Thunderclap

Making Evidence Matter
Disclosures

• Paid Editorial Role JAMA’s The Rational Clinical Examination

• No other disclosures or conflicts of interest
Objectives

• Recognize the evidence cycle and “hierarchy” of studies for answering clinical questions
• Connect the process of finding and appraising evidence to direct patient care
• Reflect on engaging teaching tools and strategies (including how to engage your patients)
Fundamental Principles

• Not all evidence is created equal

  A Hierarchy of evidence helps us differentiate information more likely to be valid or true

• Evidence alone is never enough

  Decisions are informed and guided by patient values and preferences.
Ask

Acquire

Appraise

Evidence-based medicine cycle

Values & Preferences

Hierarchy of Evidence

Patient dilemma

Apply
Written informed consent was obtained to share this story...
Patient Interview…

• Listen to the audiotape.
• Please decide what is the most important question being posed in this case…
Debrief Audio…

• What was the most important question being posed in this case?
What is AA’s Prognosis?

• “...on a scale of these things that I’ve seen you seem to be on the good end of things”

• What level of confidence do you have in this estimate?

• What else do you need to know?
Audience Participation

- Open envelopes
- Thunderclap Headache CARDS—Please Raise Cards as I name your color
  - PINK
  - WHITE
  - YELLOW
  - ORANGE
  - GREEN
- All of you had a Thunderclap headache. We will return to this.
Patient Interview (2)…
What is AA’s Prognosis?

• “… 19 out of 20 times when there is bleeding in your brain, it’s an aneurysm. We think you might be the 1 out of 20 times where a vein bled.”

• What level of confidence do you have in this estimate?

• Reflections on the communication strategy?
Audience Participation

• Everyone please stand

• I’m sorry. You have a cerebral aneurysm (please sit)
  • PINK
  • ORANGE
  • YELLOW

• NOT a Cerebral Aneurysm (remain standing)
  • GREEN
  • WHITE

• What are you feeling?
Patient Interview (3)
Audience Participation

- Cerebral Aneurysm CARDS
  - PINK
  - ORANGE
  - YELLOW
- RCVS vs. Vein Bleed CARDS
  - GREEN
  - WHITE
- How did this interaction change your perspective?
Just a simple request

• AA: I want to see another Neurologist for another opinion…
• SK: Why?
• AA: So many questions…What is RCVS? What will happen? I don’t understand what this means or what I am supposed to do.
• SK: (inside voice: Ugh…)}
Now what?

- AA’s questions…What is RCVS? What will happen? I don’t understand what this means or what I am supposed to do.

- Background vs. Foreground question?
Summary of critical elements for the diagnosis of reversible cerebral vasoconstriction syndromes

1. Recurrent acute, severe headaches, with or without additional neurologic signs and symptoms.
2. Transfemoral angiography or indirect (CT or MR) angiography documenting segmental cerebral artery vasoconstriction.
3. No evidence for aneurysmal subarachnoid hemorrhage.
4. Normal or near-normal cerebrospinal fluid analysis results (total protein content <80 mg/dL, white blood cell count <10/mm³, normal glucose content).
5. The diagnosis cannot be confirmed until reversibility of the angiographic abnormalities is documented within 12 weeks after onset or, if death occurs before the follow-up studies are completed, autopsy rules out conditions such as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest as headache and stroke.

RCVS: reversible cerebral vasoconstriction syndromes; CT: computed tomography; MR: magnetic resonance.

