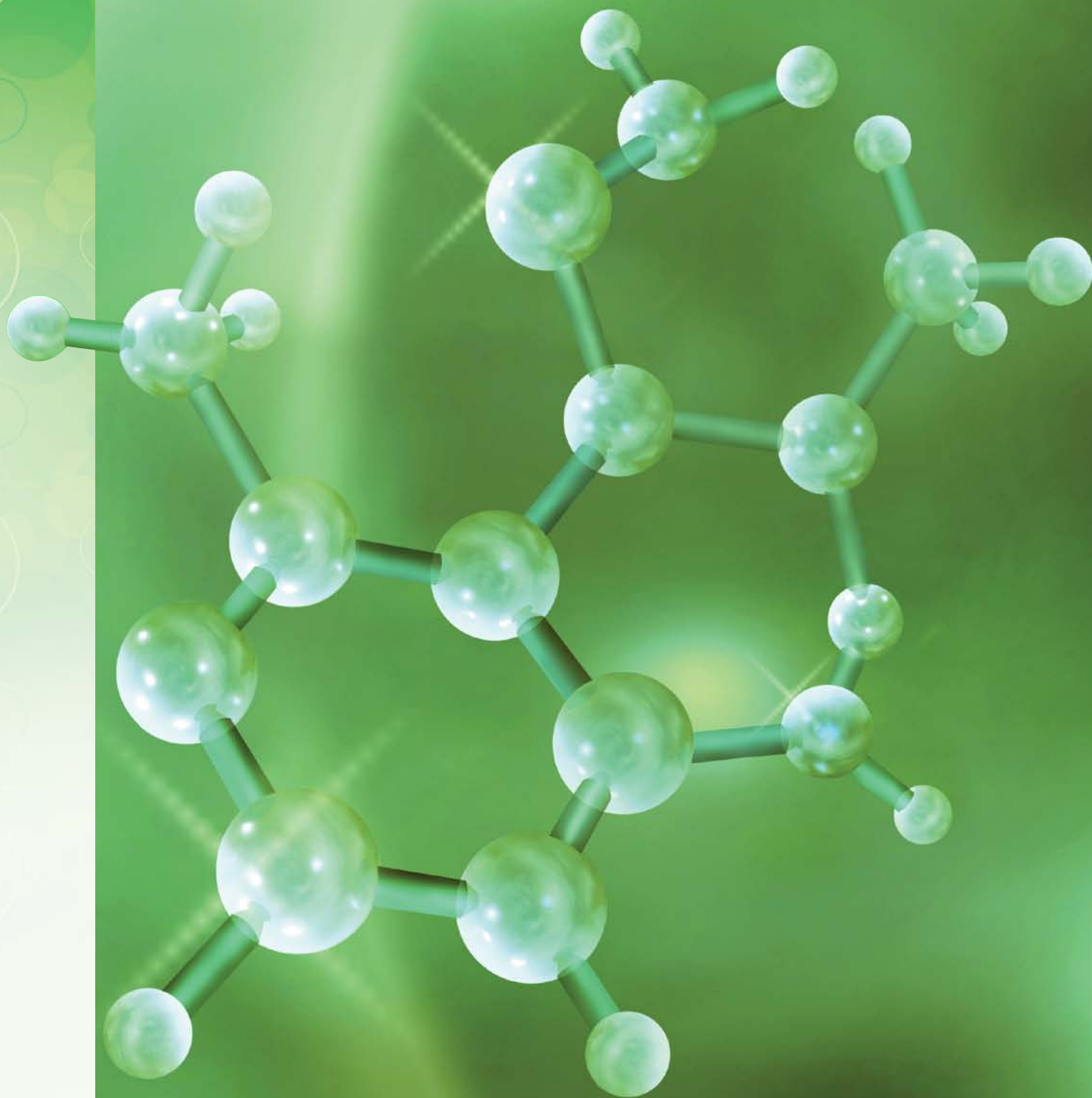


The Role of a Point-of-Care Protease Activity Diagnostic Test in Canadian Clinical Practice

A Canadian Expert Consensus



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Published as a supplement to *Wound Care Canada*.

Canadian Association of Wound Care  Association canadienne du soin des plaies

Publisher:
BCS Communications
255 Duncan Mill Rd, Suite 803
Toronto, ON M3B 3H9

The authors would like to thank Joanna Gorski of Prescriptum Health Care Communications Inc. for taking notes during the consensus meeting and drafting the manuscript for critical review and revision by the authors. Translated by Brisson & Sedgwick Inc. The authors would also like to thank Chantal Labrecque for reviewing the translation.

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Foreword

An interdisciplinary group of Canadian wound care clinicians met in Toronto, Ontario in June 2011, to review the role of proteases in wound healing. The goals were to discuss and assess the role of a protease activity point-of-care diagnostic test, develop a Canadian evidence-informed consensus on use of a protease activity point-of-care diagnostic test and create a practice algorithm incorporating the protease activity point-of-care diagnostic test.



