History of Antibacterial Drug Development

Anti-Infective Drugs Advisory Committee Meeting

December 4, 2014

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Outline

- Statutes and regulations
- Antibacterial drug development through the years
- Highlights from recent guidances
- Conclusions

Statutes and Regulations

Statutory Standards

- Approved drugs must meet the statutory standards for effectiveness of the FD&C Act
  - Section 505(d)(1): substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations,…"
  - 21 CFR 314.126(b): Adequate and well-controlled studies
    - Placebo-control; dose-comparison control; no treatment control; active-treatment control; historical (external) control
  - Section 115(a) of the Modernization Act: allowed for data from one adequate and well-controlled clinical investigation and confirmatory evidence to establish effectiveness

Statutory Standards

- There is flexibility within the statutory standards
  - Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*
    - Evidence of effectiveness from a single study and supportive evidence (phase 2, nonclinical, animal models)
  - 21 CFR 312.80, subpart E: "Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses"
    - "the recognition that physicians and patients are generally willing to accept greater risks or side effects from drugs that treat life-threatening and severely-debilitating illnesses, than they would accept from drugs that treat less serious illnesses"
    - "the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated"

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

Antibacterial Drug Development through the Decades

1960s through 1980s

- Subjects with a variety of infections at different body sites were all enrolled in the same trial
- Objective to demonstrate "comparable point estimates" to active control for clinical cure for each of the different infection types (no formal inference testing or unsupported NI margins, other design limitations)
- Indications based on subsets of body sites of infection from within the trials
- Less specific indications e.g.
  - Respiratory tract infections, later lower (included bronchitis and pneumonia) and upper (sinusitis)
  - Skin infections

1990s through 2000

- Move towards more site specific trials
  - Natural history of the disease may differ
  - Endpoints and treatment duration may differ
  - Drug efficacy may differ at different sites of infection
  - Dosing regimen may differ for different sites as well
- 1992 IDSA Guidelines
- 1992 FDA Points to Consider document – Clinical Development and Labeling of Anti-Infective Drug Products*
- Recognition of the aforementioned differences noted in these documents represented an advance in clinical trial design

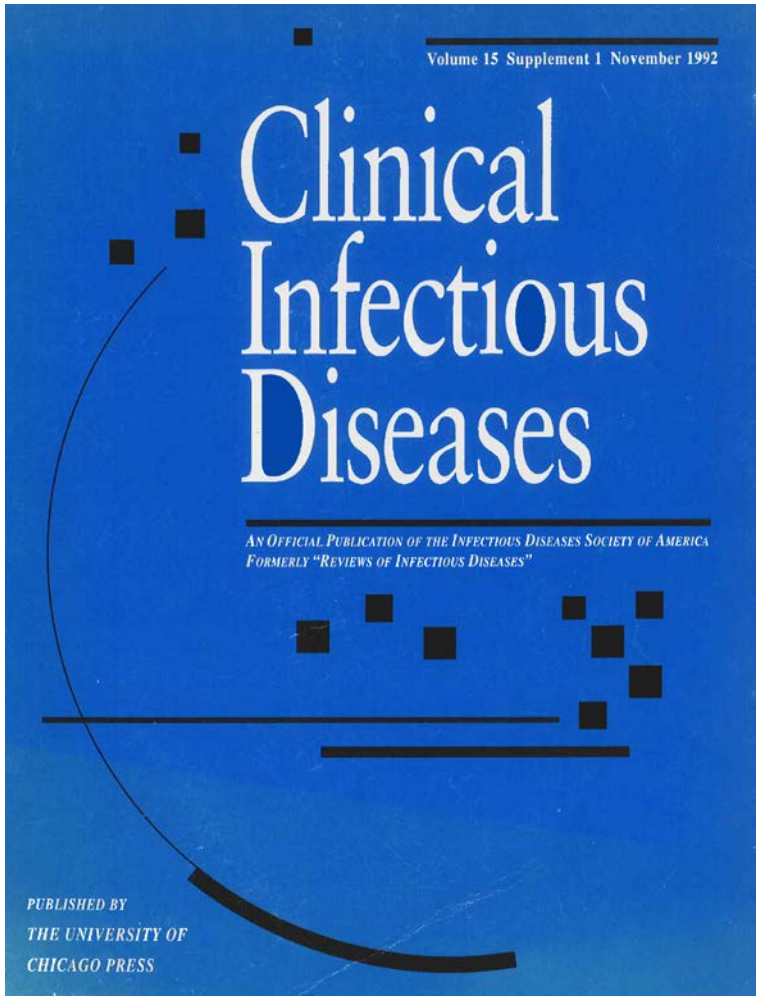
* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070975.pdf

1992 IDSA/FDA Guidelines

Clear need to improve the design and conduct of clinical trials of anti-infective drugs;

(1) provide clearer definition of disease states and their clinical and microbiological endpoints;

(2) take into account changes in the diagnosis and management of specific infectious diseases; …



