Overview of Antibiotic Spectrum and Use

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07/19/02

Neat logical categories are necessary if one is to think profitably about the real world, and to derive from it lessons for broader application and use.

Categories are only a place to start. Clinical decisions will be different for each patient.

Samuel Huntington

Firmness in decision is often merely a form of stupidity. It indicates an inability to think the same thing out twice.

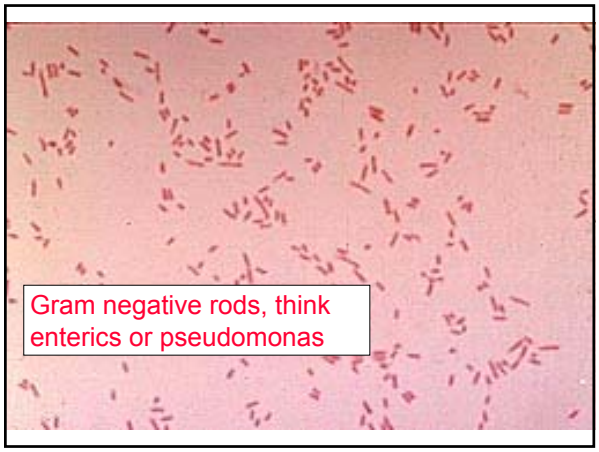
H.L. Mencken
1880-1951

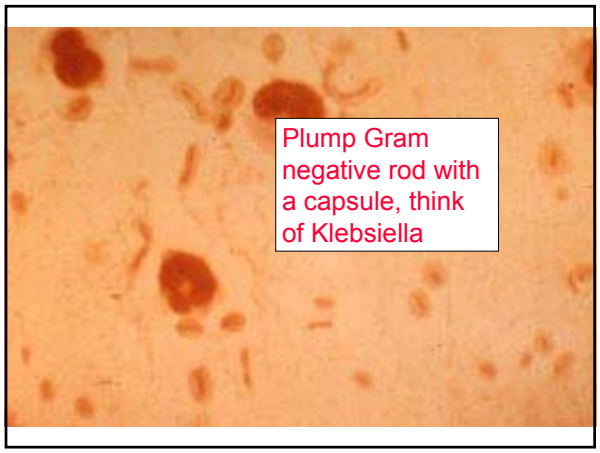
Microbiology

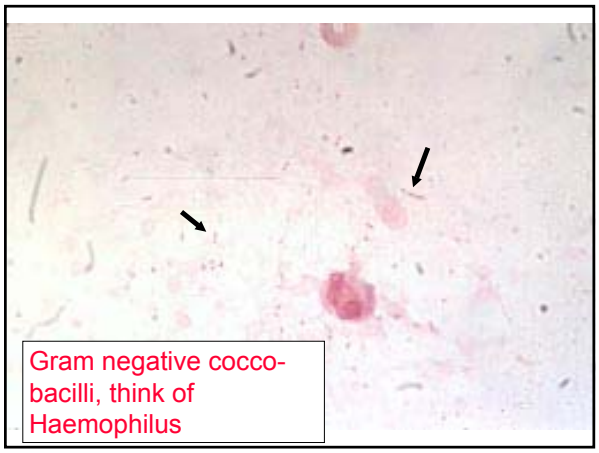
- **Bacteria/Fungus/Virus**
- **Bacteria**
  - **Color**
  - **Shape**

Gram positive cocci: Staph or strep
Clusters suggest Staph

Gram positive cocci, think strep
Chains, think enterococcus, viridans strep
Lancet-shaped diplococci, think pneumococcus







Antibacterials

- **Penicillins, extended spectrum penicillins**
- **Cephalosporins**
  - **1st , 2nd, 3rd generation**
- **Aminoglycosides, Aztreonam**
- **Quinolones**
  - **Gram negative focus (Cipro)**
  - **Gram positive focus (Gati/Moxi/Gemi)**
- **Carbapenems (Imipenem, meropenem)**
- **Others: Clinda, metronidazole**

8 yo, T=38.7, sore throat, headache, abdominal pain, Right tender tonsillar node with exudate

