Can We Predict Who Will Heal? The Validation and Use of the Wound Healing Index
Session 201 Saturday, October 26, 2013

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RCTs in Wound Care

- Review of all wound related RCTs of past 10 years
- Among 8,611 wound center out-patients, > 50% would have been excluded from 15/17
- 88% wound related RCTs at the "first pass"
  - Excluded patients on the basis of co-morbid conditions, previous surgeries or medications -- even before further tests are performed

Exclusion criteria for all wound RCTs 1996 – 2006

- For DFU studies, no ulcers > Wagner Grade II
- Diabetes as a co-morbid condition for any study other than DFU
- Venous stasis except in VSU trials
- Alcohol/drug abuse
- Anticoagulant treatment
- Cellulitis or local wound infection
- Cancer or recent cancer treatment
- Collagen vascular disease/connective tissue disease
- Rheumatoid arthritis/autoimmune disease, any type
- Scleroderma/lupus, any autoimmune disease
- Charcot foot changes in DFU
- Corticosteroid treatment any reason
- Deep venous thrombosis/pulmonary embolus
- Gastrointestinal disease of any kind /any Liver disease/Hepatitis
- Renal impairment/ESRD/Renal dialysis/Renal transplant
- Any organ transplant
- In diabetics, HbA1c > 8-10
- Nutritional impairment/Albumin < 3.0 mg/dl
- Osteomyelitis
- Peripheral arterial disease

These are common to all studies but some have additional ones
Who is the “Usual Wound Care” Patient?

- 8,611 patients (15,499 wounds) from the U.S. Wound Registry
- Average patient age: 60.4 (1 - 104) years
- Average wound duration at consultation = 189 days (6 months)
- Average number of co-morbid conditions = 6
  - 16% with CAD
  - 10% current smokers
  - 8.4% on steroids
  - 5% have renal failure or transplant
  - 26% of wounds that were not specifically diabetic foot ulcers were in patients who had diabetes
- 54% of wounds were considered “infected”

Efficacy vs. Effectiveness

- RCTs have done a good job of proving that wound care modalities are efficacious
  - --- successful under controlled conditions
- But since the inclusion criteria of these studies do not reflect the typical wound center patient, RCTs can’t prove that these modalities are effective
  - --- successful among the compromised patients in real world practice

NPWT for a leg ulcer patient with NIDDM on immunosuppressives

- 72 y.o. LAF
- * Rheumatoid arthritis
- On * prednisone and methotrexate
- * NIDDM
- 5 month history of leg ulcer due to trauma

Why does it matter whether we understand effectiveness?

Why do we care whether studies are generalizable to real patients?
Summary of Study Exclusions for All CTP Trials (cellular and tissue derived products)

[Pollak, Veves, Edmonds, Neizgoda]

- No exposure of tendon, bone, or joint
- Free of necrotic debris
- No PVD
- No fibrin or debris or necrotic material
- No systemic steroids, no transplant drugs
- No autoimmune disease
- No osteomyelitis
- Good perfusion demonstrated by TCOM, etc.
- No infection

RCT exclusion criteria

“...not involving tendon, muscle, joint capsule, or exhibiting exposed bone or sinus tracts.”

“Elimination of underlying cellulitis, osteomyelitis, or other infection”

“Appropriate debridement of necrotic tissue

“Only applied to wounds with adequate circulation/oxygenation”

“. . .must not be provided to patients with:

- uncontrolled diabetes
- vasculitis
- rheumatoid arthritis or rheumatoid ulcers
- radiation and/or chemotherapy within one month immediately preceding application
- ongoing use of high-dose corticosteroids or immunosuppressants

Quoted from the Novitas LCD on skin substitutes

I Committed Fraud to Heal This Patient

A patient with diabetes, rheumatoid arthritis, on steroids whose leg ulcer (non-healing for > 5 months) was healed with bioengineered skin. This product was used inappropriately based on the LCD because patients like this were excluded from the trial.

