Every Bite Matters: Incorporating Bite-sized Morsels of Evidence-Based Medicine (EBM) into Clinical Education

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Minneapolis VAMC, University of Minnesota

Jess Delaune MD
University of Florida

March 18, 2018
<table>
<thead>
<tr>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
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</tbody>
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NNT 76
LR 3.6
Specificity 78%

**The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**

Mervyn Singer, MD, FRCP, Clifford S. Deutschman, MD, MS, Christopher Warren Seymour, MD, MSc, Manu Shankar-Hari, MSc, MD, FFICM, Djillali Annane, MD, PhD, Michael Bauer, MD, Rinaldo Bellomo, MD, Gordon R. Bernard, MD, Jean-Daniel Chiche, MD, PhD, Craig M. Coopersmith, MD, Richard S. Hotchkiss, MD, Mitchell M. Levy, MD, John C. Marshall, MD, Greg S. Martin, MD, MSc, Steven M. Opal, MD, Gordon D. Rubenfeld, MD, MS, Tom van der Poll, MD, PhD, Jean-Louis Vincent, MD, PhD, and Derek C. Angus, MD, MPH

**JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT**

**Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest**

Paul S. Chan, MD; Robert A. Berg, MD; Yuanyuan Tang, PhD; Lesley H. Curtis, PhD; John A. Spertus, MD, MPH; for the American Heart Association’s Get With the Guidelines-Resuscitation Investigators

**PPV 70%**

**NPV 35%**

**Sensitivity 90%**
Case

- A 76 year old woman is seen on morning rounds after being admitted overnight.

  - Patient has a hx of Alzheimer’s dementia and lives at home with her husband who provides her care
  - For the past 48 hours, her husband notes she has appeared more “lethargic” and her memory may be a little worse than normal
  - She developed a productive cough last night
  - She may have been chilled this morning
  - She denies chest pain, shortness of breath
Past History

Medical/Surgical History:
- Type II DM
- Osteopenia
- Alzheimer's dementia (last MOCA 15/30)
- Hypothyroidism
- L Hip fracture (1 year ago)

Social/Family History:
- 10 year smoking history but quit in her 40s
- Lives at home with husband
- No significant family history
Physical Exam

Temp 99.7          HR 102          BP 129/87          Resp Rate 16          O2 94% (RA)

**General:** Not in acute distress, appears tired

**HEENT:** Moist mucous membranes, sclera anicteric

**Cardiac:** Tachycardic, no murmurs

**Lungs:** ? Crackles at the posterior left lung base

**Ext:** Warm, well perfused, no edema

**Neuro:** Alert, oriented to person, place and year, not month or day. No focal deficits noted.
Out of Curiosity

• How confident are you that this patient has CAP?

76 year old woman
- For the past 48 hours, “lethargic”
- Worse memory
- She developed a productive cough last night
- She may have been chilled this morning
- She denies chest pain, shortness of breath

Temp 99.7  HR 102  BP 129/87  Resp Rate 16  O₂ 94% (RA)

General: Not in acute distress, appears tired
HEENT: Moist mucous membranes, sclera anicteric
Cardiac: Tachycardic, no murmurs
Lungs: ? Crackles at the posterior left lung base
Ext: Warm, well perfused, no edema
Neuro: Alert, oriented to person, place and year, not month or day. No focal deficits noted.
Labs and Imaging

UA: Negative

CXR (2 view): Negative for pulmonary opacifications

Admitting team overnight:
- Possible pneumonia vs PE vs viral upper respiratory tract infection
- Monitor for now
- PT/OT for functional evaluation

ANC: 8.9
Bands: 0

Ammonia: 16
TSH: 1.9
Free T4: 1.2
Procalcitonin: 0.39
Flu Swab: negative
Bite Sized EBM Pearl

“Does a negative chest x-ray rule out pneumonia?” – your medical student

How do you respond?

Let’s take a look at our 4 x 4 boxes!
The 4 x 4 Square!!!

