Goals

- Examine misconceptions regarding antimicrobial therapy.
- Develop a plan or algorithm for the rationale use of empiric antimicrobial therapy, including:
  - When to use.
  - How to follow the patient.
  - What to do when things go wrong.

Part 1:
Misconceptions About Antimicrobial Therapy

"The pharmacology of antibiotics is unlike most other therapeutic agents, therefore our usual prescribing habits don’t apply."

Five common misconceptions:

5 Misconceptions About Antimicrobial Therapy

1. Purpose of Rx:
   - Equation of infection
   - Bacteriostatic vs Bactericidal
2. Dose response
3. Host response
4. Response time
5. Treatment of choice

#1: The Purpose of Antimicrobial Therapy

Question: “What is the purpose of antimicrobial therapy? ...is it to kill bugs?”

The Purpose of Antimicrobial Therapy

“...is to tip the ‘equation of infection’ in favor of the host.”
Equation of Infection
Infection is a competition between the host and the pathogen. The pathogen combats the host with virulence factors and numbers (inoculum). The host defends itself with host defenses.

Equation of Infection
The purpose of antimicrobial Rx is to tip the equation of infection in favor of the host.

IT IS NOT TO KILL THE MICROBE BY ITSELF

"Since the purpose of antimicrobial therapy is NOT to kill bugs, then...

Bacteriostatic therapy is good therapy in all situations except:"

- Name 3 'static & 3 'cidal drugs.
- Name 3 clinical conditions requiring bactericidal therapy.

Bactericidal Therapy
...is required for:
- Endocarditis.
- Sepsis in a neutropenic host.
- Meningitis.
- Undrained abscess & osteomyelitis.

#2: Dose Response
Question: “If a little bit of drug is good, isn’t a lot more a lot better?”

#2: Dose Response
Answer: “NO! Antimicrobial therapy is not stoichiometric (meaning dose response); it is sufficient or insufficient.”
**#2: Dose Response**

The patient has a **dichotomous** response
NOT a scalar response.

"You have to give enough."
"Too little is not enough."
"Too much is excessive."

**#2: Dose Response**

How do you know how much to prescribe?

*Handbooks & textbooks.*
[codified clinical experience]

*Drug levels & serum killing powers.*
[patient specific]

---

**#3: Host Response**

Many practitioners note:

"Most of my patients get better with a shorter course of therapy than the recommended course. Can this possibly be a correct observation?"

**#3: Host Response**

Many practitioners note:

"Most of my patients get better with a shorter course of therapy than the recommended course. Can this possibly be a correct observation?"

**YES**

---

**#3: Host Response**

"**WHY** do most of my patients get better with a shorter course of therapy than recommended?"

"Because therapy is directed to curing the sickest patients. To cure these patients we routinely overtreat."

**#3: Host Response**

No. of pts. with X'itis responding to Y'mycin Rx

Therapeutic Response of X'itis to Y'mycin.

| Amt. of Y'mycin | 
|---|---|

---

3
#3: Host Response

"If this is correct, why do I need to give a FULL course of therapy to patients with infections?"

Because it may be impossible to predict the host response for your patient.

#4: Response Time

"I have started antibiotic therapy, but the patient has not responded. Shouldn’t I change antibiotics?"

Answer: "If it has been less than 72 hours, NO!"

Predicting the Host Response - Examples:

- Management of soft tissue infection (cellulitis)
  versus
- Management of *S. aureus* bacteremia
  versus
- Management of osteomyelitis, meningitis, & endocarditis.

Response Time Explanation

Since the host determines the clinical response, by convention we wait at least 72 hours before concluding that the antimicrobial therapy is ineffective.

Normally, in the absence of a definitive diagnosis or significant toxicity, you should not change therapy unless it is to add therapy for an important therapeutic omission.
Empiric Rx Includes:

- Therapy before definitive diagnosis and patient too ill for observation only.

Empiric Rx Includes:

- Therapy when unsure of the definitive diagnosis and the patient is at risk if not treated.

Before you know the sensitivities:

when you have to be right from the start.

48 HOURS OF DOUBT?

positive it's negative?

Uncertainty due to: not performing appropriate diagnostic tests, administrative misadventure, concern for false positive or negative results.
#5: Treatment of Choice

"The [attending physician, infectious diseases consultant, fellow, senior house officer, textbook] says my therapy is not the best therapy.

Shouldn't I change therapy?"

**Answer:** Unless there has been a significant therapeutic omission or clinical error... **NO!**

Consistency is better than elegance.

The treatment of choice is treatment.

---

**THERAPEUTIC GOAL:** drug concentration at the site of infection should exceed the MIC by at least 2-4x.

2-4x MIC

---

4 drug doses to achieve blood-level.

- Continuous IV infusion
- Multiple IV doses
- Single IV dose

---

"Switching antibiotic therapy before achieving the desired blood level often delays the administration of effective therapy."
Have a plan!

Antimicrobial Therapy

1. Make a diagnosis.
2. Make a diagnostic and therapeutic plan.
3. Follow the patient for response.
4. Conclude therapy.
The Diagnostic Paradox

When is it easiest to diagnose sepsis?
When the patient is in a coma with shock, ARDS, DIC, and acidosis?
Or when the patient just has some confusion, nausea, mild tachycardia, and mild tachypnea?

