Treatment Effect of Antibacterial Drugs in Community-Acquired Pneumonia

A Historical and Regulatory Perspective

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Objectives

- Discuss the problem with non-inferiority trials for CAP
- Discuss approach to estimation of antibacterial drug treatment effect in CAP
- Show estimates of the treatment effect
- Discuss limitations of the data
- Present issues for further discussion

Recent CAP Studies

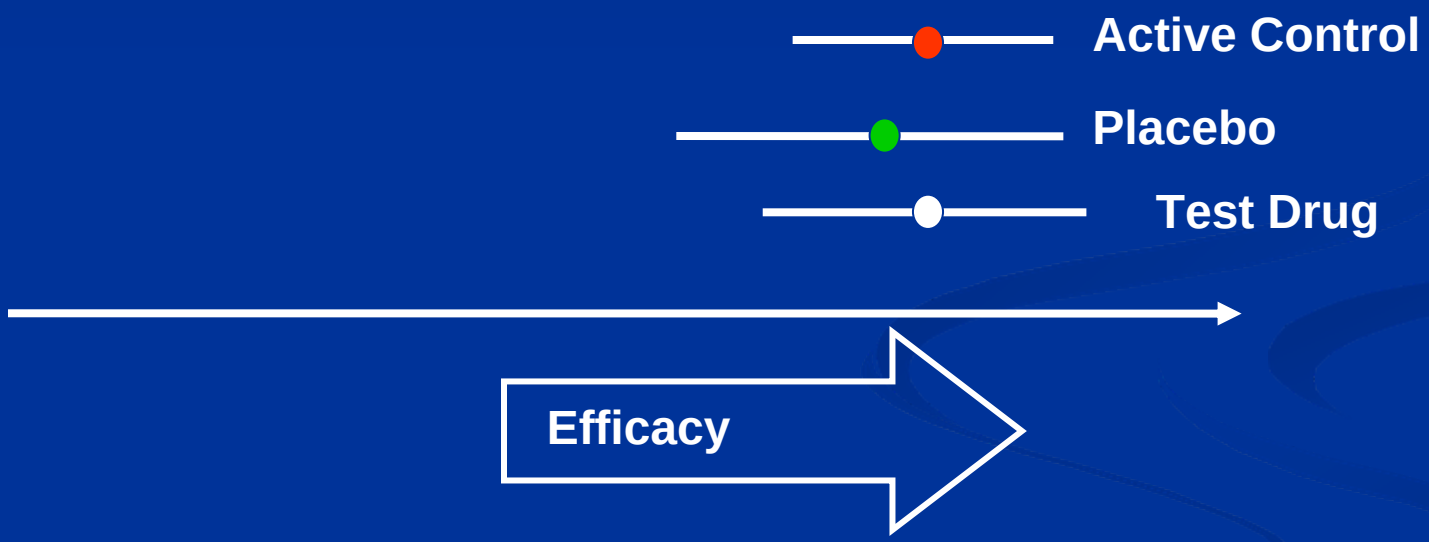
- Approximately 30 antibacterial drugs approved for CAP
- Recent studies all based on non-inferiority trials (10 or 15% margin)
- Most were studies in patients with mild-moderate CAP treated in the outpatient setting (oral drug)
- Pneumococcal pneumonia: Documented in 5-20% patients in outpatient (oral drug) studies; and in 20% hospitalized patients in studies of initial IV therapy
- Bacteremia: Documented in 0-6% patients in oral drug studies; and in 8-10 % (4-9% pneumococcal bacteremia) patients in IV drug studies
- High efficacy rates (clinical response endpoint)
- Mortality rates: < 1% patients died in oral drug studies; 2-4% died in IV drug studies

What is the Problem?

