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?*

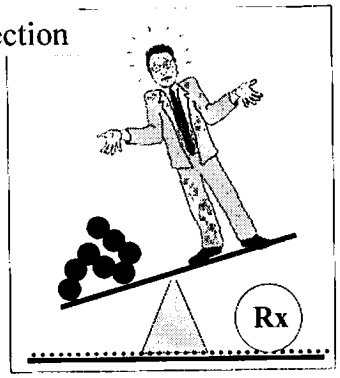
...is it to kill bugs?"

The Purpose of Antimicrobial Therapy

"...is to tip the ***'equation of infection'*** *in favor of the host."*

Equation of Infection

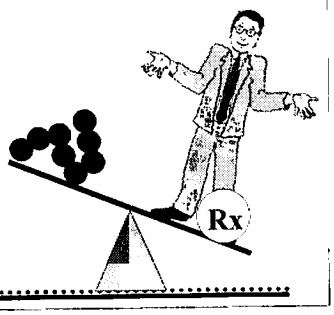
Infection is a competition between the host and the pathogen. The pathogen combats the host with virulence factors and numbers (inoculum). The host defends itself with host defenses.



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:

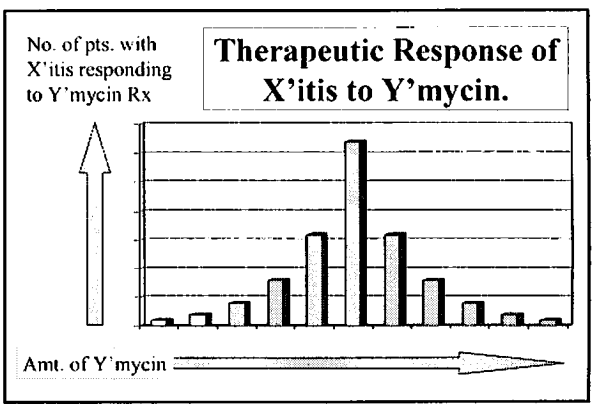
"Most of my patients get better with a shorter course of therapy than the recommended course. Can this possibly be a correct observation?"

YES

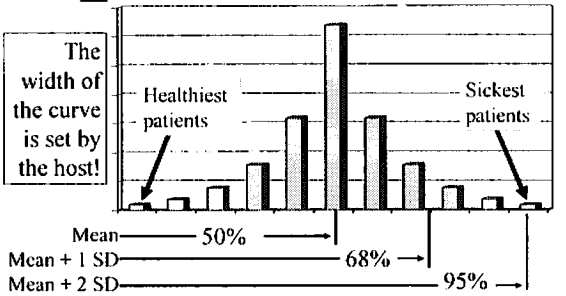
#3: Host Response

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

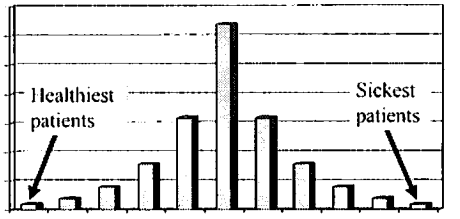
"Because therapy is directed to curing the sickest patients. To cure these patients we routinely overtreat."



Most patients respond to less than full therapy. Therapy is designed to cure the sickest patients.



Drug companies recommend therapeutic courses that routinely cure 90-95% of patients, thus over-treating most patients.



#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.**

Predicting the Host Response - Examples:

Management of soft tissue infection (cellulitis)

versus

Management of *S. aureus* bacteremia

versus

Management of osteomyelitis, meningitis, & endocarditis.

