A five-level model for wound analysis and treatment

KEY WORDS
- Analysis
- Five-level wound model
- Processes
- Super system
- Wound healing

Too often wound care consists of selecting a dressing based on what a wound looks like. Most challenging wounds are the result of one or more underlying conditions. If a wound does not heal, it makes sense to have a deeper look at those conditions to discover the causes for the delay. Such analysis will have to entail not only the cause of the wound but also other factors that influence the wound-healing process. A five-level model developed based on common medical and scientific themes may allow for thorough analysis leading to new possibilities for research, prevention and the treatment of wounds.

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Lack of knowledge of the processes related to wound healing currently prevents us from describing in detail those processes in a patient, organ, tissue or cell that are causing the wound or delaying its healing (Franz et al, 2000; Gottrup et al, 2010). Some authors, indeed, do not believe current knowledge allows for evidence-based medicine in wound care (Helberg et al, 2006; Karavan et al, 2015). This article presents a framework that may help to support the diagnosis, improve communication between professionals and allow for information exchange with other medical fields.

WOUND HEALING AS A 'SUPER-SYSTEM'

The replacement, repair and regeneration of tissues and cells is key in maintaining homoeostasis (Gurtner et al, 2008). Tissue homeostasis, i.e. the maintenance of tissue integrity, is well conserved and robust because these processes must proceed under all circumstances (Blanpain and Fuchs, 2009; Lech et al, 2012). A super-system of independent but interrelated structures and processes results in robustness that leads to successful wound healing (Tada, 1997). The system runs at every organisational level — from molecular to cellular to tissue and upward to the entire body (Samanta et al, 2017). This results in a process that is resilient to manipulation, even if it is malfunctioning (Hackam and Ford, 2002).

There is an extensive body of literature outlining the normal wound healing process (Clark, 1996; Singer and Clark, 1999). As a subset of individuals with existing comorbidities and different wound aetiologies suffer from non- or slow-healing wounds, it is important to realise that many factors are independent of the wound and exist before, during and after the wound has formed.

Examining all of the pathological factors that influence wound healing allows for a more inclusive description of events. These factors may exist on one or more levels, from the molecular to the population level (Vodovotz, 2010) and it is helpful to classify them according to how they present clinically *(Table 1)*. These four groups of factors appear to be ranked on an organisational level, but in reality they are the levels at which problems present themselves and are commonly used in clinical and scientific practice (Ziraldo et al, 2015). The dual character of these factors (following nature's organisational levels and clinical practice) enables information to be exchanged between research and clinical practice (Qu et al, 2011; Jinawath et al, 2016).

THE FIVE-LEVEL WOUND MODEL

A theoretical framework has been developed that proposes a new categorisation for all types of wounds or tissue damage (*Table 2*, *Figure 1*). The intention is that this separation into levels may help to identify difficulties and opportunities in wound medicine.

Table 1. Factors that influence wound healing	
Factor	**Examples of groups of factors**
General factors usually not causing a wound but enabling tissue damage	Social factors (stress, social groups, marital status) Demographic factors (age, gender, race) Comorbidities (disease and related medication) General health factors (condition, nutritional status, lab values)
Local factors usually not causing damage but are affecting closure of a lesion.	Location (where and involved tissue(s)) Dimensions Aspect (colour, exudate) Duration, Microbiome Local skin
Systemic factors are usually, apart from trauma, causing the wound. Systemic factors may also affect wound closure	Cardiovascular system Immune system Neural system Muscular system (sarcopenia) Endocrinological system Renal system Connective system
Molecular/cellular factors can be causing damage but can also be enabling factors or affecting wound closure.	Genetic factors (genes, transcription, translation, mutation) Epigenetic factors (methylation, histones) Migration and proliferation (transformation from one function to another) Intracellular events (endoplasmatic reticulum stress, deformation, mitochondrial stress, autophagy, apoptosis) Signalling factors (gradients, proteins and ions) Systems factors (controls, adaptation and responses)

LEVEL 0

Level 0 entails 'normal' healing as nature has intended. This is important because current wound models are based on healing without underlying pathology and, in general, research is carried out on healthy organisms (Winter, 1962). This level may be used as a benchmark for the speed of wound healing. Level 0 wounds are usually the result of trauma in individuals under the age of 50 (Brøchner and Toft, 2009; Kruger et al, 2013).

