CLINICAL RESEARCH CURRICULUM

Critical appraisal of the medical literature

Why read?

"It is astonishing with how little reading a doctor can practice medicine, but it is not astonishing how badly he may do it"

Why read?

- It is highly likely that your clinical practice will reflect your residency training for a long time; practice patterns remain constant
- However, medical and surgical treatments and techniques are constantly changing; only constant is change
- Physicians have a fiduciary responsibility to continually update one's knowledge of diseases and their treatment
- Ways of expanding your knowledge and skills:
  - Journal articles
  - Specialty meetings and CME activities
  - Colleagues in your own practice
  - Colleagues in other practices and specialties
  - Instruction Courses

Why read?

- The uncertainty of medical practice only begins after residency training
- Reading journal articles allows a surgeon to "experience" treatment and outcomes in patients not commonly encountered
- Reading journal articles allows a surgeon to compare one's experience with that if others
  - Should be an impetus for improving one's practice
- Continue CME to reduce uncertainly of medicine

Why read critically?

- Most surgeons “read” journal articles by scanning the abstracts
- Abstracts rarely tell the whole story, do not contain enough details or nuances, and are frequently biased
- Abstracts are the appetizers that should get your interest up, but it cannot be the main course (Methods, Results, and Conclusions)
  - The rest of the article contains the important nuances
- Beware of reading only abstracts, especially if you plan to change your practice based on the study!

Why read critically?

- "Most medical articles are biased in some way"
  - Has mostly to do with levels of evidence
  - Who writes most of the journal articles?
  - What are the associated biases?
- Bottom line:
  - Do NOT believe anything people write until you've convinced yourself it was a well done study with valid conclusions.
  - The data holds the truth. The review process is supposed to weed out poor studies but it is not always the case.

Critical appraisal of the Literature

- What is the objective/hypothesis of this manuscript?
  - Is it relevant for clinical care?
- What outcomes are being measured?
  - What is the data type gathered?
- Is the study biased, is there confounding, can the results be explained by chance?
  - Subject selection, data collection proper?
- Are the conclusions supported by the study data?
  - Appropriate statistics, adequate power?
- Was the study ethical and without conflict of interest?
- Are the findings clinically relevant?

Types of Medical Articles

- **Original Scientific Research**
- **Reviews (Scientific, meta-analysis)**
- **Short (Rapid) Communications**
- **Case Reports**
- **Clinical photographs**
- **Letters to the Editor**
- **“How I Do It”**

Step 1:
Assess if the article is relevant?

- Can the information in this study be used to improve patient care and public health?

Step 2: What type of study is it?

- Descriptive studies
  - Data used for descriptive purposes and not used to make predictions
  - Correlational studies, case reports or series, cross sectional surveys
  - Measures of central tendency (mean, median, mode)
- Inferential studies
  - Use data from study sample to derive conclusions and/or make predictions about the population
  - Statistics used to prove or reject hypothesis

Step 2: What type of study is it?

- Therapeutic studies
  - Investigate the results of treatment.
- Prognostic studies
  - Investigate the effect of a patient characteristic on the outcome of the disease
- Diagnostic studies
  - Investigate a diagnostic test
- Economic and decision analysis
  - Develop an economic or decision model

Step 3: What is the intervention?

- What are the dependent, independent, and confounding variables of the study?

Step 4: Who are the subjects

- Who are the subjects?
  - The ideal patients to study is from a random sample
  - In fact, most studies do not use a totally random sample, thus introducing selection bias
  - Review subject inclusion/exclusion criteria carefully to determine if the subjects are similar to your patients and to assess external validity

Step 5: Is the study internally valid? aka Do I believe the study?

- Internal validity
  - Credibility of the findings for the study sample
  - Look at objectives then conclusions
  - Then need to assess if the conclusions are supported by the study by confirming:
    - Proper study design (Methods)
    - Unbiased measurements of outcome measures (Methods)
    - Appropriate statistical analysis of data (Results)

Internal validity
Assess hypothesis/objective of the study

Hypothesis/Objectives

- Research hypothesis → what the researcher predicts
- Null hypothesis (Ho) → there is no difference in outcome between the two groups; in general expect the null hypothesis to be rejected because researcher usually predicts a difference between groups
- Alternate hypothesis (H1) → there is a difference between the groups; typically, researcher expects this to be supported so this is the research hypothesis

What type of study is it?