#4: Response Time

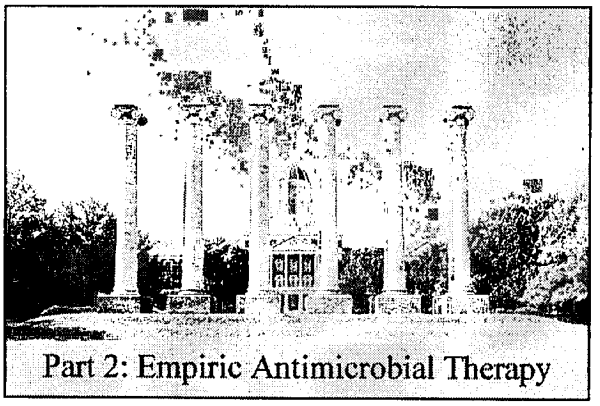
"I have started antibiotic therapy, but the patient has not responded. Shouldn't I change antibiotics?"

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

Response Time Explanation

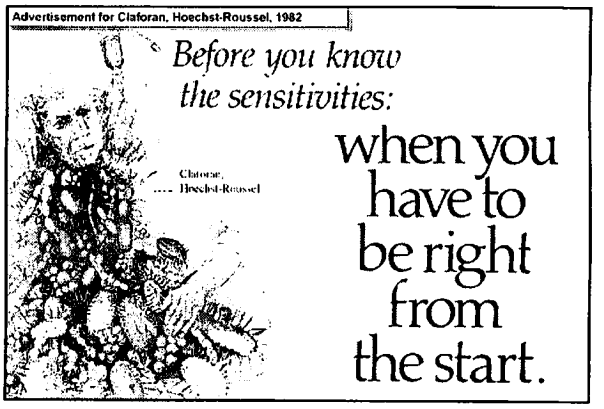
Since the host determines the clinical response, by convention we wait at least 72 hours before concluding that the antimicrobial therapy is ineffective.

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.



Part 2: Empiric Antimicrobial Therapy

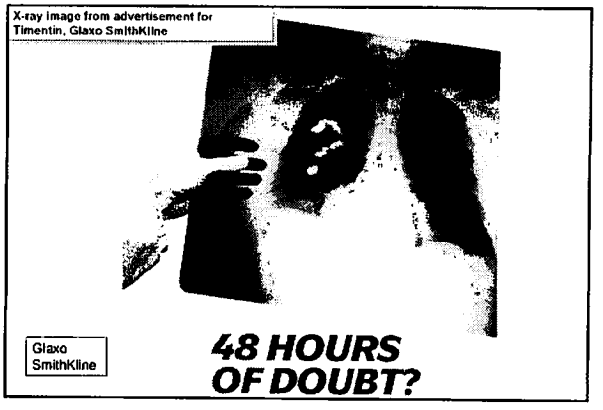
Advertisement for Claforan, Hoechst-Roussel, 1982



Empiric Rx Includes:

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

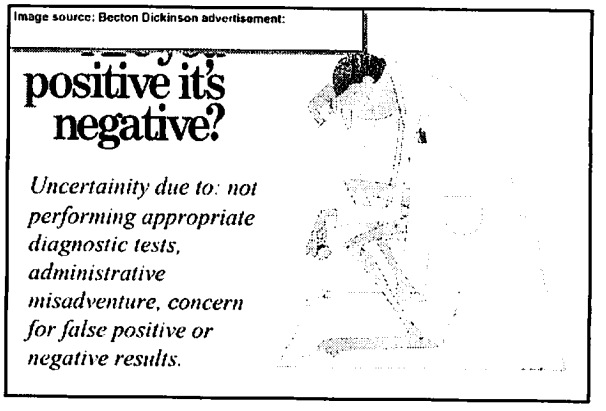
X-ray image from advertisement for Timentin, Glaxo SmithKline



Empiric Rx Includes:

- Therapy before definitive diagnosis and patient too ill for observation only.
- Therapy when ***unsure*** of the definitive diagnosis and the patient is at risk if not treated.