LEVEL 1

Level 1 wounds will heal over time but the wound healing process is impaired due to general patient factors that have an impact on wound healing processes. Level 1 pathology encompasses general and social factors that rarely directly cause a wound. General factors include:

- Age (Ashcroft et al, 2002; Heyer et al, 2016)
- Stress (Britteon et al, 2017)
- Nutrition (Molnar et al, 2016)
- Metabolic syndrome
- Mobility
- Medication (Levine, 2017).

Compliance, psyche, smoking and alcohol consumption are examples of social factors (Anderson and Hamm, 2012).

Delays in wound healing are caused by general issues, such as inflammation (Sgonc and Gruber, 2013), poor mobility (Gerrits et al, 2015), frailty (Edsberg et al, 2014; Lebrasseur et al, 2015) and the presence of metabolic diseases such as diabetes (Palmer and Kirkland, 2016). Other factors such as stress (Broadbent and Koschwanez, 2012; Archie and Article, 2013), mental status (compliance) or a limited metabolic capacity (Ferrando et al, 2006) also have a negative influence on the healing processes.

Laboratory results, such as C-reactive protein, lymphocyte count, electrolytes, creatinine, glucose and albumin, provide other clues as to general patient-related factors (Benbow, 2009). Since many drugs influence the wound healing processes, medication analysis is relevant (Beitz, 2017; Levine, 2017).

Examples of Level 1 interventions include good regulation of diabetes, improving nutritional status, treating anaemia and reviewing medications. Many more Level 1 interventions have yet to be identified and evaluated. Reducing factors that impair the wound healing process may increase the speed of healing.

LEVEL 2

Level 2 pathology initially arises from local events and encompasses the characteristics of the wound: location (Berke, 2016), dimensions (Margolis et al, 2004), tissue and structures involved (Farahani and Kloth, 2008), debris (Wilcox et al, 2013) and the microbiome (Wolcott et al, 2015). Interestingly, Level 2 factors do not cause the wound, since they result from it.

Our knowledge about the interaction between the microbiome and the body is increasing rapidly (Roth Flach and Czech, 2015; Pugliese, 2016). This interaction is highly influenced by Level 1 factors, such as how an impaired immune system may allow common bacteria to become a problem.

Level 2 diagnosis and intervention is mainly directed towards providing a clean, moist environment and managing the microbiome, mostly with antimicrobials. The TIME model is a typical Level 2 diagnosis and intervention model (Schultz et al, 2004). Regular debridement appears

Table 2. The five-level wound framework	
Level	**Wound type**
0	'Normal' without underlying pathology
1	With generalised pathology
2	With focal pathology
3	With systemic pathology
4	With cellular and/or molecular pathology

to be effective (Wilcox et al, 2013). Intervention aimed at the (peri)wound tissue also appears to be useful (Ribet and Cossart, 2015; Sorg et al, 2017). Research on local tissue loss and regeneration and from other fields has provided unexpected treatment options (Alexander et al, 2015).

LEVEL 3

Level 3 factors can directly or indirectly cause wounds. Pathology results from systemic issues, where systems are compromised. Level 3 wounds include pressure ulcers, leg ulcers and diabetic foot ulcers. The cardiovascular system, first and foremost, leads to problems with tissue perfusion (Singer and Clark, 1999). The lymphatic (Rasmussen et al, 2016), immune (Portou et al, 2015; Zhao et al, 2016), fascia (tensegrity) (Wong et al, 2011), neurological (Stelnicki et al, 2000), nephrology (Shishehbor and Demirjian, 2016) and endocrine (Terao and Katayama, 2016) systems – which all have a structural and/or integumental nature – can also be involved (Nash et al, 2004; Alkhouli et al, 2013; Ashrafi et al, 2016; Gefen and Weihs, 2016).

Level 3 intervention is usually directed towards removing the cause by means of pressure relief, surgical intervention, compression therapy or another treatment. Interventions aimed at reducing the effect of problems with other system can increase the speed of wound healing (Morton and Phillips, 2016).

LEVEL 4

Level 4 pathology results from dysfunction at the cellular and molecular level. Apart from the cellular and molecular manifestation of problems associated with other levels, many factors act exclusively at this level. For example, epidermolysis bullosa would be considered a Level 4 event (Barshir et al, 2014; Saldanha et al, 2015).