- Levels of evidence
  - 1. Level 1: Randomized controlled trial
  - 2. Level 2-a: Controlled trial without randomization
  - 3. Level 2-b: Cohort or case-control studies
  - 4. Level 2-c: Uncontrolled trials, nonrandomized cohort
  - 5. Level 3: Case series, case reports, expert opinion, conclusions extrapolated indirectly from scientific studies

- Randomized trial
  - Interventions are randomly allocated
  - Both treatment and control groups are equally eligible subjects
  - Best design is when neither the investigator nor the subject know which group they are in (double blinding)
  - Usually the best research approach
  - However, bias is likely to occur if the hypothesis has not been generated *a priori*

- Cohort study
  - A cohort is a group of subjects followed forward in time
  - Best for defining the incidence of and potential causes of a condition
  - Expensive and inefficient way to study rare outcomes
  - Prospective cohort studies become more efficient as the outcomes become more common

- Case-control studies
  - Select a group of subjects with a condition (cases), then look for risk factors, and compare with a group of similar subjects without the condition (controls), then look for similar risk factors
  - Much cheaper to do this type of study than cohort or cross sectional studies
  - Potential biases include sampling bias and differential measurement bias (because data collection begins after the event of interest)

- Case series and reports (most articles in otolaryngology journals are of this type)
  - Has a high probability for bias
  - These studies must present
    - A priori protocol to collect and analyze date
    - Include all eligible subjects in a specified time period
    - Have follow-up data for at least 80% of enrolled subjects
    - Follow-up duration must be adequate
    - Present complete outcomes

Internal validity
Reject or support the hypothesis?

- Need proper Statistics ☹
- Research involves measurement of data
- Evaluation of the data for significance (hypothesis testing) requires knowledge of statistical principles
- The data type that is collected decides the type of statistics that should be used for hypothesis testing

Assess data measurement

- How was the data measured?
  - Who measured it?
    - Typically want the individual collecting and interpreting the data to have no knowledge of the treatment rendered
    - Always assume bias if that is not the case
    - Then have to decide how much bias there may be in collection, analysis, and interpretation of data
    - If the unblinded treating individual is also collecting and interpreting the data there is potential for bias.

Assess adequate sample size

- Especially important for descriptive statistics
  - 83% success rate in 6 patients is different from same success rate in 600 patients
- In general, inferential statistics take sample size into consideration
  - Results may trend towards significance ($p = 0.05$) with low sample size but become significant if more subjects were enrolled
- In research design, however, power calculations should be done to assess adequate sample size

Look for Sources of Bias in the Study

- Bias
  - Things that may influence the research and lead to a systematic deviation from the truth
  - May occur in each stage of data manipulation:
    - Collection
    - Analysis
    - Interpretation
    - Publication
    - Review

Few examples of Bias

- Design bias
- Ascertainment bias
- Selection bias
- Observer bias
- Reviewer bias

- See next week's article to get the list of different types of bias

Look for Confounding Variables

- A confounding variable is one that is associated with the predictor variable and is a cause of the outcome variable
  - Example: An association was seen in a study between coffee drinking and MI.

  However, if more coffee drinkers were also smokers then smoking is the confounding variable

  - So need to know other risk factors for disease

  - Randomization reduces confounding but this research design is not always possible

Look for adequate follow-up

- In general the follow-up should be at least 80%.
- Inadequate follow-up or too many loss to follow-up is a serious flaw in research;
  - What if only the happy patients followed up with the study?
- The authors should account for all patients lost to follow-up, and at least discuss the potential bias and data scenarios

Assess statistical measures used and findings

- What is the data type measured for outcomes?
  - Nominal (categorical)
  - Ordinal (rank order)
  - Continuous
  - Ratio

- Check that proper statistical analysis was performed; example,
  - Categorical date → chi square
  - Ordinal data → Mann - Whitney U Test, spearman's rho, weighted kappa
  - Continuous data → t-test, Z-test
- Keep a statistical reference book handy to review new statistical terms while reading journal articles until familiar with it

- When a difference is shown, it could be due to (1) chance or (2) a true finding:
  - Chance (Type I error), False positive
  - Generally we accept less than 5% chance of type I error; so check that alpha level (P value) is set at ≤0.05 for level of significance.

- When no difference is found (accept null hypothesis), it could be the truth or it could be false negative (Type II error, beta)
  - Beta is typically set at 20%
  - Power of the study is defined as the probability of true positive (accept alternate hypothesis), typically 0.80 (i.e. there is an 80% chance of detecting the difference if one truly exists)

Step 6: Is there external validity?

- External validity
  - Generalizability of the study to other population across
  - Can you safely generalize the internally valid findings to the general population
  - Was the study sample chosen appropriately and described in adequate detail for results to be generalized
  - Requires good sampling scheme, subject selection criteria, descriptive characteristics of the study sample

Step 7: Was the study ethical?

- Was the study original, approved by an IRB, and free of conflicts of interest?

Do authors report financial relationships that can bias findings?

- Most important to report financial relationship in industry supported research
- Industry supported research is 3-4 times more likely to reach pro-industry conclusions
- Editors, reviewers, and readers must all assess if a competing interest causes bias

Is there Disclosure?

- Disclosure
  - "the act of revealing something"
- Medical Disclosure
  - Author, editor, and reviewer must disclose any financial or personal relationships that inappropriately influence (bias) his or her actions

Step 8: Final thoughts
Did I get something out of this?

- Does the article significantly improve the knowledge base beyond what is already published on this topic?
- Is the statistically significant difference clinically significant?
  - Use research findings to meet the clinical needs of the patients
  - In clinical practice patient factors determine the treatment course; however, be well informed