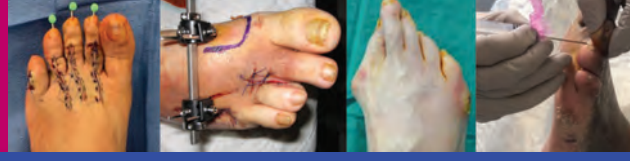

How Can Research Data Be Used to Treat DFUs?

Here's how to apply clinical study results to real-world patients.

BY ADAM LANDSMAN, DPM, PHD

Introduction

Between 2009 and today, the number of advanced biologic products cleared by the FDA for wound treatments has mushroomed from about 20 to over 80 different products. In other words, the number of amniotic and placenta-derived materials, various types of collagen, living tissue preparations, and various polymers field quadrupled in only 12 years. With each new product, doctors will comb over the flurry of data that inevitably follows, comparing these materials through a variety of clinical and scientific studies.

Studies published in peer-reviewed journals often promise levels of success that are rarely seen in a true clinical practice. Studies that demonstrate over 90% closure rate must be considered with real skepticism. After all, how many wound care specialists in clinical practice have ever achieved anywhere near that level of success, with any wound care product? It is well known that the wound healing process in patients with diabetes is complex and involves a variety of factors including blood flow, mechanical off-loading, bony deformities, chronic hyperglycemia, neuropathy, exposure of deep structures, location, infection, and others.

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When reviewing the literature, it is rare for clinicians to dive in to the heart of a given research study to examine the inclusion and exclusion criteria of

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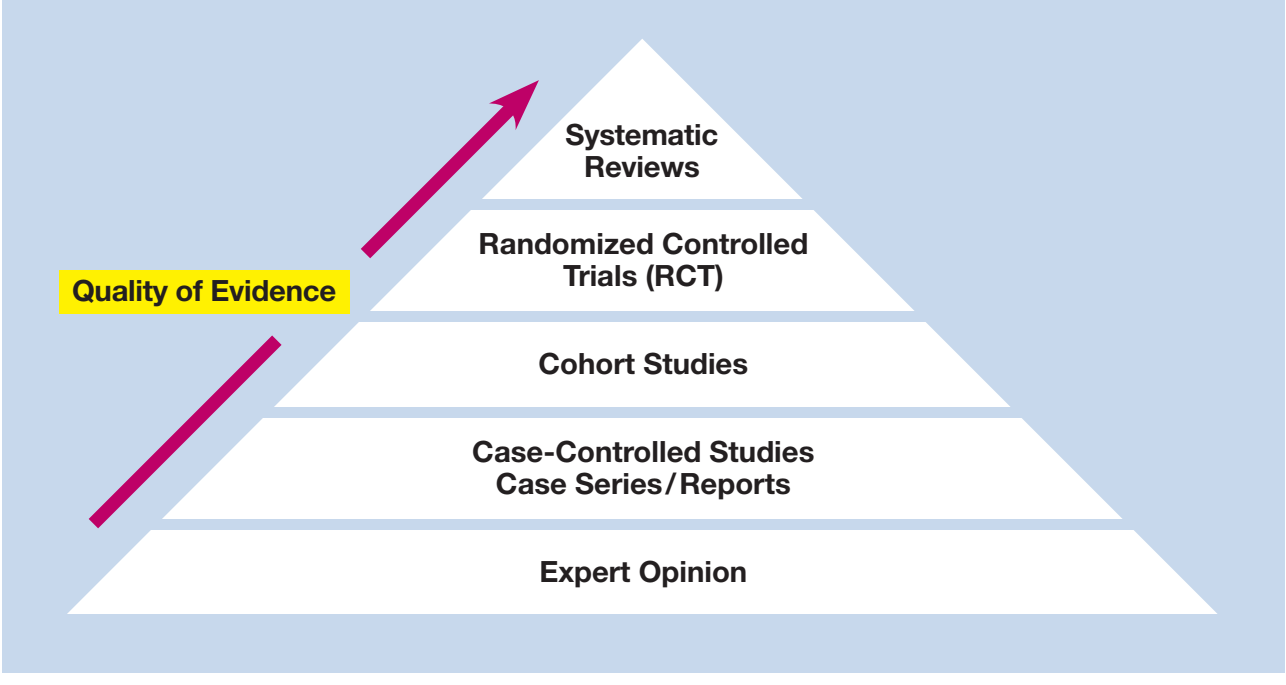
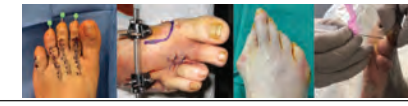


Figure 1: Evidence-Based Research Pyramid



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a particular study? Often, this information will illustrate how constrained the study population actually is. Many studies exclude patients with exposed muscle/tendon/bone, wounds larger then 10cm^2, or patients with high A1C levels, and yet this is very common in clinical practice. How many clinicians appreciate the difference in study design, or grasp the value of statistical significance from a clinical trial perspective? In essence, it becomes quite clear that the outcomes from many clinical research studies do not translate well to the types of patients that are actually seen in clinical practice.

