ISSUES IN CLINICAL TRIALS FOR CABP

Anti-infective Advisory Committee
November 3, 2011

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University of Washington
Public Citizen

OUTLINE

Background

1. Endpoints
2. Noninferiority margin
3. Study population
4. Conduct of trial

MOVING IN THE RIGHT DIRECTION

- 2009 FDA Draft Guidance
- 2011 Foundation for the NIH Biomarker Consortium recommendations
- Briefing materials for today's Advisory Committee meeting

TRIAL DESIGN FOR CABP

- There are a number of options
  - Superiority: EXP vs. active-control
  - Superiority: EXP vs. placebo as add-on therapy
  - Noninferiority: EXP vs. active-control

ELEMENTS OF A NI TRIAL

- Reliable evidence of a treatment effect of the active control
- Choose clinically meaningful NI margin
- Similar patient characteristics, concomitant treatments, and outcome
- Design and conduct trial to minimize bias toward similar treatment effect

ENDPOINTS

- Proper endpoint for an efficacy trial should measure how a patient feels, functions, or survives (21 CFR 314.500)
- Biomarkers can serve as surrogate endpoints if validated
  - IOM Report on Evaluation of Biomarkers and Surrogate Endpoints, 2010
  - Effects on surrogate must reliably establish important effects on meaningful endpoints

SURROGATE ENDPOINTS

Drug	Surrogate endpoint	Clinical endpoint
Clofibrate	↓ Lipids	↑ Death
Encainade	↓ PVCs	↑ Sudden death
Flecainide	↓ PVCs	↑ Sudden death
Rosiglitazone	↓ Hemoglobin A1c	↑ Myocardial infarction
Bevacizumab (Avastin)	↓ Tumor size (breast)	↑ Death
Sibutramine	↓ Weight	↑ CV events, death

Unvalidated surrogate endpoints cannot be used to determine the efficacy of new drugs

ENDPOINTS: CABP

- Mortality
  - Strongest evidence for a treatment effect in patients at high risk of death
- Improvement in symptoms at Day 3-5
- Test-of-cure (TOC)
  - Poorly-defined outcome that includes biomarkers such as fever
  - Not a valid endpoint

NONINFERIORITY MARGIN

- First, need reliable statistical evidence of a treatment effect for the active control (M1)
- Next, how much harm is tolerable (M2)
  - A margin of 10% is LARGE, difficult to justify without ancillary benefit (cost, safety, etc…)
- For context, look at absolute risk reduction with highly-effective treatments
  - ASA for STEMI (ISIS-2[1]): 2.4% ↓ CV death
  - PCI for STEMI (DANAMI-2[2]): 7.5% ↓ death/MI/stroke

[1]Lancet.1988;2:349.

[2]NEJM.2003;349:733.

STUDY POPULATION

- Subjects must have evidence of infection with typical bacterial pathogens
  - Micro ITT as primary analysis with M2 of ≤10%
  - Sequential designs can be used to ensure adequate power
- Subjects must be at high risk of death for constancy assumption to hold, and for a NI comparison to be valid
  - Enrich with older patients, high severity scores

TRIAL CONDUCT

- Prior antibiotics – an exclusion criterion
  - Pertel 2008 (Clin Infect Dis;46:1142)
  - Presume prior antibiotics bias findings towards NI
- Examples of early randomization: time from symptom onset
  - ASA for STEMI (ISIS-2[1]): 50% within 5 hours
  - PCI for STEMI (DANAMI-2[2]): 72% within 4 hours
  - tPA for stroke (NINDS[3]): 100% within 3 hours

[1]Lancet.1988;2:349.
[2]NEJM.2003;349:733.
[3]NEJM.1995;333:1581.

TRIAL CONDUCT

- After randomization
  - Use of non-study antibiotics with activity against typical bacterial pathogens should be limited to true treatment failures
  - If rate of rescue therapy is high with experimental drug, might falsely conclude noninferiority when drug is worse than active control

AN EXAMPLE: CETHROMYCIN

Analysis Population	Cethromycin cure/N (%)	Clarithromycin cure/N (%)	Treatment Difference, (95% CI) [a]
ITT (n=510)	213/257 (82.9)	224/253 (88.5)	-5.7 (-12.1, 0.8)
CE (n=445)	205/224 (91.5)	212/221 (95.9)	-4.4 (-9.3, 0.5)

Excluding patients with PORT = 1, atypical pathogens, and prior antibiotics:

ITT (n=510)	86/113 (76.1)	90/105 (85.7)	-9.6 (-20.9, 1.6)
CE (n=445)	85/98 (86.7)	86/92 (93.5)	-6.7 (-16.2, 2.7)

CONCLUSION

- FDA has made great advances in the regulation of CABP trials
- Endpoint must be valid
- NI margin must be justified (≤10%)
- Study population should be valid (micro ITT, high risk of treatment failure)
- Use of non-study antibiotics should be restricted

Community Acquired Pneumonia drug studies in Emergency Departments: the perspective from a practicing emergency physician

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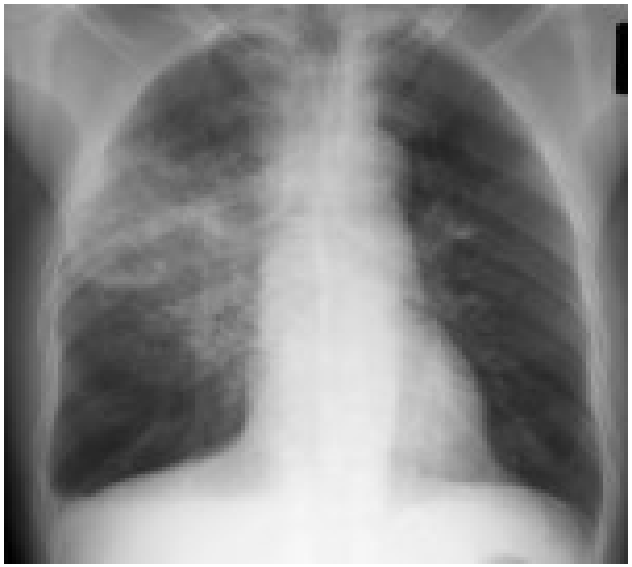
Emergency



Agenda

- Discuss Opportunities and Barriers to enrolling patients with community acquired pneumonia in drug studies in the emergency department

Opportunities

- Over 124 million annual ED visits in the US
- Estimated 500,000 hospital admissions for community acquired pneumonia

- National Center for Health Statistics, Toledo, Ohio. 2008
- **Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group.**
- Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, Kolczak MS, Breiman RF. Arch Intern Med. 1997 Aug 11-25;157(15):1709-18

Barriers

- Overcrowded Hospitals
- CMS/TJC Core Measures
- Antibiotic use prior to emergency department visit
- Operational Constraints

Overcrowding: Lack of inpatient bed capacity and rising ED volumes leads to increased wait times for patients

Centers for Medicare and Medicaid/The Joint Commission

- Pay for Performance
- CMS/TJC Core Measures data collection started in 2003
- Started publishing data on Hospital Compare Website in 2007

PN-5b

- November 2003
- Pneumonia patients who receive their first dose of antibiotics within **4** hours after arrival at the hospital

- **Emergency department operational changes in response to pay-for-performance and antibiotic timing in pneumonia.**
- Pines JM, Hollander JE, Lee H, Everett WW, Uscher-Pines L, Metlay JP.
- Acad Emerg Med. 2007 Jun;14(6):545-8. Epub 2007 Apr 30.

Liberal dispensing of antibiotics for ED patients with potential for pneumonia

PN-5c

- March 2008 CMS “relaxes” requirements
- Pneumonia patients who receive their first dose of antibiotics within **6** hours after arrival at the hospital

Liberal dispensing of antibiotics for ED patients with potential for pneumonia

CMS will no longer require timely antibiotics starting January 2012

But old practices may take some time to change

Prior Antibiotic Use

- Exists, but is not a big issue in urban emergency department
- Many patients with community acquired pneumonia present to the ED without first seeing their primary care doctor
- Patients who feel they are pretty sick tend to go directly to the ED instead of PMD or clinic

Operational Constraints

- Emergency Departments are busy
- Long waits during peak times
- Physicians/Departments are measured on markers such as door to doctor time, decision to admit/discharge time and total ED length of stay
- Having physicians stop workflow to enroll patients in studies is difficult

Opportunities

- 24/7 Business Model
- Study coordinators facilitate patient enrollment
- ED physicians need only page/call coordinator
- CMS/TJC requirements have resulted in MDs/RNs being vigilant for suspected pneumonia patients →increased likelihood of early detection for study enrollment
- ED triage RNs already trained to identify patients with time sensitive diagnoses such as stroke and MI

Conclusion

- Patients with community-acquired pneumonia who are sick enough to require admission most often first present to the emergency department
- Despite operational challenges, the emergency department is a prime site to enroll patients in drug studies for treatment of severe acute infectious diseases

Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia

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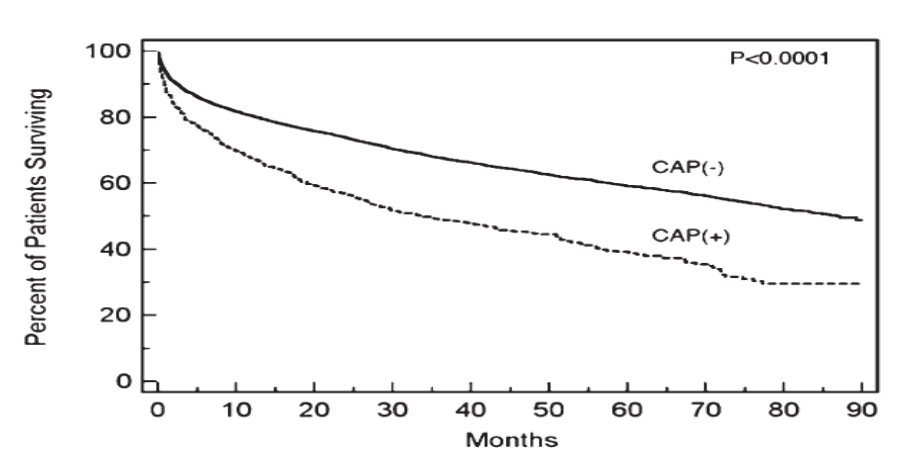
Disclosures

- Recent research funding– Boerhinger Ingelheim, Cerexa/Forest, Gilead, Pfizer, Tibotec
- Scientific Advisory Board/Consultant—Astellas, Bayer, DaiichiSankyo, Cerexa/Forest, Merck, Nabriva, Pfizer, Tetraphase

Community-acquired Pneumonia (CAP)

- Leading cause of morbidity and mortality
  - No. I cause due to infection
- 5-6 million cases/year
  - > 75% treated as outpatients
  - Approx. 1 million admissions/year
    - » **40% one year mortality; Kaplan et al. Arch Intern Med 2003; 163: 317-323)**
    - » **50% mortality at 30 months (Bordon et al. chest)**



- Cost of treating CAP exceeds $17 billion/year

File T. *Lancet* 2003; File and Tan *JAMA* 2005

File T and Marrie T *Postgrad Med*. 2010

CAP in adults

- "Despite extensive studies, there are few conditions in medicine that are so controversial in terms of management"
  - Bartlett JG et al. IDSA CAP Guidelines 1998/2000. Clin Infect Dis. 1998/2000
- Use of antimicrobials for CAP preceded RCTs
  - Therefore, hypothesis that antimicrobials are necessary component of the management of CAP has not been rigorously tested-especially in mild pneumonia*
  - However, observations suggest antimicrobials are beneficial*

*Read R. J Infect. 1999; 39: 171

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Cefamandole Nafate Therapy of Respiratory Tract, Skin, and Soft Tissue Infections in 74 Patients

Robert L. Perkins, Robert J. Fass, John F. Warner, Richard B. Prior, Thomas M. File, Robert R. Tight, William G. Gardner, Daniel E. Ruiz, and Thomas G. Slama

From the Division of Infectious Diseases, Department of Medicine, The Ohio State University, Columbus, Ohio