Image source: Becton Dickinson advertisement:



#5: Treatment of Choice

"The [attending physician, infectious diseases consultant, fellow, senior houseofficer, textbook] *says my therapy is not the best therapy. Shouldn't I change therapy ?"*

#5: Treatment of Choice

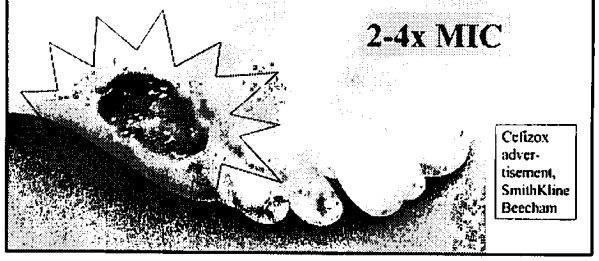
Answer: *Unless there has been a significant therapeutic omission or clinical error...* **NO!**

Consistency is better than elegancy.

The treatment of choice is treatment.

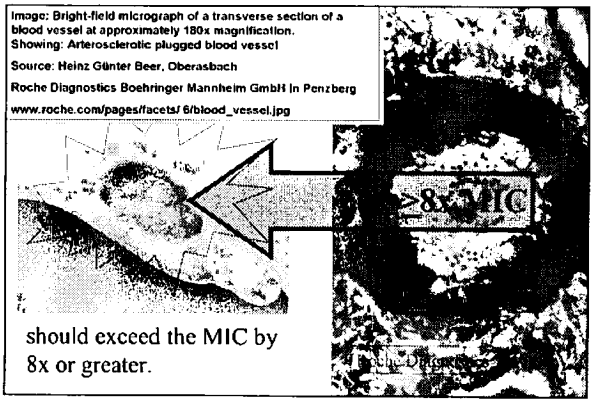
Image: advertisement for Ceftzox, circa 1988+

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



Ceftzox advertisement, SmithKline Beecham

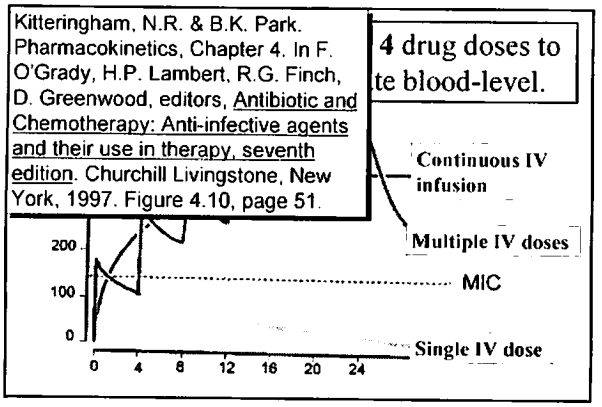
Image: Bright-field micrograph of a transverse section of a blood vessel at approximately 180x magnification.
Showing: Arteriosclerotic plugged blood vessel
Source: Heinz Günter Beer, Oberasbach
Roche Diagnostics Boehringer Mannheim GmbH in Penzberg
www.roche.com/pages/facets/ 6/blood_vessel.jpg



should exceed the MIC by 8x or greater.

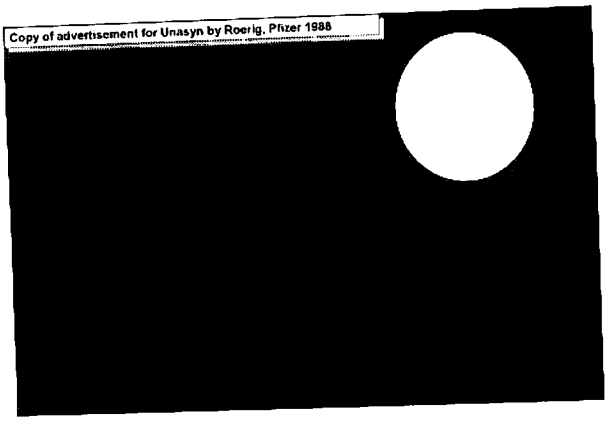
Kitteringham, N.R. & B.K. Park. Pharmacokinetics, Chapter 4. In F. O'Grady, H.P. Lambert, R.G. Finch, D. Greenwood, editors, Antibiotic and Chemotherapy: Anti-infective agents and their use in therapy, seventh edition. Churchill Livingstone, New York, 1997. Figure 4.10, page 51.