The advent of wound diagnostics has the potential to initiate a paradigm shift in wound management protocols. Awareness of the wound microenvironment could lead to earlier appropriate intervention, faster healing, and more cost-effective treatment. The consensus panel affirmed that the availability of a protease activity test could facilitate this paradigm shift by providing an evidence-based rationale for early selection of targeted therapies. Incorporating a protease activity test into wound assessment may ultimately lead to a change in the standard of care for managing stalled, complex wounds.

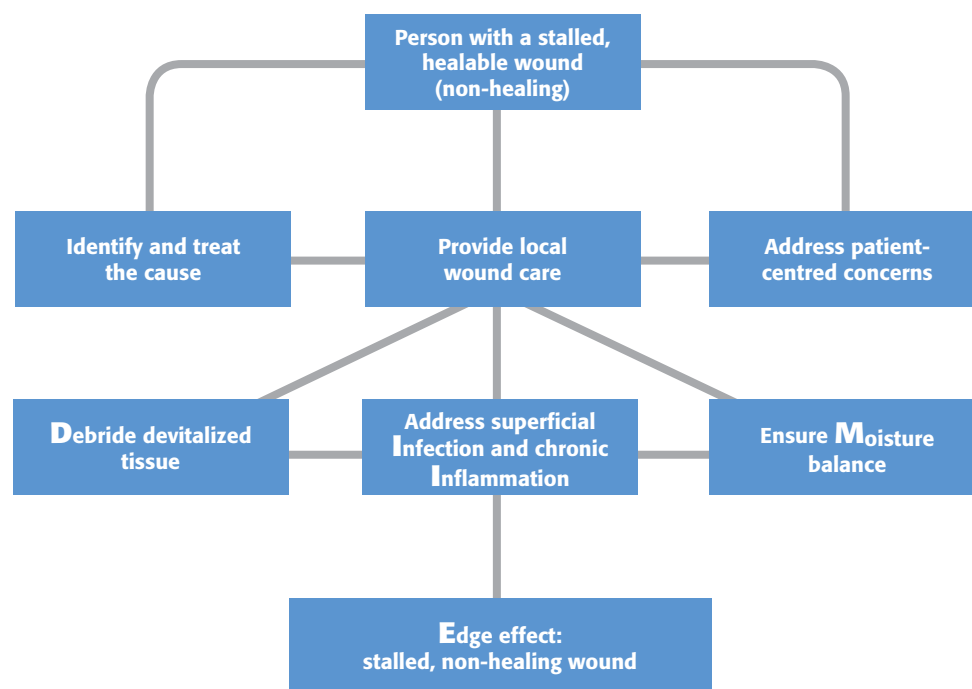
Supported by an unrestricted educational grant from Systagenix.

Clinical challenges in wound care: the stalled, healable wound

Wound bed preparation is an organized approach to wound healing that includes holistic care of the patient before addressing the components of local wound care (Figure 1).⁽¹⁾ Among the challenges facing the wound care clinician today is the paramount need to diagnose and treat the cause of the wound. In addition, patient-centred concerns, including pain, need to be acknowledged and controlled before attending to local wound care. The local wound contains three key components for assessment and potential treatment: debridement

(D), infection versus abnormally prolonged inflammation (I), and moisture balance (M). Appropriate topical treatment needs to be matched to the wound characteristics. Despite appropriate management, wounds with the ability to heal may become stalled.⁽²⁾ Advanced, active local wound care therapies are then used to stimulate a stalled wound edge (E) to heal.

Figure 1. Wound bed preparation paradigm for holistic patient care. Sibbald et al, 2011.



At the local wound bed, delayed healing may be due to a variety of underlying defects:

- Deficiency of growth factors or their receptors
- Local tissue hypoxia
- Damaged extracellular matrix
- Inflammatory environment, often with high protease activity levels
- Biofilms and associated superficial critical colonization or deep and surrounding infection
- Senescent (aging) cells
- Non-migratory, often cliff-like, hyperproliferative epithelial edge

Currently, however, no point-of-care tests are available to assist in determining the local reason for delayed

wound healing, and therefore, no benchmark can determine the appropriate targeted therapy to stimulate healing. Because more costly targeted therapies are often selected without considering clinical and biological criteria, they may be ineffective. As a result, instead of being used as early targeted therapy, active local wound treatments tend to be used as a last resort. A point-of-care test, however, could demonstrate the presence

“By providing specific information that ... a particular intervention is suitable ... the ideal diagnostic tool may promote more accurately timed and targeted care.” (3)

of specific biologic factors that prevent healing and may allow clinicians to select the appropriate targeted therapy earlier, in the expectation of its effectiveness.

On June 17–18, 2011, an interdisciplinary group of Canadian wound care clinicians met in Toronto, Ontario to review the role of proteases in wound healing with the following objectives:

- Discuss and assess the role of a protease activity point-of-care diagnostic test
- Develop a Canadian evidence-informed consensus on use of a protease activity point-of-care diagnostic test
- Create a practice algorithm incorporating the protease activity point-of-care diagnostic test.

Successful wound management depends on the ability of the wound care clinician to identify and treat the underlying cause, patient-centred concerns and local wound factors that may delay healing. A prompt and accurate assessment of inflammatory protease activity may assist clinicians to accelerate healing by identifying an appropriate treatment regimen confidently, precisely, and sooner.