2000 through Today

- Greater emphasis on the evidence base for noninferiority trials
  - Public concern about the scientific validity of antibacterial drug trials
- This has generally led to larger trials
- Continued trend towards more specific indications:

Respiratory tract infection (RTI)

⇩

Lower RTI + Upper RTI (ABS, ABOM)

⇩

CABP + ABECB +/- Nosocomial pneumonia

⇩

HABP + VABP

- More specific indications scientifically reasonable because information about ABECB doesn't inform about HABP/VABP

Recent Guidances

Concepts Underlying Guidances

- Recommend trial designs that are scientifically well-grounded and feasible
  - Allow some use of prior antibacterial drugs
  - Use ITT population for certain indications
  - Use of a comparator drug that is SOC but doesn't have a labeled indication, i.e. HABP/VABP
  - NI margin >10% possible , i.e. for CABP
- Enroll patient populations with the diseases of interest
- Endpoints that reflect benefit to patients
- Noninferiority margins based on historical evidence of sensitivity to drug effect and clinical judgment

Highlights-HABP/VABP*

- Enroll hospitalized subjects with:
  - New onset or worsening pulmonary symptoms or signs
  - Hypoxemia or need for acute changes in ventilatory support
  - At least one of fever, hypothermia, WBCs>10,000 or <4500, >15% bands
  - Plus chest radiograph showing new or progressive infiltrate suggestive of bacterial pneumonia
- Primary endpoint of all-cause mortality alone or ACM plus no disease-related complications at day 14-28
- Primary analysis population depends on spectrum of activity (micro-ITT for narrow and ITT for broad)
- NI margin 10%

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf

Highlights-cUTI*

- Enroll subjects with conditions associated with risk for cUTI plus at least two signs and symptoms:
  - Indwelling urinary catheter, urinary retention (≥ 100 mL of residual urine after voiding), neurogenic bladder, obstructive uropathy, azotemia or
  - Pyelonephritis
- For IV drug, primary endpoint of resolution of symptoms and $<10^4$ CFU/mL of pathogen isolated at baseline at day 5
- Primary analysis population is microbiological intent-to-treat (micro-ITT)
- NI margin 10%

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf

Highlights-cIAI*

- Enroll subjects with one or more systemic sign or symptom:
  - Hospitalized and operative procedure completed or scheduled to occur within 48 hours
  - Intra-abdominal abscess, appendicitis or diverticulitis complicated by perforation or abscess, cholecystitis with perforation or empyema, intestinal perforation with abscess or fecal contamination, gastric or duodenal ulcer perforation, peritonitis with fecal contamination
- Primary endpoint of complete resolution of baseline signs and symptoms at day 28 and no failure
- Primary analysis population is microbiological intent-to-treat (micro-ITT)
- NI margin 10%

*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321390.pdf

When Considering Unmet Need Development Programs

- Keep in mind statutes and regulations
- Recall how antibacterial drug development evolved over the decades and trial designs improved
- Consider recently issued guidances for specific bacterial indications
  - Patient populations
  - Endpoints
  - NI margins
- Benefit/risk for unmet need

Thank you!

Clinical Development Issues for Antibacterial Drugs for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases

Anti-Infective Drugs Advisory Committee Meeting

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December 4, 2014

Overview of Recommendations for Clinical Development of Antibacterial Drugs for Unmet Medical Need

- Recognition that patients and physicians are generally willing to accept greater risks for drugs that treat life-threatening illnesses
- Benefits of the drug need to be evaluated in light of the severity of the disease being treated

21 CFR 312.80: subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

Overview of Antibacterial Drug Development: Unmet Medical Need

- Definition of unmet medical need
  - Patients who have a serious bacterial disease for which effective antibacterial drugs are limited or lacking
    - Includes patients who have bacterial diseases in which in vitro susceptibility testing shows resistance to several antibacterial drugs

Overview of Antibacterial Drug Development: Unmet Medical Need

- Characteristics of new antibacterial drugs
  - New mechanism of antibacterial action
  - Added inhibitor that neutralizes a mechanism of resistance
  - Alteration in structure such that a particular mechanism of resistance does not affect the new drug
  - Other characteristic to enhance effectiveness

Overview of Antibacterial Drug Development: Unmet Medical Need

- Drug intended to treat a single species of bacteria can be a candidate for streamlined development:
  - Frequency of infection with single species
  - Use of a rapid diagnostic to reliably and promptly identify patients with the infection
  - Co-development of a rapid diagnostic for use in clinical practice

Overview of Antibacterial Drug Development: Unmet Medical Need

- Nonclinical considerations
  - In streamlined clinical development involving smaller, shorter, or fewer clinical trials, nonclinical data may take on a more important role in the overall data submitted for review to demonstrate safety and efficacy
  - Nonclinical evaluations should not be streamlined or smaller

