Clinical Epidemiology I: Deciding on Appropriate Therapy

Clinical Scenario [UG2B]

- 65 yo man
- controlled HTN
- 6-mo Hx cardioversion-resistant afib
- Benefit vs risk of long-term anticoagulation:
  - ? prevent embolic stroke
  - ? induce hemorrhage

What is Clinical Epidemiology?

- Applying population-based information
- … to optimize patient care
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- Information source: peer-reviewed medical literature
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- Problem 1: Finding relevant information
- Problem 2: Assessing quality of information found

Finding relevant information

- Colleagues
- Textbooks
- Review articles
- Medline
  - Sources
    - CD-ROM
    - On-line library services (ovid at UofC)
    - Grateful Med
  - Focused searches
    — PT = Publication Type

A Model for Evidence-Based Practice

- Clinical Scenario
- The Search
- The Framework
  - Are the results of the study valid?
  - What were the results?
  - Will the results help to to care for my patients?

What color is evidence?

"Unfortunately, evidence comes in shades of gray. Often, results may be valid, perhaps demonstrate an important effect, and might improve patient care."

— Oxman, et al (1993): 2093.

Types of clinical questions

From Oxman, et al, JAMA 1993; 270: 2093–2095

- **Primary Studies**
  - **Therapy**
  - **Diagnosis**
  - **Harm**
  - **Prognosis**
- **Integrative Studies**
  - **Overview**
  - **Practice Guidelines**
  - **Decision Analysis**
  - **Economic Analysis**

What counts as evidence?

- Evidence depends upon the question being asked
- For instance, “How effective is a therapy likely to be?”
- “Therapy” here includes
  - Treatment of disease
  - Interventions to prevent disease
  - Interventions to lower risk
- “Effective” = produces better outcomes (on average)

Reader's Guide: Articles about Therapy

Recap:

- Are the results valid?
  - Primary Guides
  - Secondary Guides
- What were the results?
  - Describing effects of treatment
- How will the results help my patients?

Are the results valid?

What is “validity”?

- Does the effect of treatment as reported accurately reflect the actual size and direction of the treatment's effect?
- Does the study provide an unbiased assessment of effectiveness, or could it plausibly be distorting the picture in a systematic way?

Primary Guides for validity

- Was assignment of patients to treatments randomized?
- Were all patients who entered the trial properly accounted for and attributed at its conclusion?
  - Was follow-up complete?
  - Were patients analyzed in groups to which randomized (ITT)?

Primary Guides for validity

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Randomized Clinical Trials—Issues

- Randomized allocation to treatment
- Blinding
- Placebo controls

Randomization & Concurrent Controls

- Randomized vs nonrandomized assignment to Rx
- "The randomized clinical trial is the epitome of all research designs because it provides the strongest evidence for concluding causation."
- Nonrandom assignment of treatment
  — differences in outcome could be due to
  - Factors associated with the treatments under test, or
  - Factors associated with the assignment to treatment

clinical outcomes result from many causes, and treatment is just one of them: underlying severity of illness, the presence of comorbid conditions, and a host of other prognostic factors (unknown as well as known) often swamp any effect of therapy. Because these other features also influence the clinician's decision to offer the treatment at issue, nonrandomized studies of efficacy are inevitably limited in their ability to distinguish useful from useless or even harmful therapy.

useless or even harmful therapy. As confirmation of this fact, it turns out that studies in which treatment is allocated by any method other than randomization tend to show larger (and frequently false-positive) treatment effects than do randomized trials.[10-13] The beauty of randomization is that it assures, if sample size is sufficiently large, that both known and unknown determinants of outcome are evenly distributed between treatment and control groups.

Primary Guides for validity

- Was assignment of patients to treatments randomized?
- Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Complete follow-up

- "Where did all of the patients go?"
- Validity depends on knowing outcomes of all (or most) patients enrolled
- Why?
- Outcomes and availability for followup are often related
- Examples:
  - Regular visits vs PRN visits for asthma
  - Dropout a precursor of death

The intention-to-treat principle:

“Patients must be analyzed in the groups to which they were randomized”

Intention-to-treat

- Not necessarily the only analysis
- Comparing "all-treated" to "all-randomized"
- Why might it be bad to exclude noncompliant patients?

Secondary Guides for validity

- Were patients, health workers, study personnel blind to treatment?
- Were groups similar at the start of the trial?
- Aside from experimental intervention, were groups treated equally?

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Blinding

- Good practice: factors that can affect the evaluation of outcome should not be permitted to influence the evaluation process
- Double-blind design
  - Neither patient nor outcome evaluator knows Rx to which patient was assigned
- Single-blind
  - Patient or evaluator is blinded as to Rx, but not both
- Triple-blind
  - Patient, Physician, and Data analyst are blinded as to Rx identity

Are unblinded trials invalid?
— NO !!

- Blinding may not be possible
  Medical vs surgical treatment for CHF
- Outcome assessment may not be subject to bias
  Lab results
- Assessor of outcome may not be able to influence outcome
  Length of stay

Secondary Guides for validity

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Similarity of comparison groups

- Randomization tends to produce this
- Imbalance can often be adjusted for in analysis
- Major differences between groups on prognostic factors can influence interpretation

Secondary Guides for validity

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Example: Differential Followup

- Outcome:
  - Time to metastatic disease in prostate cancer
- Treatments:
  - Watchful waiting
  - Radical prostatectomy
- RP pts evaluated every two months; WW pts PRN
- RP pts “relapse faster”
- BUT — RP patients were more likely to have their relapse discovered early