Have participated in RCTS of CAP since 1975

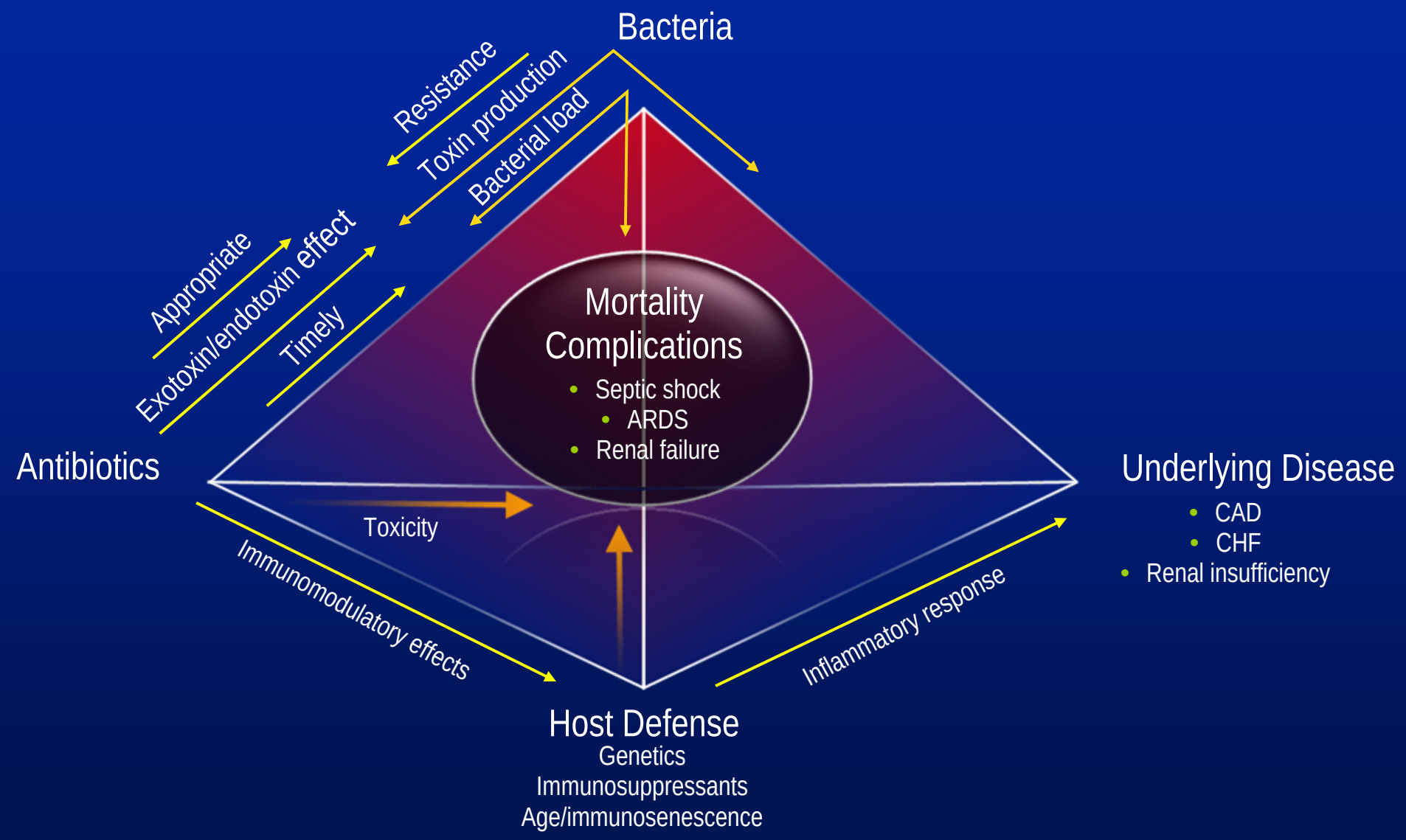
- Significant change in Clinical Trial process
  - » Pathogens
  - » Consent process; Study implementation; Report Forms
  - » Increasing Confounders
    - Timing of initial dose; Prior dose; Decreasing LOS, Early switch from IV to po
  - » ID vs ED; performance measures
  - » CAP vs HCAP

Community-acquired Bacterial Pneumonia (CABP)

- "To better identify individuals most likely to have bacterial pneumonia and hence benefit from antimicrobial therapy"
- defines CABP (adult patient) as acute infection associated with symptoms such as fever or hypothermia, chills, rigors, cough, chest pain, or dyspnea, accompanied by the presence of a new infiltrate. …to demonstrate an effect of therapy on the clinical course caused by bacterial pathogens such as *S. pneumoniae, H. influenzae, S. aureus, or M. catarrhalis*
- *BUT NOT HOW WE TREAT PATIENTS*

Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment
http://www.fda.gov/cder/guidance/index.htm .

CAP: Multiple Determinants of Outcome

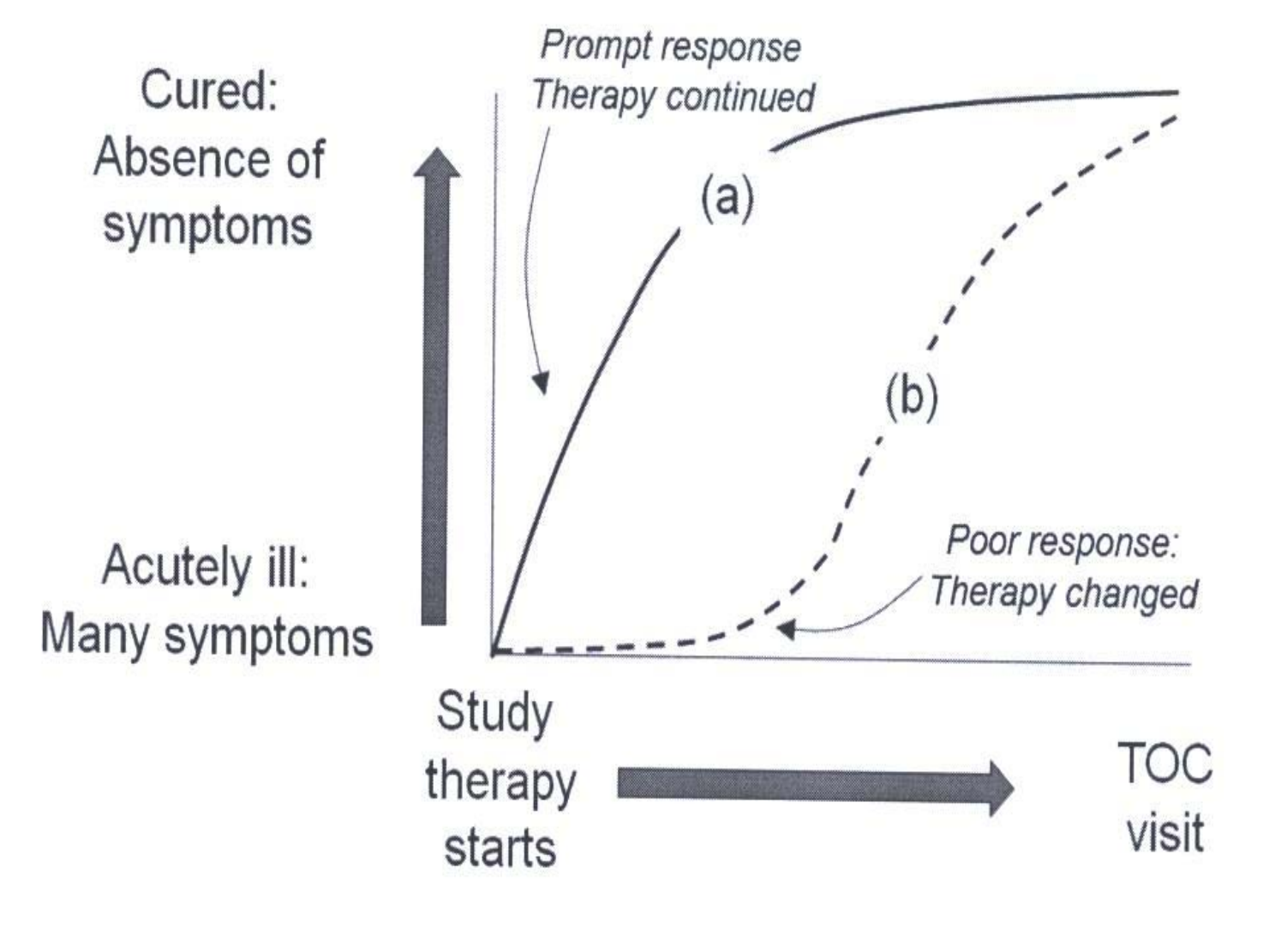


Waterer G, Rello J,Wunderink R *Am J Respir Crit Care Med*. 2011;183:157-164

CAP Trials in adults

- Merits and limitations of endpoint based on improvement of at least 2 of 4 symptoms at day 3 to 5.
- Consider proposed trial designs
- Other trial designs
  - Prior ABX therapy
  - Endpoints
  - Enrichment of micro-ITT
  - Overcoming barriers

Comparing two drugs for clinical efficacy



2011 August 26 FNIH Biomarkers Consortium Project Team: CABP Interim Recommendations Document

Interim Recommendations from FNIH

- Study Design
  - Non-inferiority
- Endpoints
  - Early assessment at Study Day 4
    - » One point improvement at least 2 symptoms; no worsening (cough, dyspnea, pleuritic pain, sputum production)
  - Later assessment time TOC
- Enrollment criteria
  - Minimum of 2 symptoms
  - Severity, prior ABX not addressed

2011 August 26 FNIH Biomarkers Consortium Project Team: CABP Interim Recommendations Document

Early Endpoints

- Already assessed (Ceftaroline trials)
- Specified day # vs Time to Clinical Stability
  - Latter is well described in guidelines and part of Standard of Care
- Clinically relevant to patient
- Combine with later TOC assessment to assure (continued) resolution

2 Recent CAP Studies

	Tigecycline v Levofloxacin	Ceftaroline v Ceftriaxone
# pts (mitt)	846	1153 (MITTE) *(ITT 1240)*
PORT	53 % I or II	All III or IV
Age (mean)	51	61
% 'bacterial' pathogen	29% (40% with 'atypicals')	26.1% (37% with 'sole atypicals')
Mortality	2.7%	2.2%
4 day response	72%	69.3% vs. 59.9%
TOC response	89.9% v 87.8%	82.6% v 76.6% (1.6-11.8)
S pneumoniae	84/91 (92.3%) vs 88/99 (88.9%)	59/69 (85.5%) vs 48/70 (68.8%)
Bacteremia: response	20/22 (90.9%) v 13/18 (87.8%)	15/21 (71%) v 10/17 (58.8%)

