Evidence Based Medicine (EBM)

Study Types

- Meta-analysis
  - Combines the data from several different individual studies and analyzes them as a group

- Systematic review
  - Summarizes and assesses studies that address a similar issue
  - Often includes a meta-analysis

- Randomized controlled trial (RCT)
  - A trial which randomly assigns participants to ≥ 2 groups

- Cohort study
  - A prospective study
  - Follows a group of participants that either has a condition or receives a treatment and compares them to those who do not

- Case-control study
  - Starts with the outcome (one group has the outcome and the other does not) and looks retrospectively to see what experiences they had

- Cross-sectional study
  - Observes a population at a single point in time to see who had the outcome and who had the exposure

- Case reports and case series
  - Description of a single patient or series of patients with the outcome

- The pyramid from least to most rigorous quality of evidence, with the least bias theoretically being at the top, goes from
  - Case reports / series
  - Case control studies
  - Cohort studies
  - RCT
- Systematic review and meta-analysis
  - Does not actually hold true in practice because meta-analyses are not necessarily the least biased
    - Each study included has to be done without bias and measured similarly

![Diagram of clinical study levels]

**PICO Question**

- Helps you formulate a specific research question related to patient care, so you know what to search
- **PICO**
  - **P** = Patient / problem
  - **I** = Intervention
  - **C** = Comparison
  - **O** = Outcome
- **Example**
  - You are taking care of a child with a facial laceration and wonder if skin glue or sutures have lower rates of infection and better cosmetic appearance
- **Patient problem**
  - Description of the patient or population with the problem of interest
    - E.g. children under age 8 with facial lacerations
- **Intervention**
  - Intervention or exposure of interest
    - E.g. tissue adhesive
- **Comparison**
To what we are comparing the intervention
  - E.g. sutures

**Outcome**
  - What is being measured
  - E.g. rates of infection and cosmetic appearance

### Sensitivity & Specificity

**Sensitivity**
- The proportion of patients with the disease who test positive (see formula below)
  - How good is the test at picking up anyone who might have the disease
  - E.g. using troponin to test for ACS
    - Newer troponins are even more sensitive than prior generations
    - But this does not mean that everyone with a slightly elevated troponin is having an MI

**Specificity**
- Proportion of patients without the disease who test negative
  - How good is the test at confirming the diagnosis?
  - E.g. using troponin to test for ACS
    - Many patients who have heart failure, renal disease, or some other cardiac issue such as myocarditis can have an elevated troponin
    - Troponin is not very specific to ACS -- it still needs to be used in the right clinical setting

**Calculating sensitivity and specificity**
- Set up a 2 x 2 table as shown in table 1
  - Sensitivity = true positive / (true positive + false negative)
  - Specificity = true negative / (true negative + false positive)

**Example with made-up data:**
- There are 100 patients, 10 have ACS, of those 10 only 9 have a positive troponin
- 90 Patients do not have ACS, but 30 have a positive troponin
- See table 2 to see the example 2x2 table
  - Sensitivity = 9 / (9+1) = 90%
  - Specificity = 60 / (60+30) = 67%

- In this example, troponin is fairly sensitive but not very specific

<table>
<thead>
<tr>
<th></th>
<th>Disease +</th>
<th>Disease –</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test +</strong></td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td><strong>Test –</strong></td>
<td>False negative</td>
<td>True negative</td>
</tr>
</tbody>
</table>
### Positive and Negative Predictive Value

- **Positive Predictive Value**
  - If the test comes back positive, how likely is it that the patient has the disease?
  - PPV = true positive / (true positive + false positive)

- **Negative Predictive Value**
  - If the test comes back negative, how likely is it that the patient does NOT have the disease?
  - NPV = true negative / (true negative + false negative)

### Risk & Number Needed to Treat

- **Risk**
  - Many terms for evaluating risk
    - Absolute risk, absolute risk reduction, relative risk, and relative risk reduction
    - These terms are very confusing, similar, and can also be used to manipulate data to give it the appearance you desire
    - These formulas are all included in the EBM Review Sheet
  - **Relative Risk**
    - Ratio of an event's occurrence rate in the exposed group compared to the non-exposed group
    - Used for prospective studies
    - RR = Experimental Event Rate / Control Event Rate
      - RR = EER / CER
  - **Relative Risk Reduction**
    - Percent change in risk of the event that is obtained through exposure
    - RRR = (EER - CER) / CER
  - **Absolute Risk Reduction**
    - Difference in event rates between the control group and experimental group
    - ARR = EER - CER

- **Number Needed to Treat**
  - How many patients need to be treated with this intervention before someone benefits from it?
Low NNT is good! If NNT is 2, this means you only need to treat two patients before one patient benefits. In other words, 50% of patients benefit.

Less bias and manipulation of statistics

NNT = 1/ARR

Example
- Risk of heart attack is 3% in control group and 2% in experimental group
- RRR = 3-2 / 3 = 33% → that sounds great!
- ARR = 3-2 = 1% → that doesn’t sound as great
- NNT = 1 / 0.01 = 100 → I’m not impressed

