Therapy

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Orlando

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Miami
Outline

• The Evidence Cycle
• Case Scenario
• RCT appraisal
  • Did the groups start with a similar prognosis?
  • Did we maintain the similarities?
  • What are the outcomes?
• MATH!
• Closing the Case
• Take Home Points
Therapy first impressions:
The Evidence-based Medicine Cycle

The 5 A’s

- ASSESS
- ASK
- ACQUIRE
- APPRAISE
- APPLY

THE PATIENT
Case scenario

- Martin lived in Iowa for 3 ½ years
- Lots of good things happened in Iowa
Iowa is beautiful
But Iowa can be cold
Hawaii is beautiful... and warm

Recruiters convince him to come for a visit.
The visit is a success...

He’s about to sign a new contract
But then there’s this:

Man Of War jellyfish

(You don’t see this in Iowa)
Case scenario

- Martin is stung by a jellyfish
- Brought to lifeguard station
- Pain over his right leg
- No nausea
Case Scenario

• An expert at evidence based medicine who has come to the Duke workshop many times,

• Martin wonders

He thinks there might have been an episode of Friends that addressed this…
Evidence-based Medicine Cycle

The 5 A’s

THE PATIENT

ASSESS

ASK

ACQUIRE

APPLY

APPRAISE
ASK: PICOTT

- Population
- Intervention
- Comparison
- Outcome
- Type of question
- Type of ideal study

• Adults stung by jellyfish
• Hot water
• Cold water
• Improvement in pain
• Therapy

Type of ideal study

Type of question
5. A randomized controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in jellyfish stings.

Lofthus C, Stoltes B, Worby E, Seymour JE, Jiang S, Ibestad GK.


PMID: 18184306

Similar articles
A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings

Conrad Loten, Barrie Stokes, David Worsley, Jamie E Seymour, Simon Jiang and Geoffrey K Isbister

Thousands of bluebottle (Physalia sp.) stings occur each year in Australia.1 Stings cause immediate, intense pain that usually resolves within an hour and is associated with a characteristic linear erythematous eruption (Box 1).2 The first aid management of bluebottle stings is a daily problem for surf lifesavers. Currently, most first aid bodies, including the International Life Saving Federation,3 recommend treatment by topical application of ice packs. There is little scientific evidence to support this,4 and the only study to investigate ice packs was observational with no objective measure of pain, or control or comparator treatment.5

Many marine venoms are heat-labile in vitro.5,8 It is feasible that heat penetrates the human dermis to the estimated depth that nematocysts inject toxins (100–1000 μm),4 and recent clinical research suggests heat may be effective for treating jellyfish stings.9,10 However, previous studies of heat therapy were small10,11 or not randomised,11,12 and only one was published in full.1,2 A randomised controlled trial showed that, compared with ice packs, hot showers significantly reduced pain and treatment duration for bluebottle stings.10

If heat is to be used, it needs to be applied

ABSTRACT

Objective: To investigate the effectiveness of hot water immersion for the treatment of Physalia sp. (bluebottle or Portuguese Man-of-War) stings.

Design: Open-label, randomised comparison trial. Primary analysis was by intention to treat, with secondary analysis of nematocyst-confirmed stings. One half-way interim analysis was planned.

Setting: Surf lifesaving first aid facilities at two beaches in eastern Australia from 30 December 2003 to 5 March 2005.

Participants: 96 subjects presenting after swimming in the ocean for treatment of an apparent sting by a bluebottle.

Interventions: Hot water immersion (45°C) of the affected part versus ice pack application.

Main outcome measures: The primary outcome was a clinically important reduction in pain as measured by the visual analogue scale (VAS). Secondary outcomes were the development of regional or radiating pain, frequency of systemic symptoms, and proportion with pruritus or rash on follow-up.

Results: 49 patients received hot water immersion and 47 received ice packs. The two groups had similar baseline features, except patients treated with hot water had more severe initial pain (VAS [mean ± SD]: 54±22 mm versus 42±22 mm). After 10 minutes, 53% of the hot water group reported less pain versus 32% treated with ice (21%; 95% CI, 1%–39%; P = 0.039). After 20 minutes, 87% of the hot water group reported less pain versus 33% treated with ice (54%; 95% CI, 35%–69%; P = 0.002). The trial was stopped after the half-way interim analysis because hot water immersion was shown to be effective (P = 0.002). Hot water was more effective at 20 minutes in nematocyst-confirmed stings (95% versus 29%; P = 0.002). Radiating pain occurred less with hot water (10% versus 30%; P = 0.039). Systemic effects were uncommon in both groups.