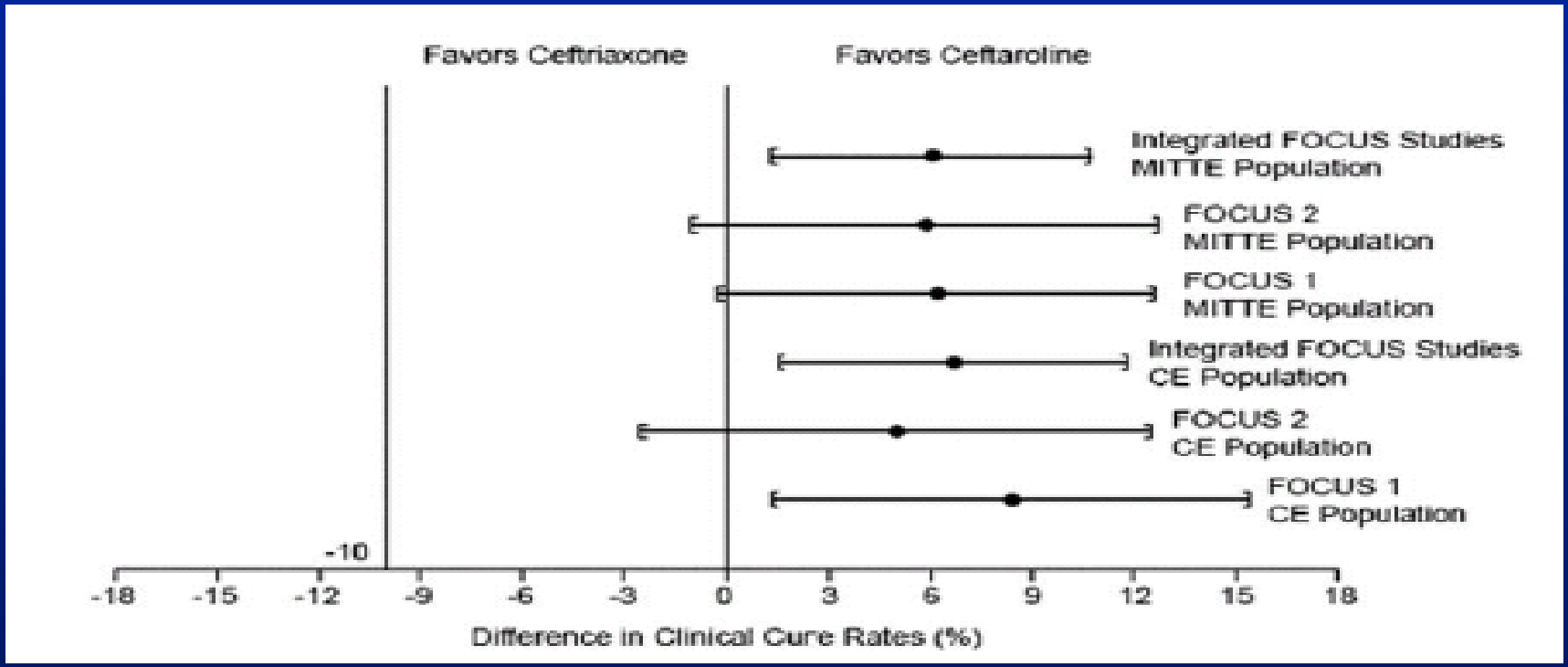
Tanaseanu et al. Diag Microb Infect Dis. 2008; 61: 329-338; File et al. Clin Infect Dis. 2010; 51: 1395-1405

2 Recent CAP Studies

	Tigecycline v Levofloxacin	Ceftaroline v Ceftriaxone
Prior Antimicrobial	1 dose non QD drug	One dose short-acting
% on prior ABX		42% (CE population)
IV to po switch	One study to levofloxacin	No
% patients from US	18%	3.8% (FOCUS 1)
Macrolide use		One study with one day of clarithromycin

- **Summary:**
  - Mortality low (2-3%; lower than non RCT study patients)
  - % with identified etiology
    - 26-29% ‘typicals’; 37-40% with ‘atypicals’ (caveat about Chlamydophila??)
  - Early end point reasonable
  - Effect of prior ABX in US
  - North American use of macrolide needs to be considered

Ceftaroline Fosamil versus Ceftriaxone Patients with Community-Acquired Pneumonia



- 1200+ patients; Ave age—61 years; all PORT III or IV
- Clinical Cure for *S. pneumoniae*:

  Ceftaroline 59/69 (85.5%); Ceftriaxone 48/70 (68.6%)

  Ceftaroline has greater affinity for PBP 2x

File T et al. Clin Infect Dis. 2010; 51: 1395-1405

Effects of Prior Therapy for CAP

- "Long acting agent" Pertel et al. Clin Infect Dis. 2008; 46 April 15

Table 6. Clinical cure rates among patients in the pooled clinically evaluable population, by prior effective antibacterial therapy.

	Daptomycin arm		Ceftriaxone arm		
Prior effective therapy	No. of cured patients/total no. of patients	Cure rate, %	No. of cured patients/total no. of patients	Cure rate, %	95% CI[a]
Yes	88/97	90.7	81/92	88.0	−6.1% to 11.5%
No	205/272	75.4	245/279	87.8	−18.8% to −6.0%

[a] For the difference in cure rates.

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[a] For the difference in cure rates.

- "Short acting agent" File T et al. Clin Infect Dis. 2010; 51: 1395-1405

Table 7. Clinical Cure Rates in Select Patient Subgroups, Integrated Clinically Evaluable Population

Patient subgroup	Ceftaroline group	Ceftriaxone group	Weighted treatment difference (95% CI)
Bacteremia	15/21 (71.4)	10/17 (58.8)	12.6 (−17.6 to 41.6)[a]
PORT risk class III	249/287 (86.8)	217/274 (79.2)	7.5 (1.3–13.8)
PORT risk class IV	138/172 (80.2)	132/175 (75.4)	4.7 (−4.1 to 13.5)
Received prior antibiotic treatment[b]	152/185 (82.2)	158/194 (81.4)	0.7 (−7.2 to 8.6)
Did not receive prior antibiotic treatment	235/274 (85.8)	191/255 (74.9)	11.2 (4.5–18.0)

Enrichment of Microbial Etiology

- Molecular Tests
- Sputum Grams stain or Urinary Antigen
- Advanced Urinary Antigen (Luminex platform)
  - Pride MW et al. 7th Intern Symp Pneumococci and Pneumococcal Diseases. 2010, Tel Aviv
- Procalcitonin

Enrichment of Microbial Etiology- PCR

- Johansson et al. Clin Infect Dis. 2010; 50: 202-9

Etiology of community-acquired pneumonia using molecular and conventional diagnostic methods

Pathogen	No. (%) N = 184	Blood Culture	Respiratory Culture	Urinary Antigen	PCR	Serology
Streptococcus pneumoniae	70 (38)	27	17	16	10	—
Mycoplasma pneumoniae	15 (8)	—	—	—	8	7
Haemophilus influenzae	9 (5)	—	7	—	—	—
Moraxella catarrhalis	7 (4)	—	7	—	—	—
Staphylococcus aureus	4 (2)	2	2	—	—	—
Legionella pneumophila	3 (1)	—	1	2	—	—
Streptococcus milleri group	1 (0.5)	1	—	—	—	—
Nocardia sp	1 (0.5)	—	1	—	—	—
Fusobacterium necrophorum	1 (0.5)	1	—	—	—	—
Mycobacterium tuberculosis	2 (1)	—	2	—	—	—
Viruses	54 (29)	—	8	—	26	20
Influenza virus	14 (8)	—	3	—	4	7
Rhinovirus	12 (7)	—	—	—	12	—
RSV	7 (4)	—	1	—	1	5
Parainfluenza virus	7 (4)	—	1	—	1	5
Coronavirus	4 (2)	—	—	—	4	—
Metapneumovirus	3 (2)	—	1	—	3	—
Adenovirus	3 (2)	—	—	—	—	3
HSV 1	2 (1)	—	2	—	—	—
Enterovirus	1 (0.5)	—	—	—	1	—

For patients with complete sampling, a microbiological agent was identified for 89% of the cases.

"We double the number of patients with *S. pneumonie* based on whole blood PCR" (Wunderink R. personal communication)

Enrichment of Microbial Etiology- Sputum Grams Stain

- Patients enrolled in six studies of oral Amoxicillin/Clavulanate (2000/125 mg)*
  - *S. pneumoniae* isolated from 15.3% (652/4264) of all patients
  - Inclusion criteria enriched patient populations with *S. pneumoniae*
    - » possible bacterial (studies 2,3,5,6): 3.1–13.1% of all patients
    - » suspected pneumococcal (studies 1,4): 18.6–20.9% of all patients
      - Required + Grams Stain or + Urinary Antigen
  - 75 DRSP isolates obtained from 10.6% (69/652) patients with *S. pneumoniae* infection
  - Bacteremia detected in 15% (micro eval population) patients with *S. pneumoniae* infection
- Conclusion: Can enhance % bacterial yield

File T et al. ICAAC 2005, San Francisco; File T et al. Intern J Antimicrob Agents 25 (2005) 110–119

Enrichment of Microbial Etiology-Procacltonin

- Procalcitonin (from Gilbert D. Clin Infect Dis. 2011: 52: (Suppl 4)
  - "Several studies have evaluated the role of elevated serum PCT levels as a way of increasing the probability of a bacterial etiology of respiratory tract infections in adults"
  - "It should be possible to use advanced molecular diagnostics to validate the ability of the serum PCT to separate viral from bacterial infection."

- Procalcitonin (from Roig et al. Abstract 979 IDSA 2011)
  - "Procalcitonin as a diagnostic tool to distinguish bacterial pneumonia in patients with pulmonary infiltrates"
    - » Using 0.55 ug/L as a cut-off, PCT showed 78.8% sensitivity for predicting bacterial infection, 78.3% specificity, PPVof 66.7 % and NPV of 87.0%.
    - » Conclusion: Serum procalcitonin >0.55 ug/ maybe a useful diagnostic test in evaluating patients admitted with new pulmonary infiltrates.
-

Enrichment of Microbial Etiology-Procalcitonin

Table 1. Randomized Controlled Trials That Used Procalcitonin (PCT) Serum Levels to Guide Antibiotic Therapy in Adult Patients With Respiratory Tract Infections

			No. of evaluable patients		Percentage of patients who started antibiotic therapy		Duration of antibiotic therapy, mean days	
Reference	Clinical syndrome(s)	Study site (location)	Control group	PCT group	Control group	PCT group	Control group	PCT group
[21]	Pneumonia, AECOPD, acute bronchitis	Emergency department (Basel, Switzerland)	119	124	77.3	44.4	12.8	10.9
[22]	Community-acquired pneumonia	Emergency department (Basel, Switzerland)	151	151	99	85	12	5
[23]	AECOPD	Emergency department (Basel, Switzerland)	106	102	72	40	...	...
[24]	Rhinosinusitis, tonsillitis, pharyngitis, acute otitis media, tracheobronchitis, AECOPD, community-acquired pneumonia	General practices at multiple outpatient facilities (Switzerland)	226	232	97	25	7.1	6.2
[25]	Community-acquired pneumonia	Hospitals (Denmark)	107	103	79	85	6.8	5.1
[26]	Acute bronchitis, AECOPD, community-acquired pneumonia	Emergency departments at 6 hospitals (Switzerland)	688	671	87.9	75.4	3.8	3.2

Gilbert D. Clin Infect Dis. 2011: 52: (Suppl 4

Clinical Trials: Barriers

Barrier	Response
Prior ABX	OK if prior to presentation; Allow short-acting agent prior to enrollment; Have study personnel in ED
Timing of initial ABX	No longer will be quality measure by CMS, but there is evidence of effect. Study personnel in ED
Early discharge; Early IV to po switch	Allow short course of IV and switch to po
Enrich for ‘bacterial’ etiology	Require Sputum; Molecular tests, Advanced Urinary Ag; Procalcitonin; Include validated ‘atypicals’
Consent Forms (Intimidating), time consuming	Well trained Study staff

Clinical trials Networks

- NIH Networks (based on ACTG model)
- NIH funded CAP Trial*
  - 5 center Prospective study
  - PIs: ID, ED, Microbiology
  - Study nurses in ED 18 hr/day
  - Diagnostic tests (all results in 1 hour)
  - Anticipate > 6000 patients enrolled in 2 years
  - Focused therapy (e.g., Pen G if pneumococcus)
- Other cooperative groups (CAPO, EPIC,ED network)

*Yu V. Comparing narrow-spectrum antimicrobial therapy to standard of care in patients with community-acquired pneumonia [Press release]. Available at: www.nih.gov/news/health/oct2010/niaid- 19.htm.

Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia

- Need Feasible, Valid studies
  - Unmet need: Severe CAP
- Suggest:
  - Early and TOC endpoints
    - » Early: Specific D# vs Time to Stability
  - Allow use of prior short-acting ABX
    - » Provide optimal care for patients, but acknowledge and assess effect
  - Enrich Microbiology with sputum assessment, molecular tests, Procalcitonin

PhRMA

New Medicines. New Hope.