From Annals of Internal Medicine, Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: Reversible cerebral vasoconstriction syndromes, Volume 146, Issue 1, Pages 34-44. Copyright © 2007 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.
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Patient dilemma

Ask

Acquire

Appraise

Evidence-based medicine cycle

Hierarchy of Evidence

Apply

Values & Preferences
Your Clinical Questions

- **P**: Patient, population, problem
- **I**: Intervention, exposure, prognostic factor
- **C**: Comparison
- **O**: Outcome
- **T**: Type of question
- **T**: Type of study design
My First Clinical Question

• **P**: Headache and intracranial vasospasm
• **I**: Followed over time
• **C**: --
• **O**: Rebleed, headaches, mortality
• **T**: Prognosis
• **T**: Cohort or Follow up Study (Prospective)
Evidence-based medicine cycle:

1. Ask
2. Acquire
3. Appraise
4. Assess
5. Apply
6. Values & Preferences
7. Hierarchy of Evidence
8. Patient dilemma
My First Clinical Question

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<td>#1</td>
<td>Headache</td>
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<td>#2</td>
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<td>#3 AND #4</td>
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Another Search

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<th>#1</th>
<th>“reversible cerebral vasoconstriction syndrome”</th>
<th>71,156</th>
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<tbody>
<tr>
<td>#2</td>
<td>Cohort Study</td>
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<td>#5</td>
<td>#3 AND #4</td>
<td>7</td>
</tr>
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</table>

Chen et al. Neurology 2015; 84(15):1552-8
My Paper’s MeSH Terms

- Follow up studies
- Headache
- Recurrence
- Vasospasm

MeSH Terms
- Adult
- Female
- Follow-Up Studies
- Headache/diagnosis
- Headache/epidemiology*
- Headache/etiology
- Humans
- Male
- Middle Aged
- Recurrence
- Sexual Behavior
- Syndrome
- Taiwan/epidemiology
- Time Factors
- Vasospasm, Intracranial/complications
- Vasospasm, Intracranial/diagnosis
- Vasospasm, Intracranial/epidemiology*
Searching for Cohort Studies

- Cohort Study
  - Follow-up Studies
  - Longitudinal Studies
  - Prospective Studies
  - Retrospective Studies
Ask
Acquire
Appraise

Evidence-based medicine cycle

Values & Preferences

Hierarchy of Evidence

Patient dilemma

Apply
Critical Appraisal Framework

I. How serious is the risk of bias? (*used to be called are the results valid?)

II. What are the results?
   • Magnitude of effect
   • Confidence / precision of estimate

III. How can I apply to patient care
Cohort Study

How Serious is the Risk of Bias?

• Was the sample of patients representative?
• Were patients classified into prognostically homogeneous groups?
• Was follow-up sufficiently complete?
• Were outcome criteria objective and unbiased?
Cohort Study
What Are the Results?

• How likely are the outcomes over time?
• How precise are the estimates of likelihood?
Cohort Study
How Can I Apply to Patient Care?

• Were the study patients and their management similar to those in my practice?
• Was the follow-up sufficiently long?
• Can I use the results in the management patients in my practice?
Evidence Summary: Chen 2015

• Representative?
  • Prospective cohort of 210 RCVS patients from Tai Pei Veteran’s Clinic: initial thunderclap between 2000-12
  • Tertiary care referral filter

• Prognostically homogeneous? Yes. All with first thunderclap (early and uniform)

• Objective and unbiased outcomes?
<table>
<thead>
<tr>
<th>Investigations for patients with suspected RCVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive history-taking and headache intake form</td>
</tr>
<tr>
<td>Neurologic examination</td>
</tr>
<tr>
<td>Complete blood counts, biochemical panels, thyroid function, autoimmune profiles</td>
</tr>
<tr>
<td>Blood testing</td>
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<tr>
<td>MRI</td>
</tr>
<tr>
<td>Sequences include T1, T2, FLAIR, CUBE FLAIR, T1 with contrast, T1-FLAIR with contrast, T2∗ gradient echo and/or SWI, DWI, ADC, MRA, and magnetic resonance venography</td>
</tr>
<tr>
<td>Extracranial and transcranial duplex sonography</td>
</tr>
<tr>
<td>Extra- and Trans-cranial Duplex</td>
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<tr>
<td>CSF studies</td>
</tr>
<tr>
<td>Xanthochromia, cell counts, glucose, protein, cultures</td>
</tr>
</tbody>
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Abbreviations: ADC = apparent diffusion coefficient; DWI = diffusion weighted image; FLAIR = fluid-attenuated inversion recovery; MRA = magnetic resonance angiography; RCVS = reversible cerebral vasoconstriction syndrome; SWI = susceptibility weighted image.

