg, measuring, undermining, or tunneling) which need to be developed and will require collaboration between clinicians and digital technology experts.

Additional areas that will improve with standard protocols and guidelines developed by a center of excellence include standardization of debridement techniques with proof of efficacy and guidance for use of systemic antibiotics. Currently debridement of wounds is quite variable depending upon the wound type, the clinical site, and the capability of the clinician. The overuse of systemic antibiotics causes several issues, including bacterial resistance, adding complexity to future therapeutic approaches. Even currently, surgical site infections are a huge health-care issue with mortality rate of 75%.[32–34] Finally, the center of excellence can facilitate clinicians' decision-making about the need for amputation by providing data for risk stratification and quality of life outcomes. Interestingly, some reports revealed that the lack of access to specialized wound care centers increases the rate of amputation.[35–37]

Education

Traditionally, wound care has been led by nursing. Yet formal wound care training in the basic nursing curriculum

is lacking.[38] Tissue viability nurses in the UK receive specialized training that includes multifaceted roles and skills (ie, both communication and technical skills) to manage chronic wounds, while in the US the scope of practice for nurses, which varies by state and by hospital policy, may limit highly skilled and knowledgeable nurses with wound care certification from performing even the most basic procedures.[32,39] Lack of basic wound care training is not limited to nursing. A retrospective analysis of 50 US medical schools determined that the medical school curriculum devoted fewer than 10 hours of education to wound-care related topics.[40] The US is not alone, as these findings were mirrored in studies conducted in Germany and the UK.[41] While it is true that wound care may be taught as a formal elective or as part of a surgical rotation, this is highly dependent upon the local expertise and there are no minimum or standard requirements in the medical school curriculum.[42] Wound care education in the basic medical school and nursing curriculum should be revisited to reflect the multi-billion dollar expense of chronic wounds to the global health-care systems.

However, the generalist cannot be expected to keep up with the rapidly evolving science in the wound-healing field. Programs that provide specialty training in wound care are expanding rapidly. The Wound Ostomy and Continence Nursing Board certification is offered at both a basic and advanced practice level. This is a highly respected and rigorous program with a stringent recertification process, yet, in the current state, only wound certified advance practice nurses (WOC-APRN) are afforded autonomy that includes authority to prescribe and bill independently for their services.[32] Billing and reimbursement is critical because that allows hospitals and outpatient clinics to justify hiring and recoup costs. Within the physician community, there are now several fellowship programs in the country, but none of these are formally accredited by the American Board of Medical Specialties. Both the American Board of Wound Medicine and Surgery and the American College of Wound Healing and Tissue Repair are leading efforts to standardize the curriculum and achieve specialty board certification for physicians which will go a long way towards legitimizing wound care.[31,43] Meanwhile, there is a plethora of wound care certification courses, both online and in person. These do not provide a true board certification and there is no agreement regarding what constitutes the appropriate background training to become wound care certified. These certification courses are poorly differentiated from the rigorous and legitimate training that is required to treat complex patients with difficult wound healing problems.[44,45]

Another major issue in chronic wound care is the knowledge gap among patients and the general population and the lack of educational materials designed for patients. Recent analysis of Medicare expenses revealed that outpatient costs ($9.9–$35.8 billion) are much more than inpatient costs ($5.0–$24.3 billion).[46] This means that an effective campaign to educate patients and their caregivers is of crucial importance to reduce the outpatient costs.[5,47] Development of strategies, including electronic modalities to educate patients, family members, caregivers, and home health nurses, can substantially decrease the overall cost of outpatient wound care management while increasing the success rate of treatment. One example is the American College of Surgeons' Wound Management Home Skills Program (https://www.facs.org/education/patient-education/skills-programs/wound-care). Similar programs are needed that can reach all sectors of the population.