Design of Clinical Trials in CABP

Barry Eisenstein, MD, FACP, FIDSA

Senior VP, Scientific Affairs, Cubist Pharmaceuticals

FDA AIDAC, Nov 3, 2011

PhRMA Key Observations

- **Regulatory uncertainty and infeasible study requirements decrease the likelihood that our patients will have needed new antibiotics in the future**
- **PhRMA supports trial designs**
  - That are ethical, scientifically valid, and feasible
  - Are optimally informative for prescribers
  - That harmonize with regulators internationally
  - That employ the best locally-recognized standards of good clinical practice
  - And that balance data quantity and quality
- **The March 2009 FDA draft guidance on CABP and the recent FNIH work on endpoints establish some common ground**

PhRMA Key Recommendations

- **Clinical response as the primary end point**
  - Test of cure evaluation is 3-7 days after EOT (~study day 13-17)
  - As has always been the case, failures at study day 4 (i.e., after 72h Rx) are carried forward
- **ITT (or the CE/PP) should be the primary population for analysis**
- **Permit a single phase 3 trial [with caveats]**
- **Age is the key severity & patient-selection attribute**
- **Permit short-acting prior antibiotics for <24 hours pre-enrollment**

PhRMA response to FDA AIDAC Question 1

- **Please discuss the merits and limitations of an endpoint based on improvement in at least 2 of the 4 symptoms of cough, amount of sputum production, chest pain, and difficulty breathing (and no worsening or no new symptoms) … at day 3 to 5 as the primary endpoint for CABP trials**
  - This approach makes good biological sense. These measures capture the sense of early failure that has been present <u>and used in every antibiotic registration trial we know of insofar as standard clinical practice incorporates this evaluation</u>. Patients not improving at this point are often switched to different treatment, which is why all the prior CABP trials have been good trials.
  - However, late endpoints are important, too!

Early Clinical Endpoints have Meaning to Patients (as reviewed by the FNIH)

- **Pre-antibiotic era:**
  - Osler 1910:
    - When seen on the second or third day …in typical pneumonia…
      - The patient lies flat in bed
      - The breathing is hurried, accompanied often with a grunt
      - The expression anxious
      - The temperature may be 104° or 105°
    - After persisting for seven to ten days, the crisis occurs, and with a fall in the temperature the patient passes from the condition of extreme distress and anxiety to one of comparative comfort
  - Bullowa 1937:
    - $\geq$ 95% of 662 untreated survivors were still febrile on day 3
- **With antibiotics:**
  - Petersdorf 1957: By day 3, 94% feel better and ~80% are afebrile
  - Moussaoui 2006: By day 3, patient-reported symptom score shows improvement
- **The early clinical effects of antibiotics are powerful!**

Osler W. The Principles and Practice of Medicine. New York: D. Appleton and Company, 1910:164-192; Bullowa JGM. The management of pneumonias. New York, NY: Oxford University Press, 1937:36-76; Petersdorf RG et al. Bull Johns Hopkins Hosp 1957; 101:1-12; Moussaoui. Chest 2006; 130;1165

But *Later* Clinical Endpoints have Meaning Too!

- **Early improvement is important, but may not predict overall drug efficacy (which for acute infections should be cure).**
- **Here's a good example (Agranat et al, 1939)**
  - Initial improvement with sulfapyridine is followed by persistent fever due to empyema. Drug treatment made the patient better early but failed later:

*Case 8332….admitted on the fourth day of illness, with a right-lower lobe pneumonia…. **[Sulfapyridine]** treatment was begun on admission. **Temperature reached normal on the third day; then a secondary rise due to an empyema occurred, persisting for twenty days** … The drug, continued to the day of operation and amounting to 130 tablets, **had no effect on the course of the empyema**.*

Case from Agranat, Dreosti, and Ordman, Lancet 1939, page 309-317

Primary endpoint and study design

- **What endpoints should be used in clinical trials of CABP?**
  - **Clinical response** as proposed in the March 2009 draft guidance
  - And, mortality alone should not be the primary endpoint for non-inferiority clinical trials in CABP, but rather an important signal to examine
- **Is the rationale provided in the draft guidance on the use of clinical response as the primary endpoint scientifically sound?**
  - Clinical response is well justified. The rationale has been supported by extensive analyses and by the FNIH. Thus, the response on study day 4 is a validated point of sensitivity to significant drug effect. If not met, patient "fails" (and therapy is usually changed in clinical practice).
  - **But, patients aren't yet out of the woods at day 4! Early endpoints can define failure, but not success, which means CURE.**
  - **To fully conform with clinical practice and global harmonization, we recommend that the test-of-cure visit occurs 3-7 days after EOT (when relapse can occur in the absence of ATBs in the body), with failures on day 4 onward carried forward.**
  - **IF sponsor/agency negotiation leads to separate analyses at two time points (as regulatory science evolves with more data), only one should be powered statistically as the primary endpoint**

PhRMA response to FDA AIDAC Question 2

- Please discuss the merits and limitations of each of the pathways and trial designs….
- All three approaches could be used, assuming that enrollment is feasible and representative of the population of interest
- Some points to consider:

Primary analysis population

- **Should the micro-ITT population be a primary analysis population for non-inferiority trials in CABP?:**
  - Either ITT or CE/PP (which may be preferred by the EMA) from each of two phase 3 trials should be the primary endpoint
  - And, the pooled micro-ITT from these two trials should be a secondary endpoint whose results are consistent with the primary
    - Culture-positive pathogens will be identified in only ~1/3 of patients
    - Results from micro-ITT data should be consistent across trials
- **What is the role of serologic or other diagnostic tools for identification of baseline pathogens and inclusion in micro-ITT population (part of question 3)?**
  - Sponsor should endeavour to obtain as much culture-proven microbiology as possible
  - Non-culture-based, validated diagnostics should be permitted as supplemental tools to prove bacterial etiology (including those due to “atypicals”, where appropriate and informative)

A Single Phase 3 Trial: Focus on Quality rather than Quantity

- **Require only a SINGLE phase 3 trial of feasible size for CABP**
  - With at least one additional phase 3 trial (e.g., ABSSSI, HABP/VABP), in part to get adequate aggregate human safety data and in part to validate drug efficacy in a supportive clinical setting. (Note: HABP/VABP presentation on November 4.)
- **Regardless, such a single registration trial would need the TOTALITY of supporting clinical and non-clinical evidence:**
  - Human PK and tissue penetration studies (e.g., ELF data for CABP), plus phase 2 data
  - Animal modelling of human infection with correct pathogens
    - Pathogenesis of model infection represents the human infection
    - PK/PD evaluation of drug effect that mirrors human exposure
    - Target organs are appropriate (e.g., lung via inhalational inoculum)
  - Appropriate *in vitro* studies including the potential for inhibitors of antibiotic efficacy (e.g., surfactant in the lung)

Additional points relevant to question #2

- The proposed margins in each approach make good sense
  - But, the trials should be powered for a single primary endpoint evaluated at a single time point in the trial
  - More will be discussed during the HABP/VABP discussion
- What is the role of a PRO endpoint to measure clinical benefit in the evaluation of new drugs for CABP?
  - Whereas hypothetical future PROs face a severe validation problem – it will be difficult to obtain or estimate meaningful placebo-controlled effect size information - we support FNIH's proposed symptoms of cough, chest pain, dyspnea, and sputum production, based on FNIH's extensive review of the literature and the long tradition of using these in clinical practice and prior ATB trial evaluations.
- Let's remember: antibiotics have a profound positive effect on treating pneumonia
- SAFETY of research subjects, in the context of best clinical practice, is our first priority in a clinical trial

AIDAC Question #3: Other Issues: Severity assessment

- **Should age >50 years rather than scoring systems such as PORT or CURB-65 be used to enroll a patient population with disease of sufficient severity for a non-inferiority clinical trial in CABP?**
  - Yes, age is preferred to PORT or CURB-65. Just being over age 50 gives a ≥ 50% mortality rate in the historical data
  - The draft guidance offers a very reasonable idea (line 1020):
    - IV drugs should be studied in a population where at least 75% are 50 years of age or older
    - Oral drugs should be studied in a population where at least 50% are 50 years of age or older
  - Enrollment of a subset below age 50 ensures that the study population is more representative of the patient population and simplifies the enrollment process at the point of acute care

AIDAC Question #3 (cont.): Prior therapy

- **Should the use of prior or concomitant antibacterial drugs be permitted in clinical trials of CABP?**
  - Two separate issues. Agree that concomitant antibiotics should not have activity against pathogen(s) of interest. The bigger issue is the role of prior potentially effective antibiotics:
  - (Long-acting) prior effective antibiotics can have a major effect on outcomes, therefore, these long-acting antibiotics should be avoided to get the most informative trial data
  - But, prior antibiotics are incredibly hard to avoid in CABP patients because good treatment practices demand ATB treatment within 4-6h of suspicion of CABP in the ER
  - Complete forbiddance of prior antibiotics (short-acting as well as long-acting) as an exclusion criterion could therefore lead to trial infeasibility, particularly in the US (and the EU)

Informative Trial Designs: Lessons from Daptomycin for CABP[1]

- **Two double-blind studies using the clinical outcome endpoint**
  - 79% (Daptomycin) vs. 88% (Ceftriaxone) (CI: -14 to –3%)
  - Mortality: 4.6% vs. 2.6% (CI: -4.4 to 0.4)
  - Consistent results in each of the two independent Phase 3 studies
- **But, daptomycin has significant activity and is NOT a placebo in blood or tissue:**
  - Pathogens are susceptible in vitro and the antibiotic worked well in necrotizing lung infection models and in hematogenous lung infections (both in animal models and in human clinical trials)
  - Rather, it was found to be inactivated by lung surfactant, which became apparent in more refined animal models
- **Two key lessons:**
  - This inferiority difference is, therefore, a MINIMUM effect size
  - The proposed **late** TOC endpoints functioned well in demonstrating clinical inferiority (and mortality did not demonstrate statistically significant inferiority)

[1]Pertel: CID 2008; 46: 1142..

Informative Trial Designs: Lessons from Daptomycin for CABP[1] (cont.)

- **Of equal note:**
  - Patients treated in the US and Western Europe with daptomycin succeeded almost as often as those treated with comparator
  - Further analysis showed that results in these patients were confounded by a high rate of treatment with prior antibiotics (limited to <24h total use, unless patient had failed prior tx)
  - Importantly: This effect (shown overall) was limited to patients treated with long-acting (half life >8 hrs; macrolides, quinolones, ceftriaxone) BUT NOT SHORT-ACTING (half life ~ 2-3 hrs), antibiotics (e.g., other beta-lactams, trim-sulfa, tetracyclines)
- **But the 2009 draft guidance overcompensates:**
  - Any use of prior effective antibiotics, even short-acting ones, could confound outcome results and should be eliminated
- **This lesson was "over-learned" in that it did not discriminate between long-acting and short-acting prior antibiotics**
  - To eliminate ALL prior antibiotics will virtually eliminate the US from future patient enrollment!

[1]Pertel: CID 2008; 46: 1142.

Different effects of short- and long-acting prior antibiotic therapy on the clinical cure rates (%) [CE population]

- Long-acting antibiotics reduced the treatment difference
- Daptomycin was inferior in the rest of the population

	Daptomycin		Ceftriaxone		
Prior effective therapy?	n/N	Cure rate	n/N	Cure rate	95% CI
Yes: long-acting[1]	88/97	91%	81/92	88%	-6.1 to 11.5
No: none OR short-acting[2]	205/272	75%	245/279	88%	-18.8 to -6.0

1. Macrolides, quinolones, ceftriaxone; half life > 8 hrs., as defined by Pertel et al.
2. Other ß-lactams, tetracyclines; half life ~ 2-3 hrs.

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2. Other ß-lactams, tetracyclines; half life ~ 2-3 hrs.

Different effects of short- and long-acting prior antibiotic therapy on the clinical cure rates (%) [CE population]

- Similar cure differences with no prior and only short-acting

	Daptomycin		Ceftriaxone		
Prior effective therapy?	n/N	Cure rate	n/N	Cure rate	95% CI
Yes: long-acting[1]	88/97	91%	81/92	88%	-6.1 to 11.5
No: none, short-acting	205/272	75%	245/279	88%	-18.8 to -6.0
• None	164/215	76%	205/233	88%	-18.8 to -4.65
• Short-acting[2]	40/55	73%	40/45	89%	-31.1 to -1.23

1. Macrolides, quinolones, ceftriaxone; half life > 8 hrs., as defined by Pertel et al.
2. Other ß-lactams, tetracyclines; half life ~ 2-3 hrs. NB.: Unable to classify 3 patients as “none” or “short-acting”.