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Consensus on the role of protease activity testing in wound care

Consensus statements

The expert panel developed several statements describing the role of proteases in delayed wound healing and incorporating a protease activity point-of-care diagnostic test into the wound bed preparation paradigm. After the panel meeting, the members participated in an independent, electronic, modified Delphi process to

generate the following final consensus statements. It is important to note that at least 80% of the panel members had to strongly agree or somewhat agree with each statement.

Quick Reference Guide: Consensus on the Role of Protease Activity Testing in Wound Care

No.	Consensus Statements
Background statements	
1	High protease activity is a key factor delaying wound healing in complex, stalled, healable wounds.
2	Clinical signs cannot accurately predict excess wound protease activity.
Treat the cause and patient-centred concerns	
3	Address the cause of complex stalled wounds and patient-centred concerns before considering use of the protease activity test.
Provide local wound care	
4	Wound care clinicians with the knowledge and ability to direct treatment should be the individuals to order and interpret protease activity testing. Any appropriately trained individual may perform the test.
5	Assess and optimize local wound care: debridement, infection or persistent inflammation (e.g., excess protease activity), and moisture balance.
6	Use protease activity testing as part of the assessment of complex, stalled, healable wounds.
7	Integrate protease activity testing results into local and systemic treatment.
8	Re-evaluate wound progress at regular intervals, using the protease activity test as appropriate.

Background statements

1

High protease activity is a key factor delaying wound healing in complex, stalled, healable wounds.

Defining terms

The expert group gave special attention to the terminology used to describe non-healing wounds. Labelling a stalled, healable wound *chronic* can be a misleading descriptor, as the healing trajectory of acute wounds, including post-surgical wounds, may also stall. In some wounds, a biochemical imbalance may be present from the beginning. Intrinsic and extrinsic factors in patients with chronic disease may promote delayed healing. Describing non-healing (but healable wounds) as *complex, stalled, healable* wounds encompasses all healable wounds that do not heal at the expected rate, regardless of duration, thus increasing the precision of the description of a non-healing wound.

- *Healable*: A healable wound is one in which the cause has been corrected, the blood supply is adequate for healing, and no local or systemic factors that could prevent healing are present.
- *Healable versus maintenance versus non-healable*: Specifying healable excludes maintenance and non-healable wounds, including palliative wounds. A maintenance wound has the ability to heal but is not healing due to patient factors, such as a refusal to wear compression, or system inability to provide a needed element of care, such as a specialized device to redistribute pressure on the foot. A non-healable wound lacks systemic or local factors for healing, such as an adequate blood supply or a correctable cause.
- *Complex*: No simple definition of a complex wound exists, but in practice, the term describes a wound with one or more complicating factors that contribute to the cause or prevent response to local wound care. In addition, comorbidities, such as co-existing diseases or concomitant drug therapy, may affect wound healing.

- *Stalled*: A stalled wound does not follow the expected healing trajectory. The wound is either not healing or healing more slowly than expected. Research suggests that a reduction in the wound area by weeks 2 to 4 is a predictor of the ability to heal by week 12. For diabetic foot ulcers, a decrease in size of at least 50% within 4 weeks is predictive of healing by week 12.^(4,5) For venous leg ulcers, a 20 to 40% reduction in size by 2 to 4 weeks has correlated to healing by week 12.⁽⁶⁾ The panel commented that a wound requiring the clinical intervention of a wound care expert is often a complex or stalled wound, as uncomplicated wounds heal on their own in accordance with the initial treatment plan.

Wound-associated mortality

The consensus group emphasized the medical significance of wounds, as they are frequently perceived to be less serious than they really are. The 5-year mortality rate associated with diabetic neuropathic ulcers or with amputation is in the same range as that for some common cancers, such as colorectal cancer, and higher than for breast and prostate malignancies.⁽⁷⁾ It is therefore critical to treat wound healing as an important medical issue and to provide early, aggressive management to maximize the chance of healing and reduce the risk of complications. The longer a stalled wound remains stalled, the more difficult it becomes to transform it into a healing wound.

It is therefore critical to treat wound healing as an important medical issue and to provide early, aggressive management to maximize the chance of healing and reduce the risk of complications.

Proteases and normal wound healing

Proteases, enzymes that digest protein, are critical to wound healing. Two main categories of proteases exist: serine proteases (elastase, plasmin, urokinase, and chymase) and matrix metalloproteinases (collagenase and gelatinase).⁽⁸⁾ A variety of cell types, including inflammatory cells, vascular endothelial cells, fibroblasts, and epithelial cells, normally produce proteases in an inactive form. They are then activated by other enzymes. Tissue inhibitors of metalloproteinases are normally present in wounds and can both prevent activation of inactive matrix metalloproteinases and inhibit activated matrix metalloproteinases.⁽⁸⁾

During normal wound healing, a delicate balance exists between activation of a protease to degrade its specific substrate and eventual inhibition of the same protease once it has served its purpose. During the normal process of wound healing, proteases serve to: ^(2,8)

