

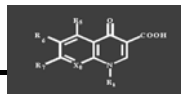
Advances in Fluoroquinolones Therapy

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Background:	Mechanism of Action Microbiology Clinical indications
Discussion	Advantages Liabilities
Unsolved questions:	Safety profiles differentiating efficacy Resistance development

Fluoroquinolones



Synthetic antimicrobial agents with the characteristic 4-quinolone ring structure containing a fluorine moiety at the 6-position. Some members also have a 1-piperazinyl group at the 7-position.

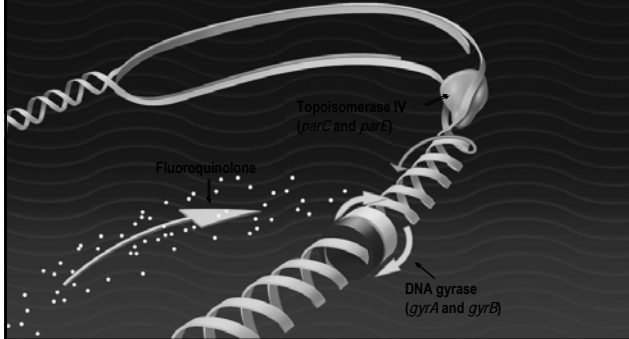
Fluoroquinolone agents have greater intrinsic antibacterial activity and a broader antibacterial spectrum than the quinolone agents (their precursors)

Fluoroquinolones in the US

<ul style="list-style-type: none"> ⇒ Ciprofloxacin (IV/PO) ⇒ Levofloxacin (IV/PO) ⇒ Grepafloxacin ⇒ Trovafloxacin ⇒ Moxifloxacin (IV/PO) ⇒ Gatifloxacin (IV/PO) ⇒ Clinafloxacin ⇒ Sparfloxacin ⇒ Gemifloxacin (PO) ? ⇒ Sitafloxacin ⇒ Garenoxacin ⇒ ABT 492 	}	New Fluoroquinolones
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Mechanism of Action of Fluoroquinolones

(Fluoroquinolones bind to two nuclear enzymes inhibiting DNA replication)



Activity of Fluoroquinolones vs. Typical Respiratory Pathogens

Pathogens	MIC ₉₀ (µg/mL)				
	Cipro	Gati	Levo	Moxi	Gemi
<i>S. pneumoniae</i> (PenS)	2	0.5	1	0.25	0.03
<i>S. pneumoniae</i> (PenR)	2	0.5	1	0.25	0.03
<i>H. influenzae</i>	<0.03	<0.03	<0.03	≤0.03	≤0.03
<i>M. catarrhalis</i>	<0.03	<0.03	<0.03	≤0.03	≤0.03

Zhanell GG, et al. *Drugs*. 2002;62:13-59.

Activity of Fluoroquinolones vs. *Atypical* Respiratory Pathogens

Pathogens	MIC ₉₀ (µg/mL)				
	Cipro	Gati	Levo	Moxi	Gemi
<i>C. pneumoniae</i>	2	0.13	0.5	1	0.12
<i>L. pneumoniae</i>	0.06	0.016	0.03	0.02	0.008
<i>M. pneumoniae</i>	2	0.06	0.5	0.12	0.12

Felmingham et al. ICC. 1999.
Zhanel GG, et al. Drugs. 2002;62:13-59.

In vitro Activity of New Fluoroquinolones vs. Gram-Negative Bacilli

Pathogens	MIC ₉₀ (µg/mL)				
	Cipro	Gati	Gemi	Levo	Moxi
<i>E. coli</i>	0.12	0.1	0.015	0.12	0.5
<i>K. pneumoniae</i>	0.06	0.1	0.12	0.25	0.5
<i>Ps. aeruginosa</i>	4	16	8	16	8
<i>B. fragilis</i>	16	1	2	8	1

Zhanel GG, et al. Drugs. 2002;62:13-59.

Fluoroquinolone Indications

DISEASE		LEVO	GATI	MOXI	GEM
RTI	ABECB	X	X	X	X
	Sinusitis	X	X	X	
	CAP	X/HAP	X	X	X
GU	Cystitis	X	X		
	Complicated UTI	X	X		
	Acute pyelonephritis	X	X		
	STD		X		
SSSI	Uncomplicated	X	X	X	
	Complicated	X			

Advantages of New Fluoroquinolones:

1. Activity vs. common respiratory pathogens, including atypicals
2. Activity vs. resistant organisms (*S.pneumoniae*)
3. Good respiratory tissue uptake
4. OD dosing
5. IV/PO formulation
6. Safety ?