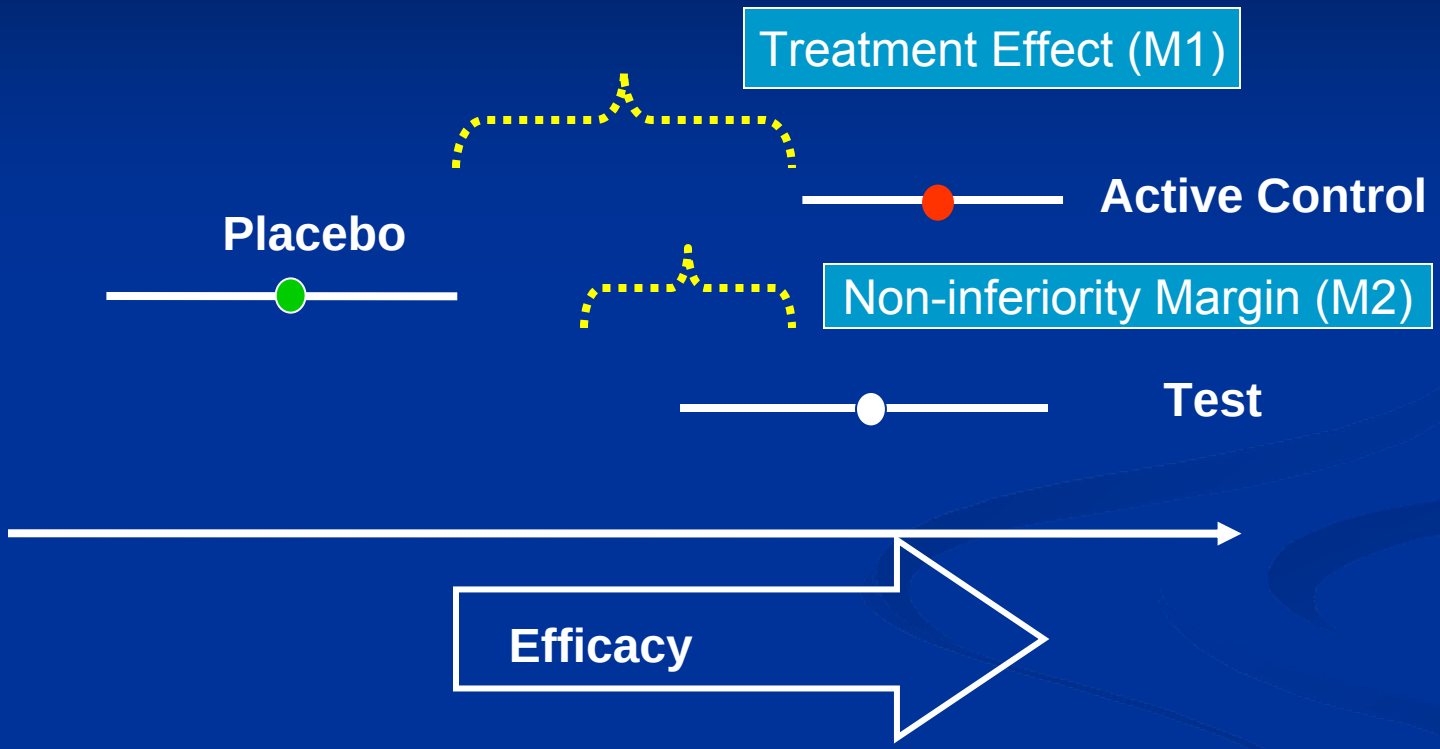
Non-inferiority trials: How much less effective is test drug than the active control drug?

- Efficacy of test drug must fall within bounds of a pre-specified non-inferiority margin relative to active control drug.
- Assumption: Treatment effect is known, i.e. active control is more effective than placebo for treatment of the disease by some known difference (M1)
- If treatment effect is known, a clinically acceptable non-inferiority margin (M2), which can be chosen (M2 ≤ M1).
- Magnitude of the treatment effect is not known for antibacterial drugs for treatment of CAP; so there is some uncertainty about the appropriate non-inferiority for CAP studies.

Treatment Effect in Disease with High Spontaneous Resolution Rate or no Effective "Active Control"



Treatment Effect in Disease with Low Spontaneous Resolution Rate and Effective Active Control



Goal: Estimate the magnitude of the treatment effect of antibacterial drugs in CAP

Approach to Estimation of Treatment Effect for Antibacterial Drugs in CAP

1. Historical Data

- Published studies performed pre- and post -introduction of antibacterial drugs
- Most were studies of pneumococcal or lobar pneumonia
- Hospitalized patients
- Mortality Endpoint
  - Observational studies (treated vs. untreated)
  - Controlled trials: antibacterial drugs vs. untreated controls
    - No true placebo-controlled studies
    - Patients not randomized ; treatment not blinded

Approach to Estimation of Treatment Effect for Antibacterial Drugs in CAP (continued)

2. Alternative Sources of Data which might show a treatment difference between antibacterial drugs:

- "Negative" non-inferiority studies
- Superiority studies (none)
- Dose response
- Pharmacokinetics/pharmacodynamics
- Discordant therapy:
  - Resistant organisms
  - Guideline-concordant vs. discordant
  - Delayed vs. immediate treatment
  - Broad vs. narrow spectrum empirical treatment

Natural History of CAP

"Recovery followed the 'crisis' - an abrupt decrease in temperature over 12 hours, accompanied by passage 'from a condition of extreme distress and anxiety to one of comparative comfort' - and occurred in a large proportion of cases. A fatal outcome was noted in 20-35%. Worse prognosis was evident in 'drunkards' and the elderly, with fatality increasing to 50-65% in the elderly in those in their 6th and 7th decades."