• **Differential diagnosis**	Adenovirus, Mycoplasma, EBV, Gonorrhea, Diphtheria, Coxsackie (vesicles)
• **History**	Laryngitis=viral
• **Exam**	Group A, C, G Strep
• **Labs**	Sister with Group A Strep pharyngitis
• **Differential diagnosis**	Rapid strep screen negative, culture positive
• **Organisms to consider**	
• **Antibiotics to start with**	Penicillin G Na: IV Penicillin G K: IV
• **Best treatment**	Penicillin V K: PO

Infant <1 mo, with fever. CSF gram stain = Gram positive rods

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Listeria monocytogenes

Ampicillin plus gentamicin for synergy

Acute onset of dysuria, right flank pain, T=39, vomiting liquids and solids, decreased urine output with dark urine

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Pyelonephritis
No prior UTI
Flank tenderness, dehydration
Pyuria
Plump GNR on stain=E. coli
Gracile GNR=Pseudo
Capsule=Klebs
now many E.coli resistant to Amp
Ampicillin IV
Amoxicillin PO

Acute onset of dysuria, right flank pain, T=39, vomiting liquids and solids, decreased urine output with dark urine

- Differential diagnosis
- History Just finished ampicillin/amoxicillin Rx for pyelonephritis
- Exam
- Labs Urine grows *Pseudomonas aeruginosa*
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Acute onset of dysuria, right flank pain, T=39, vomiting liquids and solids, decreased urine output with dark urine

- Differential diagnosis
- History
- Exam
- Labs Urine grows *Klebsiella, Enterobacter, Serratia, or Proteus*
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Vomiting followed by right lower quadrant abdominal pain, complained of rough roads on the way to the hospital. T=38.6. Delay in being seen, then decided to watch overnight, now with shock and severe diffuse abdominal pain

- Differential diagnosis
- History
- Exam
- Labs
- Differential
- Organisms
- Antibiotics
- Best treatment

Ruptured appendicitis
Rebound tenderness
Fecal flora
Aerobic GNR
Enterococcus
Anaerobes
Ampicillin/sulbactam
Ticarcillin/clavulanate
Piperacillin/tazobactam

To kill anaerobes

Penicillin/Ampicillin (mouth anaerobes)

Clindamycin
Metronidazole
BL/BLI
Cefoxitin
Imipenem
Meropenem
chloramphenicol

48 hr post-op abdominal surgery, with pus draining from wound but stable vital signs

Gram stain: GPC, clusters
Staphylococcus aureus
<24 hr: Group A strep
>24 hours: Staph aureus
Staph aureus:
MSSA: Oxacillin, Nafcillin
MRSA:
Community acquired: Clinda, Vanco, Bactrim
Hospital: Vanco
Mixed GNR/GPC on stain: Cefazolin, Cefalothin

- Best treatment

1 cm pustular lesion right calf, sunburn-like rash (blanching erythroderm) and shock

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Toxic Shock Syndrome:

Use an antistaphylococcal beta-lactam (or Vancomycin)

plus clindamycin

Vomiting followed by right lower quadrant abdominal pain, complained of rough roads on the way to the hospital. T=38.6. Delay in being seen, team decided to watch overnight, now with shock and severe diffuse abdominal pain

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Cefoxitin is OK, but won't kill Enterococci, and selects for resistant organisms really fast

No cephalosporin kills enterococci

Cefotetan=cefoxitin

Cough, fever, RLL consolidation

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Community Acquired Pneumonia

- **No co-morbidity: Mycoplasma, Chlamydia pneumoniae, viral, Streptococcus pneumoniae (uncommon)**
- **Smoker: SP, Moraxella catarrhalis, Haemophilus influenzae**
- **Post-influenza: SP, MC, HI, Staphylococcus aureus**
- **Alcohol: SP, anaerobes, KESP**
- **Birds: Psittacosis**
- **Rabbits: Tularemia**
- **Livestock: Coxiella burnetii**
- **Water exposure: Legionella**

Beta-Lactam Resistance: Pneumococcus vs Haemophilus/Moraxella

	Streptococcus pneumoniae	*Haemophilus Moraxella*
Resistance Mechanism	Change PBP	Produce ß-Lactamases
Treat with	3 gen ceph macrolides TMP/SMX, FQ	ß-lactamase inhibitor combo 3 gen ceph macrolides TMP/SMX, FQ

Penicillin Susceptibility of *Streptococcus Pneumoniae:* Clinical Implications

NCCLS Category	MIC (mcg/mL)	Clinical Implications
Susceptible	≤ 0.06	penicillin OK
Intermediate	0.1-1.0	penicillin usually* OK
Resistant	≥ 2.0	cefotax, vanco,clinda**