Overview of Antibacterial Drug Development: Unmet Medical Need

- Nonclinical considerations
  - Characterization of properties to assess its potential to address an unmet medical need
  - Mechanism of action
  - Guidance for Industry available
    - ICH guidance M3(R2) Nonclinical Safety Studies
    - FDA “Pharm/Tox” guidance webpage
      - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm

Overview of Antibacterial Drug Development: Unmet Medical Need

- Nonclinical considerations: microbiology
  - In vitro activity of the investigational drug
    - Activity in animal models of infection
    - Minimum inhibitory concentration from samples of target bacterial pathogens
  - Mechanisms of resistance
    - Enzymatic, decreased permeability, altered target site, efflux
    - Cross-resistance

Overview of Antibacterial Drug Development: Unmet Medical Need

- Nonclinical considerations: PK/PD
  - In vitro evaluation of PK/PD relationships
  - Target value of PK/PD index in animal models
    - AUC/MIC
    - Cmax/MIC
    - Time above MIC
  - Appropriate levels of antibacterial drug in certain tissue sites
  - Comparison of human PK to the data obtained in animal models

Overview of Antibacterial Drug Development: Unmet Medical Need

- Early Clinical Development: PK/PD
  - Drug distribution in relevant tissue sites
    - e.g., epithelial lining fluid
  - Characterize PK in patients with co-morbidities, guide dosing recommendations
    - Renal impairment
    - Hepatic impairment
  - Sparse sampling of patients enrolled in trials

Overview of Antibacterial Drug Development: Unmet Medical Need

- Labeling: **21 CFR 201.56 21 & CFR 201.57**
  - INDICATIONS AND USAGE
    - Appropriate level of detail on population for whom drug is indicated
    - Statement if drug should be reserved for certain situations
    - Limitations of use (e.g., patient subgroups)
    - First list of bacterial pathogens
      - Evaluated during clinical trials
    - Statement about antibiotic resistance
      - see 21 CFR 201.24(b)

Overview of Antibacterial Drug Development: Unmet Medical Need

- Labeling: **21 CFR 201.56 21 & CFR 201.57**
  - MICROBIOLOGY (e.g., subsection 12.4)
    - Second list of target bacterial pathogens
      - Guidance on microbiological data: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf
    - Mechanisms of resistance and cross-resistance
    - Susceptibility test methods and interpretive criteria
      - Phenotypic in vitro antibacterial susceptibility testing is very important because clinical isolates may have the presence of more than one resistance mechanism!

Overview of Antibacterial Drug Development: Unmet Medical Need

- Labeling: **21 CFR 201.56 21 & CFR 201.57**
  - CLINICAL STUDIES (section 14)

  "…any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b)" [21 CFR 201.57(c)(15)(i)]
    - Provide primary support for effectiveness
    - Other important supporting evidence of effectiveness
    - Prospective evaluation of a safety endpoint

Guidance on Clinical Studies Section of Labeling:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf

Overview of Antibacterial Drug Development: Unmet Medical Need

Thank you!

Statistical Considerations in Evaluating Products for Unmet Medical Need

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Unmet Need and Statistical Considerations

- Unmet need:
  - Presentation will focus on evaluating new antibacterials for patients with serious or life-threatening infections who lack safe and effective regimens due to drug resistance

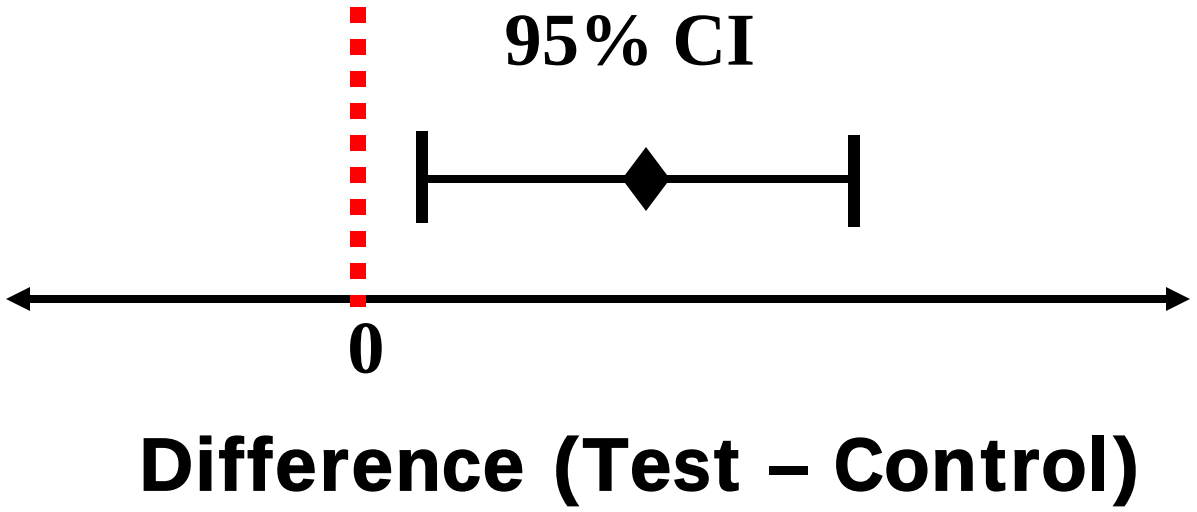
- Statistical considerations:
  - Presentation will discuss statistical properties of pathways in the meeting background materials and 2013 draft guidance