<table>
<thead>
<tr>
<th></th>
<th>Disease Present</th>
<th>Disease Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>True Positive</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>False Positive</td>
<td></td>
</tr>
<tr>
<td><strong>Test Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>False Negative</td>
<td></td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>True Negative</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = \[ \frac{A}{A+C} \]

Specificity = \[ \frac{D}{D+B} \]
### The 4 x 4 Square!!!

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<td>True Positive</td>
<td>B</td>
</tr>
<tr>
<td>C</td>
<td>False Negative</td>
<td>D</td>
</tr>
</tbody>
</table>

- **Sensitivity** = $\frac{A}{A+C}$
- **Specificity** = $\frac{D}{D+B}$
EBM Opportunity!

• A 2012 study published in the American Journal of Emergency Medicine (Wesley et al) looked at chest x-rays and CT scans for diagnosing a “pulmonary opacity.”
<table>
<thead>
<tr>
<th></th>
<th>CT Scan +</th>
<th>CT scan -</th>
</tr>
</thead>
<tbody>
<tr>
<td>pulmonary opacity</td>
<td>83</td>
<td>206</td>
</tr>
<tr>
<td>CXR + opacities</td>
<td>118</td>
<td>1825</td>
</tr>
</tbody>
</table>

Sensitivity: 43.5%
Specificity: 89.9%

But how do we use these clinically?
<table>
<thead>
<tr>
<th></th>
<th>CT Scan + pulmonary opacity</th>
<th>CT scan – pulmonary opacity</th>
</tr>
</thead>
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</tr>
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<td>1825</td>
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Sensitivity: 43.5%
Specificity: 89.9%

Simplify!!!!!
<table>
<thead>
<tr>
<th>CXR + opacities</th>
<th>CT Scan + pulmonary opacity</th>
<th>CT scan − pulmonary opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>CXR − opacities</td>
<td>120</td>
<td>1800</td>
</tr>
</tbody>
</table>

Round
<table>
<thead>
<tr>
<th>CXR + opacities</th>
<th>CT Scan + pulmonary opacity</th>
<th>CT scan − pulmonary opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

Remove some 0’s!
<table>
<thead>
<tr>
<th></th>
<th>CT Scan + pulmonary opacity</th>
<th>CT scan − pulmonary opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR + opacities</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>CXR − opacities</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Divide by 2!
<table>
<thead>
<tr>
<th></th>
<th>CT Scan + pulmonary opacity</th>
<th>CT scan – pulmonary opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR + opacities</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>CXR – opacities</td>
<td>6</td>
<td>9</td>
</tr>
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</table>

Sensitivity: 40%
Specificity: 90%
From these findings, we can calculate an important clinical metric:

**Likelihood Ratios**

**Sensitivity** = % of people with the disease who test positive

40%

**Specificity** = % of people without disease who test negative

90%

Kelleher et al. “Teaching the Un teachable. Linking EBM and Technology to Teach Diagnostic Reasoning.” 2017 AAIM Conference, Baltimore MA.
Sensitivity = % of people with the disease who test positive

Specificity = % of people without disease who test negative

If the test is positive test, how likely is it that they have the disease?

Answer: 4 for every 1 = 4x more likely to have the disease (so, a LR+ of 4).

LR+ = \frac{\text{Sensitivity}}{1 - \text{Specificity}}
If the test is negative, how likely is it that they do NOT have the disease?