- Sir William Osler, 1894, who succumbed to Haemophilus influenzae pneumonia in 1919

History of Effective Treatment for Pneumococcal Pneumonia

1881	*Streptococcus (Diplococcus) pneumoniae* identified as 'the' cause of pneumonia
1913 - 1940	Serum Therapy
1938-1939	Sulfapyridine
1940 - 1945	Penicillin and other antibiotics

OBSERVATIONAL STUDIES

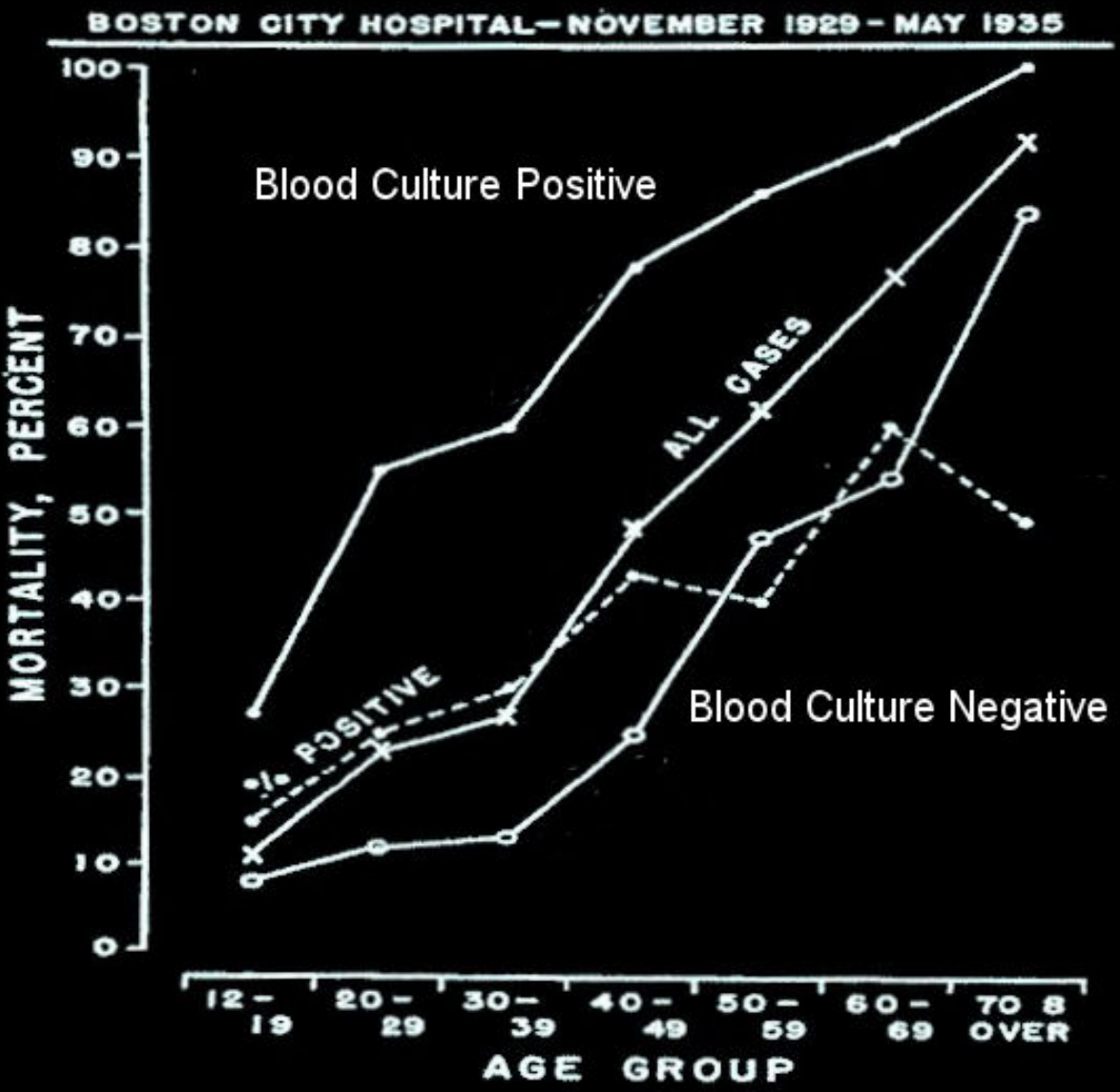


FIGURE 1. *Mortality in Pneumococcal Pneumonia in Relation to Age and Bacteremia (Based on 1586 Cases Reported by Tilghman and Finland[1]).*

The percentages of cases with bacteremia in the age groups are connected by the dotted line.