Many other processes and networks at this level have regulatory (Fang et al, 2013) and mechanical (Simpson et al, 2011) roles at the cellular interface that have an impact on wound healing. (Epi) genetic issues (Zhang and Duan, 2015), neutrophil extracellular traps (Fadini et al, 2016), senescence, proliferation, cell division and migration (Guo et al, 2015), reperfusion injury (Eltzschig and Collard, 2004) and hypoxia (Hamada et al, 2016) are all primary Level 4 factors. The dysregulation of local signals (Byun and Gardner 2013), growth factors and cellular processes (Andersson et al, 2011; Serras, 2016) as well as redox issues (Dhall et al, 2014) may be implicated.

Our knowledge of Level 4 causal factors is still in its infancy (Kondo, 2007) and wound care is often not the primary goal of articles providing insight into such factors (Laschober et al, 2010). Despite this, the number of Level 4 interventions is increasing rapidly due to the availability of modern diagnostic techniques, such as genetic screening, proteomics (Sabino et al, 2015) metabolomics (Kalkhof et al, 2014) and translational medicine (Kassab et al, 2016), which provide deeper insights into the processes involved in cellular damage and subsequent repair. Level 4 research is leading to new therapies aimed at cellular and molecular processes, such as stem cell therapy, artificial matrixes, drugs and miRNA (Fahs et al, 2015). Although rarely clinically relevant, translation from other fields of medicine like cardiology or ageing may lead to dramatic breakthroughs in Level 4 wound healing (Clevers et al, 2014).

APPLICATION IN CLINICAL PRACTICE

Homeostasis, repair and regeneration of tissue are resilient processes; therefore most wounds will heal (Wilcox et al, 2013). The proposed five-level framework could help diagnose events related to the wound healing process and help quantify the effects that separate events have on it. Even though in most, if not all, wounds aspects of all five levels play a role in the outcome, clinically the levels can be seen as a staged trajectory and function like a sieve. A Level 0 or 1 wound will require minimal attention and should heal by itself. A Level 2 wound is a complicated Level 1 wound that requires debridement and a moist environment for optimum healing. A Level 3 wound usually requires intervention to address the underlying pathology.

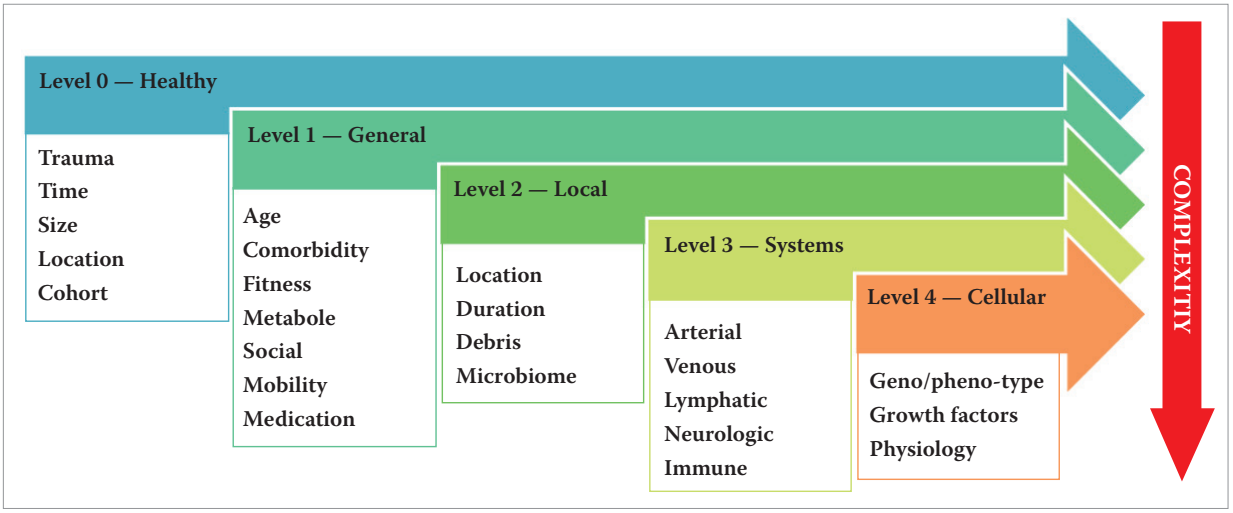

Figure 1. Five-level, schematic overview

After successful intervention, a Level 3 wound can downgraded to Level 1 or 2; a wound that does not heal after interventions should be considered Level 4.