* Exceptions=meningitis, ?pneumonia with effusion, abnormal host (sickle cell)

* po cephalosporins no better than penicillin. Cross resistance: TMP/SMX, others

Penicillin Susceptibility of *Streptococcus Pneumoniae:* Clinical Implications

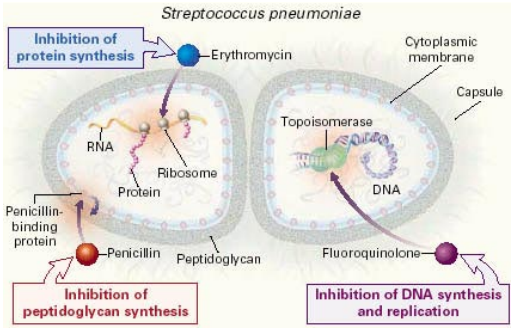
	Susceptible	Intermediate	Resistant
MIC	<=0.06	0.1-1.0	>=2.0
Penicillin susceptible or intermediate	Treat with Penicillin		
Penicillin nonsusceptible		No interpretation for treatment	
Penicillin resistant			Do not treat with Penicillin

Macrolide Resistance

Resistance Type	Abbreviation	Mechanism	Gene	Erythro	Clinda
Macrolide	M	Efflux pump (low or high)	mefE	Resistant	Susceptible
Macrolide-Lincosamide-Streptogramin B	MLSb	Change Ribosome Binding	erm	Resistant	Resistant

Does Azithro/Clarithro resistance follow Erythro or Clinda?

Streptococcus pneumoniae: three sites of resistance to antimicrobials



Swartz, MN. Attacking the pneumococcus—a hundred years' war. NEJM 2002;346:722

PRSP are Resistant to Many Antibiotics: Resistance of Streptococcus pneumoniae by Penicillin Resistance

	Percent Resistant		
	Pen S (61%)	Pen I (22%)	Pen R (17%)
Cefotaxime	0	8 (48% I)	42 (58% I)
Clindamycin	3	8	0
Erythromycin	7	48	79
Tetracycline	0	17	37
TMP/SMX	23	64	79

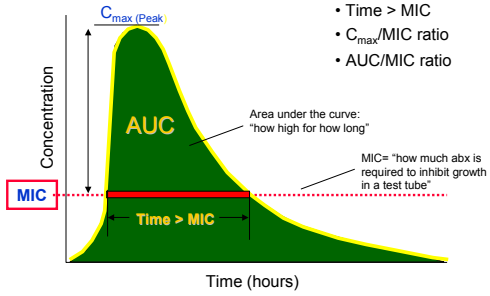
N=113 respiratory isolates CHW, 1998

Streptococcus Pneumoniae %Resistance to Antibiotics: CHW, 1996-2000: Ear / Respiratory Isolates

Yr	N	Pen	Cefotax	Eryth	T/S	Clinda
96	65	15	17	16	36	5
97	141	18	9	21	46	3
98	111	16	10	26	43	3
99	125	23	8	33	47	10
00	212	20	8	30	46	11

Pharmacokinetic/Pharmacodynamic Predictors of Efficacy

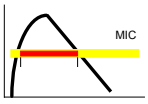
Parameters of Interest:
- Time > MIC
- C_{max}/MIC ratio
- AUC/MIC ratio



Craig W. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. *Clin Infect Dis.* 1998; 26:1-12.

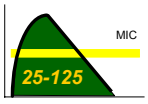
Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

Time >MIC
(non-concentration-dependent)



- Penicillins
- Cephalosporins
- Erythromycins
- Clarithromycin

AUC_{24}/MIC
concentration-dependent



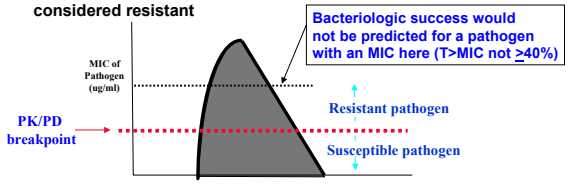
- Quinolones
- Aminoglycosides
- Azithromycin

25 (gram-positive)
125 (gram-negative)

Craig W. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. *Clin Infect Dis.* 1998; 26:1-12.