**Answer:** 6 blue for every 9 blue = 0.66x likely to have the disease (so, a LR- of 0.66).
<table>
<thead>
<tr>
<th>LR</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Increases the pretest probability of disease by ~45%</td>
</tr>
<tr>
<td>5</td>
<td>Increases the pretest probability of disease by ~30%</td>
</tr>
<tr>
<td>2</td>
<td>Increases the pretest probability of disease by ~15%</td>
</tr>
<tr>
<td>1</td>
<td>No change in the likelihood of disease</td>
</tr>
<tr>
<td>0.5</td>
<td>Decreases the pretest probability of disease by ~15%</td>
</tr>
<tr>
<td>0.2</td>
<td>Decreases the pretest probability of disease by ~30%</td>
</tr>
<tr>
<td>0.1</td>
<td>Decreases the pretest probability of disease by ~45%</td>
</tr>
</tbody>
</table>
Big EBM bite

• So, let’s put likelihood ratios into action
• Back to our case.
Next Day

Temp 101.3°F  HR 108  Blood pressure 98/53

- Cough progressive overnight
  - Levofloxacin started
  - 2L NS given

- Emesis + large Aspiration at breakfast causing hypoxic respiratory failure
  - Emergent intubation
  - Ampicillin/Sulbactam

- Chest x-ray: opacification of the right lower lobe
- WBC count is now 22,000, predominantly neutrophils.
Continued

• In the ICU the patient is given 2 additional liters of normal saline
• 6 hours after admission to the ICU:
  • HR 105, MAP is 55 and norepinephrine is initiated → MAP 65.
    • Norepi @ 0.15 mcg/kg/min
EBM learning opportunity!

• Given the patient’s ongoing hypotension/pressor requirements, should the patient receive more fluids?
  • 4L total fluid
  • Norepinephrine @ 0.15mcg/kg/min

Discussion

How would we answer this question clinically?

Static vs dynamic measurements:
  • Static: CVP or wedge pressures
  • Dynamic: echocardiogram, IVC measurement, leg raising, positive pressure breaths during ventilation
Introducing: likelihood ratios and the JAMA Rational Clinical Exam!

Likelihood ratios (LRs):
- Positive LR: Sensitivity/1 – specificity
- Negative LR: 1-Sensitivity/specificity

All in the context of your “pre-test probability.”
Choose 1:

- CVP < 5
- JVD not present
- Passive Leg Raise with >10% increase in VTI
- PCWP < 11 mmHg
- CVP & PCWP < 8 mmHg & < 12 mmHg, respectively
- Pulse Pressure Variation >12%
Let’s put this in context

JAMA:

• 50 studies
  • Population: Refractory hypotension, HD unstable vs ongoing s/s of end organ perfusion in adults.
  • Overall fluid responsiveness: 50% (i.e. your pre-test probability)

• Likelihood ratios calculated showed the following:

<table>
<thead>
<tr>
<th>Maneuver, Exam, Measurement</th>
<th>+ LR</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive Leg Raise (w/10% increase SV)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Pulse Pressure Variation &gt; 12%</td>
<td>9</td>
<td>0.13</td>
</tr>
<tr>
<td>CVP &lt; 8</td>
<td>2.6</td>
<td>0.5</td>
</tr>
<tr>
<td>PCWP &lt; 11</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>PCWP &lt; 12 &amp; CVP &lt; 8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

https://jamanetwork.com/journals/jama/fullarticle/2556129
So, for our patient what does this mean?

- Let’s start with physical exam. The ICU team feels that the patient appears “dry” and has flat JVD.
What does this mean?

- CVP is estimated to be 5 mmHg
- CVP <8 has a +LR of 2.6
JVD

- JVD is distended
  - JVD + and – LR are ~1
Passive Leg Raise

- PLR $\rightarrow$ cardiac output increases 12%
  - PLR increase $> 10\%$ has a $+$LR of 11
Back to our patient..

• After evaluation, it is felt that the patient needs further fluid resuscitation.

• Proposing treatment and management options!
  ✓ Type of study (RCT best for original studies, SR, meta analysis etc...)
  ✓ CASP evaluation for thorough (or rapid) evaluation of studies

What type of fluids would you give?
Our Question!

• If we were to give this patient more fluids, should we order normal saline or balanced crystalloids?

• How would you evaluate this journal article to determine if you should incorporate the findings into your clinical practice?
1. Are the results of the study valid?

2. What are the results?

3. Will the results help locally?
Are the results of the trial valid?

• Did the trial address a clearly focused issue?
  • PICO statement

• Was the assignment of patient to treatments randomized?
  • How was this carried out?