The Diagnostic Paradox

When is it easiest to treat sepsis?
When the patient is in a coma with shock, ARDS, DIC, and acidosis?
Or when the patient just has some confusion, nausea, mild tachycardia, and mild tachypnea?

The Diagnostic Paradox

Physicians are charged with diagnosing disease at its earliest presentation.
- This is the time when the presentation is the most subtle, with the greatest number of false negatives and positives.
- But the best time to treat.
- Ergo: Dx trepidation & Rx bravado!

Step 2: Making a Dx & Rx Plan

"The choice of empiric therapy requires the clinician to anticipate the infecting agent. This is done in the following manner in the order of importance."
1. Gram stains and rapid diagnostic smears & assays.
2. Prior culture data (when available).
3. Epidemiological or clinical setting. (The WHO, WHEN, & WHERE of illness.)
**Step 1: Diagnosis**

*Antibiotic therapy follows diagnosis.*

*Antibiotic therapy should only be used when the patient has a diagnosis of infection.*

*If a patient does not have a diagnosis, then antibiotic therapy should not be used.*

---

**Diagnosis indicates:**

- Organ system involved (syndromic diagnosis). *This tells you how to evaluate the patient.*
- Most likely pathogens (etiologic diagnosis). *This tells you what antibiotics to use.*
- Clinical evidence of infection. *This guides your management by indicating whether or not the patient is improving or failing.*
Step 2: Making a Dx & Rx Plan

"The decision to start empiric antimicrobial therapy is based on an assessment of RISK."

---

### Example of Lowest Risk

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Healthy [WARD CLERK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen</td>
<td>None [Example: insignificant exposure to <em>Neisseria meningitidis</em>]</td>
</tr>
<tr>
<td>Risk</td>
<td>NONE</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>None</td>
</tr>
<tr>
<td>Therapy</td>
<td>None</td>
</tr>
</tbody>
</table>

---

### Example of Higher Risk

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Healthy [FIRST AID PROVIDER]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen</td>
<td>None [Example: exposure to <em>Neisseria meningitidis</em>]</td>
</tr>
<tr>
<td>Risk</td>
<td>YES</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Significant exposure</td>
</tr>
<tr>
<td>Therapy</td>
<td>Prophylaxis</td>
</tr>
</tbody>
</table>

---

### Example of Low Risk

- (≥38°) and a bright red pharyngitis, enlarged tonsils with purulence.
- You get a throat culture, but the 'rapid strep test' is unavailable.

**What do you do?**

---

Pharyngitis picture: www.clinical.com/ctim/images/STREPTO.jpg

Example of High Risk

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Pharyngitis with fever [$\geq 38^\circ$] in a postsplenectomy patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen</td>
<td>Viral versus streptococcal.</td>
</tr>
<tr>
<td>Risk</td>
<td>YES</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>At risk for post-splenectomy sepsis.</td>
</tr>
<tr>
<td>Therapy</td>
<td>Empiric therapy.</td>
</tr>
</tbody>
</table>

Step 3: Follow the patient for a response

Empiric Therapy is a Prospective Trial

Clinical Hypothesis

Treatment Over Time

For Better or Worse

Protocol to following the patient over time

Presumptive Diagnosis

Dx confirmed

Dx not confirmed, but Pt. improved

Don't know

No response & no diagnosis

Dx demonstrated to be wrong

Dx confirmed

Complete definitive Rx

Dx not confirmed, but Pt. improved

Continue empiric Rx

Dx confirmed

Dx not confirmed, but Pt. improved

Continue empiric Rx & reassess daily

No response & no diagnosis

Reevaluate patient

Dx demonstrated to be wrong

Stop empiric Rx
### Truth: Clinical Dx

<table>
<thead>
<tr>
<th>Clinical Observation</th>
<th>COMPLETE &amp; CORRECT</th>
<th>LACKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT RECOVERS</td>
<td>Diagnostic &amp; therapeutic success!</td>
<td>Lucky or spontaneous success</td>
</tr>
<tr>
<td>PATIENT FALTERS</td>
<td>Failure due to complication or therapeutic malfunction</td>
<td>Diagnostic &amp; therapeutic failure</td>
</tr>
</tbody>
</table>

### Clinical Failure of Empiric Therapy

**Most likely:** Failure due to complication
- Undrained abscess
- Secondary infection
- Super-infection
- Emergence of resistance
- Drug reaction
- Complication (i.e. DVT & PE)
- Resurgent underlying disease

**Possible:** Failure due to therapeutic malfunction:
- Lapse in drug administration
- Wrong dose, interval, or route of administration
- Poor penetration at the site of infection
- Drug incompatibility

**Possible:** Failure due to diagnostic error
- Wrong etiologic and/or syndromic diagnosis of an infectious disease
- Unrecognized non-infectious disease

### "What do you do when drug reactions develop?"

Ask yourself what is the [presumptive or definitive] diagnosis, then cover the [presumed or demonstrated] pathogens.

### "What do you do when you don’t know when to stop therapy?"

Ask yourself what is the [presumptive or definitive] diagnosis, then continue antimicrobial therapy until the recommended course is complete.

**Remember:** "A bad diagnosis (meaning no diagnosis) does not deserve bad therapy!"