Superiority and Organism-Specific Clinical Trials of Anitbacterial Agents

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On behalf of the

Infectious Diseases Society of America

Disclosures

- In the last 12 months, Dr. Boucher has served as a consultant/advisor to:
  - Basilea, Durata, Merck (adjudication committee), Paratek, and Rib-X

IDSA Advocacy: 2003 – Today

BAD BUGS, NEED DRUGS
The 10 X '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020

http://www.idsociety.org/10x20

IDSA

The Stakes Are High
www.AntibioticsNow.org

Rebecca Lohsen
(17 yr)--Dead

Mariana Bridi da Costa
(22 yr)--Dead

Bryce Smith (14 mo)—survived, $1 million hospital bill

Tom Dukes—8” of colon resected, colostomy

Carlos Don
(12 yr)--Dead

Ricky Lannetti
(21 yr)--Dead

IDSA
Meeting Regulatory Challenges - Guidance

- Predictable, feasible guidance needed on
  - Standard antibiotic indications – often the initial development pathway
    - FNIH process
    - Feasibility key – consider the "costs" of various options (e.g., inclusion criteria that limit enrollment)
  - Pathways for new Gram-negative antibiotics (e.g., urinary tract, intra-abdominal infections, and pneumonia)
    - For newly-emerging resistant pathogens these studies can't easily be done
    - Tiered approach (efpia) and LPAD

Meeting Regulatory Challenges Guidances – Speed is Key!

To address the "unmet need" gap, IDSA proposed several program designs that could allow approval of new drugs for resistant Gram-negative infections

- Small, well conducted studies, to enable conditional approval for drugs of critical public health need while placing limitations on the use/promotion of such drugs until follow-up studies are completed
- Superiority pathways
  - less feasible as new drugs emerge
- Bacteria- or "organism-specific" rather than disease-specific approval
- Pathway must permit development of multiple drugs over time

White Paper: Recommendations on Conduct of Superiority and Organism-Specific Clinical Trials

- Recognized need for means to overcome ethical and practical barriers to studying drugs for infections caused by drug-resistant pathogens
  - Parenteral drugs for MDR pneumonia, BSI
  - Oral drugs for UTI/pyelonephritis

Spellberg et al. CID 2012

Study Design Options

- Heirarchical Noninferiority-superiority Clinical Trials
- Monotherapy Superiority Clinical Trials
  - Less severe infection with possible rescue therapy
    - e.g. Uncomplicated UTI
  - Trials of extreme drug-resistant and pan-drug resistant infections
    - No effective comparator
  - Safety endpoints
    - Study of new, potentially less toxic agent

Spellberg et al. CID 2012

Study Design Options (continued)

- Nested superiority-NI trial design
- Combination therapy or “add on” trial design
  e.g., salvage HIV
- Historical control superiority studies
  - Data less robust
  - Explicitly discussed in ICH E10
    - “well documented population”
    - Limit to “situations in which the effect of treatment is dramatic and the usual course of disease highly predictable.. Objective endpoints”
  - May fit many MDR/XDR infections!

Spellberg et al. CID 2012

Challenges in Superiority Studies of Infections Caused by Drug-Resistant Bacteria

Challenges:

- **Diagnosis**
  - **Need for molecular diagnostics is GREAT!**
- **Need for rescue therapy**
- **Site selection**
  - **Need high prevalence of resistant pathogens AND clinical trials expertise**
    - **Hope: increased networks/NIH resistance group**
- **Empirical vs targeted enrollment**
  - **Empirical enrollment – risk: bias**
  - **Targeted enrollment – risk: effect of prestudy abx**

Spellberg et al. CID 2012

Meeting Challenges in Superiority Studies of Infections Caused by Drug-Resistant Bacteria

- Bias in historical control studies
  - Pharmacometric approaches to defining historical control response rates
- Informed consent in critically ill patients
  - Emergency exception
- Patient identification to ensure enrollment
  - Strategies to mitigate:
    - Organism specific enrollment – i.e., allow inclusion of infections at multiple sites caused by the resistant pathogen
    - Smaller development programs
    - Alternative statistical methods (Bayesian design)

Spellberg et al. CID 2012

Organism Specific Superiority Clinical Trials

- Established precedent – invasive fungal infections

- Key design issues:
  - Justify types of diseases to enroll
  - Drug should be known to penetrate relevant tissues
  - Pk in relevant populations should be understood
  - Drug activity in relevant tissues

Spellberg et al. CID 2012

Superiority Clinical Trials Design Considerations

- Endpoints
  - Clinically relevant, objective
  - Should reflect how patient “feels, functions or survives”
  - In life-threatening disease, composite to include mortality
  - Historical control – mortality likely primary
- Sample size
  - Flexibility key
  - One phase 3 trial may suffice in certain circumstances
    - Depends on trial design, conduct, objective endpoints, robust results
    - Postmarketing studies likely required

