The Gap Between Biomarkers and Surrogate Endpoints in the Development of Anti-Infectives

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Chronology of attempts to Improve ABX development and bring forth more antibiotics

- Guidance for current ABX trials dates to 1992, when both FDA and IDSA participated in a trial design harmonization effort
- Numbers of NDAs submitted to FDA have been declining, perhaps even before this document, but decline has accelerated since.
- Industry is blamed by clinicians for exiting development; Clinicians say there are no new ABX, Industry replies that clinicians will not preferentially use the new ABX they develop.

Review of Antimicrobial Drug Development

MAJOR ARTICLE

Trends in Antimicrobial Drug Development: Implications for the Future

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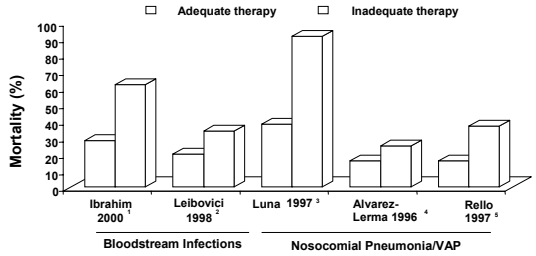
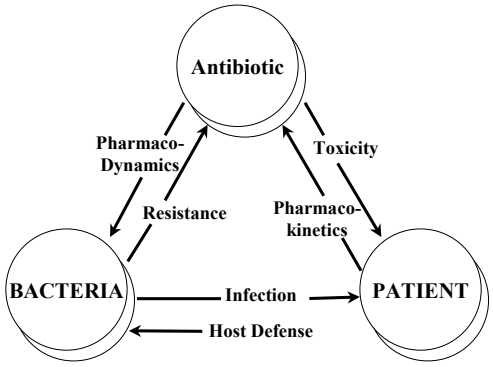
Clinicians Viewpoint: Inadequate Antibiotic Therapy Increases Mortality



1. Ibrahim et al. *Chest*. 2000;118:146–155.
2. Leibovici et al. *J Intern Med*. 1998;244:379–386.
3. Luna et al. *Chest*. 1997;111:676–685.
4. Alvarez-Lerma et al. *Intensive Care Med*. 1996;22:387–394.
5. Rello et al. *AJRCCM*. 1997;156:196–200.

Chronology, part II

- HIV drug development, by contrast, has enjoyed massive investment and nearly complete industry participation.
  - Some of this credited to use of surrogates and thus a more clear path to early efficacy – encourages risk taking.
  - Paradox is that HIV drugs are not cures, so they are used for long time periods and thus generate returns consistent with treatment of chronic disease conditions…
- Several Public Advisory Meetings (IDSA-FDA-PHRMA) since 2002 to "fix antibiotic drug development" to make it more efficient or less costly.
  - Wide ranging discussions (2002-2004) of issues such as trial design, incentives to bring industry back into the process and the role of surrogates and other alternative strategies to make the development of anti-infectives more rapid or less costly.



The Gap in Antibiotic development is Large by these Definitions:

- Biomarkers are :
  - analytical tools used to assess biological parameters
  - useful for many purposes (not just endpoints)

1) diagnostic tool - use of test as an inclusion criteria to define the disease based on presence of organism (increases specificity of diagnosis)

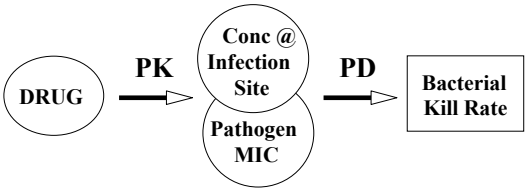
2) describe mechanism of action of drug - effect on organisms is mechanism, not goal of therapy

3) risk factor for acquisition of disease - colonization with particular organisms may be risk factor

4) risk factor for outcome - indicator of disease prognosis (HIV viral load and CD4 in HIV)
   - *Sande MA et al. NIH Consensus Conference on HIV, JAMA 1993;270:2583-89.*

5) surrogate endpoints – substitute for clinical endpoints

Optimizing Antimicrobial Therapy



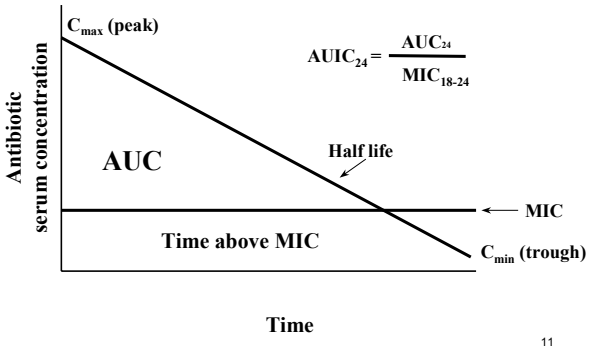
Bacteria as Genomic Targets?