Gathering Real-World Data from Clinical Research Studies

Evidence-based research (EBR) refers to the pyramid diagram that helps one to visualize both the quality and quantity of research evidence (Figure 1). Historically, this pyramid has been a way to gauge the value of a study from the perspective of evidence quality. But evidence quality is really a measure of how solidly the answer to a research question is known. Part of arriving at that answer, however, involves comparing study subjects with as little variability as possible. As the eligible study population becomes narrowed down, the translatability of the data to actual patients also begins to decrease.

Systematic Review

Systematic reviews are typically at the top of the research pyramid, and refer to studies like those found in the Cochrane Database, where numerous studies are combined and analyzed for scientific value based on numerous criteria selected for the specific topic at hand. By reviewing all of the data available on a specific topic, the authors can find commonalities, and group studies of acceptable quality that meet their criteria for inclusion. This results in large databases that can reduce the effect of potential bias found in a single study. Well-conceived systematic reviews in wound care are rare due to the amount of labor and expertise needed to perform this type of study, as well as a shortage of quality studies to be analyzed.

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Randomized Controlled Trials

Randomized controlled trials (RCTs) are more commonly found in the peer-reviewed literature, and involve a formal structure governed by the inclusion and exclusion criteria, type and quantity of data collected, and the quality of the statistical analysis performed. A cursory examination of some of the best known RCTs in wound care help one to understand exactly what was studied. Marston, et al. published a large RCT on the use of a biologic material for treatment of diabetic foot ulcers[1]. A quick review of the inclusion and exclusion criteria of this study reveals that in order to be included in this study, the patient had to have an ulcer with no exposed muscle, tendon, bone or joint capsule, free of necrotic debris, with palpable pulses. Furthermore, they were excluded if the ulcer was over a Charcot deformity, was larger then 20cm^2, or had any evidence of infection. When thinking about clinical patients who may be candidates for this treatment, it is possible that few will meet these criteria. The question is how much of the data coming from this well constructed RCT will actually translate to the patients that are seen in the real-world clinical setting.

Cohort Studies

Cohort studies are studies in which a group of study subjects are assembled, and then followed retrospectively or prospectively, to determine what has happened to them in relation to other members of their group. For example, a prospective cohort study by Naemi, et al.[2] considered a group of 1810 people with diabetes and followed them for an average of 133 days, and recorded 28 differ-

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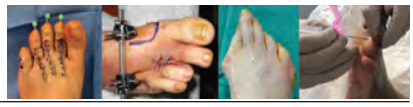

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ent parameters to determine which if any would correlate with the occurrence of a foot ulcer.

Similarly, a retrospective cohort study by Landsman, et al.[3] examined 214 consecutive patients with either diabetic foot ulcers or venous leg ulcers who also were treated with a cryopreserved human skin allograft to determine the closure rate as well as other factors that may have had an impact on those who closed their wounds versus those who did not.

Although some would argue that the quality of evidence of a cohort study is inferior to the RCT, the cohort study data is much more likely to represent the types of patients that are seen in the clinical setting.

Cohort studies examine a broadly defined population, and then, either retrospectively or prospectively examines the outcomes of the intervention to be studied. Depending on how the cohort is defined, these data sets are usually large and contain a variety of patients with multiple co-morbidities that may not be included in the typical RCT.

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Case-Controlled Studies, Case Series, and Reports

These types of studies are often described as pilot studies, and will lack the statistical rigor associated with the larger and more robust cohort studies. Frequently, these case series are designed to follow a population under treatment, similar to a cohort study, and will have various treatment options, similar to an RCT. But usually the sample size is inadequate to draw meaningful statistically significant conclusions.

Ironically, the case series papers often do translate to the types of patients seen in the clinic and are excellent for teaching new techniques, or introducing new treatment options. A case series by Flood, et al.[4] demonstrated the utility of a biologic product for coverage over ulcers with exposed muscle, tendon, and/or bone. The series is designed to demonstrate a treatment option and the author's experiences without making definitive conclusions about where and when this product should be used.

Expert Opinions

These are just that—opinions. The expert opinion is based on a combination of experiences. Not unlike this very paper, the thoughts given here are based on a combination of thoughts, literature, and prior activities. These opinions may open the door to future, higher levels of quality evidence, but generally are a (admittedly bias) recap of past and present thoughts.