Outline

- **Randomized superiority design**
- Non-inferiority design
- Pooling body sites
- External controls
- Lessons from combination trials

Randomized Superiority Design

- Evaluate whether a new treatment leads to better clinical outcomes than a control regimen



Randomized Superiority Design

- Rationale:
  - Answers the most relevant question
  - Provides the most statistically reliable answer

- Possible inducements:
  - Pooling of infections at different body sites
  - Less stringent statistical significance level
  - Allow cluster randomization

Randomized Superiority Design

- Challenges:
  - Must hypothesize large effect over best current therapy

Control failure rate	Treatment failure rate	Sample size per arm
50%	30%	N = 91
50%	35%	N = 167
50%	40%	N = 385

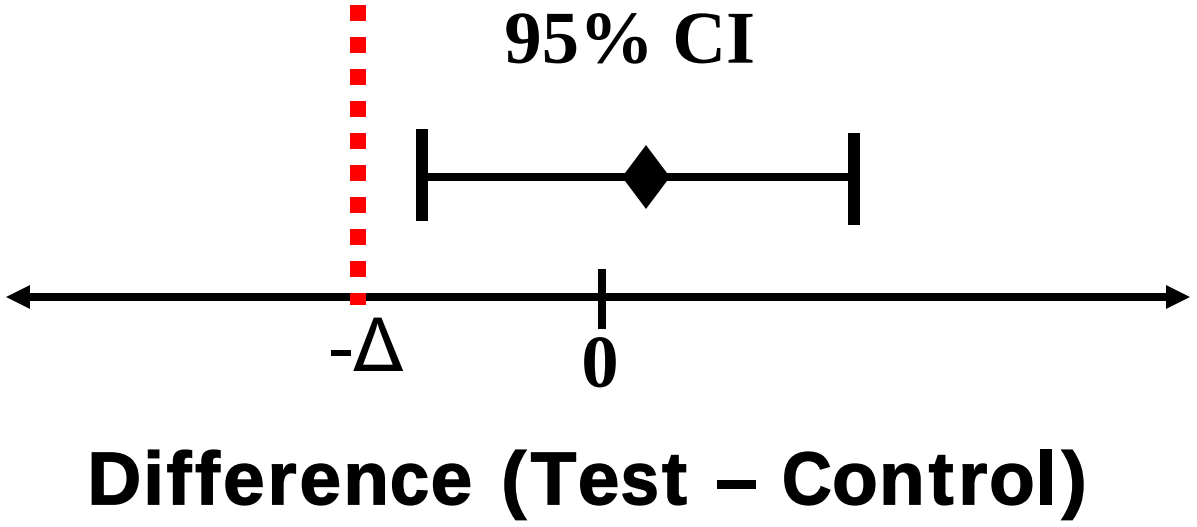
Assumes one-sided $\alpha = 0.025$ significance level, 80% power

Outline

- Superiority design
- **Non-inferiority design**
- Pooling body sites
- External controls
- Lessons from combination trials

Non-inferiority Design

- Must determine whether the test drug is unacceptably worse than the active control, according to margin Δ



Non-inferiority Design

- Rationale: Unethical to administer placebo when patients have effective or partially effective therapy
- Traditional, well-characterized method for antibacterial drug development is to conduct a non-inferiority trial for infections at a specific body site
- Challenges in design and analysis:
  - Dependence on historical evidence of sensitivity to drug effects, constancy assumption, assay sensitivity
  - Similar challenges will present for external controls

Non-inferiority Design

- Unmet need guidance discussion:
  - Conduct trial in patients with acceptable current options
  - Wider than normal non-inferiority margin
  - Extrapolate efficacy to group with unmet need

- Challenges of extrapolation:
  - Patient factors differ between those with susceptible pathogens and those with resistant pathogens
  - Patient factors are prognostic of outcomes and can modify treatment effects

Non-inferiority Design

Table 1. Demographics and Outcomes of Sensitive vs Resistant ICU-Acquired Infections

Demographics and outcomes	Sensitive	Resistant	p Value
n	1,669	739	—
Age, y, mean ± SEM	52.8 ± 0.4	53.7 ± 0.5	0.16
Male sex, %	61.5	61.5	1.00
Body mass index, kg/m^2, mean ± SEM	30.4 ± 0.2	31.4 ± 0.3	0.007
APACHE II score, mean ± SEM	19.2 ± 0.1	20.2 ± 0.2	<0.001
WBC, maximum, mean ± SEM	15.7 ± 0.2	15.0 ± 0.3	0.06
Trauma, %	49.4	35.9	<0.001
Transplant recipient, %	12.3	21.9	<0.001
Transfused, %	82.8	93.2	<0.001
Hemodialysis, %	17.1	28.1	<0.001
Ventilator dependence, %	68.8	73.2	0.01