Fluoroquinolones Liabilities

- **Safety:**
 - Hepatic
 - Cardiac
 - Glucose homeostasis
 - Photosensitivity
- **Drug Interactions**
 - Metabolized drugs
 - Antacid Interactions
- **Low doses and resistance development**

Landmarks in Fluoroquinolone Safety

June 1992	Temafloxacin	Voluntarily withdrawn 0.3yrs post-marketing due to HUS (<i>hemolytic uremia syndrome</i>)
March 1993	Lomefloxacin	Post-marketing phototoxicity labeling
mid-1990's	Several FQs	Tendonitis/tendon rupture warning labels
December 1996	Sparfloxacin	Phototoxicity and QTc prolongation labeling
June 1999	Trovafloxacin	Public health advisory warning on hepatotoxicity and black box 2 years post-marketing (2.5 million patients)
October 1999	Grepafloxacin	Voluntarily withdrawn for QTc prolongation and deaths
November 1999	Cinafloxacin	Development is discontinued due to severe phototoxicity and glucose homeostasis
December 1999	Moxifloxacin Gatifloxacin	QTc prolongation labeling at time of marketing
May 2002	Gatifloxacin	Glucose homeostasis labeling revisions (March 2001 and May 2002)

US Cases of Torsades de Pointes Jan 1, 1996 – May 2, 2001

Quinolone	FDA cases	Rx's (millions)	Cases/10 million Rx's
Ciprofloxacin	2	66	0.3
Ofloxacin	2	9.5	2.1
Levofloxacin	13	24	5.4
Gatifloxacin	8	3	27
Moxifloxacin	0	1.4	0

Spontaneous Reporting System (1969-1997)
Adverse Events Reporting System (1997 -)

Frothingham. Pharmacotherapy 2001; 21:1468-72.

Unresolved Questions With New Fluoroquinolones

- potency of individual agents against *S.pneumoniae*
- resistance development
- safety
- clinical data on:
 - nursing home pneumonia
 - pneumonias in high risk patients
 - fluoroquinolones vs macrolides
 - treating inpatient pneumonia orally
- what to do with gatifloxacin and moxifloxacin
- what role will gemifloxacin have

How do we compare activity and maximize efficacy of individual fluoroquinolones?

How do we compare activity and maximize efficacy?

- * The drugs are very similar in spectrum. Clinically it comes down to activity vs the following two organisms where differences are seen:
 - *S. pneumoniae*
 - *P. aeruginosa*

* Use of **Pharmacodynamic principles** to differentiate

between the different fluoroquinolones

Fluoroquinolone Pharmacodynamics

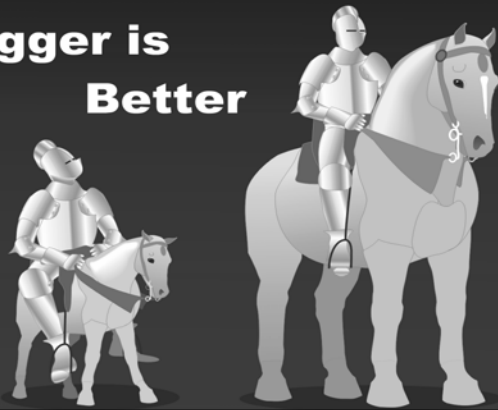
Concentration dependent bacterial killers
prolonged persistent effects
bacteriological eradication:

- AUC/MIC (AUC)
- C_{max}/MIC

Give large doses less frequently (eg. OD)

Turnidge. Drugs 1999.
Pickerill et al. Pharmacother 2000.
Zhanel et al. Drugs 2002.

Bigger is Better



Pharmacodynamic Targets for Fluoroquinolones in Respiratory Infections

Nosocomial pneumonia:

AUC/MIC ≥ 125 Target for bacterial eradication

Community acquired pneumonia:

AUC/MIC ≥ 30 Target for bacterial eradication
 AUC/MIC ≥ 100 Target for preventing resistance

Andes and Craig, ICAAC 2000.
 Preston et al. JAMA 1998.
 Forrest et al. AAC 1993.
 Thomas et al. AAC 1998.