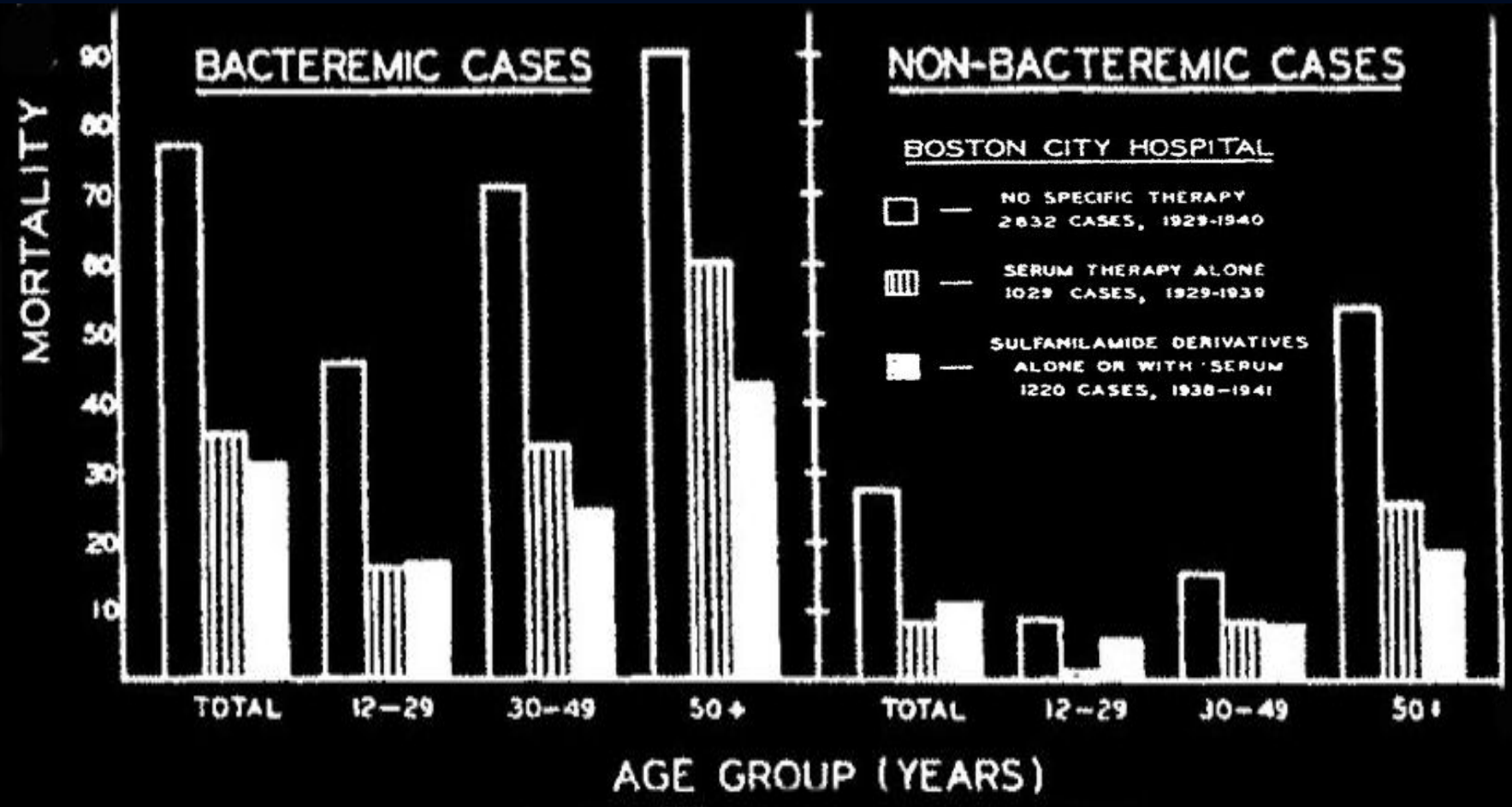


FIGURE 2. *Mortality in Patients with Pneumococcal Pneumonia of Different Age Groups in Relation to Treatment with Serum or Sulfonamides and to Bacteremia (Reproduced from Finland[4] with the Permission of the Publishers).*

Treatment of Pneumococcal Pneumonia with Penicillin

Meads, et al. (1945)

Observational Study in patients with moderate-severe pneumococcal pneumonia

Severity	Penicillin N=37	Penicillin after sulfa treatment N=17
Grade 2 (moderate)	15	1
Grade 3 (acutely ill/irrational)	9	5
Grade 4 (shock &/or CHF)	13	11