Different effects of short- and long-acting prior antibiotic therapy on the clinical cure rates (%) [CE population]

- Short-acting, treatment <24h behaved like no prior antibiotics!

	Daptomycin		Ceftriaxone		
Prior effective therapy?	n/N	Cure rate	n/N	Cure rate	95% CI
Yes: long-acting[1]	88/97	91%	81/92	88%	-6.1 to 11.5
No: none, short-acting	205/272	75%	245/279	88%	-18.8 to -6.0
• None	164/215	76%	205/233	88%	-18.8 to -4.65
• Short-acting[2]	40/55	73%	40/45	89%	-31.1 to -1.23
• Short-acting < 24h	34/45	76%	35/39	90%	-29.9, 1.57
• Short-acting > 24h	6/10	60%	5/6	83%	-65.9, 19.23

1. Macrolides, quinolones, ceftriaxone; half life > 8 hrs., as defined by Pertel et al.
2. Other ß-lactams, tetracyclines; half life ~ 2-3 hrs.

Different effects of short- and long-acting prior antibiotic therapy on the clinical cure rates (%) [CE population]

- A small number of short-acting >24h were in patients FAILING prior treatment

	Daptomycin		Ceftriaxone		
Prior effective therapy?	n/N	Cure rate	n/N	Cure rate	95% CI
Yes: long-acting[1]	88/97	91%	81/92	88%	-6.1 to 11.5
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1. Macrolides, quinolones, ceftriaxone; half life > 8 hrs., as defined by Pertel et al.
2. Other ß-lactams, tetracyclines; half life ~ 2-3 hrs.

Prior therapy (cont.)

- **Should the use of prior antibacterial drugs be permitted in clinical trials of CABP?**
- **No perfect solution:**
  - We acknowledge that prior ATBs MIGHT confound the effects of study drug (and comparator) and thereby diminish assay sensitivity to drug effect
    - (see: File T et al. Clin Infect Dis. 2010; 51: 1395-1405)
  - BUT, delaying treatment is not feasible according to modern practice guidelines

Prior therapy (cont.)

- **Is there a way out?**
- **YES – Allow prior ATBs but have them be limited to brief courses of SHORT-ACTING agents:**
  - Allow minimal dose(s) of short-acting antibiotics since there was no rescue effect relative to longer-acting antibiotics in the (Pertel et al) trials
  - Therefore, to enable US (and EU) enrollment, thereby providing the FDA the most representative population sample of patients treated according to best US (and EU) standards, limited (<24h) short-acting antibiotics should be permitted and recorded as baseline study information
  - Such information by subgroup should be reviewed for qualitative success results but not for statistical confirmation as it is not feasible to power these subgroups for such analysis
  - Allow enrollment of patients judged to have been failing prior >24h treatment

While we're discussing Microbiology, Let's not forget BREAKPOINTS

- **Recent regulatory interactions have not used all data: microbiological surveillance, clinical and PK-PD data to set breakpoints**
  - The focus has been mainly on clinical data
- **The challenge is that breakpoints should often be set at or above the population MIC90, if supported by PK-PD analysis, so that the wild-type population is effectively identified as susceptible**
  - The number of culture-proven cases is always going to be relatively small at the margins of a distribution
  - When analyzed at the species level (e.g., *S. pneumoniae),* there will be even fewer cases per group
  - Setting a breakpoint that divides the wild-type population results in erratic test performance
- **When there are small numbers of cases, there will by definition be VERY small numbers of cases at or near the population MIC90**
  - If breakpoints are set based solely on cases observed, the resulting breakpoints will make little clinical or biological sense
  - PK-PD data offer strong guidance and should be incorporated

One more point: Atypical pathogens

- **Can patients hospitalized with *L. pneumophila* pneumonia be included in a noninferiority clinical trial of CABP that enrolls patients with *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *M. catarrhalis*?**
  - Yes. See the March 2009 Tigecycline CABP approval for an example of this very thing.
  - Obviously should be limited to agents with in vitro activity
- **How should patients with pneumonia due to other "atypical" pathogens be studied in clinical trials? How should such trials be designed? (e.g., noninferiority or superiority)**
  - This setting has reports of very good placebo-controlled & ineffective-drug-controlled studies for treating *Mycoplasma pneumoniae*
    - References: Gooch AAC 1970; Kingston JAMA 1961; Rasch AAC 1965; Shames Ann Int Med 1970; Smilack JAMA 1974
  - Non-inferiority studies using clinical response measures are more than justified

It is Time for Progress

- **Don't let the perfect be the enemy of the (very) good**
  - Clinical trials should be feasible to do in the US and, therefore, relevant to US clinical practice

- **Unlike any other therapeutic area, antimicrobials are depreciating assets**
  - Resistance emerges steadily
  - Antibiotic stewardship can delay but cannot prevent resistance
  - Individual antibiotics become obsolete
  - We must have a continuous supply of replacements

- **The greater danger is that we err on the side of too few new antibiotics approved in the US rather than too many**

Summary

- **Continued delay decreases the likelihood our patients will have effective new medicines when needed**
- **PhRMA seeks ethical, informative and feasible trials**
- **Refinement is the next challenge**
  - **Clinical endpoints capture the antibiotic benefit**
  - **Use ITT (or CE/PP) as the primary endpoint**
  - Use pooled micro-ITT population as a secondary endpoint with non-culture-based diagnostics
  - **Allow a single phase 3 trial under circumstances where the totality and quality of the data is strong**
  - **Age (rather than PORT scores) should be used**
  - **Allow <24h of prior short-acting antibiotics**
  - Rational evaluation of susceptibility breakpoints
  - Permit enrollment of patients with atypical pathogens

PhRMA

New Medicines. New Hope.

Thank you

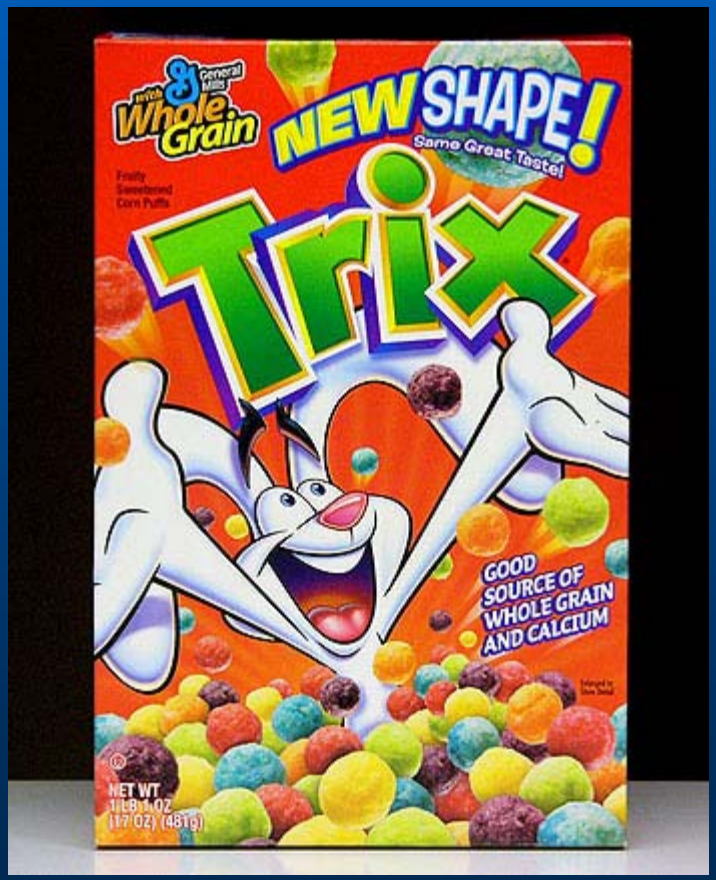
For Women & Families

Antibiotics: A Public Health and Consumer Perspective

Diana Zuckerman, Ph.D.
President
National Research Center for Women & Families
www.center4research.org

New ≠ Improved

We like new things, but that doesn't mean they are good for us



Study Design Can Save Lives

- Don't study drugs on relatively healthy patients if they will be used for patients who are seriously ill.
- Tigecycline warning: FDA is reminding healthcare professionals of an increased mortality risk associated with the use of the intravenous antibacterial Tygacil (tigecycline) compared to that of other drugs used to treat a variety of serious infections.

Study Design Issues

Allowing prior antibiotics in trials makes drugs appear more similar.

- Prior medication use should not be allowed in studies of antibiotics. They are not allowed in other clinical trials.

Confirmation of Disease

Ethics 101: Do not expose people to an experimental drug if they don't have the disease.

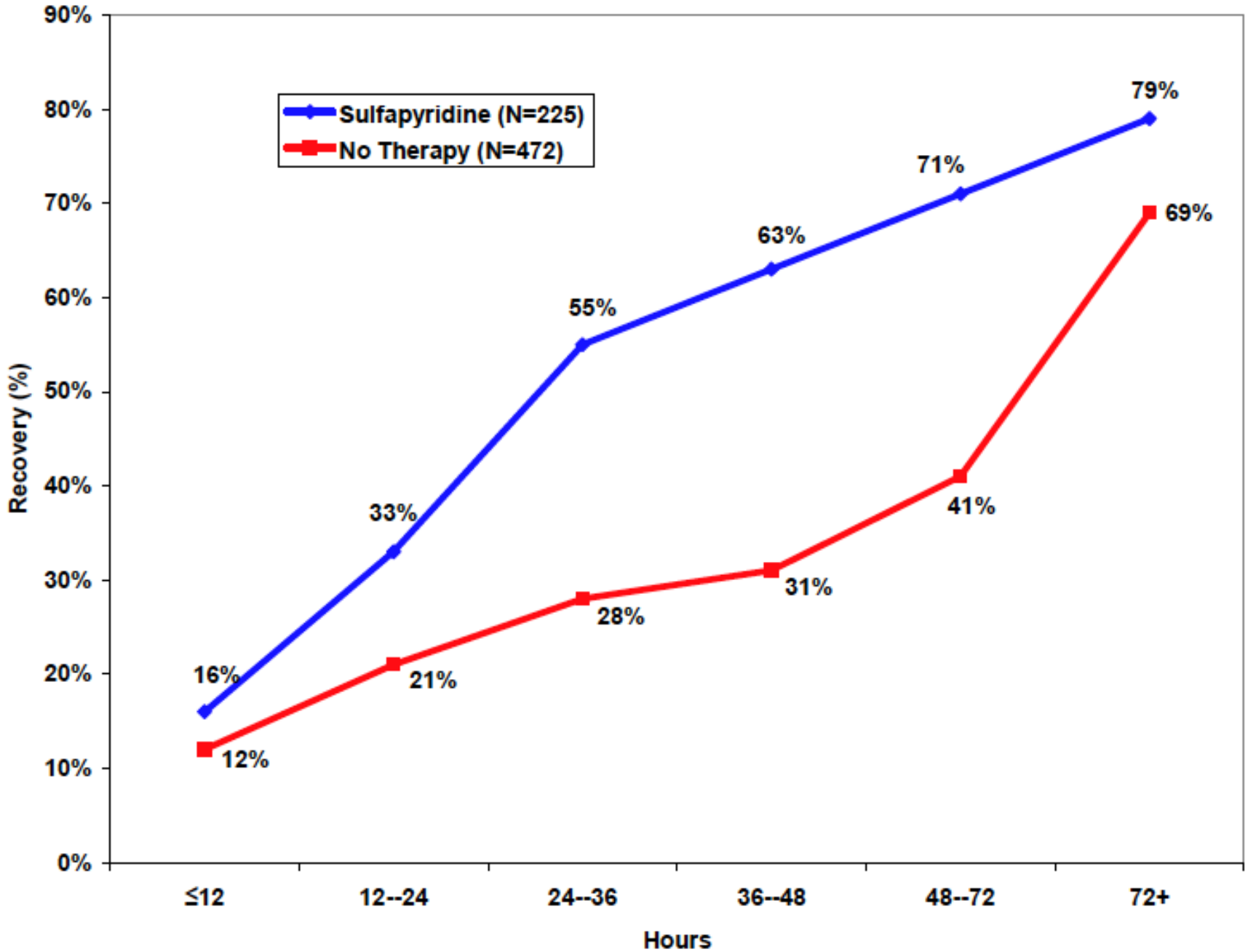
- If some Ss don't have the disease, then drugs that are inferior will look non-inferior
- Allergic disease and heart failure can look like pneumonia on a CXR and clinical presentation