Contrary to the cause of the wound, which is usually straightforward and is often lack of perfusion, a mixture of factors lead to reduced healing. These factors have to be evaluated at all five levels. Diagnosis starts with the pre-clinical situation, where the causes of the wound and their impact on have to be defined. After a wound has occurred, these causes are supplemented by factors resulting from the lesion. Even though issues may present at a specific level, the processes involved may be at various levels, from molecular to social. For example, stress may impair the immune system and increase blood pressure (Vitlic et al, 2014). A wound has the potential to develop into a larger defect, depending on the tissues involved and processes therein. Deteriorating tissue is linked to Level 3 issues, such as peripheral arterial disease, but factors at other levels may play a decisive role in the events leading to a larger or problematic defect.

It is clear from *Figure 1* that any single intervention in clinical practice, other than reducing or removing the cause of tissue damage, will only influence some of the factors involved and likely only have a limited impact on the outcome. This observation might help explain why although providing a moist environment increases the speed of healing in the absence of other factors known to affect wound healing (Winter, 1962; Hinman and Maibach, 1963), unidentified causative factors can reduce its effect to an undetectable level in meta-analyses (Ubbink et al, 2008). This problem is aggravated by a lack of specificity in describing wounds and their healing trajectory.

QUANTIFYING 'EVENTS' IN RELATION TO THE FIVE-LEVEL MODEL

Casting a wider and finer net dramatically increases the number of factors that need to be considered in wound healing.

First, we need to know the impact a given factor has on wound healing, which requires an ability to quantify the contribution of factors to wound healing processes (Khalil et al, 2015).

Relative quantification involves describing healing speed as a percentage, where normal wound healing speed is 100%. This focuses attention on how fast a particular wound is healing compared to how fast it should be healing. Even a simple equation based upon observation versus expectation will allow for quantification (Lecomte du Noüy, 1919).

Second, we need to sum up all factors that may influence healing speed and assess the contribution of each factor to the delay. Considering factors beyond the most obvious may reveal novel treatment options. Interventions should target treatable factors and have a larger impact than other options. If a treatment is not available in the current setting, the patient may need to be treated elsewhere.

The intention is for the framework to be used as a checklist. It could help promote a more holistic view of the patient and demonstrate the relative impact of any intervention that is implemented.

DISCUSSION

Many articles describe how wound healing works; however, there are few tools for analysing how the wound healing process or its subprocesses is/are dysfunctioning. Most guidelines describe the wound and not the process that caused it, which may have existed prior to the lesion. It is not uncommon to see a description of Level 2 dimensions that underestimates or ignores events at the other levels and may result in misdiagnosis.

The five levels represent a framework for clinicians to use in wound care. By connecting generalised, systemic, cellular and molecular events, organisational levels and clinically-relevant topics, it allows us to draw a holistic map of the processes involved in wound healing, highlighting what we know, do not know and current practice. It also allows for better communication between research and practice, enabling the incorporation of evidence-based wound care and its variants into current practice. The levels are applicable to everyday wound care and can be used as a checklist. It allows triage and diagnosis as well as increasing the number of interventions available. By quantifying factors, it focuses attention on the relative impact of interventions. Finally, by providing a framework for all types of wounds, it solves practitioners' 'multi-aetiology' dilemmas, such as which protocol to use for a patient with diabetes and a necrotic heel (Twilley and Jones, 2016).

Lacking a framework to describe and act upon the entire process — prior to, during and after the occurrence of damage — may be a major cause of the under- or mistreatment of wounds. However, it is acknowledged that this framework could complicate matters because all the factors/events that may have an impact on wound healing need to be considered. The complexity of the concepts may be a barrier to its use in clinical practice, however not using them may mean treatments are overlooked.

CONCLUSION

The five-level model may shed new light on how we diagnose and treat wounds and applies to all wound types. The levels are theoretically independent, however, in practice they are connected and function like a sieve. Providing wound care based on consideration of the five levels could broaden the diagnostic and interventional toolbox, help clarify healthcare professionals' roles and lead to a more comprehensive picture of what we know and should know about wound healing.

The next step is to acknowledge that a Level 2 diagnostic tool such as TIME has to be considered in the context of events and factors at other levels. Informal initial feedback suggests that the application of the five-level model in practice is a natural process for most caregivers, as it complements, supports and underpins their current practice of holistic care. WUK

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