FDA Standards

Another issue, that makes the wound healing market in the US crowded with too many overlapping and redundant products, is the 510(k)-approval process. The majority of treatments for wounds are devices and, therefore, achieve approval through 510(k) clearance by the FDA. Unlike the Premarket Approval (PMA) mechanism, which requires comprehensive clinical trials—if a new device can be demonstrated to have substantial equivalence to a previously marketed device or predicate, it can be marketed without undergoing further clinical trials. This pathway is much more rapid and less expensive than the PMA mechanism.[48,49] The postmarket trials of the approved products tend to be company sponsored and are therefore biased, small and do not compare similar products head to head. Because the products are already on the market, the sponsors have little motivation to cover the huge costs of large, unbiased randomized trials. One of the issues with the 510(k)-approval mechanism is that many companies may emphasize only the aspect that shows substantial equivalence and not disclose the novel aspects of their products that makes them more qualified for the PMA-approval lane. FDA can play a critical role in minimizing the complexity and ambiguity around PMA and 510(k) approval procedures and limit the entrance of additional "me too" products into the already saturated chronic wound market.

Funding Agencies

Research funding for chronic wound studies is surprisingly limited, compared to the huge impact of chronic wounds on global health care.[9,50,51] Part of the reason could stem from the fact that the chronic wound is viewed as a symptom rather than a disease entity, therefore a large portion of funding goes to research of the comorbid diseases associated with chronic wounds. To improve the field of chronic wounds, the funding agencies should allocate specific and meaningful funding strategies and consortiums for chronic wounds. Recent efforts by the National Institutes of Health in establishment of the national Diabetic Foot Consortium (NIDDK; FOA: DK17-014; NOT-DK-18-017)[52] is a good example for the proposed strategy.

Research

The lack of funding and other resources in the wound healing field created a breeding ground for low quality research. A recent comprehensive study on the published papers in the field of chronic wounds revealed a low proportion of the publications in the field with high quality, robust information, and suitable statistical significance that makes them useful and reproducible for the scientific community.[53] Even a large portion of the well-conducted and robust research papers contain conclusions that are susceptible to bias and/or misinterpretation of data. The other major problem with current wound research is the limited sample size (both animals and human) and lack of suitable animal models to recapitulate chronic wounds.

Another major problem in the current research approach is the lack of interdisciplinary teams of experts and a knowledge gap between the critical disciplines (eg, lack of multidisciplinary teams composed of vascular surgeons, bioengineers, podiatrists, dermatologists, wound healing clinicians and researchers, and infectious disease experts). To address this major issue and achieve the 360 degree view of wound healing complexity, any design team should include the required expertise to overcome the major problems of chronic wounds including improvement of circulation, debridement, controlling infection, depressurizing the wound site, fixing impaired healing mechanisms such as angiogenesis, cell migration, and proliferation (comprehensive approach to the patient), identifying infection and use of structured, integrated reporting mechanisms. Another major stakeholder that needs to be included in the design team is the patient. Until very recently, patient-centered outcomes have been overlooked and the patient perspective is rarely included in developing new products. The FDA has encouraged patient engagement in drug development for the past 15 years. The agency has now developed a roadmap to include patient-focused outcome measurement in clinical trials that includes both drug and devices.[54] Embracing patient engagement at all levels of wound healing drug and device development will ensure that new treatments are clinically relevant and consumer friendly.

Currently there is a huge gap between diagnostic and therapeutic research with a major impact on clinical practice. Development of robust diagnostic biomarkers or biomolecular patterns from wound exudates will provide a unique capacity to select the most relevant and efficient therapeutic approaches to assess the wound and monitor treatment progress. These diagnostics, especially point of care diagnostics, have the potential to relieve patient suffering and alleviate the crushing financial burden for both patients and the entire health-care system. Therefore, realignment of the importance of diagnostics alongside therapeutics is a desperate need for the current research and clinical strategies. Funding agencies can play a critical role in facilitating this path by allocating more funding to diagnostic approaches. This will promote future research on the development of diagnostics to define biomarkers (eg, through exudates) with enough sensitivity and specificity to monitor the progress of therapeutic approaches in chronic wounds. Such biomarkers may enable clinicians to choose the most appropriate therapeutic path. We also need to develop fast and sensitive approaches for (i) early detection of bacterial infection (current strategies rely heavily on clinical appearance/observations), and (ii) detection of tissue damage with markers of severity at the very early stages.