Treatment of Pneumococcal Pneumonia with Penicillin: Outcomes

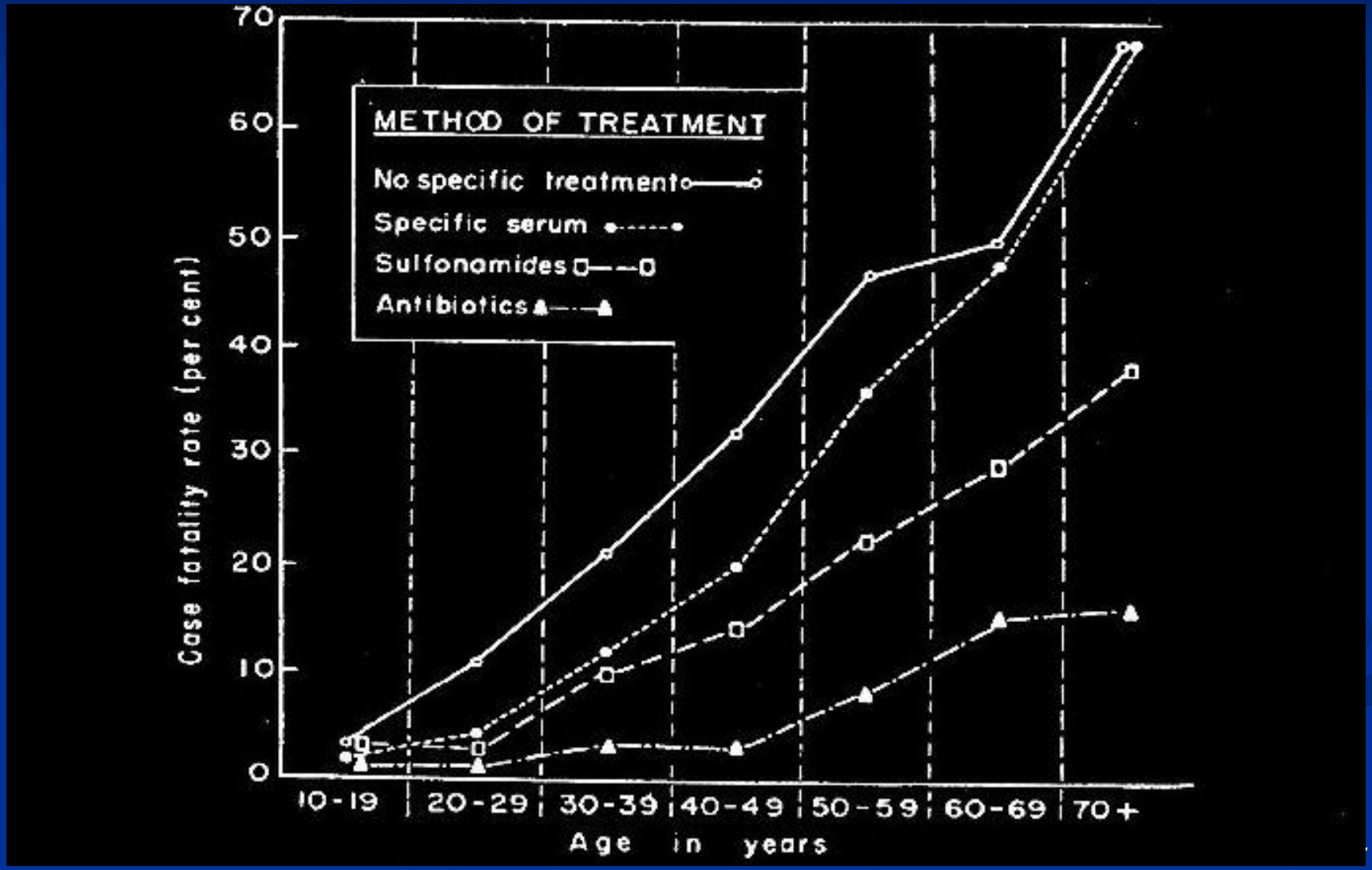
Meads, et al. (1945)

Outcome	Penicillin (N=37)	Penicillin after sulfa failure or intolerance (N=17)
Death	7 (19%)	3 (18%)
Relapse	2	1
Complications	0	0
Bacteremia after penicillin treatment	0/12	4/6
Duration of acute symptoms* < 48 hours	27/30 (90%)	9/14 (64%)
Duration of fever < 48 hours	24/30 (80%)	8/14 (57%)

*symptoms such as delirium, prostration, and dyspnea

Case Fatality Rate in Pneumococcal Pneumonia treated with Serum, Sulfonamides or "Antibiotics"

- Dowling and Lepper (1951)



Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum

Austrian and Gold (1964)