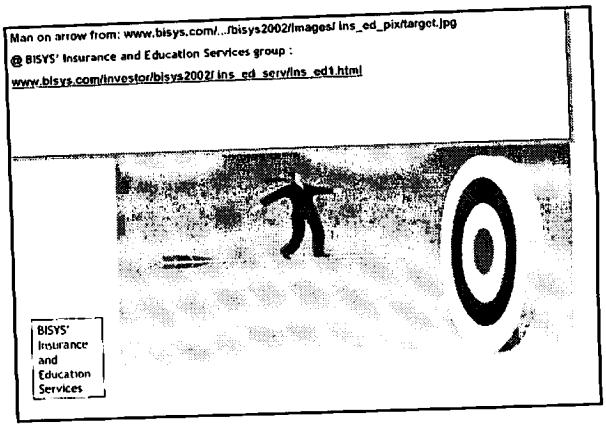
4 drug doses to te blood-level.



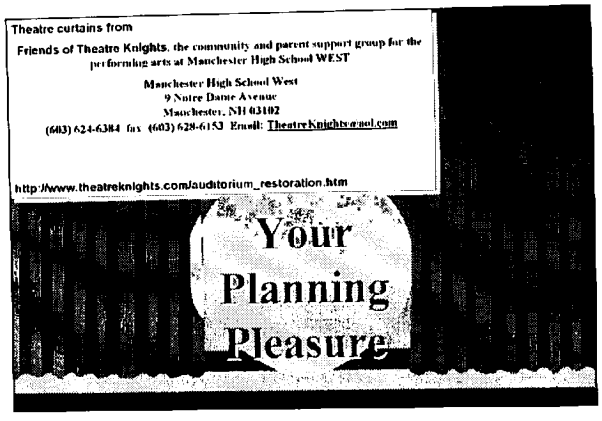
#5: Treatment of Choice

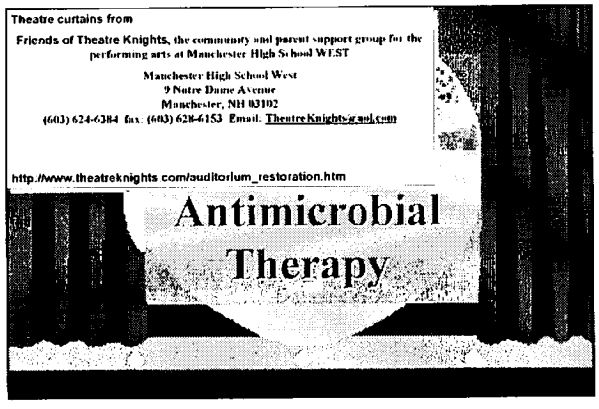
"Switching antibiotic therapy before achieving the desired blood level often delays the administration of effective therapy."


Copy of advertisement for Unasyn by Roerig, Pfizer 1988


Man on arrow from: www.bisys.com/.../bisys2002/images/ ins_ed_pix/target.jpg
@ BISYS' Insurance and Education Services group :
www.bisys.com/investor/bisys2002/ ins_ed_serv/ins_ed1.html
BISYS' Insurance and Education Services


Target with scalpels and syringe: Emergency Medicine, November 1978, page 160
Have a plan!
Emergency Medicine


Theatre curtains from
Friends of Theatre Knights, the community and parent support group for the performing arts at Manchester High School WEST
Manchester High School West
9 Notre Dame Avenue
Manchester, NH 03102
(603) 624-6384 fax (603) 628-6153 Email: TheatreKnights@aol.com
http://www.theatreknights.com/auditorium_restoration.htm
Your Planning Pleasure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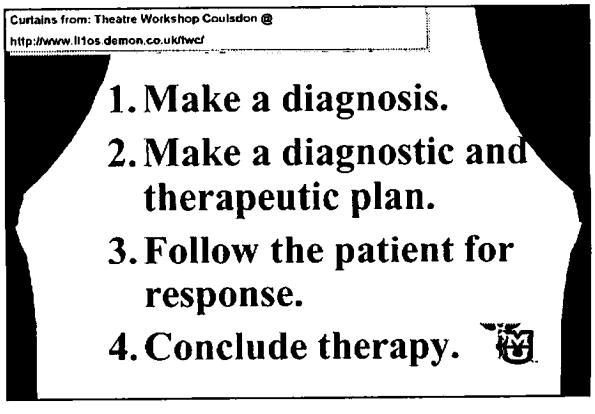
9 Notre Dame Avenue
Manchester, NH 03102
(603) 624-6384 fax (603) 628-6153 Email: TheatreKnights@aol.com
http://www.theatreknights.com/auditorium_restoration.htm
Antimicrobial Therapy