Future research should also shed more light on our limited understanding of the complex orchestration between different cell types and the extracellular matrix during the normal healing process. In addition, as many of the therapeutic bioengineered products are wound dressings, researchers must consider the role of exudates in changing the biological identity of these dressings (specifically if the dressing contains nanoscale objects such as nanoparticles and nanofibers). This is mainly because the biological fluids can interact with nanomaterials, cover their surfaces, and give them a new biological identity, which is significantly different from their original formulation.[55–58] The biological identity of the dressings

will then dictate their interactions with biosystems (eg, cell) and may have a critical role on safety and therapeutic efficacy of dressings.[55]

We recently found that the biological identity of nanoparticles, created by plasma proteins of various diseases, provides useful proteomic information about the diseases and, therefore, can be used for disease diagnosis.[59] This approach may also be usable in biological identity of nanoparticles by exudates (as the exudates contain important proteomics, metabolomics, and paracrine factor biomolecules) and provide critical information on wounds (eg, type, stages, and inflammation status) which can pave a way for selection of the appropriate therapeutic approaches.

Meta-analysis and clinical research reports should carefully consider the diversity and geographical variation in patients (eg, poverty, transportation, and comorbidity) and clinicians (freedom to select and use treatment approaches; motivation; expertise, eg, differences between podiatric, surgical subspecialties, and nonphysician wound care experts; private practice vs academic institutions). Otherwise, the outcomes would not be reliable and may cause misprediction in establishing a long-term plan to solve the issues of chronic wounds. For example, studies of interventions for chronic venous leg ulcers take place in many different practice and cultural settings involving a variety of disciplines, including nursing, dermatology, vascular surgery, and internal medicine. This heterogeneity combined with the excessive variety of methods caused problems in achieving reliable and robust wound healing data.

Comorbidity

Comorbid illnesses induce adverse effects on the healing process of wounds and may need different strategies such as modification of drug therapy, diet, or behavior to promote wound healing. Diabetes, obesity, autoimmune diseases, malnutrition, cardiovascular disease, end-stage renal disease and cancer with the need for chemotherapy and/or radiation therapy are the most common comorbidities that impact wound healing. A full discussion of each of these is beyond the scope of this article, however, for illustration we will focus on diabetes and obesity as the rise in these two conditions has had a major impact on the burden of chronic wounds and they are linked to many of the other comorbid illnesses.[5] Because there are regional variations in some comorbid illnesses and their treatment, it is important to consider the demographics of the patients with diseases that may have a direct effect on the development and persistence of the chronic wound. For example, the demographics of obesity and the associated morbidity assessment are very important in training and therapeutic purposes; eg, the southern US requires more training and clinical expertise in obesity-linked illness compared to the west and east. However, obesity is a global problem, as demonstrated by a threefold increase in worldwide obesity from 1975 to 2016.[60] Thus, future research targeted at alterations in healing of injured adipose tissue compared to skin or muscle will facilitate development of strategies that can improve healing in obese patients. The impact of obesity on wound healing is multifactorial and can be magnified by the difficulties inherent in devising dressings appropriate for the morbidly obese patient. This increases the associated costs for wound management compared to nonobese populations, and persists even after surgical procedures targeted at reducing obesity.[61]

Compounding the problem is that obese populations are at higher risk of getting other diseases (eg, cardiovascular and diabetes), which add more complexity to the chronic wounds.[62,63] Obesity also increases the complexity of infectious diseases, compared to healthy people, mainly due to the poor infiltration of immune system to the infectious sites.[64–66] Thus a comprehensive research strategy is needed that includes the metabolic abnormalities as well as addressing the practical issues of the need for different clinical procedures in wound management and strategies and products that facilitate the ability for obese patients to do their own wound care.