Free AUC – *S. pneumoniae*

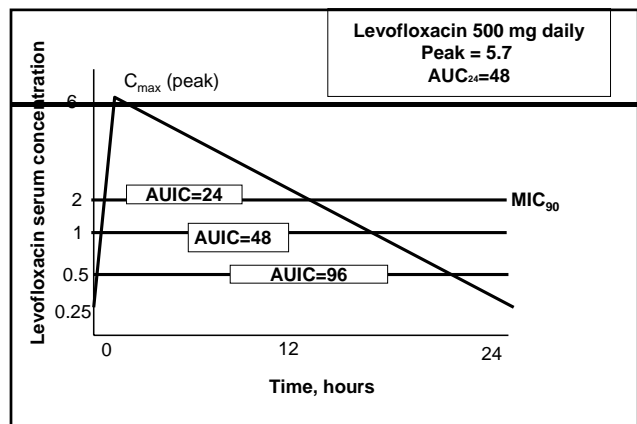
	AUC ₀₋₂₄ (mg-hr/L)				MIC (mg/L)
	Total	Free	AUC	AUC	
Cipro	20 ± 2.4	14 ± 1.2	10	7	2
Levo	48 ± 5.8	35 ± 3.1	48	35	1
Gati	30 ± 2.9	24 ± 2.0	60	48	0.5
Moxi	30 ± 3.3	15 ± 1.2	90	60	0.25

CLSI (NCCLS) Breakpoints: Cipro none, levo ≤ 2 , gati ≤ 1 , moxi ≤ 1

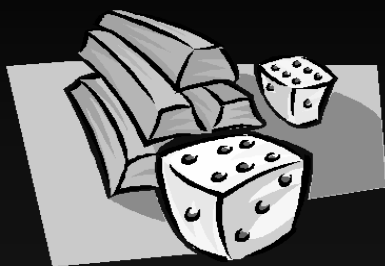
Free AUC – *P. aeruginosa*

	AUC ₀₋₂₄ (mg-hr/L)				MIC (mg/L)
	Total	Free	AUC	AUC	
Cipro	20 ± 2.4	14 ± 1.2	5-80	<4-56	0.25 – 4
Levo	50 ± 5.8	35 ± 3.1	12.5-100	<9-70	0.5 - >4
Gati	30 ± 2.9	24 ± 2.0	<7.5	<6	> 4
Moxi	30 ± 3.3	15 ± 1.2	<4	<2	8

NCSL (NCCLS) Breakpoints: Cipro ≥ 4 , levo ≥ 8 , gati ≥ 8 (urinary tract only), moxi none
 NCSL (NCCLS) 2002, Blondeau JM JAC 1999 43: suppl B, 1-11.



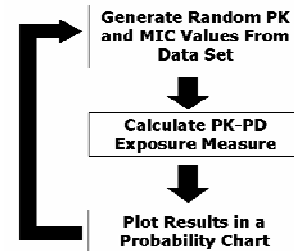
Monte Carlo simulations



R. Wise, 11th ECCMID, 2001

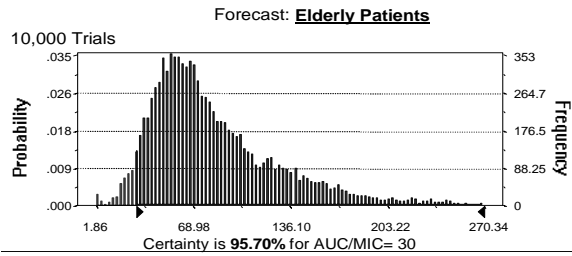
MONTE CARLO SIMULATION

Applied to PK-PD



Dudley MN, Ambrose PG. Pharmacodynamics in the study of drug resistance and establishing in vitro susceptibility breakpoints: ready for prime-time. Current Opinion in Microbiology 2000;3:515-521

Monte Carlo Simulation Analysis



Courtesy of Dr. Noreddin

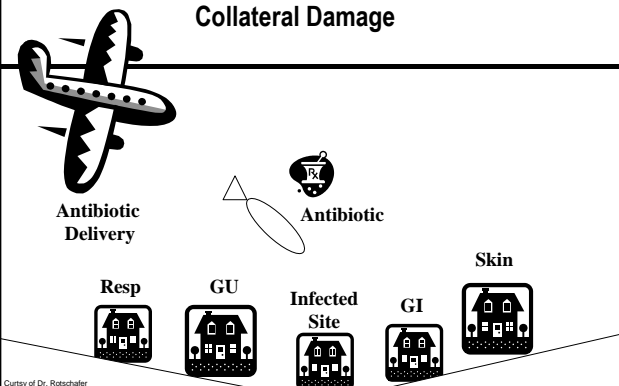
Target attainment potential of **levofloxacin** administered once daily to various patient populations