- Even within species, each organism is uniquely susceptible to antibiotics, and may express resistance genes to varying degrees
- MIC and MBC are tests to detect drug specific resistance genes, useful as Biomarkers
- Predictive models incorporating PK and MIC are successful in predicting the outcomes of antibiotic therapy on the organism itself (sometimes on the patient, but this can depend on pathogenicity and host responsiveness)

Overview – Strategies to go beyond Biomarkers and Develop useful Surrogates

- Proposal to co-model pathogen replication and death, the time-course of severity of disease manifestation & the effects of drug therapy, on these processes (PD)
- PD endpoints, in ID, which might be modelled
  - Advantages/disadvantages
  - Current status in drug development
- Difficulties in studying PK/PD of anti-infectives in humans
- Enabling study designs for human trials

AUIC as enabling technology



Why focus on AUC and AUIC?

- All of these PK parameters change in parallel with each other, as the dose changes in relationship to the patient's clearance
- None of the data used to justify once daily use is based on optimized peaks
- Whenever you raise the dose, you increase the peak, but also the AUC

Optimal PK and PD attributes

- For optimal antimicrobial effect:
- C_{max}/MIC ratio should be > 8 to 10
- AUC/MIC ratio should be > 125 for cure
- AUC/MIC should exceed 250 for rapid killing of organisms
- To minimize resistance development: -AUC/MIC ratio should exceed 100

Patient Studies Modelling Biomarkers, Surrogates and Their Linkages: MIC, Clinical Scoring and PK/PD Indices of Antimicrobial Effect

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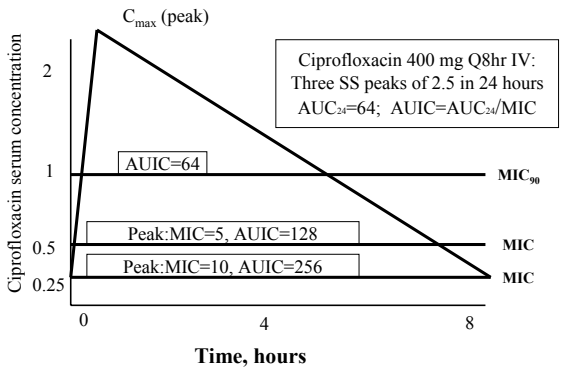
Population PK/PD of IV Ciprofloxacin - LRTI

- Relating drug exposure to infectious outcome
- 74 patients, in ICU with pneumonia
- Treated with IV ciprofloxacin 200 mg q12h to 400 mg q8h
- 2-19 blood samples to derive PK as AUC, and PK/PD as time > MIC and AUIC
- Daily cultures to derive time to bacterial eradication and speed of eradication
- Most important predictor for clinical and microbiological cure was the AUIC

Forrest A, et al. Pharmacokinetics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073-81.

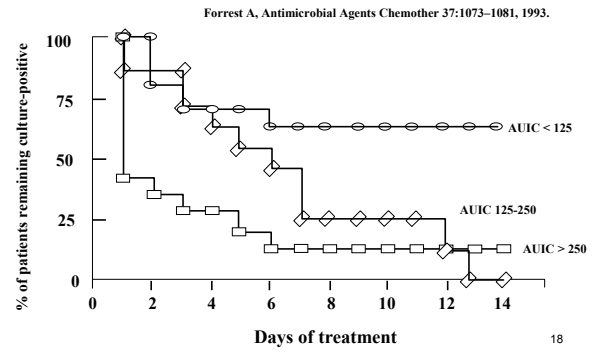


Cure vs Ciprofloxacin AUIC

		Cure Rate	
AUIC	**No.**	**Bacteriologic**	**Clinical**
0-125	**19**	**29%**	**42%**
125-250	**16**	**81%**	**88%**
250-1000	**14**	**78%**	**71%**
1000-5541	**15**	**87%**	**80%**

Forrest A, et al. Antimicrob Agents Chemother 1993;37:1073-81.