Curtains from: Theatre Workshop Coulsdon @
http://www.ll1os.demon.co.uk/twc/
1. Make a diagnosis.
2. Make a diagnostic and therapeutic plan.
3. Follow the patient for response.
4. Conclude therapy.

Picture of Galveston beach from: ssh.tamu.edu/news.htm

Back to Joe Blow

Rx: "Triples"

Is this bad medicine?

Diagnostic Trepidation & Therapeutic Bravado

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!

The Diagnostic Paradox

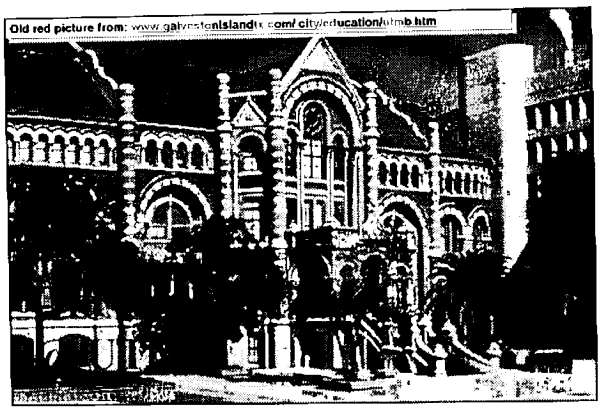
Therefore it is important to document the signs and symptoms prompting therapy so that the patient can be followed for a response.

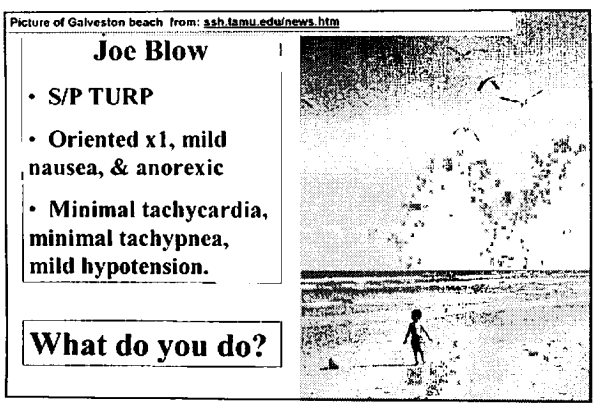
There is an understandable reluctance to commit oneself to a diagnosis at this time, but if it merits therapy, it merits documentation.

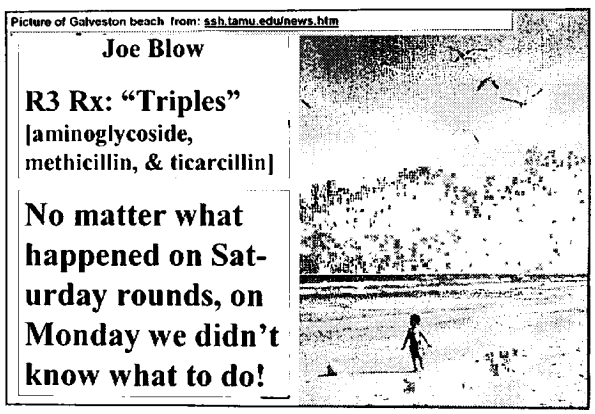
Step 2: Making a Dx & Rx Plan

"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.)
4. Codified clinical experience.