Target Free-Drug AUC ₀₋₂₄ /MIC ₅₀	30	40	100
Elderly	95.9%	88.8%	28.2%
Immunocompromised	82.1%	65.2%	10.7%
Healthy Volunteers	78.9%	13.6%	0.00%

Target attainment potential of **gatifloxacin 400mg** administered once daily to various patient populations

Target Free-Drug AUC ₀₋₂₄ /MIC ₅₀	30	40	100
Elderly patients	59.5%		
Immunocompromised patients	30.2%		
Healthy Volunteers	23.3%		

Collateral Damage



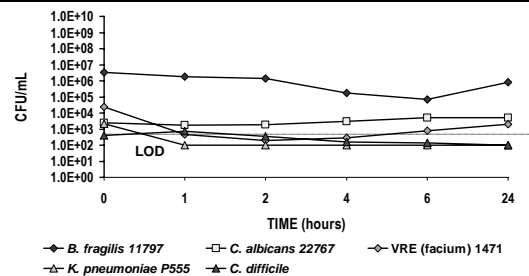
Courtesy of Dr. Rotschaller

Ecological Issues With New Fluoroquinolones (Respiratory Infections)

Question:

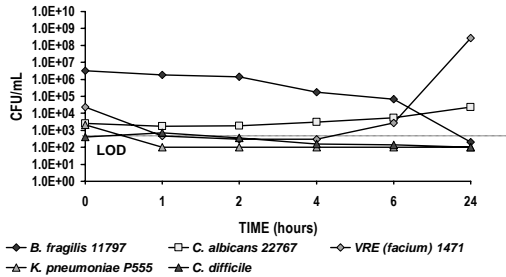
In treating CAP are there any potential negative consequences in using anaerobic fluoroquinolones that also kill anaerobic colonic flora (*B. fragilis*)?

Exposure of Colonic Flora to Non-Anaerobic Agents (Ciprofloxacin 500 mg BID or Levofloxacin 500 mg QD)



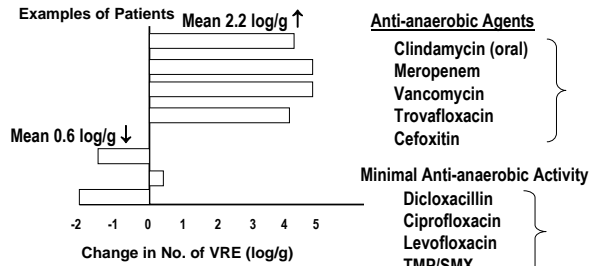
Zhanel GO, et al. Presented at the 102nd General Meeting of the American Society for Microbiology, May 19-23, 2002, Salt Lake City, Utah.

Exposure of Colonic Flora to Anaerobic Agents (Gatifloxacin 400 mg QD or Moxifloxacin 400 mg QD)



Zhanel GG, et al. Presented at the 102nd General Meeting of the American Society for Microbiology, May 19-23, 2002, Salt Lake City, Utah.

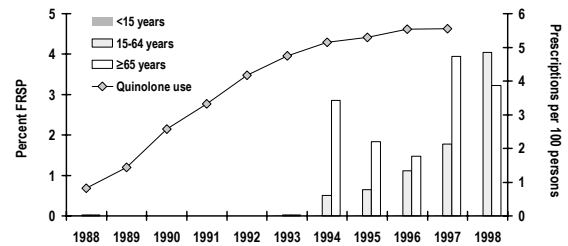
Effect of Antibiotic Therapy on the Density of VRE in Stool of Colonized Patients



Donskey CJ, et al. *N Engl J Med.* 2000;343:1925-1932.

Resistance Development

Fluoroquinolone (Ciprofloxacin) Use and Ciprofloxacin Resistant *S. pneumoniae* (Canada, 1988-1998)



Chen DK, et al. *N Engl J Med.* 1999;341:233-239.