Source: Rosenberger et al. (2012)

Outline

- Superiority designs
- Non-inferiority designs
- **Pooling body sites**
- External controls
- Lessons from combination trials

Pooling Body Sites

- Rationale:
  - Small sample sizes per body site with resistant pathogens
- Trials already pool across various factors:
  - Pathogens, regions, demographic factors, etc.
  - Indications originally separated due to clinical heterogeneity
- Pooling discussions mainly for major Gram-negative indications:
  - HABP/VABP, BSI, cIAI, cUTI
- Several ongoing trials pooling HABP/VABP and BSI:
  - Plazomicin versus colistin (NCT01970371)
  - Colistin+meropenem versus colistin (NCT01597973)

Pooling Body Sites

- Some statistical methods such as Bayesian hierarchical models attempt to borrow strength across body sites

- Model-based estimation for site-specific treatment effects

Pooling Body Sites

- Challenges:
  - Pooled trial would have little power to precisely estimate treatment effects in each body site, or detect heterogeneity across body site subgroups
  - Examples of possibly decreased efficacy in respiratory infections or more severely ill patients (e.g., tigecycleine, doripenem, daptomycin, ceftobiprole, see references).

Pooling Body Sites (Tigecycline Mortality Data)

Patients with outcome of death by infection type

Infection Type	Tygacil deaths/total patients (%)	Comparator Antibiotics deaths/total patients (%)	Risk Difference* (95% Confidence Interval)
cSSSI	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
cIAI	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
CAP	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
HAP	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-VAP†	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
VAP†	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
RP	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)
DFI	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1, 1.2) **

Source: FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm.

Pooling Body Sites (Halted Doripenem VABP Trial)

Analysis Population	Doripenem Group %	Imipenem Group %	Difference %	2-sided 95% CI %
Clinical Cure Rates				
MITT	45.6	56.8	-11.2	-26.3 to 3.8
ME	49.1	66.1	-17	-34.7 to 0.8
All Cause 28-day Mortality Rate (MITT)	21.5	14.8	6.7	-5.0 to 18.5

Source: FDA Statement on recently terminated clinical trial with Doribax (doripenem). http://www.fda.gov/Drugs/DrugSafety/ucm285883.htm.

Outline

- Superiority designs
- Non-inferiority designs
- Pooling body sites
- **External controls**
- Lessons from combination trials

External Controls

- Rationale:
  - Increases power when resistant pathogens are scarce
  - Allows a more principled analysis than a descriptive single arm case series
  - A controlled comparison is necessary because patients with resistant infections cannot be assumed to uniformly die or fail to recover

- Draft unmet need guidance recommends still conducting a randomized trial, possibly with disproportionate randomization, but augmenting the control group with external data

External Controls

- Selected summary of literature reports of pandrug-resistant (i.e., resistant to all antibiotics) Gram-negative infections

First author	Year published	Sample size	Recovery/survival rate
Falagas	2005	n = 7	5/7 (71.4%)
Beno	2006	n = 10	3/10 (30.0%)
Mentzelopoulos	2007	n = 5	4/5 (80.0%)
Falagas	2008	n = 24	14/24 (58.3%)
Elemam	2009	n = 2	1/2 (50.0%)
Tsioutis	2010	n = 14	9/14 (64.3%)
Giamarellou	2013	n = 3	3/3 (100%)
Oliva	2014	n = 3	2/3 (66.7%)
Total		n = 68	41/68 (60.3%)

External Controls

- Challenges encountered putting idea into practice:
  - Selection of the control group (Chart review? Literature?)
  - Ensuring patient comparability with matching or adjustment
  - Minimizing bias in the analysis with pre-specification of selection of controls
  - Heterogeneous outcomes across studies
  - Underlying co-morbidities predictive of outcomes

Outline

- Superiority designs
- Non-inferiority designs
- Pooling body sites
- External controls
- **Lessons from combination trials**

Combination Trials

- Three recent randomized, pathogen-specific trials comparing colistin monotherapy to combinations for cabapenem-resistant *A. baumannii* infections

First author	Country	Period	Sample size	Combination
Durante-Mangoni	Italy (5 centers)	11/2008-7/2011	N = 210	Colistin + Rifampicin
Aydmir	Turkey (1 center)	03/2011-03/2012	N = 43	Colistin + Rifampicin
Sirijatuphat	Thailand (1 center)	01/2010-03/2011	N = 94	Colistin + IV Fosfomycin

Combination Trials

Trial location	Percentage of trial subjects with infections at different body sites					
	Pneumonia	Bacteremia	Intra-abdominal	Urinary tract	Other	Total
Italy	77.5%	20.1%	2.4%	0%	0%	100%
Turkey	100%	0%	0%	0%	0%	100%
Thailand	76.6%	5.4%	6.4%	5.4%	6.4%	100%