Outcome Measures

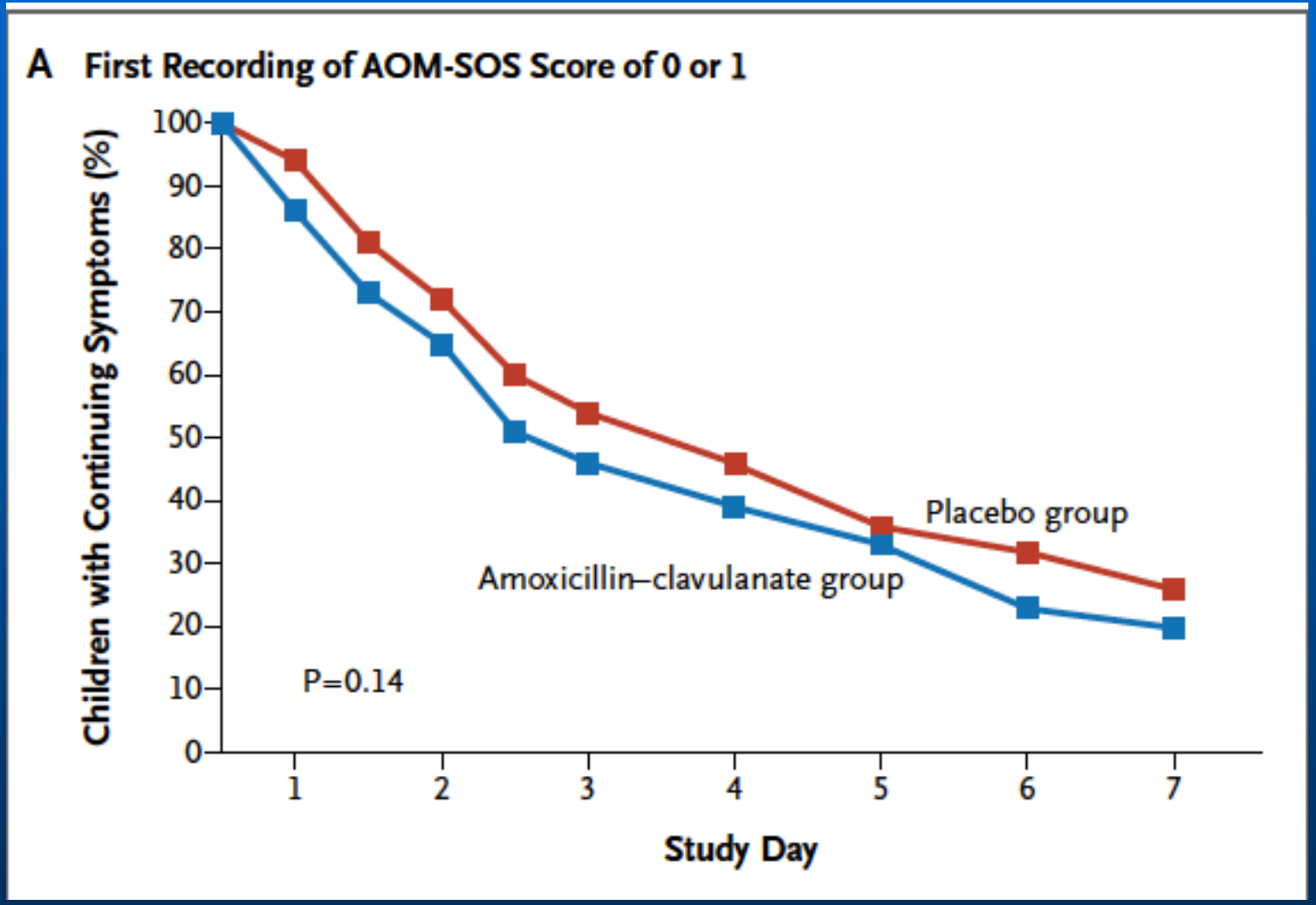
Studies should focus on health and recovery, not unimportant signs.

- The effects of antibiotics occur early, so the primary outcome should be measured early.
- Longer outcome time makes drugs appear more similar, since some people get better anyway.

Figure 2: Rates of clinical recovery of acute bacterial pneumonia (Finland 1940)



Is this drug effective?



Myths

#1: Our **animal models** are so good that we don't have to worry about doing studies in people

But only 28% of antibiotics are approved according to a Tufts study and the other 72% all had promising animal studies

Myths

#2. **Test tube** results are good enough

- But test tube studies don't predict side effects and safety for humans

- But most antibiotics are not approved and they all have to look great in a test tube to get to the IND stage

Myths

#3. **Current trial designs** work well, so “if it ain't broke, don't fix it"

- But non-inferiority trials done today violate basic standards of clinical trials, do not follow FDA's own regulations for "adequate and well-controlled.“
- But Ketek and tigecycline show that current trial designs are a problem.

Myths

#4. **Antibiotics are different** "because they attack bacteria instead of binding to a human receptor."

- But the goal is to prolong life and improve function or symptoms -- regardless of mechanism of action and how the drug gets you there.

Myths

#5. “Don’t let the **perfect be the enemy of the good**"

- But it is not good when people are dying unnecessarily from antibiotics that are not as safe or as effective as other available antibiotics.

Myths

#6. “It can’t hurt” to take an antibiotic unnecessarily.

- But new research suggests that altering normal bacterial flora can cause long-term harm.

Research or Hype?

- Hype sells antibiotics that are often more expensive but not as safe as older antibiotics.
- Research should focus on outcomes that matter. Compare new antibiotics to placebo (if possible) or to existing drugs used by appropriate patients to see if they truly are a good alternative.

Research or Hype?

- Compare different lengths of treatment to compare effectiveness and determine the impact on recurrence.
- Compare short-term results **and** compare long-term results. Do not replace one with the other or pool them together.

FDA Approval Caveats

- Studied on a few thousand people, **used by millions**
- Approved for one use and widely **used off label** with few warnings
- Risks are inevitable. **Reduce risks** by comparing antibiotics in unbiased studies of the patients who will use it
- Small risks don't feel small if **you** are the one harmed

Conclusions

- Non-inferiority studies don't protect patients from less effective and less safe antibiotics. But some non-inferiority trials are better than others.
- Risks are real and labels and ads to doctors need to be clearer.
- Don't expect doctors or patients to read the fine print or the studies.

Diana Zuckerman, Ph.D.
President

National Research Center
for
Women & Families

www.center4research.org

COMMUNITY-ACQUIRED PNEUMONIA

John G. Bartlett
Johns Hopkins University
School of Medicine

Conflicts – None

CAP: FDA TRIAL ISSUES

Trial location: US preferred

- Unique microbiology & care standards

Pre-randomization micro: Not realistic

- No pathogen in 80-90%
- Must start Abx <6 hrs (medicare & mortality)
- Single dose short acting Abx: reasonable
- Randomization: Should simulate practice (Empiric therapy)

Clinical response

- Signs & sx at 3-5 days & 13-17 days – reasonable
- Objective vs. subjective: PRO (?)

Microbiology: Study new diagnostic tests simultaneously – Need POC test w/ CLIA waiver

CAP: MORTALITY IN PRE-ANTIBIOTIC ERA*

	Cases	Mortality
Townsend 1889**	1,000	25%
Shattuck 1918**	1,176	27%
Kelly 1926**	6,531	36%
Cecil, 1927**	1,107	31%
Alperin 1933**	1,385	24%
Finland 1933**	1,271	37%
Greenwood 1911	5,116	20%
Maynard 1913	1,809	39%
Huss 1855	2,710	14%
Rogers 1925	14,266	26%
Meta-analysis	67,677	36%
Meta-analysis**	19,540	33%

*Limited to reports >1000/cases

**US cases

PROGNOSTIC FACTORS FOR A DEATH RATE >30%

Variable	%	Cases	Source
WBC <10,000	66%	463	Avery 1917
Fever >106ºF	36%	768	Cole 1920
Heavy ETOH	48%	1,003	Cohn 1935
Age >60 yrs	71%	2,882	Shattuck 1918
Bacteremia	50%	1,003	Cohn 1935
Resp. Rate >50	41%	768	Cole 1920

RISK OF DEATH: AGE*

Age	No.	Mortality
<10	476	14%
10-19	329	10%
20-29	626	18%
30-39	580	29%
40-49	431	36%
50-59	292	50%
≥60	148	71%

*Shattuck, MGH Hosp. Boston Med Surg J 1918;178:245

CAP: NATURAL HISTORY*

Acute course: 5-10 days 70%

Mean: 5.8-7.9 days

"Rare" -- ≤4 days

Clinical resolution: 20 days

X-ray resolution: 10-50 days

Mean: Day 20

*Cohn. Am J Med Sci 1935;189:457
Wu CJ. China Med J 1933;47:545
Cecil. Arch Intern Med 1934;53:481
Finland. Arch Intern Med 1934;53:481
Vitug W J. Phillipine Is 1928;8:461
Warr. Ann Intern Med 1933;6:1474

CAP: PRE-ANTIBIOTIC ERA
(Analysis based on 10,000-20,000 cases reported 1917-35)

Mortality: (mean) 33%

Risk: Age, bacteremia

Acute illness (mean) 6.8-7.9 days

Range 5-10 days

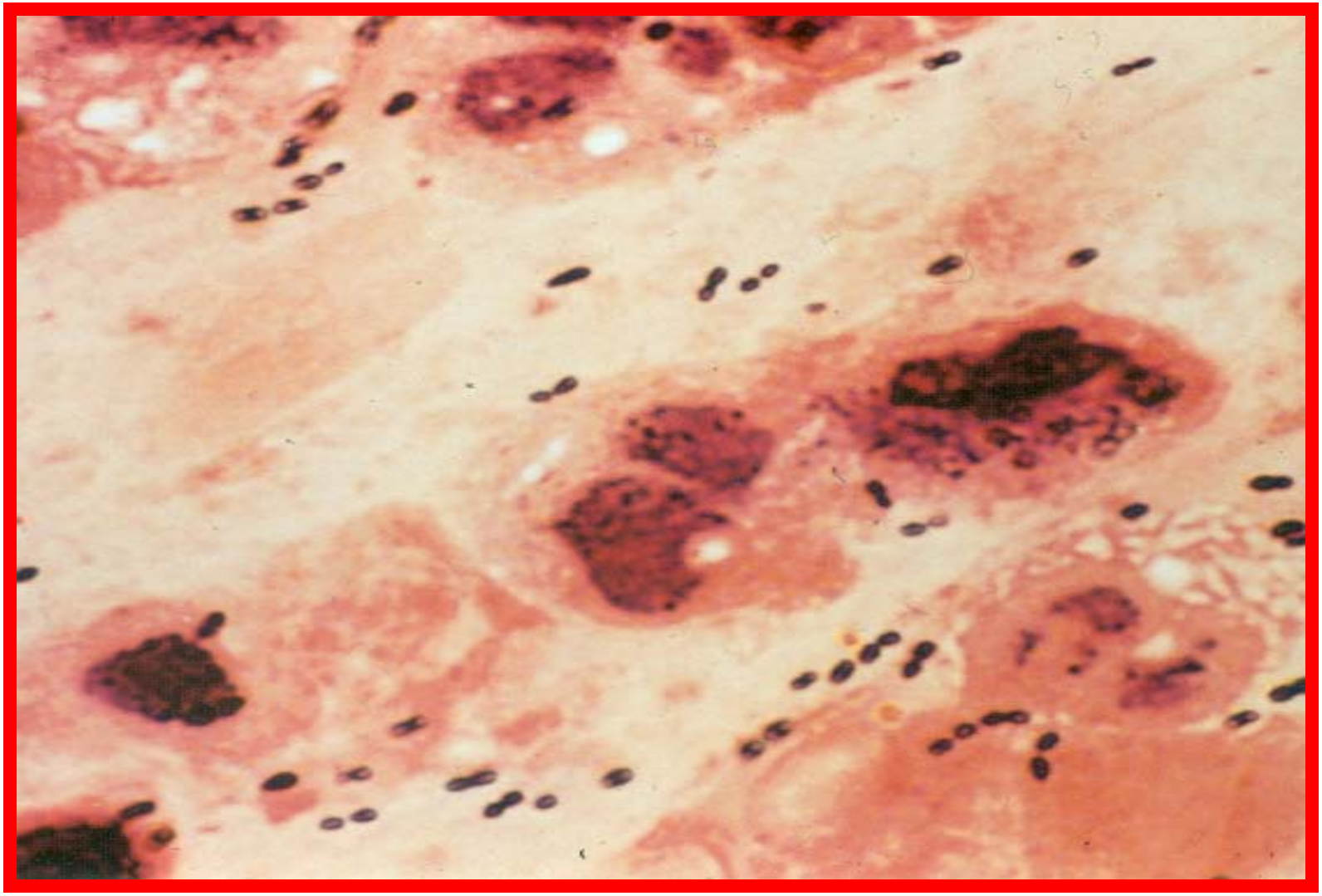
<4 days "Rare"