Clinical failure of levofloxacin reported in patients with quinolone-resistant *S. pneumoniae*

Fatal meningitis due to levofloxacin-R *S. pneumoniae* respiratory tract infection (RTI) (Wortmann & Bennett. *Clin Infect Dis* 1999; 29:1599-1600)

- 58-year-old male HIV +; splenectomy, sinus congestion plus fever
- Levofloxacin 500 mg/QD. Meningitis on day 4. Died
- Levofloxacin disc = 0

Levofloxacin treatment failure in pneumococcal pneumonia (Kuehnert et al. *Ann Intern Med* 1999; 131:312-313)

- 63-year-old male with community-acquired pneumonia (CAP)
- Levofloxacin 500 mg/QD. Persistent disease
- *S. pneumoniae* (sputum) levofloxacin MIC >32 µg/ml. Cured with ceftriaxone
- Patient exposed to levofloxacin days earlier for bronchitis

Three levofloxacin treatment failures of pneumococcal RTI (Fishman et al. 39th ICAAC, San Francisco, Abstract 825)

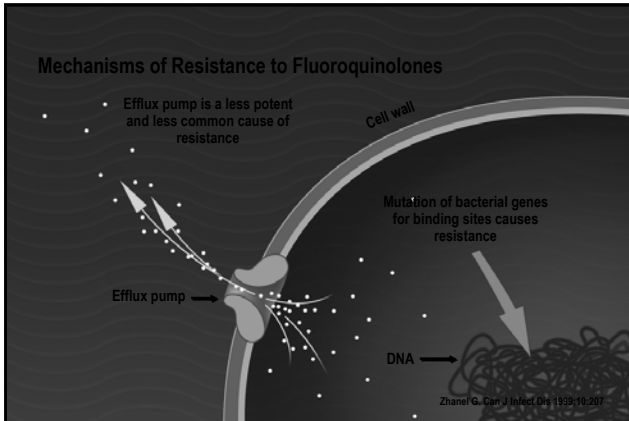
- Three cases of *S. pneumoniae* infection (CAP, sinusitis, hospital-acquired pneumonia)
- Two patients were levofloxacin-R (MICs >4 to >32 µg/ml)
- Two patients had significant history of prior fluoroquinolone use

Clinical Case of Fluoroquinolone Failure (NEJM Toronto 2002 – CAP With Empyema)

- 66-year-old woman – COPD on 8 days of Ciprofloxacin 500 mg BID for ?AECB admitted for CAP with pleural effusion
- Rx: Levofloxacin 500 mg daily
- Admission blood culture grew *S. pneumoniae*
- Pleural fluid tapped 4 days later grew *S. pneumoniae*
- The isolate was resistant to levo/gati/moxi



DO NOT USE ANY FLUOROQUINOLONE IF ON FQ IN LAST 3 MONTHS!



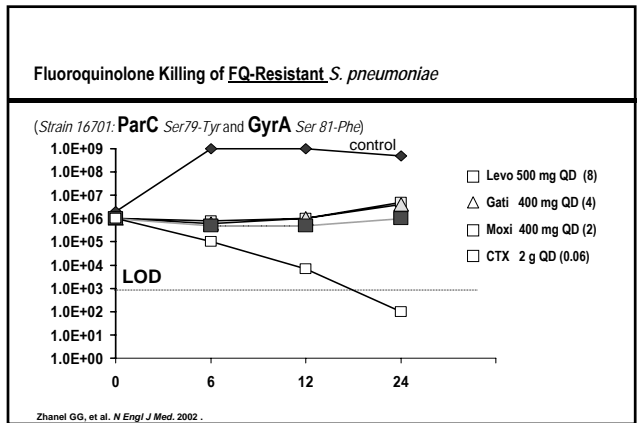
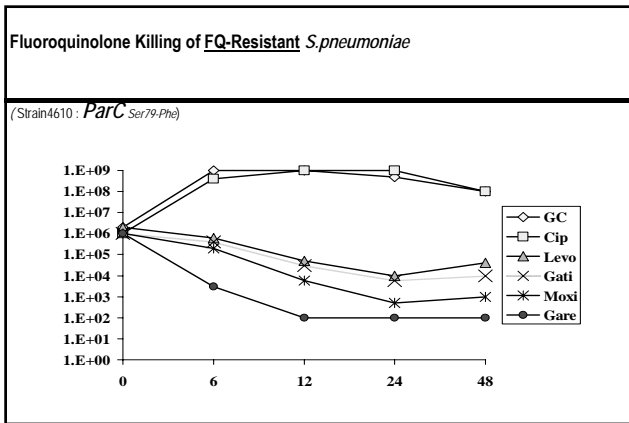
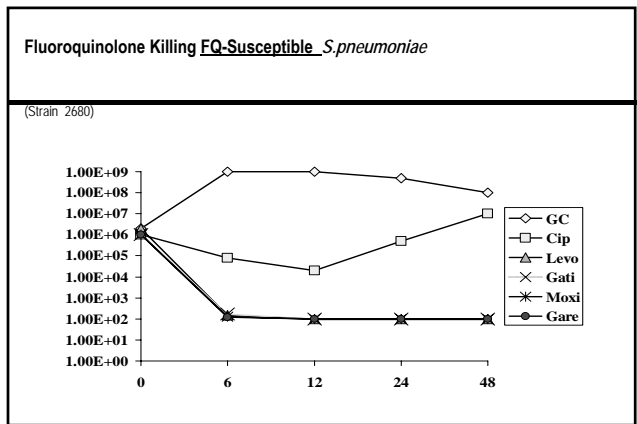
Possible Mechanisms of Fluoroquinolone Resistance (*S. pneumoniae*)