The same strategies should be considered for diabetes. For example, it is predicted that by 2030 the elderly diabetic populations (>65 year-old) in developing countries and developed countries will reach 82 and 48 million respectively.[67] This demonstrates a critical need for more robust wound care and diabetic control plans designed specifically for developing countries, compared to the developed ones, to better control the future global burden of chronic wounds.

Insurance and Reimbursement

Complexity over insurance and reimbursement procedures for wound healing products is a major burden for the clinicians (specifically the advanced healing products). The time lag for approval or share of cost of advanced therapies and other nonconventional dressings and the requirement to fail "standard of care" for 30 days results in disease progression, making treatment harder or even

impossible. Furthermore, the lack of reimbursement for treatments known to prevent wounds results in higher costs and suffering for patients at risk. A prime example is that compression stockings are not covered by Medicare unless the patient has a wound.[68]

Realigning reimbursement policy and financial incentives is an essential step to address these challenges, including research that identifies patients who would benefit from early application of advanced healing products.

Aging Population

Another major problem that wound care centers currently face is expansion of the patient population without concurrent expansion in clinician expertise, (ie, there are not enough trained experts, including nurses and geriatricians, in wound care); this is mainly because the rapid progress of medical diagnostic and treatments in various fields of medicine has increased the average life time of the people. The risk of many diseases that makes the patients prone to chronic wounds (eg, cardiovascular,[69,70] diabetes,[71,72] and neurodegenerative disorders)[11,73] significantly increases with age. The stigma and lack of understanding of the definition of palliative care also impacts allocation of resources. Palliative wound care as a separate entity can provide comfort to highly vulnerable patients while still allowing wounds to heal.[74]

Stakeholders will face a huge population of older adults in the next 10 years. With an elderly population that is more prone to chronic wounds,[2,46] handling the upcoming crisis will require a critical view of resource allocation and strategies to improve wound care for our oldest adults.

Complexity Over the Decision-making Procedures

Wound care has become an industry with commercialized management companies that help hospitals to create the wound healing centers. The companies pay for the center and equipment; they manage the wound healing centers for the hospital and take a high percentage of the profit in return. Without their contribution, especially in terms of billing with a close watch on government regulations, the wound care centers might be unprofitable. The chasm between the outcomes of hospitals and management companies confirm the complexity of the politics and decision-making procedures regarding patient treatment strategies.

Overall, we believe the main issue facing us in wound care management is that the true focus of the field, which is improving patient health through providing excellent care, was to some extent overshadowed by other powerful goals, including the pursuit of wealth and accolades. To efficiently cure chronic wounds, stakeholders need to refocus on the original goal of improving patient health and redesign strategies and interactions between all stakeholders to bring real help to patients suffering from chronic wounds.

Conclusions

This perspective article highlights a number of areas that can lead to improvement in global wound care management. One of the most critical areas is the development of strategically focused research and clinical programs that utilize a network of stakeholders with oversight by a Core Center of Excellence. The Core will facilitate and orchestrate the combined efforts of the current multiplicity of wound care and related associations and societies. Whether that means that they coalesce into larger and stronger societies or simply agree to work collaboratively, it will be the objective of the Core to present a unified voice that commands the attention of high level government agencies, including FDA, NIH, CMS and Congress. To this end, the Core Center of Excellence should take the lead in standardizing protocols across the continuum of care, including promotion of practices that prevent wounds, developing standards for education, and creating a network of clinicians and researchers who are dedicated to working in concert with government agencies to advance the science of wound care. Recognition that chronic wounds are a disease entity is a primary goal that will unify the field of wound healing, promote education for future generations, and facilitate development of new products that are tested by well-designed, robust and reproducible clinical trials with patients that are representative of the true magnitude of chronic nonhealing wounds.

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Disclosure

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