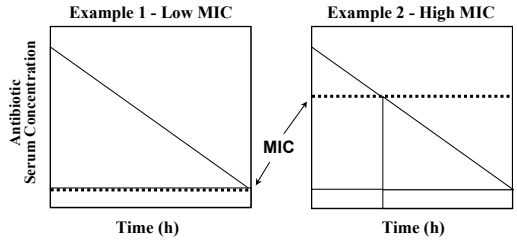
Ciprofloxacin: Eradication vs AUIC



AUIC Targets For Concentration – Dependent Antibiotics

- AUIC < 125
  - Some evidence for activity in mild infections in outpatients with normal host defenses
  - Peak:MIC = 3:1
- AUIC = 125
  - Separates cure and failure in compromised patients
  - Represents 80% of total AUC above MIC
  - Peak:MIC = 5:1
  - Threshold for avoiding resistance is 100
- AUIC > 250
  - Maximum killing rate for concentration dependent antibiotics
  - Trough concentration above MIC 100% of time
  - Peak:MIC = 10:1
  - Shortens time required for microbiological cure

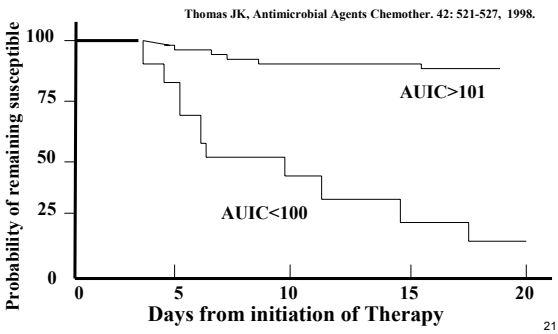
Impact of AUIC on Resistance



- Low MIC ⇒ high AUIC
- Effective dosing
- Minimal potential for resistance

- High MIC ⇒ low AUIC
- Ineffective dosing period
- High potential for resistance especially over long term use

AUIC vs Resistance



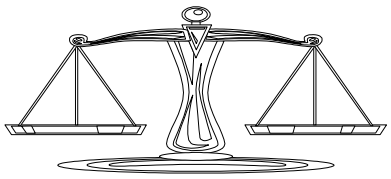
Antibiotic Use And Resistance

- Antibiotics Select Resistant Organism Sub-populations, by Eradicating Susceptible Strains
- Resistant Strains Proliferate while the Patient is treated, as They have a survival advantage when the antibiotic is present
- Link to AUICs

Choice of Empiric Agent – Choice of AUIC

MAXIMIZE COVERAGE
against most likely pathogens

MINIMIZE SELECTION
for resistance



Proposed Enabling Study Designs

- Data to be obtained when possible
  - Serial C&S from the 'site of infection' (eg, ELF, CSF, blood)
    - Quantitative or semi-quantitative titers, if possible
  - PK data from the 'site of infection'
- Data which should 'usually' be obtained
  - Plasma PK and baseline culture and sensitivities (C&S)
  - Yes/No clinical and microbiologic success/failure
  - Serial disease severity scores

Biomarkers and Surrogates for Clinical Outcomes in Phase II-IV studies

- Biomarker:
  - MIC and/or MBC (universally used in pre-clinical work)
- Surrogates proposed for clinical trials:
  - Bacterial Eradication (yes-no)
  - Bacterial Eradication Time (PK/PD)
  - Symptom Resolution (Scoring of Multiple Symptoms)
    - Fever, WBC decline, CXR resolution, Subjective expressions of well-being

Clinical Approaches

- **Dose to Trough above MIC as surrogate for AUIC > 125**
- **Increase doses for high MIC organisms and patients with high CCr**
- **When in doubt, combine antibiotics. When sure of isolates, refine regimens**
- **Gram Stain is the best monitoring tool**
- **Computer software to Estimate AUICs**

Fluoroquinolones: Agent Selection

CHOICE OF OPTIMAL AGENT

- Adverse events
- Drug Interactions
- Microbiologic activity
- Pharmacokinetics
- Pharmacodynamic profile
  - AUIC > 125, preferably AUIC > 250
  - Peak:MIC > 10:1, Preferably 25:1
  - Avoiding resistance…