- Point mutations in target sites QRDRs
 - ⇒ • GyrA
 - ⇒ • ParC
 - ⇒ • GyrB
 - ⇒ • ParE
- ⇒ □ Efflux
- Decreased permeability
- Mutations outside the QRDR (?)

Smith HJ, et al. J Antimicrob Chemother. 2002;49:893-895.

MIC changes vs mutations

Mutation	MIC levo	MIC moxi
None	1.0	0.12
par C	4.0	0.5
gyr A/par C	32	4.0
efflux	4.0	0.12



Preventing the Emergence of Resistance

- There is one mutant in every 10^7 to 10^8 bacteria
- Mutant subpopulations are present at the start of therapy
- Drug concentrations must exceed MIC of original isolate and first-step mutants

Selection of *S. pneumoniae* resistance to fluoroquinolones

Not a significant problem at the moment, but it has the potential to grow and/or spread.

Early fluoroquinolone resistance may be linked to low AUC Quinolones in the community...?

Consequences of Low Overall FQ activity vs *S.pneumoniae*

Organism sub-populations are selected rather than eradicated

Very slow decline in the numbers of organisms (i.e. bacteriostatic actions)

Host defense must be intact to resolve the infection

Residual colonization even in cured patients

PK/PD vs FQ resistance

Low doses in relation to MIC (Low AUC) are a potential problem in the development of *S. pneumoniae* resistance to the Weaker Quinolones

Resistance to one, will cross over to all

It is better to use the most active FQ from the begin

Rapid Bacterial Eradication

Ordinarily an advantage for an antibiotic

Quick eradication leads to shorter courses of therapy, and lessens the risks of emergence of selected resistant organisms

Fewer bacteria present will produce a more rapid clinical response

Shorter treatment courses are advantageous, if we assure rapid bacterial killing

- Beta Lactams and macrolides do not do this
- Fluoroquinolones do, some more than others.

Treatment of CAP: *Symptom Resolution at 3 Days* (Levofloxacin 750mg OD x 5days vs. 500mg OD x 10days)

	n/N (%) of Patients		P Value*
	750 mg x 5days	500 mg x 10days	
Fever (patient reported)	161/239 (67.4)	130/238 (54.6)	.006
Purulent sputum	97/239 (40.6)	73/238 (30.7)	.059
Shortness of breath	84/239 (35.1)	66/238 (27.7)	.132

Dunbar et al. CID 2003.

What's the Future of Fluoroquinolones

Using the safest agent

High dose/Short course

How do you make your decision?

Cost

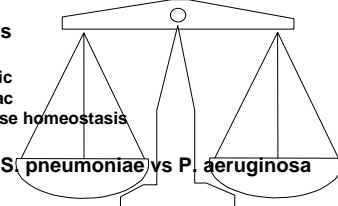
Indications

Safety

- Hepatic
- Cardiac
- Glucose homeostasis

Activity – S. pneumoniae vs P. aeruginosa

Resistance development



Hit it hard, hit it quick, and be focused