- Debride the wound
- Facilitate removal of bacteria
- Stimulate migration of cell types essential for wound healing

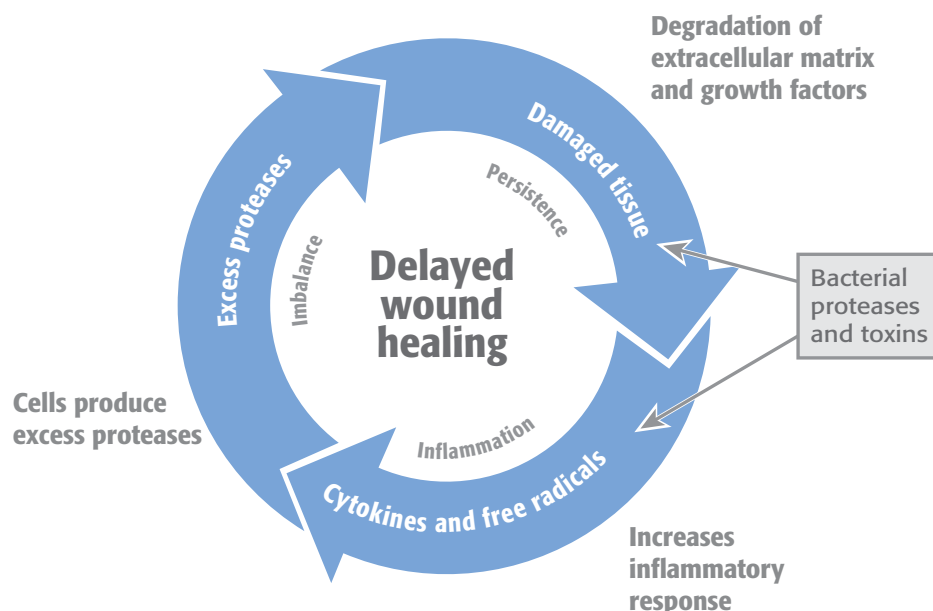
- Activate growth factors
- Remodel scar tissue.

At the start of acute wound healing, protease activity rapidly increases, peaks within a few days, and then declines to low levels by the end of the first week as the healing trajectory progresses.

Elevated protease activity and delayed wound healing

In non-healing wounds, however, disruption of the balance between protease activation and inhibition can result in excessive protease activity levels for an extended period of time. The presence of bacteria exacerbates the problem and amplifies an already hostile environment, increasing the inflammatory response with high levels of bacterial proteases.^(9,10) This imbalance promotes destruction of newly formed extracellular matrix proteins, growth factors, and receptors. A prolonged inflammatory phase and destructive wound environment delay wound healing (Figure 2).⁽⁸⁾

Figure 2. The vicious circle of inflammation, high protease activity levels, and delayed wound healing. (Cullen et al, 2009.)



A substantial body of evidence confirms the presence of much higher protease activity levels in stalled, healable

Interventions that reduce high protease activity levels and correct the imbalance could facilitate healing

wounds than in normally healing wounds.^(11–29) The presence of damaged tissue, foreign material, bacteria, and biofilms in the wound can prolong high protease activity levels.⁽²⁾ Interventions that reduce high protease activity levels and correct the imbalance could facilitate healing.⁽³⁰⁾

2

Clinical signs cannot accurately predict excess wound protease activity.

Identifying wound protease activity levels

Many, but not all, stalled healable wounds have persistent inflammation and high protease activity levels blocking progression of normal healing to the proliferation phase. During the discussion, meeting participants presented cases of complex, stalled, healable wounds (Figure 3). The panel could not accurately identify wound protease activity levels by observation or find any clinical indicators associated with either high or low

protease activity levels. As clinical expertise alone is unable to identify protease activity levels, an objective test is needed.

As clinical expertise alone is unable to identify protease activity levels, an objective test is needed.

Figure 3. What the eye cannot see: Clinical observation alone may not identify elevated protease activity. Photos courtesy of RG Sibbald.



Pressure Ulcer Level 4 Stalled



Stalled Diabetic Foot Ulcer



Stalled Venous Leg Ulcer with Critical Colonization



Venous Ulcers and vasculitis (Rheumatoid Arthritis)

As clinical inspection of a stalled wound rarely provides a definitive indication of the underlying problem and cannot identify the protease activity level, the rationale for selecting an advanced therapy is often no better

than an educated guess. A diagnostic test could help determine the underlying biochemical problem early and guide selection of the most appropriate therapy.

Wound diagnostics

In wound care, diagnostics can be divided into indicators, diagnostic markers, and theranostics, based on the parameter measured.

- *Indicators*, such as wound colour, pH, and temperature, highlight a potential problem.
- *Diagnostic markers* measure a biomarker, such as bacterial count, biofilms or virulence factors, that help assess or diagnose a disease state.
- *Theranostics* measure a biomarker that suggests the use of a particular therapy, as the test result predicts the effectiveness of that therapy. For example, a protease activity theranostic test would indicate the appropriateness of a protease-modulating (anti-inflammatory) dressing.