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Superiority Clinical Trials Design Considerations

- Comparator drugs
  - For MDR/XDR not necessary (and may be unethical) to limit comparators to FDA/EMA-approved drugs
    - Should be driven by the protocol and not left to individual site investigators
  - Goal: select agents with highest probability of demonstrating activity

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Limited Population Antibacterial Drug (LPAD) Mechanism

At least 15 drug companies as well as multiple medical societies (including AMA) and health orgs now support LPAD

http://www.idsociety.org/2012_LPAD_Proposal_Backing/

Limited Population Antibacterial Approval Pathway

- IDSA proposed this new regulatory pathway to enable conduct of smaller trials for XDR/PDR pathogens
- President's Council of Advisors on Science and Technology (PCAST) called for the establishment of a new pathway for initial approval of drugs shown to be safe and effective in a specific subgroup of patients
  - Specifically discusses a Special Medical Use pathway, using obesity and antibiotics to treat multidrug resistant infections as examples
  - This proposal aligns with IDSA's proposal for a **Limited Population Antibacterial Drug (LPAD)** approval pathway at the Food and Drug Administration (FDA)

Spellberg et al. CID 2012

Limited Population Antibacterial Drug (LPAD) Mechanism

- LPAD drugs would be studied in substantially smaller, more rapid, and less expensive trials
  - For some antibiotics to treat severe infections caused by the most resistant bacteria, pivotal trial size may be as small as 30 - 100 patients
- Narrow indications
  - LPAD drugs narrowly indicated for a small, specific population of patients for whom the drug benefits outweigh risks
- For patients with serious infections and inadequate current treatments, a greater degree of uncertainty about overall risk associated with a drug can be tolerated
- The drug would not be appropriate for use against non-serious or non-resistant infections

Spellberg et al. CID 2012

Thank You!

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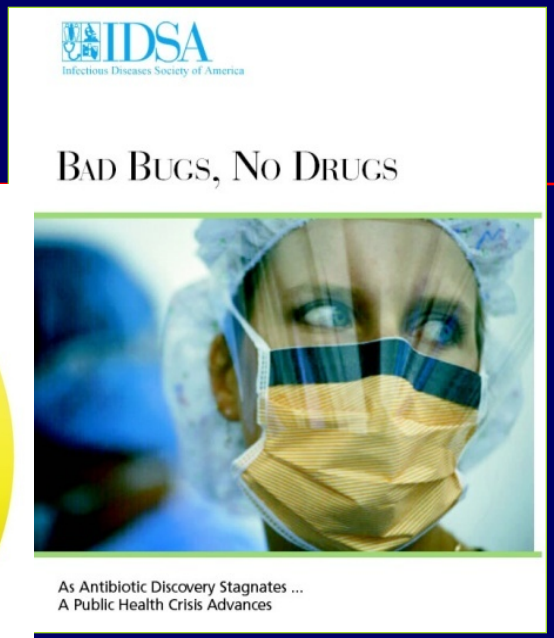

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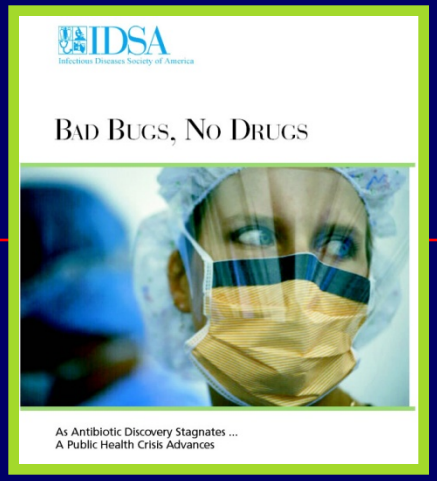
The 10 X '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020

IDSA

Additional Related IDSA Policy Reports/Continued Advocacy



Additional Reports:

- **"The Epidemic of Antimicrobial Resistant Infections: A Call to Action to the Medical Community", Spellberg et al, *CID* Jan. 2008**
- **"Bad Bugs, No Drugs; No ESKAPE"; IDSA's latest update on the antibiotic drug pipeline; Boucher et al, *CID*, January 1, 2009**
- **Numerous position papers focused on FDA clinical trial designs (CAP; cSSSI; HAP/VAP, superiority for MDR organisms)**
- **The 10 x '20 Initiative, Global Commitment, April 15, 2010**
- **Combating Antimicrobial Resistance: Policy Recommendations to Save Lives, Spellberg, Guidos et al, *CID* supp., May 2011**