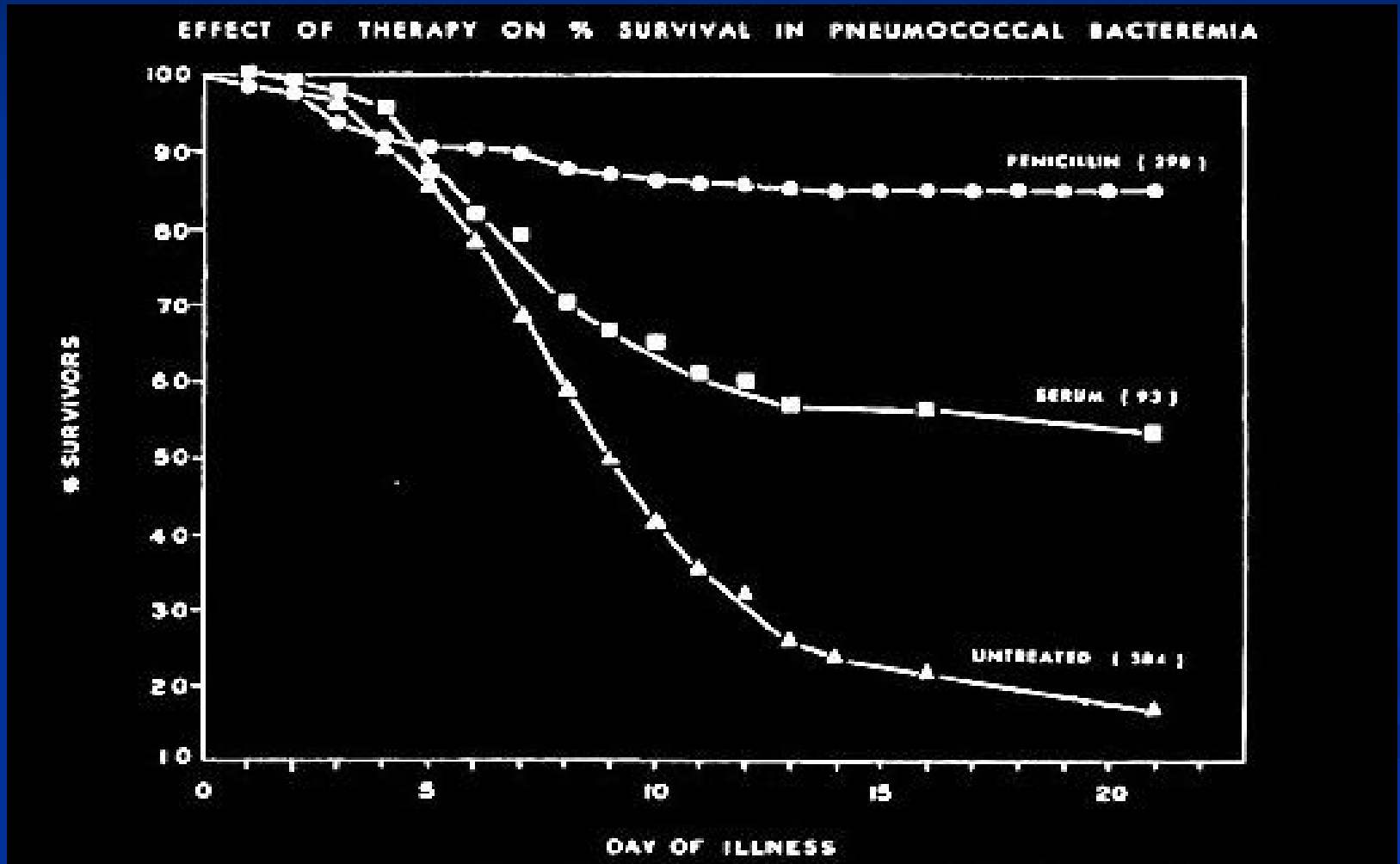
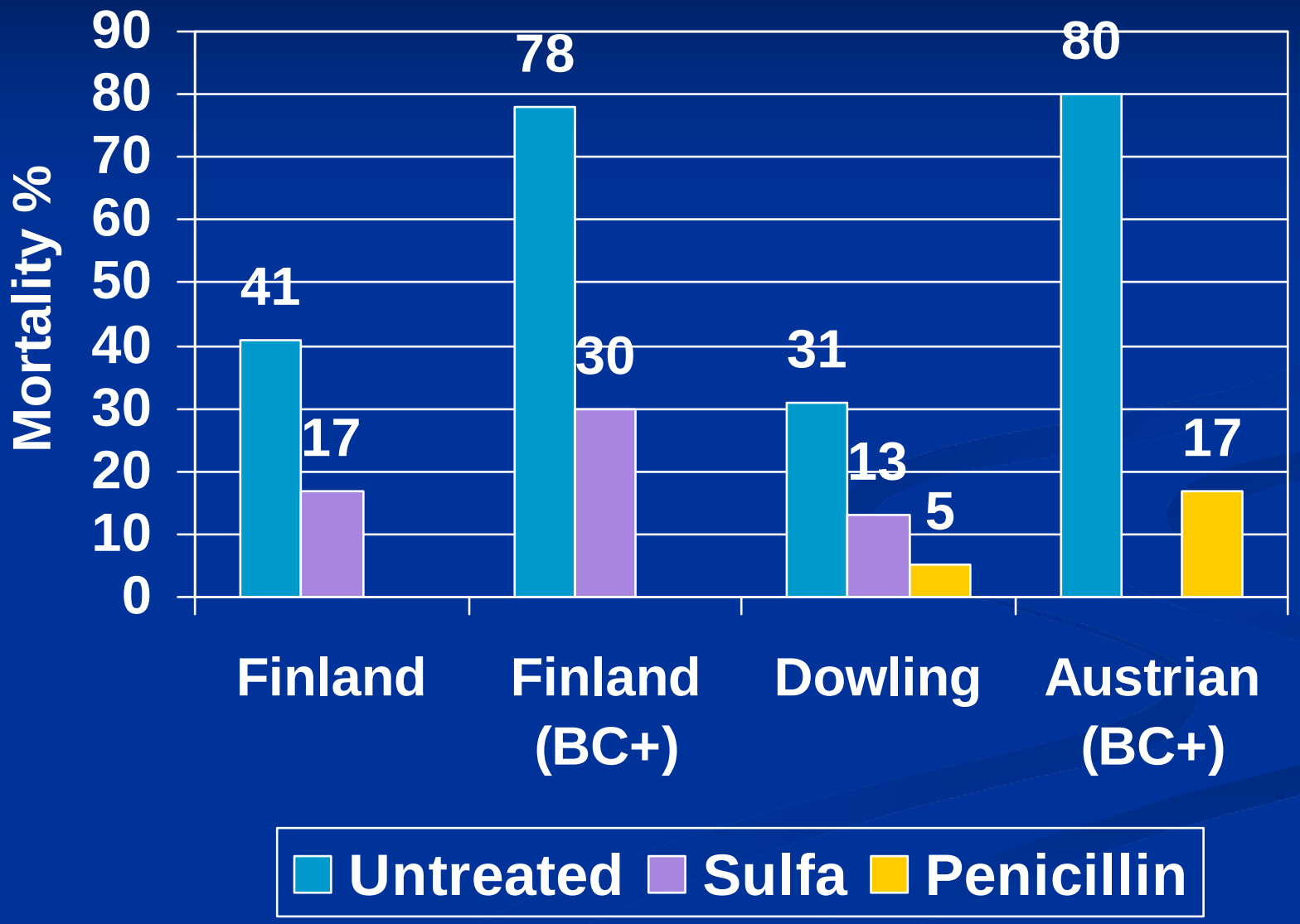