“The development of specific diagnostic tests for use in wounds has the potential to revolutionize their treatment...and help improve standards of wound care (while) aiding in the cost effective use of limited resources.”⁽³⁾

Treat the cause and patient-centred concerns

3

Address the cause of complex stalled wounds and patient-centred concerns before considering use of the protease activity test.

Assessing the patient and the wound

During the meeting, consensus panel discussion of current management approaches to complex, stalled wounds raised several important points. If a healable wound is not healing, it is essential to perform a full assessment, including a complete history and physical examination, to ensure no hidden cause or other modifying factor has been overlooked. Wound healing cannot proceed until the cause has been identified and corrected. When investigating potential causes, it is important to identify all the associated factors that can impair wound healing:

- *Patient comorbidities*, including conditions such as uncontrolled diabetes, active autoimmune disease, malnutrition, neuromuscular diseases, and cardiorespiratory problems

- *Other patient factors*, such as smoking or alcohol use, lack of adherence to the treatment plan, problems with activities of daily living, and lack of social or family support
- *Medications*, including corticosteroids, immunomodulating agents, chemotherapy, and radiation therapy
- *Wound environment*, including longer duration, larger size, poor wound bed condition, and infection or inflammation

Once these factors have been identified and addressed, appropriate therapy can accelerate wound healing.

Provide local wound care

4

Wound care clinicians with the knowledge and ability to direct treatment should be the individuals to order and interpret protease activity testing. Any appropriately trained individual may perform the test.

Communicating wound status

The expert panel concluded that the simplicity of a rapid, user-friendly, point-of-care protease activity test makes it suitable for use in multiple care settings. In many care settings, including acute-care facilities, long-term care centres, and home care, several clinicians may be involved in assessing and treating the wound at different times.

The expert group emphasized the importance of frequent communication between all wound care clinicians to ensure optimal wound care, including ordering the protease activity test and interpreting the results. This is especially true of stalled, complex wounds, which may require additional evaluations and changes in therapy.

To facilitate communication about protease activity testing and interpretation of the results, the following may be needed:

- Interprofessional education about proteases in delayed wound healing and appropriate management of elevated protease activity, including education on topical and systemic management
- Institution-specific protocols for protease activity testing
- Revision to the wound assessment portion of the patient's chart or electronic medical record to include space for recording protease activity test results
- Structure or protocol to allow appropriate action to be taken based on the test results.

5

Assess and optimize local wound care: debridement, infection or persistent inflammation (e.g., excess protease activity), and moisture balance.

Preparing the wound bed

The expert panel agreed on the importance of next optimizing local wound care, using a systematic best practice approach to wound bed preparation. After debriding the wound of necrotic, contaminated, or infected tissue, it is important to assess the wound for critical colonization or infection.

The presence of at least three of the following characteristics indicates a high bacterial population in the superficial wound compartment:^(31,32)

- **N**on-healing
- **E**xudate increasing
- **R**ed, friable granulation tissue
- **D**ebris or dead cells on the wound surface
- **S**mell

Similarly, the presence of at least three of the following clinical findings indicates a high bacterial population in the deep and surrounding wound compartment:^(31,32)

- **S**ize increasing
- **T**emperature increasing
- **O**s: probing to exposed bone
- **N**ew or satellite wounds
- **E**rythema/Edema
- **E**xudate increasing
- **S**mell

The presence of increased exudate and smell, usually indicating the presence of gram-negative and anaerobic organisms, requires an additional NERDS clinical criterion for surface critical colonization or an additional STONEES criterion for deep or surrounding tissue infection.

Protease activity levels and bacterial population are not independent variables: they are interrelated. As both infection and inflammation may increase wound protease activity levels, superficial or deep wound

infection should be treated before testing protease activity levels. It is also critical for the dressing choice to maintain the appropriate moisture balance for the wound.

6 Use protease activity testing as part of the assessment of complex, stalled, healable wounds.

Timing of protease activity testing

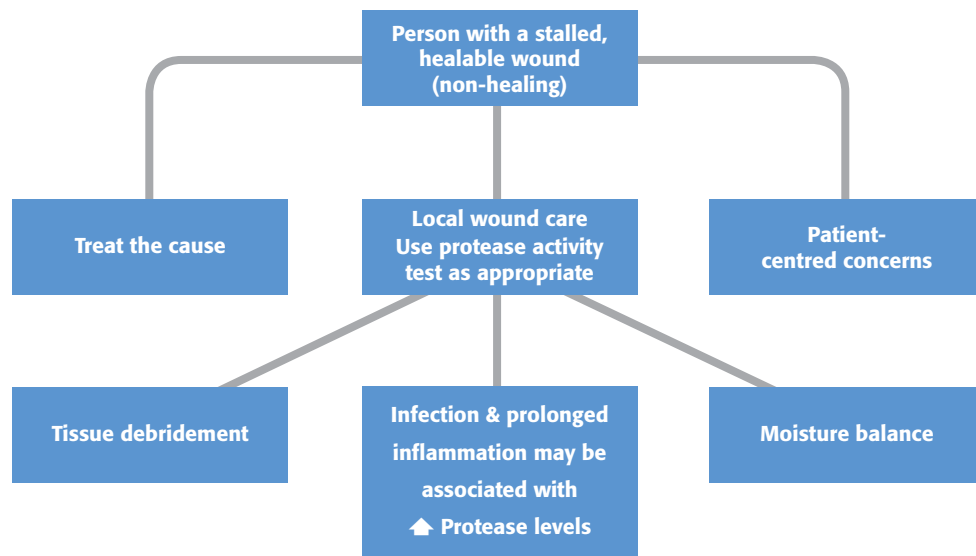
The expert group concluded that protease activity testing is an essential part of the assessment of a complex, stalled, healable wound to help determine the reason for delayed healing (Figure 4). If the wound bed is clean, a point-of-care protease activity test may be useful when the patient is evaluated on the first visit. To ensure accurate interpretation of the test results, in conjunction with administering the test, the clinician