We MUST Develop a Way to Stratify Patients by Severity or:

- RCTs will continue to be non-generalizable because the co-morbid conditions COMMON to our patients will always be excluded thus---
  - Coverage policies will mirror these RCTs, thus excluding the patients who most need the products from ever receiving them
  - And we will not be able to use “real world” data for comparative effectiveness studies

The Medicare Coverage Advisory Committee (MedCAC): March 29, 2005

- Goals:
  - Outline the extent of the knowledge base for treatment of chronic wounds
  - Promote research initiatives within the healthcare community
  - Identify meaningful outcomes and measures
  - Encourage an increase in the overall quality of evidence for wound care interventions

- Coverage and Analysis Group:
  - Ronald M. Davis, MD, Chairperson
  - Barbara J. McNeil, MD, PhD, Vice-Chairperson
  - Steve Phurrough, MD, MPA

\[ \text{MedCAC Committee} \]

**Real World Data**

- The Center for Medicare and Medicaid Services (CMS) agrees there is benefit to analyzing “real world” data to facilitate wound care research.
  - The Institute of Medicine and The Federal Coordinating Council for Comparative Effectiveness Research promote the concept that a byproduct of documenting care within electronic health records (EHRs) should be the ability to “mine” EHR data for clinical research.
- Some sort of severity score is necessary for this type of work.

**The Value of Registries**

- The strong external validity of registries is achieved by the fact that they include “typical patients,” unlike RCTs.
- Registry data can provide a good description of the course of a disease and impact of interventions in actual practice; they may be more relevant to decision making than data derived from clinical trials.

> “...well designed observational studies can approximate the effects of interventions as well as RCTs on the same topic, and in particular, in the evaluation of health care effectiveness.”

Meaningful Use Stage 2: 2015

- Public Health–Agencies or Registry data submission:
  - Registries must have some method to risk stratify patients
  - Real world data might be the way forward for wound care research.
  - The only way this works is via structured data

Structured Data: President Obama’s Linked In Page

Structured Language in an EHR

- Allergies & Adverse Reactions
  - Penicillin–Hives
  - Aspirin–Wheezing
  - Codeine–Itching and nausea

NO TYPING!
Structured data usually takes the form of menu selection.
The U.S. Wound Registry

- Data collected at point of service, during patient encounter at point of care
- All clinical information is entered (physician and nurse)
- Data collected are the legal medical chart
- Clinics must pass detailed tests of data completeness and integrity before they can contribute to the USWR
- All patient data are de-identified and pooled to become the USWR.
  - No selection bias
  - No post hoc vetting of data

USWR

- Multi-purpose registry created from EHR with a high degree of structured-language usage
  - Medications prescribed by eRx or computer generated
  - EHR internally audits chart to calculate physician and facility reimbursement = enhanced motivation for completeness
- USWR recognized by CMS as qualified patient registry for Physician Quality Reporting System data submission
  - 100 facilities in 34 states contribute de-identified EHR data to the U.S. Wound Registry (501c3)
- Independent IRB

Can Healing be Predicted?

- Numerous studies over the past 2 decades have identified specific wound and patient factors known to have a negative impact on healing
  - Our purpose was to develop a comprehensive stratification system for patients with wounds that predicts healing likelihood
- A comprehensive stratification system could potentially be used to---
  - Prospectively aid clinicians in selecting patients who most need advance therapeutics
  - Prospectively stratify patients in clinical trials on the basis of disease severity
  - Facilitate retrospective data analysis of real world data
Factors we know have a negative effect on healing from prior work:

- **Wound factors:**
  - size (depth, area, and diameter)
  - stage/grade
  - wound “age” (duration since onset)
  - bacterial load/presence of infection

- **Patient factors:**
  - renal failure
  - patient age
  - peripheral arterial disease
  - some medications

We knew some factors varied by **WOUND TYPE**

Methods:

- Data from 256,671 wounds examined.
  - Care spanned from July 2003 to July 2011.
- 106,272 wounds met criteria (41.4% of total) for 9 wound types (models created for 7 types)
  - At least 2 clinician encounters for each wound
  - At least 5 days between first and last encounter
  - No gap longer than 60 days between all wound encounters
  - At least 1 area measurement
  - Minimum area of at least 0.25cm²
  - Wound age
  - Specified body location of wound

Wound type was defined by ICD–9-CM (International Classification of Diseases 9th revision) codes and text fields for location:

1. Amputations/Non healing surgical wounds
2. Diabetic Foot Ulcers (chronic ulcers related to diabetes)
3. Pressure Ulcers – Body
4. Pressure Ulcers – Heels
5. Traumatic wounds (wounds related to trauma)
6. Venous ulcers (specifically coded + chronic wounds due to CVI)
7. Arterial ulcers (chronic wounds related to atherosclerosis)
8. Burns
9. Failing flaps and grafts

Models not created for wound types 7–9 due to small sample size.
## Methods:

- Healing determined by clinician at point of care or by longitudinal analysis of change in measurement from start, type of tissue exposed
  - Documented as ‘healed’ by clinician
  - If not documented as ‘healed’ by clinician then
    - Size of last area
    - Change in wound area from maximum to last
    - Last wound depth
    - Last exposed tissue type (mild, moderate, severe)

### WHI outcome

<table>
<thead>
<tr>
<th>WHI outcome</th>
<th>2nd level: Size of last area</th>
<th>3rd level: Change from maximum area to last area</th>
<th>4th level: Deep wound (last depth ≥ 0.5 cm)</th>
<th>5th level: Last exposed tissue type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not healed</td>
<td>&gt;2.5 cm²</td>
<td>Not Used</td>
<td>Not Used</td>
<td>Not Used</td>
</tr>
<tr>
<td>Not healed</td>
<td>1.25–2.5 cm²</td>
<td>&gt;50%</td>
<td>Deep</td>
<td>Not Used</td>
</tr>
<tr>
<td>Not healed</td>
<td>0.25–1.25 cm²</td>
<td>&gt;30%</td>
<td>Deep</td>
<td>Moderate</td>
</tr>
<tr>
<td>Healed</td>
<td>1.25–2.5 cm²</td>
<td>&gt;50%</td>
<td>Shallow</td>
<td>Mild or Moderate and Change from maximum area to last area &gt;80%</td>
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</tr>
<tr>
<td>Healed</td>
<td>Missing</td>
<td>Missing</td>
<td>Shallow</td>
<td>Mild and maximum area ≤ 2.5 cm</td>
</tr>
</tbody>
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</tr>
<tr>
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<td>1.25–2.5 cm²</td>
<td>&gt;50%</td>
<td>NA</td>
<td>NA</td>
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Factors known to be associated with decreased healing were evaluated.

Bivariate analyses were used to test relationship between each candidate predictor and outcome of 'healed' for each wound type.

Once 'healed' or 'not healed' was defined for each wound, we randomly selected 10% of wounds in each wound type to use for model validation.

Logistic regression models were created based on variables that were significant (p<0.05) in 90% sample, and subsequently tested on 10% hold-out sample of data.

The WHI is the predicted probability of a specified wound becoming healed.

- Created from multiplying the logistic regression parameter estimates by the values of the significant variables for each wound category type

A different model was predictive of healing for each wound type.

- Somewhat different variables predicted healing for each condition
- All models were well validated when applied to the 10% hold-out sample

Variables significant in nearly all models:
- wound size
- age of wound
- number of wounds
- tissue type exposed (Wagner grade or stage)
- being non-ambulatory
- requiring hospitalization during the course of care
- evidence of bioburden/infection

Variables significant in some models:
- renal failure, renal transplant, malnutrition, and peripheral vascular disease

Results: The WHI

- 2 WHI Models for each wound type:
  - One model based on patient and wound data available at the first visit (What’s in the patient’s “suitcase” when they arrive)
  - Second model based on patient and wound data available from all visits in which the wound was treated

Results: The WHI- NO Rx!

