



CTTI Think Tank for Anti-Bacterial Drug Development: Unmet Medical Need and HAP/VAP

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Outline

- Background
- Use of extant data to augment the control group
- Cluster randomization to facilitate trial logistics
- Other issues



BACKGROUND

CTTI Statistics Think Tank

- Held on August 20, 2012 in Bethesda
- Meeting objective: *To discuss innovative approaches to the design and analysis of clinical trials in anti-bacterial drug development.*
- Participants
 - Four biostatistics faculty members
 - Four statisticians from industry
 - Four government statisticians (external to CDER)
 - CDER statistical review team for anti-infective products

CTTI Statistics Think Tank

- Just one of a number of initiatives FDA is undertaking to promote anti-bacterial drug development
- Opportunity for input from research statisticians working in other medical areas, e.g., cancer clinical trials
- Recognized need to facilitate development of new anti-bacterials, but want to accomplish this in smart ways
- Ultimate goal is to increase the likelihood that clinical trials of promising agents are successful and to ensure that those agents, if approved, are in fact safe and effective therapies for the intended patient populations

CTTI Discussion Topics

1. One- versus two-study paradigm:
 - Design characteristics for a single confirmatory study to provide sufficient evidence
 - Types of supporting evidence also needed
2. Non-inferiority trials:
 1. Bayesian approach to meta-analysis to determine margin
 2. Bayesian analysis with historical data as prior
 3. Use of MIC data (pre-randomization) to embed superiority test between extreme subgroups in trial

CTTI Discussion Topics

3. Multiple (body) sites of infection:

- Bayesian hierarchical modeling to combine information across multiple (body) sites for a single pathogen or across multiple pathogens at a single body site

4. Trial logistics:

- Methods to efficiently account for prior medications
- Trial network to establish infrastructure
- Cluster randomization to facilitate enrollment



Discussion Area #1

USE OF EXTANT DATA

Extant Data as Control

- Shortcomings of single-arm trials are well-documented
 - Difficult to establish comparability between treated patients and external controls (re: time, geography, etc.)
 - Potential for selection bias and endpoint ascertainment bias in open label studies
- A better idea
 - Include randomization with concurrent controls, but with allocation in favor of test drug
 - Leverage historical or other external data at analysis stage

Extant Data as Control

- Randomization allocation
 - Consider 2:1, 3:1 or even 4:1 allocation in favor of test drug
 - Higher degree of imbalance reflects more confidence in the external data
- Bayesian methods for data analysis
 - Incorporate historical or external data on control agent through prior distributions

Extant Data as Control

- Frequentist methods also available for analysis
 - Match or balance external controls to trial population through covariate or propensity score adjustments
 - Apply meta-analytic methods to ‘average’ external control data with concurrent controls
 - May want to down-weight external data relative to concurrent control data
- Substantial amount of historical or external data may be required to ensure a reasonable level of balance



Discussion Area #2

CLUSTER RANDOMIZATION

Cluster Randomization

- Difficult trial logistics
 - Patients with resistant pathogens may not consent to randomization if possible to be assigned to a new and potentially effective treatment
 - Time delay in randomization results in prior therapy use, reducing efficiency of the trial
- Possible solution
 - Randomize clinics to either test drug or standard of care

Cluster Randomization

- Requires a large number of clinics with few patients per clinic, i.e., a highly stratified design
- Ideal for the clinical trial network setting, with developed infrastructure
- Degrees of freedom = number of clinics, not patients, so power implications
 - But, if eliminates the need for prior therapy, this may be a wash



OTHER ISSUES



Several Options for Discussion

- Randomized superiority trials
- Externally controlled trials
- M1-driven non-inferiority trials
- Accelerated approval



Randomized Superiority Trials

- Provides direct evidence of safety and efficacy
- Challenges:
 - Large treatment effect relative to standard of care?
 - Difficulty of locating and enrolling in MDR setting
 - Pathway for second wave of sponsors?

Randomized Superiority Trials

- New ideas:
 - Pooling body sites if not precluded by clinical heterogeneity¹
 - Bayesian hierarchical models?
 - Superiority hypothesis nested within a non-inferiority trial¹
 - Enroll general patient population for active controlled trial, but analysis set is subjects with resistant pathogens enrolled before susceptibility results
 - Cluster randomization
 - Discordant MIC analysis: would like to show superiority for pathogens with low treatment MICs and high control MICs
 - Problem: very few subjects with high MICs are usually found in trials
 - Follmann et al.: valid superiority test by estimating “response surface”



ClinicalTrials.gov

This study is currently recruiting participants.

Verified March 2012 by Kaye, Keith, M.D., M.P.H.

Sponsor:

Kaye, Keith, M.D., M.P.H.

Information provided by (Responsible Party):

Keith Kaye, M.D., M.P.H., Kaye, Keith, M.D., M.P.H.

ClinicalTrials.gov Identifier:

NCT01597973

First received: May 8, 2012

Last updated: October 1, 2012

Last verified: March 2012

[History of Changes](#)

- Purpose: Approximately 444 subjects who are greater than or equal to 18 to 95 years of age, are non-pregnant, and are in the inpatient setting of one of the six study sites will be evaluated to treatment efficacy. Analysis will include subjects with bloodstream infection or pneumonia due to *Acinetobacter baumannii*, *Kelbsiella* spp., *E. Coli*, *Enterbactor* spp., and/or *Pseudomonas aeruginosa* that demonstrates in vitro non-susceptibility defined as extensively drug-resistant Gram-negative bacilli (XDR-GNB) which includes XDR-AB, XDR-PA and CRE.
- Primary objective: Determine whether the treatment regimen of Colistimethate sodium (colistin) combined with Imipenem-cilistatin (imipenem) is associated with a decreased risk for mortality compared to colistin alone for patients with bloodstream infection and/or pneumonia due to XDR-GNB.