should follow a protocol for wound cleansing and debridement. As the test results can be used to guide therapy, results must be recorded in the assessment portion of the patient’s chart or electronic medical record to facilitate communication between the clinicians managing the wound. On later visits, repeating the test can provide evidence confirming the therapeutic choice or identifying a need to modify therapy.

Figure 4. The updated wound bed preparation paradigm (1) incorporates the use of a point-of-care protease activity test to identify elevated protease activity levels. Testing may be useful in selecting appropriate therapy, monitoring the effect of treatment, and indicating whether therapy needs to be modified. See Figure 5 for a summary of local and systemic wound treatment approaches. from Sibbald et al, 2000, 2003, 2006, 2007, WHO 2010, 2011.

Wound Bed Preparation Paradigm for Holistic Patient Care

Role of Protease Activity Testing



Integrate protease activity testing results into local & systemic treatment

Selecting wounds for testing

The panel identified clinical situations in which management of several categories of healable wounds could benefit from protease activity testing, including the following:

- Wounds in patients with underlying comorbidities, such as diabetes mellitus, peripheral arterial disease, or venous stasis
- Any wounds identified as stalled after the cause of the wound has been addressed
- Dehisced surgical wounds, to prevent complications that may result in readmission
- Pressure ulcers in at-risk patient populations, such as the elderly or diabetic patients
- Wounds in which skin grafting, tissue-engineered products, or scaffolds will be used, as matrix degradation is likely to occur in an environment with high protease activity.
- Wounds in which negative-pressure wound therapy will be initiated.

The consensus panel also identified wounds in which testing for protease activity would be *inappropriate*, including the following:

- Skin tears, unless healing has stalled
- Maintenance wounds
- Non-healable wounds, including palliative wounds.

The panel members questioned, however, whether treating elevated protease activity levels could convert a maintenance wound into a healable wound by decreasing surface protease activity. Research is needed to demonstrate the validity of the test in different wound types in clinical practice.

Identifying benefits of protease activity testing

By determining wound protease activity levels, testing can provide clinical evidence of wound biochemistry, leading to rational use of targeted therapies, eliminating guesswork, potentially speeding wound healing, and allowing faster patient discharge. From a healthcare economic perspective, appropriate use of a protease activity test could help reduce inappropriate use of healthcare system resources. The expert panel concluded a protease activity test should be considered part of a comprehensive care plan that optimizes both wound healing and cost-effective outcomes.

7

Integrate protease activity testing results into local and systemic treatment.

Correcting an inflammatory wound environment

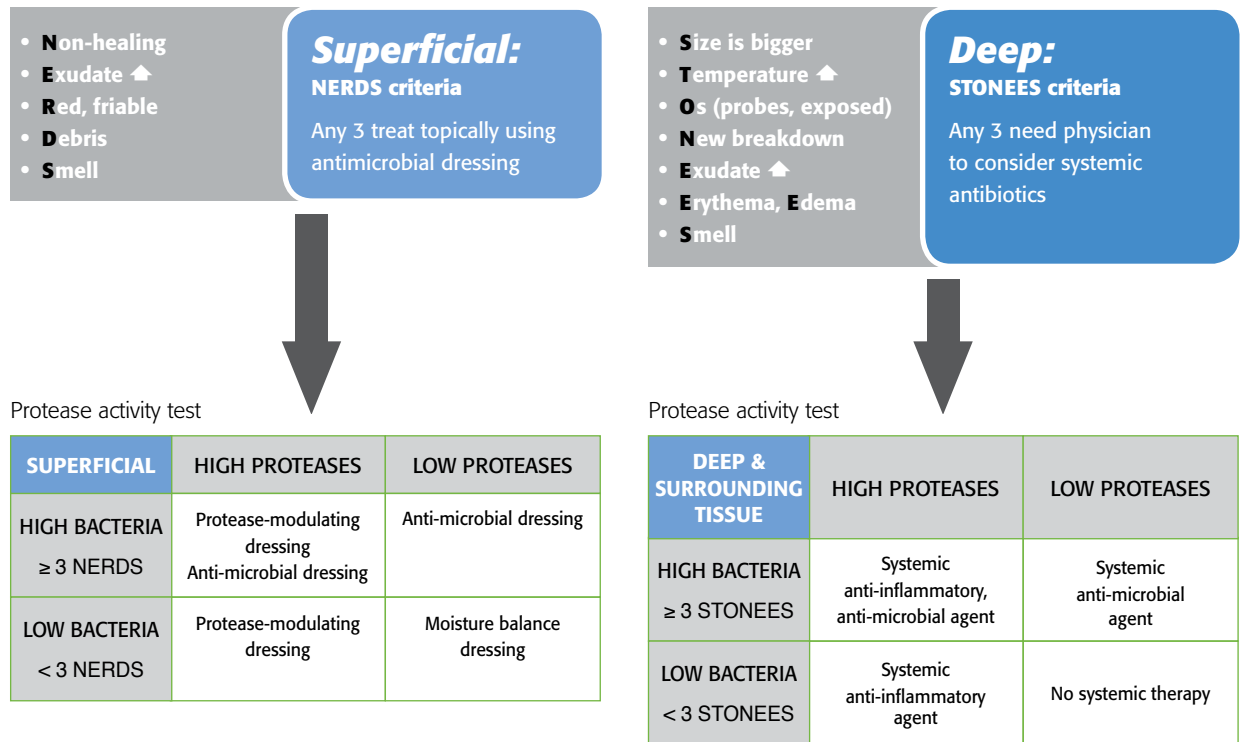
The three components of local wound care are debridement, management of infection and inflammation, and moisture balance. After adequate debridement, persistent inflammation or infection may be associated with high protease activity levels. It is then necessary to determine if abnormal inflammation is associated with bacterial tissue damage and whether the focus of the inflammation or infection is superficial, requiring