New Trends in Clinical Research

Clearly, there is a need to combine the reduction of bias found in the RCT with the real-world data typically associated with the cohort study. One technique that can be used is known as Cohort Matching. Cohort matching considers a study population and then matches them across many parameters, thus creating groups that are similar in composition on a variety of levels, and ideally only differ in the study treatment given. For example, when comparing treatment "A" to "B", a 50-year old female with type 2 diabetes, and an ulcer on the plantar aspect of her heel from group A would be compared to a similar female candidate with a heel ulcer and type 2 diabetes in group B. The larger the database available, the more factors that the investigators may choose, in order to create this match.

Some of the more popular ways to match subjects in one treatment group to another include age, gender, wound location, wound duration, concomitant use of antibiotics, Wagner classification, HgA1c, presence of Charcot deformity, smokers, and numerous others. Often times, the Charlson

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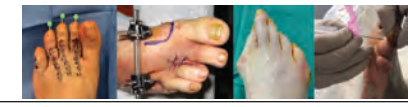

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Co-morbidity Index (CCI) is used as part of the matching strategy in order to assess the generalized health of each study subject.[5] CCI is a validated measure of one-year mortality risk and factors in the severity of diseases and 17 common comorbidities. (Figure 2) Two subgroups, liver disease and diabetes, are also factored in to the scoring strategy. The CCI score is then used as a generalized measure of patient health and can be considered as an important factor in cohort matching.

When large databases are analyzed, the matching can be very powerful. Some studies require exact matches in CCI as well as gender, geographic region, and a narrow age range (i.e., age 65-69 would be considered a match). The goal is to find study subjects that are as similar as possible, with regard to general health and wound characteristics, and only differ in the treatment rendered. In this way, the treatments can be compared. An excellent example of this technique was employed by Barbul, et al.[6] to assess the relative costs associated with two different biologic treatments.

In this study, an initial cohort of 89,341 subjects who received a biologic were identified, and went through a rigorous matching process that took in to account factors that affect a subject's ability to heal—propensity matching—to arrive at 664 well-matched subjects receiving one of three biologic treatments. Once matched, data could be analyzed to make the desired comparison of costs of treatment. The end result is a huge study with data taken from over 1800 subjects, running the spectrum of complications, all matched to isolate the value of the treatments being studied.

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After considering the research data options, RCT studies are excellent for making scientifically strong direct comparisons between treatment options, but fall short in our ability to translate those results directly to the clinical arena. The strict criteria for enrollment cuts both ways—minimizing the investigator bias, by not allowing them to select the treatment option—while greatly constraining the study population in order to eliminate and/or neutralize any extraneous factors that may influence the study outcomes. In a well-constructed RCT, there will be two nearly identical groups, with similar pathologies, that differ only in the treatment that they receive. But this type of study design sacrifices population diversity, and therefore may not be representative of the typical patient seen in clinic.

Conversely, the typical cohort study may be too broad and inclusive and fail to take into account diversification in many forms across the study population. This issue is somewhat neutralized by administering some form of propensity matching within the cohort in an effort to find data that is directly translatable to the clinical setting.

In an excellent paper by Serena, et al.,[7] they discuss the disparity between idealized RCT evidence and real-world data that can be directly translated to patient treatments. This has a direct impact on how we determine the real value of a wound care product or material. Large database information is very useful for judging a variety of factors in a real-world setting, where subjects with co-morbidities and complex wounds of varying depths and at various locations are now considered. This type of data analysis can be used to assess actual costs (including the management of related healthcare costs), relative closure rates, frequency of complications such as infection, and even recidivism.

Evidence-Based Medicine

Evidence-based medicine is a critical element of clinical practice, but the clinician has to be cautious about the type of information received. Each study should be judged on the merits of the work at hand, as well as how

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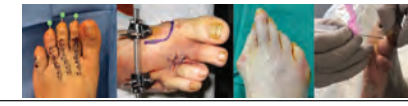
FIGURE 2

CCI Co-morbidities

• Myocardial infarction history	• Diabetes without end-organ damage
• Congestive heart failure	• Hemiplegia
• Peripheral arterial disease	• Renal disease
• Cerebrovascular disease	• Diabetes with end-organ damage
• Dementia	• Tumor without metastasis
• Chronic Pulmonary disease	• Leukemia
• Connective tissue disease	• Lymphoma
• Peptic ulcer disease	• Moderate/Severe Liver disease
• Mild Liver disease	• Metastatic solid tumor
• AIDS	

Each study should be judged on the merits of the work at hand, as well as how well it actually represents the types of patients that are seen in clinical practice.



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well it actually represents the types of patients that are seen in clinical practice. Data from overly idealized patient populations may not be applicable to the typical wound patient. Similarly, large cohorts of subjects where there are lots of unknown variations in the study groups may also be of lesser value. The new paradigm in valuation of research evidence is how well it represents the types of patients actually encountered in the clinic. In addition to wound closure rates, one must ask how this evidence translates to the clinical arena and whether or not ancillary issues such as recidivism, costs, and complications must also be considered when determining the value of a treatment regimen. **PM**

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