Externally Controlled Trials

- Challenges:
 - Patient comparability
 - Heterogeneous patient population
 - External control = open label = need objective endpoint
 - If basing “untreated” success rates on FDA margin justifications in guidances, remember discounting step
 - ICH E10: only use when withholding therapy is unethical

- New ideas:
 - Combine external data with 2:1 randomization
 - Prospective collection of MDR natural history data

External Controls Should be Recent²

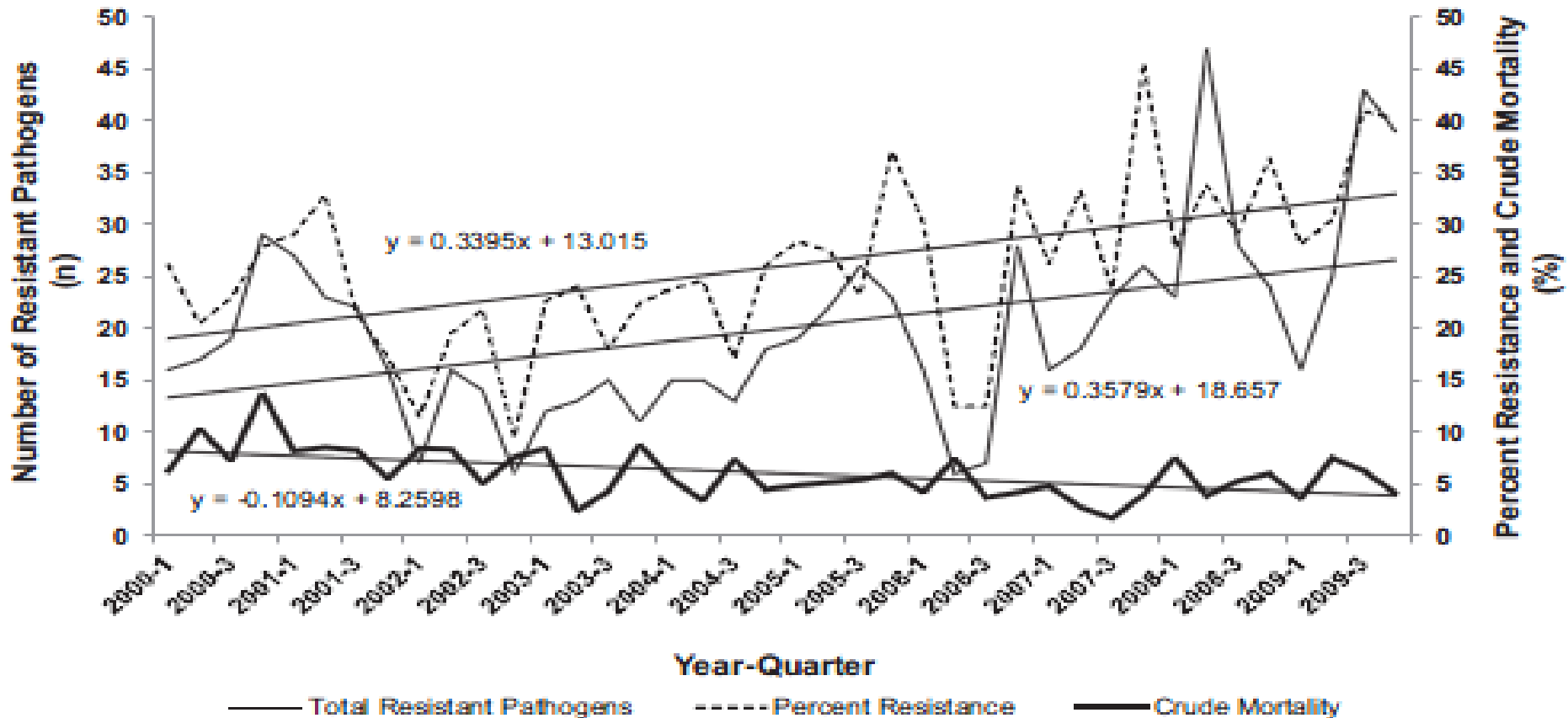


Figure 4. ICU resistant pathogens, percent resistance, and crude mortality.

M1-Driven Non-inferiority Trials

- Active-controlled trial in subjects with susceptible pathogens to indirectly show superiority to placebo.

- Challenges:
 - Extrapolation from susceptible to resistant populations
 - Limited use: Possible for diseases treated empirically?
Otherwise, loss relative to active control is important.
 - Ethics?



Patients with susceptible pathogens ≠ Patients with resistant pathogens²

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



Accelerated Approval

- Challenges:
 - No need/utility for a clinical marker with acute diseases
 - Preclinical data reasonably likely to predict benefit?
 - Ability to obtain confirmatory trials?



References

1. Infectious Diseases Society of America. 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, *Clinical Infectious Diseases*, 2012;55(8):1031-46.
2. Rosenberger LH et al. Infections caused by multidrug resistant organisms are not associated with overall, all-cause mortality in the surgical intensive care unit: the 20,000 foot view. *Journal of the American College of Surgeons*, 2012;214(5):747-55.