PK/PD Breakpoints

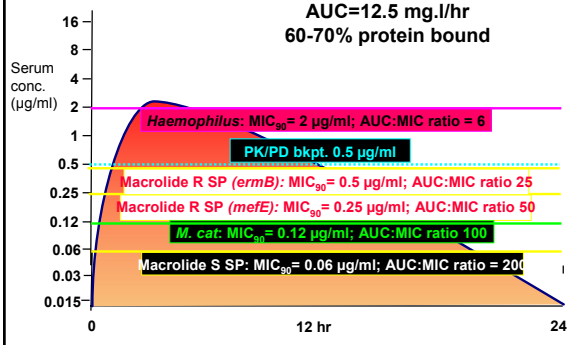
- The MIC at which the pathogen is called susceptible or resistant
  - the point at which T>MIC of 40% or AUC:MIC of 25-125 is met with a specific antibiotic
- Given the pharmacokinetics of a specific antibiotic, how low does the MIC have to be for the organism to be called "susceptible" (where the goals for T>MIC or AUC:MIC are met)?
- Any pathogen with an MIC that falls below the breakpoint is considered susceptible; MICs that are above the breakpoint is considered resistant



"Gram Positive" Quinolones: $AUC_{(0\text{-}24h)}/MIC_{90}$ and C_{max}/MIC_{90} Ratios for *S. pneumoniae*

Antimicrobial	Dose	AUC/MIC_{90}	C_{max}/MIC_{90}
Gemifloxacin (Factive)	(320 mg)	**280** 8.4/0.03	**53.3** 1.6/0.03
Moxifloxacin (Avelox)	(400 mg)	**192** 48.0/0.25	**18.0** 4.5/0.25
Gatifloxacin (Tequin)	(400 mg)	**103** 51.3/0.5	**8.4** 4.2/0.5
Levofloxacin (Levaquin)	(500 mg)	**48** 47.5/1.0	**5.7** 5.7/1.0

Telithromycin 800 mg/day qd



Adapted fromFDA Anti-Infective Drugs Advisory Committee, 4/26/2001

CAP: Outpatient

- Macrolide (erythro, clarithro)
- Azalide (azithromycin)
- Ketolide (telithromycin)
- Gram positive quinolone (levo-, gati-, moxi-, alatro-, gemi-)
- Doxycycline (age >8)
- Cepha-2 (cefuroxime, cefdinir, cefpodoxime, cefprozil NOT CEFIXIME)

CAP: Inpatient

- Cepha-3 (cefotax/ceftriax or cefepime, but not ceftazidime)
  - Plus erythro or azithro
  - Consider vanco for MRSA and PRSP/CRSP
- Gram positive quinolone (levo-, gati-, moxi-, alatro-, gemi-)

Cough, fever, RLL consolidation. 2 weeks into ICU stay for pneumonia/ARDS, on Cefotaxime/Azithro. New onset fever, hypoxemia, increase in yellow tracheal secretions, LUL infiltrate, GNR on tracheal Gram stain

Serratia
Pseudomonas
Acinetobacter
Citrobacter
Enterobacter
Yersinia

Cefepime, Pip/Tazo
Gent/Tobra/Amikacin
Imipenem/Meropenem
Cipro
Bactrim for S. malto

Stenotrophomonas maltophilia
Cefepime/gent resistant Enterobacter

Cough, initially with fever but now afebrile, 2 weeks duration. Clear CXR .

- Differential
- History
- Exam
- Labs
- Differential
- Organisms
- Antibiotics
- Best treatment

Paroxysms of coughing
Post-tussive emesis
Family members with coryza and cough

PCR of nasal secretions positive

Pertussis

Erythro

1 day old, sepsis and meningitis

- Differential diag
- History
- Exam
- Labs
- Differential diag
- Organisms to c
- Antibiotics to start with
- Best treatment

GBS
E. Coli / GNR
Listeria monocytogenes

Amp/Gent
Amp/Cefotaxime
Change when culture results known

6 month old (=50 yo), fever, stiff neck, lethargy

- Diff
- Hist
- Exa
- Lab
- Diff
- Org
- Ant
- Best treatment

Pyogenic bacterial meningitis:

Streptococcus pneumoniae
Neisseria meningitidis
(Haemophilus influenzae)