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:"

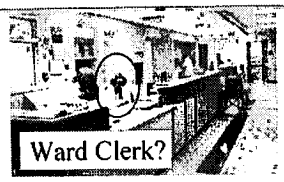
Mouth-to-mouth picture: www.mjbovo.com/Writer/ WR-MTM3.gif

Reception desk: www.st-marys.com/ Images/er.jpg

St. Mary's Healthcare Center
801 E. Sioux Ave.
Pierre, South Dakota 57501
Phone: 605/224-3100
Fax: 605/224-8339

Ambulance: www.networkoverseas.cc/ images/mouwasat/er.jpg

Al-Mouwasat Hospitals
Dammam, Riyadh, Medina



Ward Clerk?

First-Aid Provider?

Example of Lowest Risk

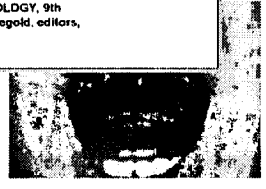
Clinical Status	*Healthy* [WARD CLERK]
Pathogen	*None* [Example: insignificant exposure to *Neisseria meningitidis.*]
Risk	**NONE**
Diagnosis	*None*
Therapy	*None*

Example of Higher Risk

Clinical Status	*Healthy* [FIRST AID PROVIDER]
Pathogen	*None* [Example: exposure to *Neisseria meningitidis.*]
Risk	**YES**
Diagnosis	*Significant exposure*
Therapy	*Prophylaxis*

Pharyngitis picture: www.vet.uga.edu/erc/WEBFILES/ graphics/STREPT2.JPG from:
BAILEY AND SCOTT'S DIAGNOSTIC MICROBIOLOGY, 9th edition. E.J. Baron, L.R. Peterson, and S.M. Finegold, editors, Moseby-Year Book, Inc., 1994.

(≥38°) and a bright red pharyngitis, enlarged ¾ tonsils with purulence.



You get a throat culture, but the 'rapid strep test' is unavailable.

What do you do?

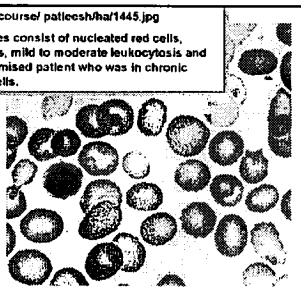
Example of Low Risk

Clinical Status	*Pharyngitis*
Pathogen	*Viral versus streptococcal*
Risk	**NO for acute illness** [R/O Risk of Rheumatic Fever]
Diagnosis	*Possibly infected*
Therapy	*None*

Splenectomy blood film: courses.nus.edu.sg/course/ patleesh/hal1445.jpg

Classical post-splenectomy blood film changes consist of nucleated red cells, Howell-Jolly bodies, acanthocytes, target cells, mild to moderate leukocytosis and thrombocytosis. This film is from a splenectomised patient who was in chronic renal failure, and therefore also shows burr cells.

(≥38°) and a bright red pharyngitis, enlarged ¾ tonsils with purulence, but the patient has no spleen.



Now what do you do?

Example of High Risk

Clinical Status	*Pharyngitis with fever* [≥38°] *in a postsplenectomy patient.*
Pathogen	Viral *versus* streptococcal.
Risk	**YES**
Diagnosis	*At risk for post-splenectomy sepsis.*
Therapy	*Empiric therapy.*

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

Empiric Rx for 72 hours

- 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
Don't know	Continue empiric Rx & reassess daily
No response & no diagnosis	Reevaluate patient
Dx demonstrated to be wrong	Stop empiric Rx

Truth: Clinical Dx

Clinical Observation	COMPLETE & CORRECT	LACKING
PATIENT **RECOVERS**	Diagnostic & therapeutic success!	Lucky or spontaneous success
PATIENT **FALTERS**	Failure due to complication or therapeutic malfunction	Diagnostic & therapeutic failure

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

Clinical Failure of Empiric Therapy

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

Clinical Failure of Empiric Therapy

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!"*

2000 Adobe Systems Incorporated, published in The Chronicle of Higher Education, Jan 26, 2001, page A7 [www.adobe.com/education]

The End