Combination Trials (Mortality Results)

Trial location	Mortality in randomized groups		
Italy	Colistin	Colistin + Rifampicin	
	45/105 (42.9%)	45/104 (43.2%)	
Turkey	Colistin	Colistin + Rifampicin	
	16/22 (72.7%)	13/21 (61.9%)	
Thailand	Colistin	Colistin + Fosfomycin	
	27/47 (57.4%)	22/47 (46.8%)	
Pooled trials	Colistin	Colistin + Add-on	Difference (95% CI)
	88/174 (50.6%)	80/172 (46.5%)	4.1% (-6.4% to 14.5%)

Lessons from Combination Trials

- Managing bias:
  - Heterogeneous mortality rates across studies
  - Non-randomized comparisons would need to match or statistically adjust for baseline factors to control confounding
  - Possible utility for a future trial network

- Managing variance:
  - No evidence of a mortality benefit for combination therapy over monotherapy, but benefit cannot be excluded
  - Definitive answers will be difficult to obtain with small sample sizes, absent dramatic treatment effects. Need for leveraging or augmenting varied data sources in a principled manner to increase precision.

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Trial Considerations for Unmet Need

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Anti-Infective Drugs Advisory Committee Meeting
December 4, 2014

Outline

- Trial design considerations for antibacterial drugs for unmet need
- Potential data packages using the following examples:
  1. Antibacterial drug with activity against Enterobacteriaceae and *Pseudomonas aeruginosa*
  2. Antibacterial drug with activity against Enterobacteriaceae
  3. Antibacterial drug with activity against *P. aeruginosa* only
  4. New beta-lactamase inhibitor combined with an approved beta-lactam antibacterial drug
  5. Adjunctive therapy

Unmet Need: Noninferiority Trials (1)

- Well-conducted noninferiority (NI) trials of antibacterial drugs are critical to maintaining a robust pipeline of antibacterial drugs so that options are available before new mechanism(s) of resistance emerge
- Developing antibacterial drugs once resistance develops and attains levels sufficient to conduct a clinical trial in patients with unmet need is not in the best interest of public health

Nambiar S et al. Clin Pharmacol Therap 2014 Aug;96(2):147-9.

Unmet Need: Noninferiority Trials (2)

- A well-conducted NI trial will provide evidence of a drug's efficacy in a given body site of infection
  - Can enroll patients infected with either wild-type or MDR phenotype microorganism(s)
  - Generally, will be limited to situations where the baseline microorganism(s) are susceptible to both test and comparator drug
    - Trial often enrolls relatively few (or no) patients infected with MDR phenotype microorganism(s)
  - Supported by evidence for the drug's activity from *in vitro* data and animal models of infection

Unmet Need: Noninferiority Trials (3)

- In general, one adequate and well controlled Phase 3 NI trial enrolling patients with infection at one body site will suffice
  - Enroll patients with severity of illness/comorbidities similar to those seen in patients with unmet need
- Willing to accept a wider NI margin than that used for a traditional development program
- Labeling from such a program will include a limited use statement
- Pooling across body sites for an NI trial can be challenging
  - Trial may not demonstrate a potential deficit in treatment effect across infection types
  - Treatment effect varies across infection types
  - Endpoints vary between infection types

Pertel PE, et al. CID 2008;46(8):1142-51;

Superiority Trials (1)

- Provides a clear finding of efficacy
- Ability to rely on superiority is likely time-limited
  - Once a new therapy becomes available, ongoing trial designed to show superiority over standard of care (SOC) will likely become unethical and would probably need to be stopped
  - Subsequent trials will be NI trials
- Pooling across body sites acceptable; larger fraction with more serious infections such as HABP/VABP where deficits in performance of an antibacterial drug have been seen

Doripenem Drug Safety Communication; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm;
Tigecycline Drug Safety Communication::http://www.fda.gov/drugs/drugsafety/ucm369580.htm;

Superiority Trials (2)

- Active comparator
  - Usually dependent upon the comparator arm of the trial representing suboptimal treatment
  - Very infrequently an antibacterial drug provides additional benefit over active SOC
- External controls
  - Controls should be as similar as possible to the study population; challenges in obtaining comparable external control group well described in ICH E10
  - At least a small number of patients should be randomized to best available therapy (disproportionate randomization)
- Add on design: Test drug + SOC vs. SOC + Placebo

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf

Nested NI/Superiority Trial Design

- An NI trial where baseline pathogens may or may not have resistance phenotype of interest
  - Demonstrate NI in the population susceptible to comparator
  - Demonstrate superiority in the subset of patients with baseline microorganism(s) resistant to comparator
  - If superiority not demonstrated, does not impact on the conclusion of noninferiority
  - No multiplicity adjustment needed to control overall type-I error
  - May be an option for less severe infections with possible rescue therapy

IDSA, White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. Clin Infect Dis, 55(8):1031-1046
Huque et al. Hierarchical nested trial design (HNTD) for demonstrating treatment efficacy of new antibacterial drugs in patient populations with emerging bacterial resistance. Stat Med. 2014 Jun 23.