FIGURE 6. Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tillghman and Finland (1).

Treatment Effect: Observational Studies



Controlled Clinical Trials

Controlled Clinical Trial- Serotherapy

Park, et al. (1928)

- Alternate patients with lobar pneumonia
- Treatment:
  - **Polyvalent antiserum:** pneumococcal types I, II, III

    or:
  - **Standard treatment:** fluids, pain relief with elastic adhesive plaster, restriction of opiates, no drastic catharsis, oxygen for cyanosis or rapid breathing, digitalization for heart rate > 120

Case Fatality Rate in Patients with Type I Pneumococcal Pneumonia by Severity

(Park, et al., 1928)

Condition at baseline	Serum-treated	Standard treatment	Treatment Difference
Any condition	20% (N=114)	34% (N= 109)	14%
Good (> 70)	9%	13%	4%
Fair (50-70)	29%	52%	23%
Poor (< 50)	64%	100%	36%

Controlled Clinical Trial of Treatment of Pneumonia

- Evans and Gaisford (1938)

Treatment: M&B 693: 2-(p-aminobenzenesulphonamide) pyridine
Control: Non-specific treatment (presumed standard of care)
Population: Hospitalized patients with lobar pneumonia (8 - 68 years old)
Location: Birmingham, England
Treatment group: Determined by enrollment on alternate day
Excluded: Patients who died within 24 hours

Case Fatality Rate

All patients	M & B 693 (Sulfapyridine)	Control
All patients	**8/100 (8%)**	**27/100 (27%)**
Age > 50	**4/18 (22%)**	**7/10 (70%)**

Controlled Clinical Trial: Treatment of Pneumococcal Pneumonia with Sulfapyridine

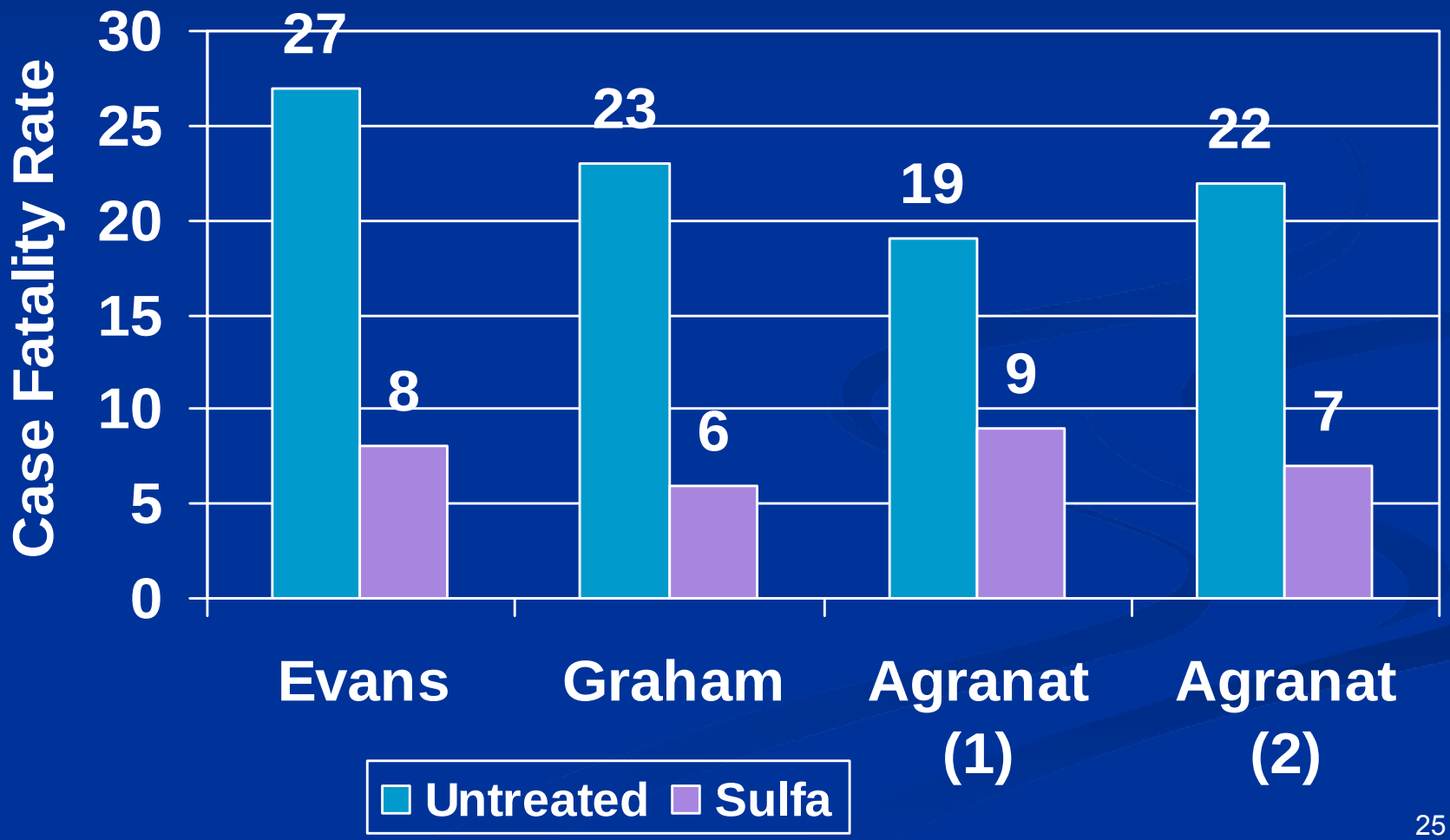
Graham, et al. (1939)