Conclusions: Immersion in water at 45°C for 20 minutes is an effective and practical treatment for pain from bluebottle stings.
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<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>How serious is the risk of bias?</td>
<td></td>
</tr>
<tr>
<td>Did intervention and control groups start with the same prognosis?</td>
<td></td>
</tr>
<tr>
<td>Were patients randomized?</td>
<td>1</td>
</tr>
<tr>
<td>Was randomization concealed?</td>
<td>2</td>
</tr>
<tr>
<td>Were patients in the study groups similar at baseline with respect to</td>
<td>3</td>
</tr>
<tr>
<td>prognostic factors?</td>
<td></td>
</tr>
<tr>
<td>Was prognostic balance maintained as the study progressed?</td>
<td></td>
</tr>
<tr>
<td>To what extent was the study blinded?</td>
<td>4</td>
</tr>
<tr>
<td>Were groups prognostically balanced at the study’s conclusion?</td>
<td></td>
</tr>
<tr>
<td>Was follow-up complete?</td>
<td>5</td>
</tr>
<tr>
<td>Were patients analyzed in the groups to which they were randomized?</td>
<td>6</td>
</tr>
<tr>
<td>Was the trial stopped early?</td>
<td>7</td>
</tr>
</tbody>
</table>
Ideal RCT

*Perfect is the enemy of good*

- Voltaire
RCT validity:

Did they start with the same prognosis?

Did they maintain it?

Did they end with it?

Patients

Intervention

Control

Outcomes

Outcomes
To keep all known and unknown prognostic variables evenly distributed between the groups
Were patients randomized in the paper?

1 RANDOMIZATION
Did they start with the same prognosis?

- To keep all known and unknown prognostic variables evenly distributed between the groups
LET’S DO OUR OWN STUDY:

When we were preparing for this talk we were nervous about people asking difficult questions.

To make it fair, we are going to randomly determine which people in the audience we will take questions from.

CAN I HAVE A VOLUNTEER?
List generation

Head: allowed to ask questions

Tail: no questions permitted
Allocation concealment:

**ENROLLER** should not be able to know, predict or manipulate which group each subject is allocated to.
List generation

Head: Hot water treatment

Tail: Ice treatment
Was randomization (allocation) concealed in the paper?

2 ALLOCATION CONCEALMENT
Were patients in the study groups similar at baseline with respect to prognostic factors?

If not similar:
• Is the difference clinically meaningful?
• If it is clinically meaningful, what is the direction of the bias?
• Which is the sicker group?
RCT validity:

Did they start with the same prognosis?

Did they maintain it?

Did they end with it?
To what extent was the study blinded?
Blinding

- Single Blinded
- Double Blinded
- Triple Blinded
Blinding

Patient

Data collector

Data Analyst

Provider

Outcome adjudicator
Did they maintain the prognosis?

Blinding
To what extent was the study blinded in the paper?
## Allocation Concealment vs Blinding

<table>
<thead>
<tr>
<th></th>
<th>Allocation Concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who?</strong></td>
<td>Enroller</td>
<td>Patients, caregivers, data collectors, adjudicators, analysts</td>
</tr>
<tr>
<td><strong>What?</strong></td>
<td>The list</td>
<td>Group assignments</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Part of randomization</td>
<td>After randomization</td>
</tr>
</tbody>
</table>
RCT validity:

- Did they start with the same prognosis?
- Did they maintain it?
- Did they end with it?
Was follow up complete?
Did they end with the same prognosis?
Loss to follow up

At the start

Patients
N=100

At the end

N=40
Outcomes
N=38
Outcomes

Where would the missing patients be? $N = 22$
Loss to follow up

- We assume they maintained the proportions.
- We carry the last observation forward

If mortality difference is 10% of the patients?
How does a loss of follow up of 1% affect the study?

If mortality difference is 1%?
How does a loss of follow up of 10% affect the study?

Sensitivity analysis:
Loss to follow up

- Patients who are lost often have different prognoses from those who are retained.
- Strategies to deal with lost to follow up: last observation carried forward, worst-case scenario, other statistical modeling.
- The best solution is to assure a good follow up.
Was follow up complete in the paper?

5 LOSS TO FOLLOW UP
Were patients analyzed in the groups to which they were randomized?

INTENTION TO TREAT
Intention-to-treat... Why??

• Preserves balance between the groups.

• Reflects real life.

• Provides a more conservative estimate of effect.
Were patients analyzed in the groups to which they were randomized in the paper?
FIVE MINUTE STRETCH BREAK
Outline

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• MATH!
• Closing the case
• Take Home Points
Math!
Math!

How can we compare the height?

9” 6”
Math!

Height Difference (subtraction) = 9” – 6” = 3”
Math!

Relative height (ratio) = 6'' : 9'' = 0.667
66.7%
Math!

Relative height (ratio) = 6” : 9” = 0.667

Risk

Relative height difference = 100% – RR = 33%
(ratio and subtraction!) 1 – 0.67 = 0.33

Risk

66.7%
Math Summary

number
needed
absolute
difference
harm
control
ratio
increase
treat
event
rate
relative
experimental
to
risk
reduction
screen
## Math Summary

<table>
<thead>
<tr>
<th>Results</th>
<th>Alternative name</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative Risk Difference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A randomised controlled trial of hot water (45\degree C) immersion versus ice packs for pain relief in bluebottle stings

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Thousands of bluebottle (Physalia sp.) stings occur each year in Australia.\(^1\) Stings cause immediate, intense pain that usually resolves within an hour and is associated with a characteristic linear erythematous eruption (Box 1).\(^2\) The first aid management of bluebottle stings is a daily problem for surf lifesavers. Currently, most first aid bodies, including the International Life Saving Federation,\(^3\) recommend treatment by topical application of ice packs. There is little scientific evidence to support this,\(^4\) and the only study to investigate ice packs was observational with no objective measure of pain, or control or comparator treatment.\(^5\)

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Conclusions: Immersion in water at 45\degree C for 20 minutes is an effective and practical treatment for pain from bluebottle stings.

