Disclosures

• Paid Editorial Role JAMA’s The Rational Clinical Examination

• No other disclosures or conflicts of interest
Objectives

• By attending the session, participants will be able to:
  • Apply the 5 elements of the evidence cycle
  • Differentiate between foreground and background questions and match information resources for each
  • Gain appreciation for the hierarchy of evidence of a prognosis question
  • Apply communication techniques for engaging patients in discussion about prognosis
Begin at the Beginning....

The Foundations
Two Fundamental EBM 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
EBM Cycle
Hierarchy of Evidence
Patient dilemma
Values & Preferences
Act & Assess
Apply
Written informed consent was obtained to share this story...
Go to Audio…

Audience Participation

• 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”

- How do you understand this description of prognosis?
Audience Participation

- Thunderclap Headache CARDS—Please Raise Cards as I name the color of your CARD
  - RED
  - WHITE
  - YELLOW
  - BLUE
  - GREEN

- All of you had a Thunderclap headache. We will return to this.
Go to Audio…
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.”

• How do you understand this description of prognosis?

• Reflections on the communication strategy?
Audience Participation

- Everyone please stand
- I’m sorry. The following color cards have a cerebral aneurysm (please sit if I call your color)
  - RED
  - BLUE
  - YELLOW
- NOT a Cerebral Aneurysm (remain standing)
  - GREEN
  - WHITE
- Observations? Comments?
Go to Audio...
Audience Participation

- RCVS OR Vein Bleed CARDS
  - GREEN
  - WHITE
- How did this interaction with the neurologist 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.

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

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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.
Evidence-based medicine cycle

Ask

Acquire

Appraise

Patient dilemma

Hierarchy of Evidence

Values & Preferences

Apply
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 Clinical Question

• **P**: Headache and intracranial vasospasm
• **I**: Followed over time
• **C**: --
• **O**: Rebleed, headaches, mortality
• **T**: Prognosis

**Background**

• **T**: Cohort or Follow up Study (Prospective)
Flow of a Cohort (Prognosis)

People with Headache

Probability of Outcomes Over Time
Flow of a Cohort (Prognosis)

People with Headache

Probability of Outcomes Over Time

Cohort at risk for outcome; measure outcome
Patient dilemma

Evidence-based medicine cycle

Hierarchy of Evidence

Ask

Acquire

Appraise

Apply

Assess

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

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

- Follow up- studies
- Headache
- Recurrence
- Vasospasm
Searching for Cohort Studies

• Cohort Study
  • Follow-up Studies
  • Longitudinal Studies
  • Prospective Studies
  • Retrospective Studies
Ask

Acquire

Appraise

Evidence-based medicine cycle

Patient dilemma

App

Assess

Hierarchy of Evidence

Apply

Values & Preferences
Critical Appraisal Framework

I. How serious is the risk of bias?

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?
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>Table 2</th>
<th>Diagnostic evaluations for patients with suspected RCVS in our headache center</th>
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<tr>
<td>Investigations for patients with suspected RCVS</td>
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<td>Comprehensive history-taking and headache intake form</td>
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<td>Neurologic examination</td>
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<td>CSF studies</td>
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**H & P**

**Neuro Exam**

**Labs**

**MRI**

**Extra- and Trans-cranial Duplex**

**CSF**

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* 

*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}.*
Patients with RCVS (N=210)

Outpatient clinic follow-up

Telephone follow-up at 6 m & 1, 2, 3, 5, 7, 10 yrs

Occurrence of new headaches

Respondents (n=168)

Death: 0
Re-bleed: 0

Died of malignancies (n=2)

Lost to follow up (n=40)

No new acute severe headaches (n=150)

New thunderclap-like headaches (n=18)

Probable RCVS (n=6)
Migraine (n=2)
Unclassified (n=1)

Recurrent RCVS (n=9)
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
Back to AA’s Questions

• 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
• 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)
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 OR Vein Bleed CARDS
  - GREEN
  - WHITE
- What are you feeling now?
Go to Audio...
Audience Participation

• What do I know about functional status?
• Everyone Raise your cards when your color is called
• Functional Status Labels
  • **RED** = DEAD (all in the SAH group)
  • **BLUE** = some level of dysfunction or deficit
    • **BLUE ON BLUE CARD** = aneurysm lives with deficit
    • **BLUE ON WHITE CARD** = RCVS has headache
  • **GREEN** = Great! NO RECURRENCE, NO SYMPTOMS

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