Clinical recovery (mean) 20 days

X-ray resolution (mean) 20 days

Range: 10-50 days

MICROBIOLOGY



CAP: MICROBIOLOGY 2011

Contemporary practice

- Diagnostic yield 7-8%
- Trials (FOCUS 1 & 2) 15-25%
- Techniques: GS/culture, urinary antigens, molecular tests – respiratory viruses

In development: Multiple new methods that could revolutionize pathogen detection

Need: rapid tests including CLIA-waived POC tests (ASSURED criteria) (Affordable, Sens, Spec, User friendly, Rapid, Equip-free, Delivered)

Comment: Simultaneous study of diagnostic tests and antibiotics should be encouraged

EXPECTORATED SPUTUM

Cytology*: Score 1-2

10-25 PMNs/LPF +2

>25 PMNs/LPF +1

10-25 SEC/LPF -1

>25 SEC/LPF -1

Geckler**: Multiple fields – 2nd spec if >25 SEC/LPF

Bacteriology***: Gram stain

S. pneumoniae ≥8/OIF

H. influenzae ≥12/OIF

*Murray & Washington: Mayo Clin Proc 1975;50:339

**Geckler RW. JCM 1977;6:396

***Baigelman W & Chodosh. Lung 1979;156:265

EXPECTORATED SPUTUM CULTURE

Quantitation of sputum pathogens based on concurrent TTA: $10^{6.6}$ cfu/mL (Bartlett JG. ARRD1978;117:1019)

Translation to sputum culture = >5 colonies in third streak (Washington JA II. Cumitech 7A ASM 1987)

CAP: MICROBIOLOGY

Report	Period	No.	Pathogen recovered
Bullowa*	1917-33	4,416	98%
Medicare**	2009	17,435	7.6%

**Bullowa. Management of Pneumonia. Oxford Univ Press 1937: p 508.

**Bratzler D. Personal communication 2011

RECOVERY RATES OF *S. PNEUMONIAE* IN SPUTUM FROM ADULT PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Source	Pts	%
Bullowa, 1937	4,416	81%
Fiala,1969	193	55%
Moore, 1971	144	47%
Fekety, 1971	100	62%
Sullivan, 1972	292	35%
Dorf, 1973	148	53%
MacFarland, 1982	127	76%
Klimek, 1983	204	36%
Dans, 1984	147	40%

Source	Pts	%
Brit Thor Soc, 1987	433	42%
Holmberg, 1987	147	39%
Woodhead, 1987	236	36%
Aubertin, 1987	247	12%
Marrie, 1987	301	9%
Levy, 1988	116	26%
Bates, 1989	153	6%
Marrie, 1989	719	8%
Fang, 1990	359	15%
Farr, 1991	245	18%
Oldach, 1992	424	16%
File, 2011	606	8%
Low, 2011	622	11%

MICROBIOLOGY: FOCUS 1 & 2
(File T. JAC 2011;66 S3:19)
(Low D. JAC 2011;66 S3:33)

	FOCUS-1	FOCUS-2	Total
Randomized	606	622	1228
Microbiology			
Atypicals	73	76	149 (12%)
S. pneumo.	51	71	122 (10%)
S. aureus	22	30	52 (4%)
Legionella	0	0	0

FilmArray RESPIRATORY PANEL

	Sensitivity	Specificity
Influenza	100%	>99%
Paraflu1-3	87-100%	99.8%
RSV	100%	89%
Adenovirus	90%	98%
Coronavirus	96%	99%
RSA	100%	89%
"Atypicals"	—	—
S. pneumoniae	—	—
TB	—	—

Results: <60 minutes

Sensitivity: >98%; Specificity – 98% for presence; 80-99% for infection

Johansson N, et al: Results (CID 2010;50:202)

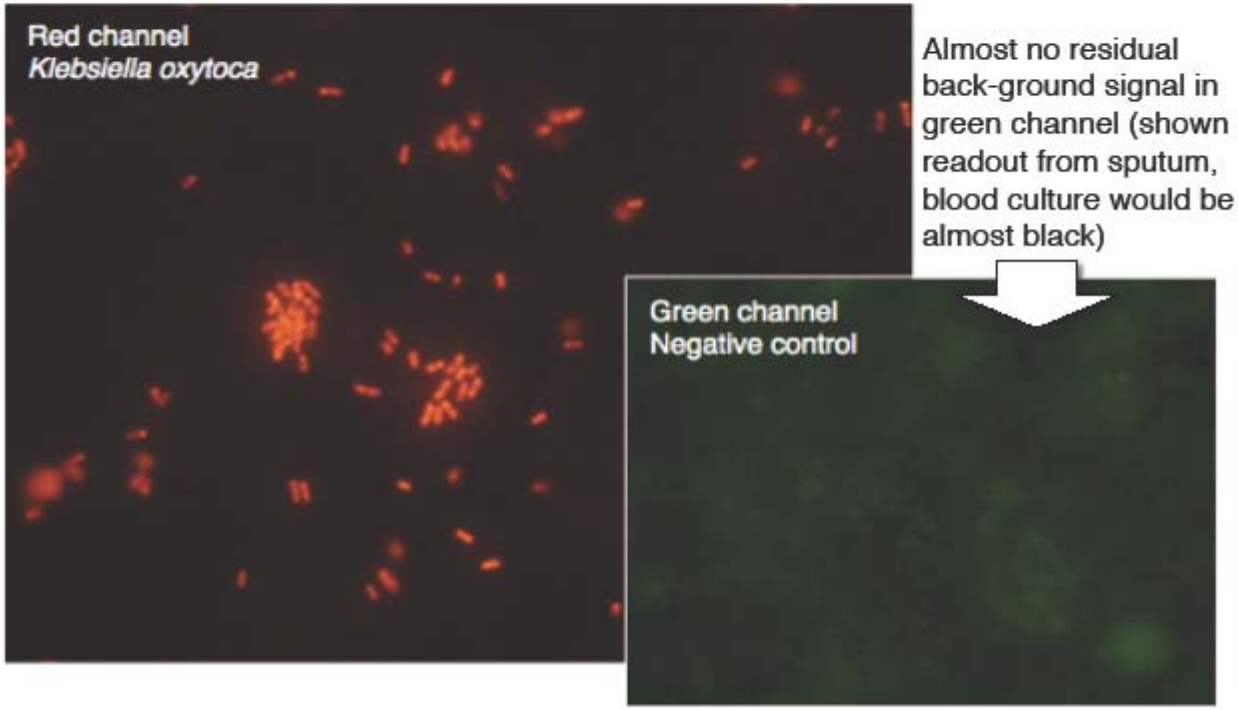
Microbial pathogen	124 (67%)*
Bacterial pathogen	106 (58%)
S. pneumoniae	70 (38%)
M. pneumoniae	15 (8%)
H. influenzae	9 (5%)
C. pneumoniae	0
Viral pathogen	53 (29%)
Influenza	14 (8%)
Rhinovirus	12 (7%)
RSV/paraflu	14 (8%)
Mixed infection	22 (12%)

*No. with all specimens 34/38 (89%)

**Quantitative: $>10^6$/mL

Fish Gram Stain with Pathogen ID, Semi-quant, 20 min, $30

UNAMBIGIOUS FLUORESCENCE in only one channel gives positive ID



Almost no residual back-ground signal in green channel (shown readout from sputum, blood culture would be almost black)

Beacons also enable pathogen identification DIRECTLY from urine, sputum or stool

Plex-ID: The Next Generation System: T5000

IBIS T5000

RT- PCR → Electon Ionization – Mass Spec

Detects bacteria, viruses and fungi

Detection <8 hr (expect 3 hrs)

Quantitative

Cost $500K, $80/sample

POINT-OF-CARE URINARY ANTIGEN IN EMERGENCY DEPARTMENT FOR CAP (Weatherall C. Emerg M J 2008;25:144)

EW vs. lab: 98% concordance

Time (mean) EW 2 hr. 39 min.

Lab 19 hr. 40 min

CAP: MICROBIOLOGY ISSUES FOR FDA TRIALS

Current methods are delayed and low yield

(Reason for difference with historic data is unclear)

Need: Tests that are rapid, specific (and sensitive)

- POC CLIA-waived
- Molecular tests
- Procalcitonin utility?

2007 IDSA/ATS GUIDELINES: ANTIBIOTIC SELECTION FOR HOSPITALIZED PATIENTS

Inpatient, not ICU

- Fluoroquinolone[1*] (moxi/levo)
- Betalactam + macrolide[1*]
  (Cefotaxime, ceftriaxone, ampicillin)

ICU patients

- Betalactam, (cefotaxime, ceftriaxone, ampicillin/sulbactam) + (azithromycin[2*] or fluoroquinolone[1*]
- Pseudomonas: Multiple options[3*]
- MRSA: Vancomycin or linezolid[3*]

*Level of evidence

IDSA/ATS GUIDELINES FOR CAP: OTHER ISSUES

IV→ PO switch: Hemodynamically stable, clinically improved and able to ingest[2*]

Duration Abx: Stop when – afebrile 48-72 hrs, Abx > 5 days and no complications (VS, O_2, MS)[2*]

Severity scoring: PSI or CURB-65[1*]

*Level of evidence

ASSOCIATION OF ANTIBIOTIC THERAPY AND DEATH**

Antibiotic	Odds Ratio*	Reduction
Cephalosporin	1.0	
Cephalosporin + macrolide	0.74	26% reduction
Fluoroquinolone alone	0.64	36% reduction