Polysaccharide-protein conjugate vaccines

Cefotaxime
Plus vancomycin for PRSP

Cancer Chemotherapy, now with fever and neutropenia

Gram positives
- viridans Streptococcus (AML)
- Staphylococcus aureus

Gram negatives
- KESP
- Pseudomonas

Fungi after 5-7 days

Naf/ox plus
Pip/Tazo or Ticar/clav or imipenem or ceftazidime or cefepime
Plus perhaps Gent/Tobra/orAmikacin or aztreonam
Vanco if indicated for positive culture (avoid VRE)

Add amphotericin lipid preparation at 5-7 days if fever persists

- Best treatment

Cancer Chemotherapy, now with fever and neutropenia

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Coagulase negative Staphylococcus
- Vancomycin

Vanco-resistant enterococcus
- Quinupristin/dalfopristin
- Linezolid

In hospital, develops diarrhea after 1 week of antibiotics for pneumonia

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to conside
- Antibiotics to start with
- Best treatment

Clostridium dificile
Rx= metronidazole
metronidazole
po vanco

Viral enteritis

6 wks of fever, lethargy, weight loss: Endocarditis

- D
- H
- E
- L
- D
- O
- A
- B

Dental work 2 months ago

New heart murmur, splenomegaly, evidence of emboli

Multiple pos blood cultures with appropriate organism
Hematuria, ↑ ESR
Vegetation on ECHO

Viridans streptococci
Staph aureus
Enterococci

Pending culture results:
Pen/Amp + Naf/Ox + gent, or
Vanco/gent (synergistically nephrotoxic)

50 yo, postal worker, with fever, stiff neck. CSF gram stain = Gram positive rods

- Differential diagnosis
- History
- Exam
- Labs
- Differential diagnosis
- Organisms to consider
- Antibiotics to start with
- Best treatment

Anthrax

Flu-like illness
Mediastinal widening perhaps only visible on chest CT

Dx easily missed

Treatment of Inhalational Anthrax

- **Treat early, continue for 60 days**
- **Doxycycline 2.2-2.5 mg/kg/dose BID (max 100 mg BID) or others in class**
- **Ciprofloxacin 30 mg/kg/day ÷ BID (max 1000 mg/day) or others in class**
- **Beta-lactamase producers: penicillin=no**
- **Pen and tetracycline resistant strains engineered by Russian scientists**

MMWR Oct 26 2001;42:909

Other drugs for treatment of inhalational Anthrax

- **Other agents with in vitro activity**
  - **Rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin**
- **Clindamycin may decrease toxin production**
- **Macrolides, cephalosporins:no**
- **CDC recommends cipro or doxy plus "one or two others" for inhalational disease**
- **Cipro or doxy alone OK for cutaneous**

MMWR Oct 26 2001;42:909

Recent Treatments for Anthrax

- **NYC infant: Ampicillin-sulbactam + clindamycin (Roche. NEJM 2001;345:1611)**
- **Florida : Vancomycin + Penicillin (high dose) (Bush. NEJM 2001;345:1607)**
- **DC area: Ciprofloxacin (400mg IV q 8 hr), Clindamycin (900 mg IV q 8 hr), Rifampin (300mg IV q 12 hr). (Mayer TA. JAMA 2001;286:2549-2553)**

Vaccination to Prevent Anthrax

- Cell-free filtrate of B anthracis
- 6-dose initial series
  - Requires yearly booster
- Military personnel only
- Inoculation at 0 and 2 weeks
  - 100% protective at 8 and 38 weeks
  - 88% protective at 100 weeks

Post-exposure Prophylaxis: 10/01

- Cipro, doxycycline (augmentin?)
- Continue for 60 days
  - Doesn't kill spores
  - Only kills germinating organisms

MMWR Oct 19, 2001;50:889

Post-exposure Prophylaxis: 12/01

- Cipro, doxycycline (augmentin?)
  - Continue for 60 days
  - Monitor for illness
- Cipro, doxy, (augmentin?)
  - Additional 40 days
  - Monitor for illness and adverse reaction
- Anthrax vaccine at 0, 2, 4 weeks plus 40 days of antibiotics

MMWR Dec 21, 2001;50:1142

We must learn to reawaken and keep ourselves awake…by an infinite expectation of the dawn, which does not forsake us in our soundest sleep

Thoreau