Example 1

- Antibacterial drug active against Enterobacteriaceae and *Pseudomonas aeruginosa*
- Active *in vitro* against several ESBLs including serine carbapenemases
- Activity in relevant animal models of infection demonstrated
- Achieves adequate levels in epithelial lining fluid
- Options:
  - Single noninferiority trial
  - Nested noninferiority /superiority
  - Superiority

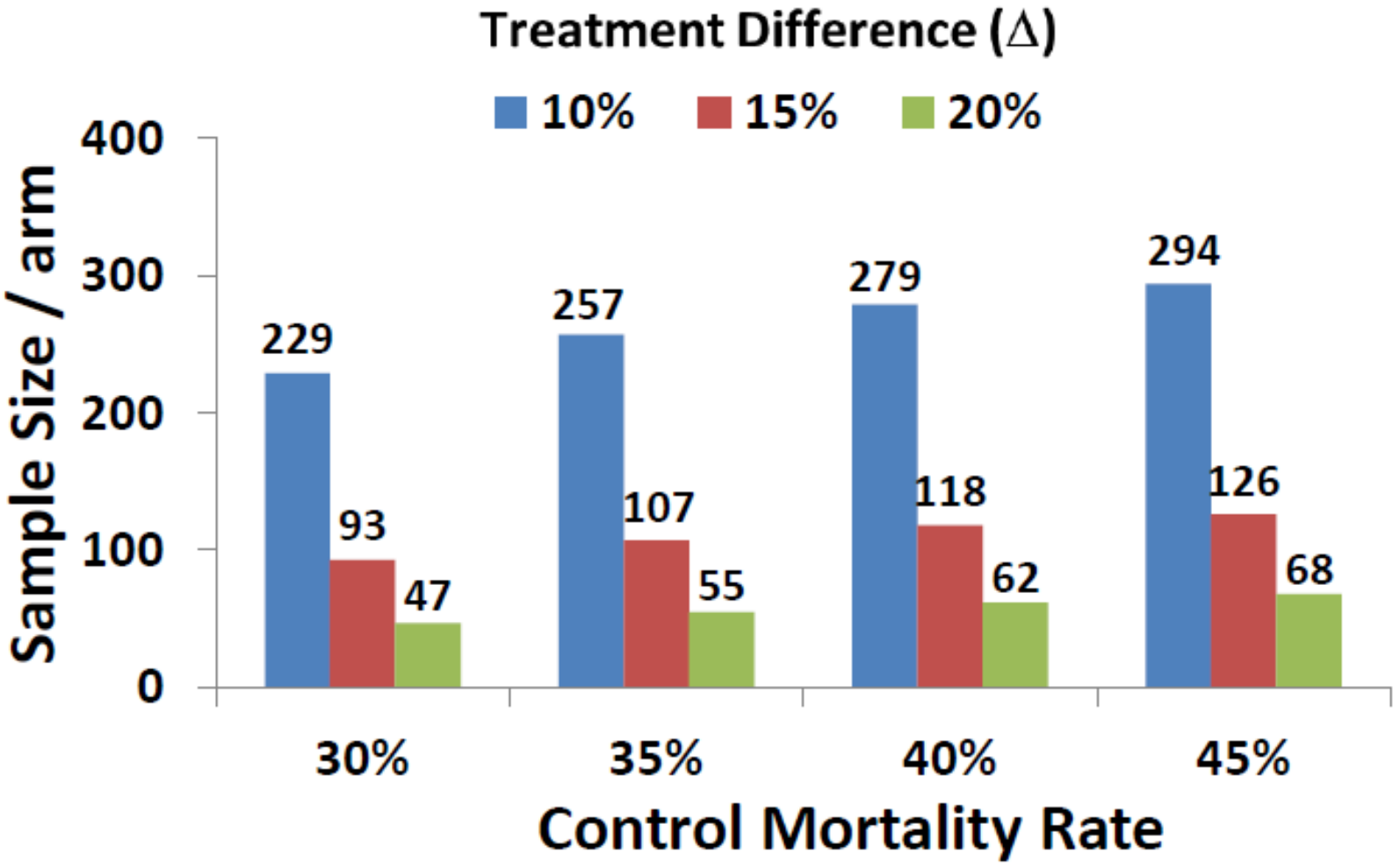
Example 1: NI Trial

- A single noninferiority trial at one body site
  - HABP/VABP
  - cIAI or cUTI
  - Wider NI margin acceptable
  - Limited use labeling
- May be supplemented with data from a study pooling across body sites in patients with unmet need
  - Provides PK data in a sicker population, likely more comorbidities
  - Will provide some clinical experience in patients with infections due to organisms with certain resistance profile
  - Could support a limited use indication across body sites if powered for inferential testing