topical treatment, or in the deep compartment or surrounding tissue, requiring systemic treatment.

The three components of local wound care are debridement, management of infection and inflammation, and moisture balance. Persistent inflammation or infection may be associated with high protease activity levels.

Figure 5. Summary of the possible combinations of infection and inflammation in the a) superficial and b) deep wound compartments and suggested therapeutic interventions. Note: Protease activity testing can identify elevated superficial protease activity levels, whereas identification of deep inflammation is based on the wound history, diagnosis, and clinical criteria. Elevated superficial protease activity levels may or may not be associated with deep inflammation, just as superficial bacterial damage with critical colonization may exist with or without deep or surrounding infection. (Adapted from Sibbald RG 2011. Modified from Sibbald et al, 2000, 2003, 2006, 2007, WHO 2010, 2011.)

Differentiation of Superficial & Deep Infection/Inflammation – Treatment Guide



Use in healable wound that is “stalled” (less than 30% decrease in size in 4 weeks.) Correct & modify cofactors using Wound Bed Preparation®. Determine critical colonization / deep and surrounding infection or both.

■ **Superficial compartment:**

- High protease activity test results indicate the need for protease-modulating (anti-inflammatory) therapy to correct an abnormally prolonged inflammatory wound environment. Therapy often includes a protease-modulating (anti-inflammatory) matrix dressing.
- If evidence of bacterial damage is present, a topical antimicrobial agent, such as silver, iodine, or honey, may also be needed, with appropriate moisture balance dressings.
- Bacterial damage can exist without protease activity elevation.

- If fewer than three NERDS criteria are present and the protease activity test is negative, only moisture balance dressings are required.

■ **Deep compartment and surrounding tissue:** The deep wound compartment and surrounding tissue of a non-healing wound (wound base and margin) comprise a compartment similar in shape to a soup bowl. The four possible outcomes have different therapeutic options:

- Negative (low) superficial protease activity test and no evidence of systemic inflammation indicate absence of infection or inflammation. No systemic treatment is required.

- The presence of three or more STONEES criteria indicates deep and surrounding tissue infection, requiring a systemic antimicrobial agent.
- Evidence of deep inflammation, in conditions such as vasculitis or pyoderma gangrenosum, requires intralesional steroid or systemic anti-inflammatory therapy.
- The presence of deep inflammation and infection indicates the need for systemic antimicrobial agents, especially agents with anti-inflammatory properties, such as doxycycline and other tetracyclines, cotrimoxazole (sulfamethoxazole and trimethoprim), metronidazole, clindamycin, and erythromycins.

Using test results to improve wound care

Protease activity testing results may provide objective clinical evidence supporting the use of advanced therapies early in the wound healing process to return the wound to a healing trajectory. The panel

recommended that clinicians consider using a protease activity test, incorporating the results into the treatment plan, and monitoring protease activity levels by repeating the test at appropriate times. This approach could help the wound clinician improve patient care by:

- Quickly identifying wounds with a developing or existing healing problem, thus preventing complications and speeding healing
- Rapidly determining the effectiveness of a treatment strategy to reduce protease activity levels
- Potentially reducing the frequency of dressing changes, visits, and total wound care clinician and nursing time
- Targeting therapy to wound biochemistry and avoiding guesswork in selecting advanced therapy, thus reducing use of ineffective therapies and the time to heal the wound.

8

Re-evaluate wound progress at regular intervals, using the protease activity test as appropriate.