The severity of vasoconstrictions on MRA was graded on a 5-point scale: 0 (0% to <10%), 1 (10% to <25%), 2 (25% to <50%), 3 (50% to <75%), and 4 (≥75%), and designated the “vasoconstriction score” of each arterial segments for computations. The vasoconstriction scores of both sides were averaged to derive a mean score. The mean scores of different arterial segments were averaged to derive a combined score.⁷

⁷ V MCA = mean flow velocity of middle cerebral artery; V ICA = mean flow velocity of the distal extracranial internal carotid artery; Lindegaard index = V MCA/V ICA.
Death: 0
Re-bleed: 0
Evidence Summary: Chen 2015

• How likely are outcomes?
  • 12 year study
  • Mean follow up 37.5 +/- 24.4 months
  • Thunderclap headaches:
    • New thunderclap: 18/168 (~10%)
    • Probable RCVS: 9/168 (~5%)
  • Re-bleed: 0
  • Dead from Neurologic Complication: 0
Evidence Summary: Chen 2015

• How precise are the estimates?
  • No 95% CI anywhere in the paper
    • New thunderclap: 18/168 (~10%)
    • Probable RCVS: 9/168 (~5%)
  • Re-bleed / death: 0; might be as high as 1.8%
  • What about lost to follow up? 40 patients-contributes uncertainty 40/210 = ~20%

*rule of 3’s for extreme results- Table 20-1
And One More…

- Second Prospective trial (Ducros Brain 2007; 130:3091)
- Paris Headache Center 67 consecutive patients
- 24/67 (35%) mild persistent headache, 2 had depressive symptoms (comparison)
- No death, no relapse, no re-bleeds in 16 +/-12.4 months of follow up
Curbside a neurology colleague

Sheri says:
  - RCVS prognosis looks good!
  - Does she have RCVS?
  - Have a look?

Neurologist verdict: Vein bleed…

Sheri (inside voice: Ugh…..)
Vein Bleed Prognosis

- Vein Bleed: Perimesencephalic SAH
- Multiple cohorts (differing quality) but all show good prognosis
- Look at Greebe et al
Life expectancy after perimesencephalic subarachnoid hemorrhage

Greebe et al. Stroke 2007; 38:1222-4
Greebe et al

• Retrospective analysis of prospectively collected data (Netherlands)

• 160 patients with vein bleed followed for 1213 patient years (1983 to 2005)

• Mean follow up 7.5 years (1 to 23 years)
Greebe et al

- 11 patients died
  - MI, cardiac failure, cerebral infarction, cancers, infection in old age
- Standardized mortality ratio that was age and sex adjusted 0.61 (95% CI, 0.34 to 1.1)
- Worst case scenario (2 patients abroad counted as dead) 0.72 (95% CI, 0.42-1.24)
- No new SAH - 0% with 95% CI (0 -0.3%)
Audience Participation

- RCVS vs. Vein Bleed CARDS
  - GREEN
  - WHITE
- What are you thinking and feeling now?
Audience Participation

• What do I know about functional status?
• Everyone Raise your cards when your color is called
• Functional Status Dots
  - PINK DOT = DEAD
  - ORANGE ON ORANGE CARD = ANEURYSM DISABLED
  - ORANGE ON WHITE CARD = RCVS HEADACHE
  - GREEN = NO RECURRENCE, NO SYMPTOMS

• Data on lifting 35 lbs? Data on exercising?
• What do you tell her?
Take home points

• Not all evidence is created equal
  A Hierarchy of evidence helps us differentiate information more likely to be valid or true

• Evidence alone is never enough
  Decisions are informed and guided by patient values and preferences.

• Evidence based medicine begins and ends with the patient.
  The evidence cycle provides a framework for integrating evidence directly into patient care.