• Were all of the patients who entered the trial properly accounted for at its conclusion?
  • Was the trial stopped early?
  • Were patients analyzed in the groups to which they were randomized?

• Were patients, health workers, and study personnel “blind”?

• Were the groups similar at the start of the trial?

• Aside from the experimental intervention, were the groups treated equally?
What are the results?

• How large was the treatment effect?
  • What outcomes were measured?
  • Is the primary outcome clearly specified?
  • What results were found for each outcome?

• How precise was the estimate of the treatment effect?
  • What are the confidence limits?
Will the results help locally?

• Can the results be applied to your context or to the local population?
  • Do you think that the patients covered by the trial are similar enough to the patients to whom you will apply this? If not, how do they differ?
• Were all clinically important outcomes considered?
• Are the benefits worth the harms and costs?
1) Did the trial address a clearly focused issue?
- PICO
  • **Population**: Critically ill adult patients
  • **Intervention**: Balanced crystalloids
  • **Comparison**: Normal saline
  • **Outcome**: Major adverse kidney event within 30 days (composite of death, new receipt of RRT, persistent renal dysfunction)
2) Was the assignment of patients to treatments randomized?
   - Patients were cluster-randomized (randomized to balanced crystalloids or normal saline by which ICU they were admitted to and which month they were admitted)

3) Were all of the patients who entered the trial properly accounted for at its conclusion?
   • Patient were analyzed by intention-to-treat analysis despite some crossover
   • The trial was not stopped early
   • No patients were loss to follow-up
4) Were patients, health workers and study personnel ‘blind’?
   • No except for the trial personnel who performed the manual chart reviews

5) Were the groups similar at the start of the trial?
   • Yes

Demographics evaluation
6) Aside from the experimental intervention, were the groups treated equally?
   • Yes
7) How large was the treatment effect?

- Absolute Risk Reduction = 1.1% in favor of balanced crystalloids for the primary outcome
- NNT = 94

8) How precise was the estimate of the treatment effect?

- Evaluate p-value and confidence intervals!
9) Can the results be applied in our context?

- Note that this was a pragmatic RCT versus a classical RCT. Essentially pragmatic RCTs ask whether an intervention works is real life. Samples sizes tend to be large. The overall design of the study is simpler. There is broad or no eligibility criteria. Study procedures are embedded into routine clinical care and they are done by clinical personnel. The study is conducted in diverse settings.
  - This results in high EXTERNAL validity
9) Can the results be applied in our context? (continued)

- However, there are caveats to take note of in this article:
  - Private health care system, predominantly white population
  - The diagnosis on ICU admission was sepsis or septic shock in ONLY ~15% of patients although in subgroup analysis the difference in outcomes appeared to be greater for patients with sepsis and those who received large volumes of isotonic crystalloid
10) Were all clinically important outcomes considered?
   • Hyperkalemia?
   • Others?

11) Are the benefits worth the harms and costs?
   • Cost different between NS and LR minimal (25 cents/liter)
   • Plasmalyte much more expensive

12) Conclusion
   • Indiscriminate use of normal saline in critically ill adults is not recommended

Thank you to Grant Jester, MD for his assistance
In Conclusion:

• EBM allows us to appropriately form our own illness scripts with numbers and of course evidence
• It allows you to choose your own adventure
Choose your own Adventure!!
Tools

- [https://www.mentimeter.com/](https://www.mentimeter.com/)
- Apps:
  - DocNomo (free) ➔
  - EBM Tools
  - Bayes
  - Medcalc 3000
  - Med Toolkit
Summary

• Bite-sized EBM can be incorporated into morning reports
• EBM tangents should be no longer than 5 minutes
• Critically appraise an article quickly (e.g. CASP)

Tools
• Make them commit (e.g. Voting app)
Questions, Concerns, Critiques, Queries

• Contact information
  • Nick Ingraham – ingra107@umn.edu