- Hospitalized patients with pneumococcal pneumonia
- Alternate patients
- Control: no specific therapy (20% bacteremic)
- Dagenan (M&B 693) = Sulfapyridine (34% bacteremic)

Case Fatality Rate

Dagenan (M&B 693)	Controls
3/50 (6%)	7/30 (23%)
3/17 (18%) bacteremic	3/6 (50%) bacteremic

Treatment Effect: Controlled Trials



Summary

Summary of Antibacterial Drug Treatment Effect in Pneumococcal Pneumonia

Observational Studies	Treatment vs. untreated controls	Mortality Difference (95% confidence interval)
Finland (1943)	Sulfonamides	24% (21, 27) 48% (bacteremic)
Dowling et al. (1951)	Sulfonamides Penicillin, tetracyclines	18.5% (15, 21) 25.4% (22, 28)
Austrian and Gold (1964)	Penicillin	63% (59, 69) (bacteremic)

Summary of Antibacterial Drug Treatment Effect in Pneumococcal Pneumonia

Controlled Studies	Treatment vs. untreated controls	Difference in Case Fatality Rate (95% confidence interval)
Evans and Gaisford (1938)	Sulfapyridine	19% (8.8, 29.2)
Graham, et al. (1939)	Sulfapyridine	17% (0.1, 36.4) 32% (bacteremic)
Agranat, et al. (1939)	Sulfapyridine	10% (-0.3, 20.6) 15% (-6.2, 35.5)

Summary

Point estimates for antibacterial drug treatment effect in pneumococcal pneumonia:

- Observational Studies: 19-25%
  - Bacteremic (48-63%)
- Controlled Trials: 10-19%
  - Bacteremic (33% in single study)

Limitations of using the Historical Data to Estimate Treatment Effect

- **Differences in Patient Populations:**
  - e.g. co-morbidities, immune status, pneumococcal vaccination
- **Differences in Organisms/Disease:**
  - Mostly hospitalized patients with pneumococcal pneumonia
  - Severity was not well-characterized
  - Most CAP now treated in outpatient setting
  - *S. pneumoniae* isolated less frequently
  - Atypical organisms common in mild CAP
- **Differences in Standard of Care**
- **Differences in Study Design:**
  - Observational data
  - Controlled trials were not randomized or blinded
  - Endpoints: mortality vs. clinical response
  - Study drugs: penicillin and sulfonamides

Issues for Discussion

- Extrapolation of historical data on treatment of pneumococcal pneumonia to estimate antibacterial drug treatment effect for:
  - Mild CAP
  - Severe CAP
- Appropriate design for CAP studies
  - Populations (inclusion/exclusion criteria)
  - Primary endpoint

Treatment Difference in Recent Studies

Study	Findings
Discordant therapy- e.g. B-lactam for penicillin-resistant *S. pneumoniae*	Review: (Falagas, et al., 2006) No difference in clinical success
Guideline concordance vs. discordance	Mortensen, et al. (2006): decreased mortality at 48 hours Mortensen, et al. (2004): decreased mortality at 30 days
Broad spectrum antibiotics (including atypical coverage) vs. narrow spectrum antibiotics	Meta-analyses: Shefet, et al. (2005); Mills (2005): no difference in cure

Treatment Difference in Recent Studies (continued)

Study	Findings
Delayed vs. immediate antibiotic treatment	Houck, et al. (2004): decreased mortality and LOS associated with shorter time to administration of antibiotics
Studies that showed inferiority	Few published or submitted for NDA
Studies that showed superiority of one antibacterial drug over another	Few; possible outliers
Dose ranging studies	Low doses which might not be efficacious generally not evaluated
PK/PD studies	Limited by few clinical failures among patients for whom PK data is available