*Analysis of 12,000 Medicare patients

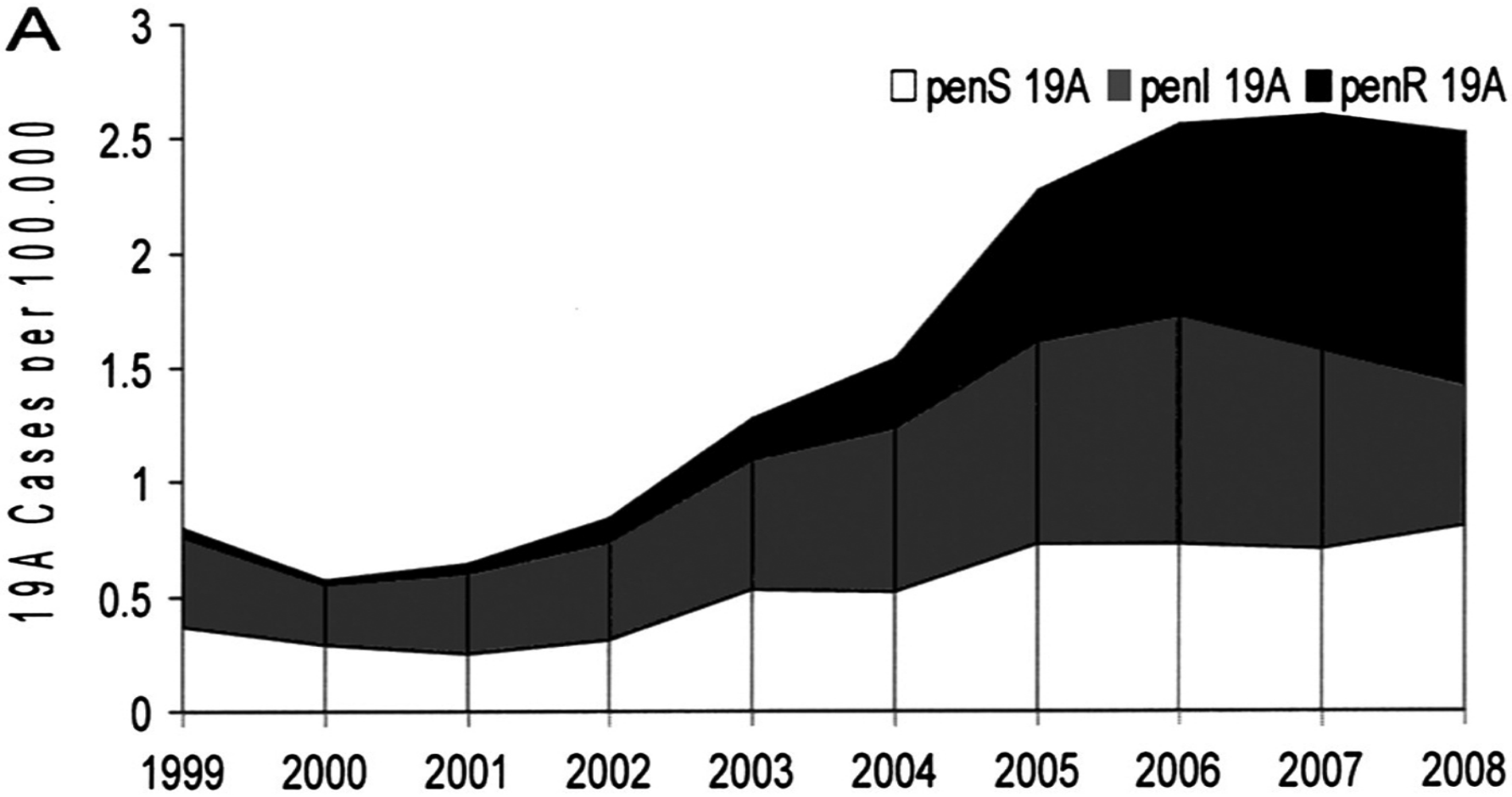
**Gleason P et al. Arch Intern Med 1999;159:2562

GLOBAL EXPERIENCE WITH CAP AND "ATYPICALS" (CAPO)*

	US Canada (3,302)	Europe (501)	Latin America (331)	Asia Africa (203)
Atypicals	22%	28%	21%	20%
Coverage	91%	74%	53%	10%

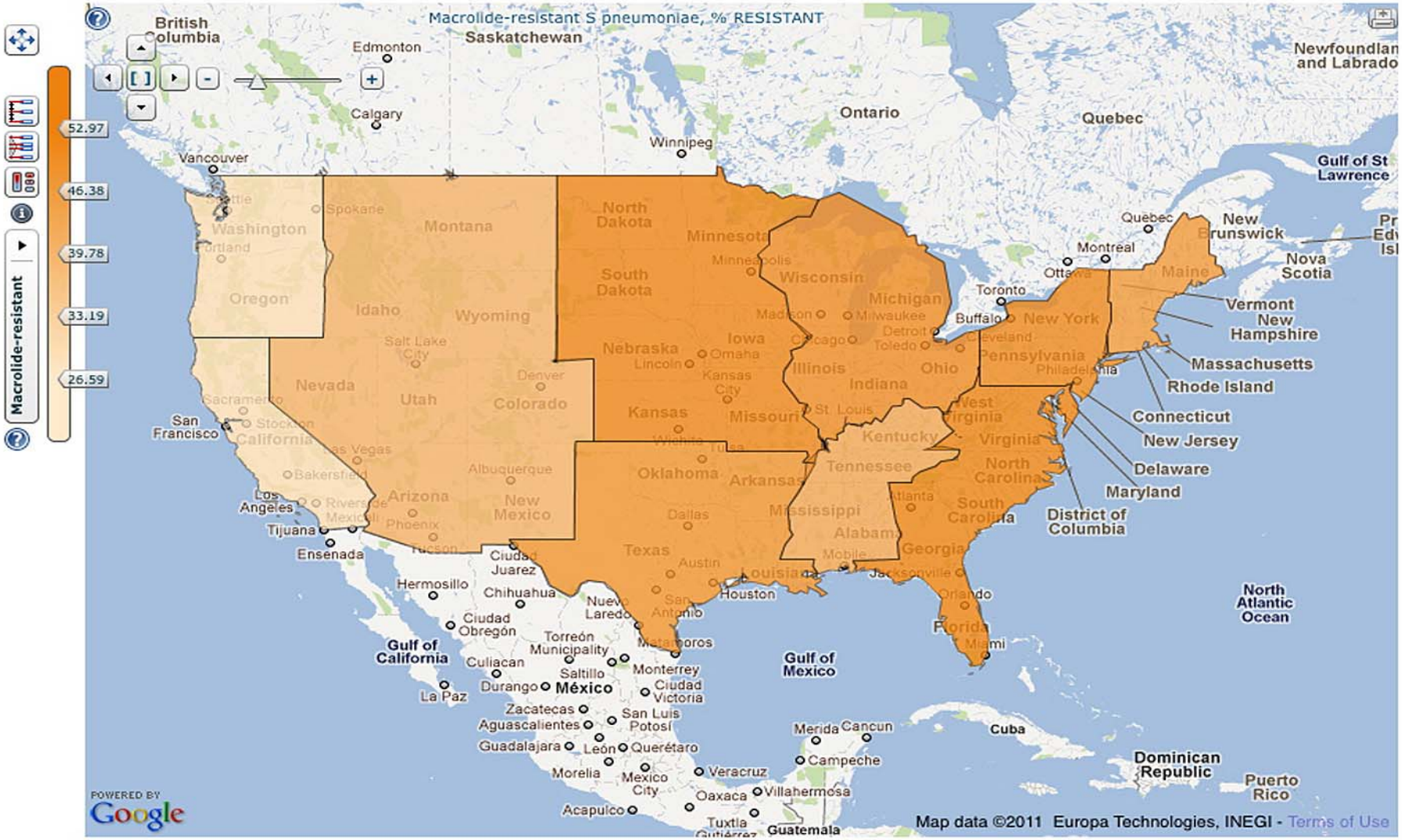
*Arnold FW. AJ Resp Crit Care Med 2007;175:1086

Beall BW. JID 2011;203:1360

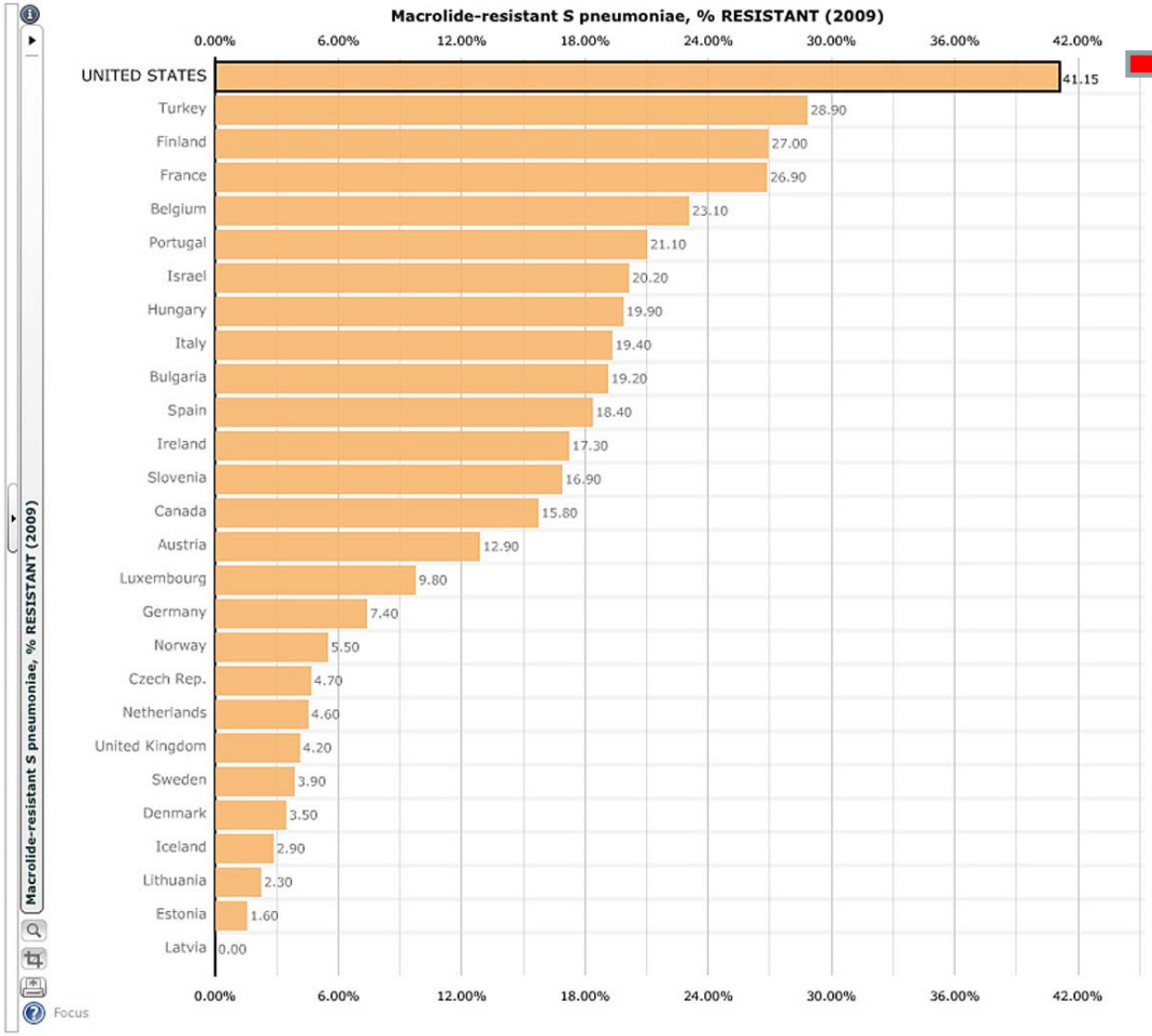


S. pneumoniae: Macrolide-resistance

RESISTANCE BY U.S. CENSUS DIVISION, 1999-2010



U.S. RESISTANCE IN THE GLOBAL CONTEXT



41%

CAP: ISSUES

Clinical presentation: Well standardized with symptoms, lab tests and imaging

Pathogen recovered:

Pre-Abx era: 98%

Current era: 7.6%*

Natural history: Mortality

Pre-Abx era: 33%

Current era: 7%**

Time to afebrile (mean)

Pre-Abx era: 7 days

Current era: <72 hrs

*Medicare data 2009 n=17,435

**Lee. Am J Med: 141/2076 hospitalized

PRACTICAL APPLICATION

CAP trials should be done primarily in US due to variations in microbiology, *in vitro* sensivity and care standards

NAID Network: Unlikely solution (funding & priorities)

Pretreatment microbiology with results will not be realistic with FDA-cleared testing – simultaneous trial of micro tests should be allowed (? retrospective analysis)

Comparator: IDSA/ATS guidelines

Requirement: Pre-randomization Abx

Evaluation: Day 3-5 & 13-17

Biomarkers: Procalcitonin to facilitate decision to start and stop

Harmonization: ?