Odds Ratio & Relative Risk

- Risk
  - Probability of an event occurring
    - Risk of rolling 1 on a die is 1:6
- Odds
  - Ratio of one outcome to another
    - Odds of rolling a 1 on a die is 1:5
- Relative risk
  - Risk in the experimental group compared to the risk in the control group
    - RR = Experimental Event Rate / Control Event Rate
    - Can only be calculated in a prospective study
    - RR cannot be used in retrospective case-control studies as we don’t know the total number of people who were at risk
    - Case-control studies can only compare known outcomes and exposures
- Odds ratio
  - Proportion of patients with the event vs those without the event in the EXPERIMENTAL GROUP compared to the proportion of patients with the event vs those without the event in the CONTROL GROUP
    - OR = (A/C) / (B/D)
    - OR = AD / BC
- What’s the difference between OR and RR?
  - Relative risk is comparing risks and odds ratio is comparing odds between the experimental group and the control group
- Example
  - Experimental group
    - After I&D of an abscess in 100 patients, all patients get antibiotics
  - Control group
    - In this group, 5 patients still have infection at 2 weeks
After I&D of an abscess in 100 patients, none of them get antibiotics
In this group, 20 patients still have infection at 2 weeks

- **Odds**
  - Odds of persistent infection in the experimental group is 5/95
  - Odds of persistent infection in the control group is 20/80
  - Odds ratio = (5/95) / (20/80) = 21%

- **Risk**
  - Risk of persistent infection in the experimental group is 5/100
  - Risk of persistent infection in the control group is 20/100
  - Relative risk = (5/100) / (20/100) = 25%

- **How do RR and OR compare?**
  - If there is no difference between the two groups both RR and OR would equal 1
  - If there is an association between the intervention and the outcome, then OR will exaggerate that relationship
    - As seen in the example above, OR makes it seem that fewer patients have persistent infection if prescribed antibiotics
  - If the event is rare then RR and OR will be nearly the same
  - As the event becomes more common the difference between RR and OR increases

### Likelihood Ratio

- Tells you how much a test should change your suspicion for the disease
- Based on the Fagan nomogram
  - >1 increase likelihood
  - <1 decrease likelihood
  - =1 is useless because it does not change your likelihood

- **LR+**
  - Tells you how much a positive test should change your suspicion for the disease
  - LR+ = sensitivity / (1 - specificity)

- **LR-**
  - Tells you how much a negative test should change your suspicion for the disease
  - LR- = (1 - sensitivity) / specificity

- **Practical application**
  - High likelihood ratio means that the test is clinically very helpful

### Confidence Intervals

- Given that the sample population will never be exactly the same as the true population, a confidence interval is a statistical way of handling sampling error
- Usually set at 95%
“We are 95% confident that the true value is within this interval”

- Influenced by variations in data and sample size
  - Very large sample size will have a smaller confidence interval
- A confidence interval that includes the null hypothesis means that it is NOT statistically significant
  - If we are using RR or OR, then we do not want the confidence interval to include the number 1, because that means there is a 95% chance that there is no difference between the two groups
  - If we are comparing data directly (e.g. blood pressures), then we do not want the confidence interval to include the number 0, because that means there is a 95% chance that there is no difference between the two groups

![Figure 2](image-url)

**Statistical Significance & P Value**

- Significance Level (alpha)
  - Number that is set before you do the experiment
  - Generally, between 0 and 1, usually set at 0.05
  - Your probability of rejecting the null hypothesis when you should not have
    - This is a type I error
    - The null hypothesis means that the two groups are the same
  - I.e. before you do the experiment you are saying that you will accept a 5% chance
that data supporting your hypothesis is due to chance (i.e. the null hypothesis is true, but this was all a fluke)

- **P Value**
  - You will not be asked to calculate this on the boards, but you must understand it conceptually
  - This is the calculated number that shows what the chance actually is that the data supports your hypothesis, but only by chance because the null hypothesis is in fact true

- **Statistical Significance**
  - If P < alpha, then there is statistical significance
  - This shows that the chance of randomly getting this data is small enough that we accept it and can reject the null hypothesis
  - Also, if your confidence interval for relative risk includes the number 1, there is not statistical significance
    - That’s like saying there is a high chance that there is no difference between the experimental group and control group
    - See chapter on Confidence Intervals

- **Clinical Significance**
  - But who cares about these numbers if it doesn’t have clinical meaning?
  - Example
    - Hypothesis
      - Lisinopril lowers blood pressure
    - Null hypothesis
      - Lisinopril does not lower blood pressure
    - Significance level is set at 0.05
    - Data collection and interpretation shows that lisinopril lowers SBP 2 points compared to placebo
    - P-value is calculated by some fancy biostatistics program and comes out to 0.04
    - There is a 4% chance that lisinopril does not lower blood pressure, but because of chance the data showed this anyway this time
    - Since our p-value was 4%, and this is lower than our significance level, that we pre-set at 5%, we will reject the null hypothesis and say that lisinopril lowers blood pressure with statistical significance
    - In practice, does lowering the blood pressure by 2 points really matter in lowering morbidity and mortality? Probably not.
  - This data is statistically significant but not clinically significant
Bias

- No matter how hard you try to make a perfect study there will always be some bias
- There are too many types of bias to define so we are picking some of the more testable types
  - Hawthorne effects
    - Subjects change their behavior when they know they are being studied
  - Lead time bias
    - If you diagnose a disease earlier in its course, it appears that patients survive longer
  - Publication bias
    - Trials with interesting or positive results tend to get published over results that are less interesting or negative for the intervention being studied
  - Selection bias
    - Any type of bias that lead the groups being studied to be different from one another
    - Sampling bias
      - When your sampling method lead the two groups to be different
      - E.g. if you only enroll patients on Monday and Wednesday mornings you will miss a lot of people who work jobs with typical hours
  - Observer bias
    - Researcher introduces bias in how they perceive their observations
    - The researcher may be seeing the outcome they want in the data
  - Recall bias
    - Participants remember events differently when they know what is being studied
  - Response (aka volunteer) bias
    - When participants volunteer to enroll in the study it creates a biased sample population
    - Randomization helps to curtail volunteer bias
  - Treatment selection bias
    - Confounders affect the outcome more than the treatment itself