Example 1: Superiority Trial

- Pooling across body sites (cIAI, cUTI, HABP/VABP); ~ 50% HABP/VABP
- Patients with documented infections due to a certain resistance phenotype, e.g. carbapenemase production
- Comparators
  - Best available therapy only or
  - Best available therapy, leveraging external control data using disproportionate randomization (3:1, 4:1)
- Endpoint: All-cause mortality or disease specific definition of clinical success
- One sided alpha of 0.05 acceptable

Sample Size: Superiority Testing
(α=.05, 1-sided; 80% Power)



Example 2

- Antibacterial drug active against Enterobacteriaceae; not active against *P. aeruginosa*; *in vitro* activity against several ESBLs including serine carbapenemases
- Options
- One NI trial at one body site:
  - Can be tested as monotherapy in cUTI
  - For HABP/VABP will need to address issue of overlapping activity of antibacterial drugs used to treat *P. aeruginosa*
- Similar to example 1
  - Nested NI/superiority
  - Superiority

Example 3

- Antibacterial drug is active only against *P. aeruginosa*
  - Difficult to study in the given paradigm
  - Low frequency of occurrence of the specific pathogen in any one body site
  - Some infections are polymicrobial; need for concomitant therapy with overlapping spectrum of activity
  - Rapid diagnostics could help some, but will not solve all these problems

Example 3: NI Trial

- NI trial at a single body site, e.g. HABP/VABP
  - Test drug would need to be co-administered with a second antibacterial drug to cover other Gram negative microorganisms, yet not obscure the treatment effect of test drug versus *P. aeruginosa*
  - Often double-coverage used for treatment of *P. aeruginosa,* further obscuring treatment effect
  - Clinicians may be hesitant to de-escalate even after *P. aeruginosa* is identified as most likely pathogen
  - Lack of a rapid molecular diagnostic test for *P. aeruginosa,* makes it difficult to enrich trial population
- Potentially study infections at other body sites- cUTI/skin(burns)?

Example 3: Superiority Trial

- Superiority trial pooling across multiple body sites
  - Superiority of test drug against best available therapy; will need to enroll patients with multidrug-resistant *P. aeruginosa*
  - Could use concurrent external control data; would it be acceptable to leverage historic control data for untreated *P. aeruginosa* infections?
- Could studies be done in populations more likely to have infections due to *P. aeruginosa* such as cystic fibrosis or bronchiectasis?
  - Can the drug be studied for treatment of pulmonary exacerbations?

Example 4

- New beta-lactamase inhibitor (BLI) being combined with an approved beta-lactam antibacterial drug
- The beta-lactam is a carbapenem that is approved for cUTI, cIAI, HABP/VABP
- Under 505(b)(2) of the FDCA, can rely in part on the Agency's finding of safety and effectiveness for the approved indications for the carbapenem
  - This information can provide part of the evidence needed for the new carbapenem-beta-lactamase inhibitor
- The combination can also be studied using an NI trial or superiority trial as discussed with prior examples

505(b)(2)

- Section 505 of the Act describes three types of new drug applications:
  - Section 505(b)(1): an application that contains full reports of investigations of safety and effectiveness
  - Section 505(b)(2): an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference
  - Section 505(j): an application that contains information to show that the proposed product is identical in active ingredient, dosage form … to a previously approved product

http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf

Types of Information That Can Be Relied On

- Agency's finding of safety and effectiveness for a previously approved drug product
- Published literature:
  - Reference to specific information (clinical trials, animal studies) necessary for approval of the application, if the applicant has not obtained a right of reference to the raw data underlying the published study or studies
- Both literature and upon the Agency's finding of safety and effectiveness for a previously approved drug product (e.g., to support a new claim).

Example 4: Data Package

- Clinical data (Phase 2 data) in patients with cIAI, cUTI, or HABP/VABP (indications for which the carbapenem is approved)
- Clinical data should include some patients with infections due to beta-lactamase producing microorganisms
- Evidence for activity against beta-lactamases available from *in vitro* studies and animal models of infection
- Adequate safety data needed for the beta-lactamase inhibitor and the combination product
- Limited use labeling for the indications studied in the Phase 2 trials with the new carbapenem and BLI combination

Example 5

- Product being developed as adjunctive therapy to standard of care (SOC)
  - Inhaled antibacterial drugs being developed for VABP
  - Immune modulators
  - Monoclonal antibody targeting a specific microorganism
- Trial design:
  - Superiority trial
  - Test drug plus standard of care versus standard of care

Summary

- Noninferiority trial at a single body site
  - Wider NI margin
  - Could include a nested superiority option
- Superiority trial
  - Pooling across body sites
  - Compared to best available therapy; may leverage external control data
  - Test drug plus SOC vs. SOC
- For a new beta-lactamase inhibitor being combined with an approved beta-lactam drug, could rely in part on Agency's finding of safety and effectiveness of the approved beta-lactam [505(b)(2)]