- No treatments were used to create the WHI
  - One cannot use treatments to define a WHI and then ask what treatments are associated with better outcome of ‘healed’

Results: The WHI

Statistics for 90% development sample

<table>
<thead>
<tr>
<th></th>
<th>Diabetic</th>
<th>Venous</th>
<th>Pressure Ulcer (Body)</th>
<th>Pressure Ulcer (Heels)</th>
<th>Trauma</th>
<th>Amputation / Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of wounds</td>
<td>5239</td>
<td>9898</td>
<td>6640</td>
<td>1909</td>
<td>9944</td>
<td>5571</td>
</tr>
<tr>
<td>Number (Percent) healed</td>
<td>3462 (66.1%)</td>
<td>7498 (75.8%)</td>
<td>4300 (64.8%)</td>
<td>1240 (65%)</td>
<td>7706 (77.5%)</td>
<td>3906 (70.1%)</td>
</tr>
<tr>
<td>Whole course model c Statistic</td>
<td>0.67</td>
<td>0.64</td>
<td>0.74</td>
<td>0.70</td>
<td>0.63</td>
<td>0.62</td>
</tr>
<tr>
<td>First Encounter model c Statistic</td>
<td>0.65</td>
<td>0.60</td>
<td>0.70</td>
<td>0.70</td>
<td>0.62</td>
<td>0.61</td>
</tr>
</tbody>
</table>

\*c Statistic: Performance metric of model discrimination equivalent to the area under the receiver operating characteristic curve.
Results: The WHI

Statistics for 10% validation sample

<table>
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<th>Pressure Ulcer (Heel)</th>
<th>Trauma</th>
<th>Amputation / Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of wounds</td>
<td>555</td>
<td>1044</td>
<td>709</td>
<td>203</td>
<td>1055</td>
</tr>
<tr>
<td>Number (Percent) heal</td>
<td>377</td>
<td>809</td>
<td>477</td>
<td>133</td>
<td>811</td>
</tr>
<tr>
<td></td>
<td>(67.9%)</td>
<td>(77.5%)</td>
<td>(67.3%)</td>
<td>(65.5%)</td>
<td>(76.9%)</td>
</tr>
<tr>
<td>Whole course model c Statistic</td>
<td>0.66</td>
<td>0.62</td>
<td>0.73</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>First Encounter model c Statistic</td>
<td>0.66</td>
<td>0.59</td>
<td>0.67</td>
<td>0.71</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Conclusions

- The first time models to predict healing likelihood for various types of wounds/ulcers have been created and validated.
- Data confirm that certain patient and wound factors affect the likelihood of healing in a predictable way.
- The prevalence of significant co-morbid conditions (e.g., diabetes among patients with non-diabetic ulcers, malnutrition, renal transplant) confirms previous observations that the majority of these outpatients would have been excluded from randomized controlled trials in wound healing.
- The next phase of research for the USWR is to use these WHI predictive models to stratify patients/wounds and analyze the effectiveness of various treatments on outcomes.

Strengths and Limitations

- Because all the medical data collected for each patient are transmitted to the registry, it is possible to analyze many contributory factors.
- Because 100% of patients seen at each clinic become part of the registry, there is no selection bias in patient enrollment to the USWR.
- The data represent the patient’s actual medical record, so there is no post hoc vetting of outcome information.
**Strengths and Limitations (cont.)**

- Data affected by the quality and consistency of clinical documentation
- Importantly, as the EHR automatically and internally abstracts the chart to calculate charges and those charges determine both clinic and physician revenue, all clinicians were highly incentivized to perform thorough documentation.

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**WHI will be used to stratify cohorts for PRP trial**

<table>
<thead>
<tr>
<th>Aim</th>
<th>DFU</th>
<th>VLU</th>
<th>PU</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Sites</td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Primary objectives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary objectives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Inclusion (&gt;18 yrs.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Exclusion Criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Subjects</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

Cohort studies approved by CMS for CED to run concomitantly beginning mid-2013.