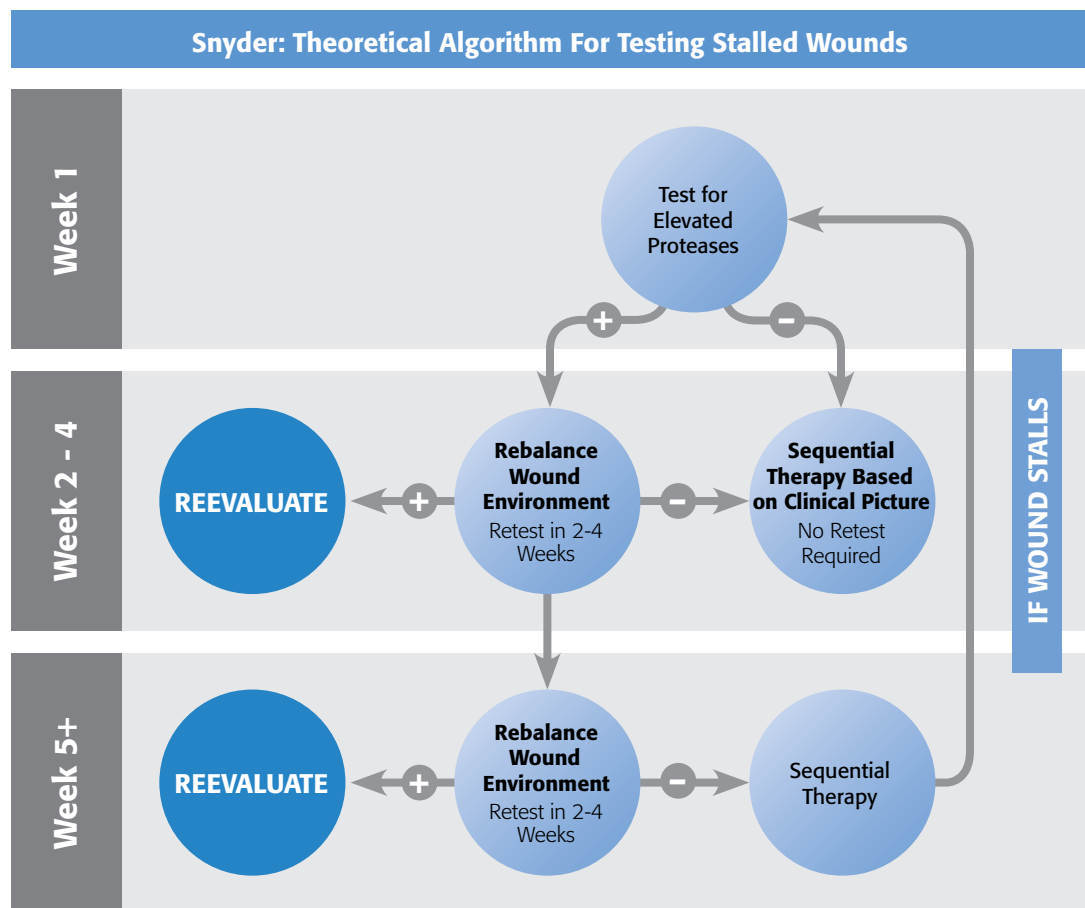
Research suggests that a reduction in wound surface area by 2 to 4 weeks is a good predictor of the ability to heal by week 12. Wounds that do not show these levels of healing within this time frame trigger the need to re-evaluate the care regimen. Treatments to rebalance a stalled, healable wound environment can include protease-modulating (anti-inflammatory) therapies. In general, protease-modulating (anti-inflammatory) dressings, such as collagen/oxidized regenerated cellulose (ORC), are used for short courses of 2 to 4 weeks followed by a full assessment of treatment effectiveness (Figure 6).

A change in protease biochemistry is a precursor to clinical change in the wound. Based on this, the consensus panel suggested that it may be logical to retest a wound for protease activity in 2 to 4 weeks. The panel also agreed that it is appropriate to repeat the test if wound healing does not proceed at the expected rate.

In this situation, both the patient and the wound should be reassessed, searching for a previously overlooked cause or other contributing local or systemic factors that need to be addressed. Thorough wound re-evaluation may be necessary when healing is not progressing.

“The simpler the diagnostic system, the more likely it will be widely used. ...diagnostic tools need to be moved into the clinic or the patient’s home to ensure optimal care is provided for patients with wounds.”⁽³⁾

Figure 6. Theoretical protease activity testing algorithm for stalled wounds. (RJ Snyder 2011.) This protease activity testing algorithm represents a theoretical model for clinical practice and may be used on the first patient encounter or at any point in the treatment regimen.



Conclusion

The advent of wound diagnostics has the potential to initiate a paradigm shift in wound management protocols. Awareness of the wound microenvironment could lead to earlier appropriate intervention, faster healing, and more cost-effective treatment. The consensus panel affirmed that the availability of a protease activity test could facilitate this paradigm shift by providing an

evidence-based rationale for early selection of targeted therapies. Incorporating a protease activity test into wound assessment may ultimately lead to a change in the standard of care for managing stalled, complex wounds.

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