MJA 2006; 184: 329–333
Executive Teaching Decision

• Because of something we learned last year...
• Let’s look at one of the secondary outcomes instead of the primary outcome.
• Box 7 on page 332.
## Results: Radiating Pain

### Table 7: Secondary outcomes at initial treatment and at 24-hour follow-up

<table>
<thead>
<tr>
<th>Clinical effects</th>
<th>Hot water immersion</th>
<th>Ice packs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Pain radiating</strong></td>
<td>5/49</td>
<td>10% (4%–22%)</td>
</tr>
<tr>
<td>Generalised pain</td>
<td>1/49</td>
<td>2% (0–11%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2/49</td>
<td>4% (1%–14%)</td>
</tr>
<tr>
<td>Crossed over to other treatment*</td>
<td>5/45</td>
<td>11% (4%–24%)</td>
</tr>
</tbody>
</table>

**Follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Hot water immersion</th>
<th>Ice packs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itchiness (24 hours or later)</td>
<td>18/42</td>
<td>43% (28%–59%)</td>
</tr>
<tr>
<td>Red mark or minor rash</td>
<td>18/42</td>
<td>43% (28%–59%)</td>
</tr>
<tr>
<td>Raised and red/wheat reaction</td>
<td>8/42</td>
<td>19% (10%–33%)</td>
</tr>
<tr>
<td>Bullous reaction</td>
<td>1/42</td>
<td>3% (0–13%)</td>
</tr>
</tbody>
</table>

* Four patients in each group did not remain for 20 minutes (after which crossover was offered). Thirteen patients could not be contacted for follow-up.
Radiating Pain

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ice packs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Radiating Pain

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot water</td>
<td>5</td>
<td>44</td>
<td>5/49 ~ 10%</td>
</tr>
<tr>
<td>Ice packs</td>
<td>14</td>
<td>33</td>
<td>14/47 ~ 30%</td>
</tr>
</tbody>
</table>
Absolute Risk Difference:
\[ \text{Risk}_{\text{con}} - \text{Risk}_{\text{exp}} = 20\% \]

Relative Risk:
\[ \frac{\text{Risk}_{\text{exp}}}{\text{Risk}_{\text{con}}} = 0.33 \]

Relative Risk Reduction:
\[ 1 - RR = \]

Radiating Pain:

- Absolute Risk Difference: \( \text{Risk}_{\text{con}} - \text{Risk}_{\text{exp}} \)
- Relative Risk: \( \frac{\text{Risk}_{\text{exp}}}{\text{Risk}_{\text{con}}} \)
- Relative Risk Reduction: \( 1 - RR = \)
Math!

Number needed to treat
How many patients do I need to treat to obtain / prevent one extra outcome in the study period.

Number needed to treat = 100% / Risk difference (%)
Radiating Pain:

Absolute Risk Difference: 30% - 10% = 20%
Relative Risk: 10% : 30% = 0.33
Relative Risk Difference: 1 − 0.33 = 0.67

Number needed to treat = 100% / Risk difference
Number needed to treat = 100% / 20% = 5
Usual stumbling block: absolute differences are usually smaller than relative differences

What if?

Risk Difference: \(3\% - 1\% = 2\%\)
Relative Risk: \(1\% : 3\% = 0.33\)
Relative Risk Difference: \(1 - 0.33 = 0.67\)

Number needed to treat = \(100 / \text{Risk difference}\)
Number needed to treat = \(100 \% / 2\% = 50\)
Done with the math
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• Take Home Points
Case Resolution

• Pain was significantly better with hot water
• Martin decided never to go back to Hawaii
• He moved with his family to Orlando instead
Take-home points

• EBM should be focused on our clinical questions about patients or populations
• Failure to do allocation concealment can overestimate the effect size and can be a major source of bias
• For “regular” therapy papers, ITT is preferred to per-protocol analysis
• Don’t be blinded by blinding!
• Make the math simple! Remember to subtract and divide!
Teaching Take-home Points

What strategies did we use to teach these concepts?
Teaching Take-home Points

• Real clinical case – make it applicable!
• Clinical question relevant to different specialties, and even non-medical learners
• Group activities
• Pre-mark article – saves time; reduces stress
• Imperfect articles (you can teach with them)
• Interactivity
• Different teaching strategies (visual learners, math lovers)
• Simplicity: one step at a time, with “no man left behind”
• Triage: you can’t do it all
Questions?