Facilitating Antibacterial Drug Development for Patients with Unmet Needs and Developing Drugs that Target a Single Species: Perspective from Academia

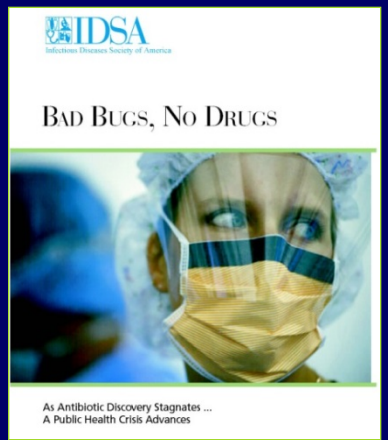
Helen W. Boucher MD FACP FIDSA

Tufts Medical Center

Tufts University School of Medicine

10x'20

Tufts Medical Center



Disclosures

- Consultant/advisor to:
  - Merck
  - Innovative Medicines Initiative of the European Medicines Agency
- Adjudication Committee – NIH
- Data Monitoring Committee
  - Actelion
  - Cardeas
- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy

Pathogen Specific Studies Perspective From Academia

We want in a perfect world:

- Scientifically justified, statistically rigorous
- Impact clinical practice
- Measure how our patients
  - feel, function, survive

What we can work with when perfection not possible:

- Good preclinical PK/PD and animal studies
- Understand needed exposure and how to dose
- Even small amount of clinical efficacy data
- Reasonable safety database
- All of which enables use of new agents in patients with limited options

Have We Returned to the Pre-antibiotic Era? Recent Case

71 year old lady with laryngeal cancer post larengectomy, chemotherapy and radiation in 2012, COPD on home oxygen, and recent admission for tracheobronchitis now transferred from rehabilitation with fever, flank pain and respiratory failure

- **Cured of cancer**

Have We Returned to the Pre-antibiotic Era? Recent Case

History:

- **12/2015 Cough, sputum production with acute on chronic respiratory failure**
- **She had no fever, chills or other constitutional symptoms**
- **Evaluation for viruses, other infections negative**
- **Blood and sputum cultures grew GNR ultimately identified as MDR *K. pneumoniae,* + metallo-carbapenemase**
- **Did well, cleared blood cultures, did not need re-intubation**
- **Treated for 2 weeks with**
  - **IV tigecycline**
  - **IV colistin**
  - **inhaled colistin**
- **January, 2016 switched from colistin IV/inhaled to IV minocycline**

Have We Returned to the Pre-antibiotic Era? Recent Case

Admitted with pneumonia again in late January and in May

She presented with respiratory failure and tracheobronchitis along with a urinary tract infection

- **Discharged on a 5 day course of levofloxacin**
- **Sputum and urine cultures subsequently grew a carbapenemase-producing *Klebsiella pneumoniae***
- **4 days later, she was found to have an increased oxygen requirement**
- **ER: reports feeling very tired, still has urinary symptoms (dark, foul-smelling, with right flank pain), T 38.5C, increased oxygen requirements**
- **Urine culture >=100,000 CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, MDR organism**

Have We Returned to the Pre-antibiotic Era? Recent Case

Culture Urine >=100,000 CFU/mL *Klebsiella pneumoniae*,
+ Carbapenem resistance, multidrug resistant (MDR) organism
<u>Resistant to:</u>

- **Ampicillin**
- **Ampicillin/sulbactam**
- **Piperacillin/tazobactam**
- **Cefazolin**
- **Cefoxitin**
- **Ceftazidime**
- **Ceftriaxone**
- **Cefepime**
- **Meropenem**
- **Amikacin**
- **Gentamicin**
- **Tobramycin**
- **Ciprofloxacin**
- **Nitrofurantoin**
- **Trimethoprim/Sulfa**
- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**

Have We Returned to the Pre-antibiotic Era? Recent Case (continued)

After discussion about limited options, predictable renal, neurological and other toxicity, patient and her family decided on hospice care

Summary:

- **Cured of cancer**
- **Dying of resistant infection**

Emerging Infections Network July, 2015

- 19 year-old renal transplant recipient with repeatedly positive blood cultures with an MDR *Stenotrophomonas maltophilia* despite source control (line removal)
  - steroid dependent for adrenal insufficiency
  - *S. maltophilia* organism highly resistant to all antibiotics except perhaps colistin, which we are using for treatment
- Does anyone do in-vitro combination testing, and is there any value in such testing if the MICs for single drugs are greater than the upper limits of the MIC test?
- The only drug not tested in-vitro is chloramphenicol, which we are not currently able to obtain at our hospital for patient use
- Does anyone have experience testing for/using chloramphenicol in this scenario?
- Other treatment suggestions?

Case

47 year old female school teacher presents with pain upon urination, lower abdominal pain

- Started on standard oral therapy - ciprofloxacin

Two days later she comes back and appears ill with new chills, nausea and back pain

- High fever, exam notable for new right flank tenderness
- Urine shows signs of infection
- Labs: elevated white blood cells with left shift

Therapy advanced to guideline therapy for pyelonephritis; she looked well enough to go home

- One dose IV ceftriaxone, then oral TMP/SMX

http://cid.oxfordjournals.org/content/52/5/e103.full.pdf+html

Case continued…
Two days later

Substantially worse, acutely ill, high fever, low BP, requires hospitalization for intravenous hydration as unable to eat or drink; 2 episodes of vomiting

- **Exam – T 38.7, BP 90/60, elevated HR, ill appearing, mild distress due to pain; worsening right flank tenderness**
- **Despite antibiotic therapy, urine culture grows > 100,000/mL *K. pneumoniae***
- ***K. pneumoniae* identified as ESBL+**
  - **Resistant to ciprofloxacin, ceftriaxone, TMP/SMX**

- **Admitted to hospital and treated with imi/meropenem**
  - **Drugs of choice for ESBLs**

Lessons from these cases

- Infections caused by resistant pathogens are serious
  - This could happen to you or your children

- The data we have is often less than what we would want
  - Data on patients with infections at standard body sites (e.g., UTI) are the foundation from which we build
  - But, clinicians have to extrapolate everyday to treat infections … patients do not always present with textbook infections!
  - We work everyday with data from a variety of sources and variety of observations

Clinical Trials for Single Species Catch-22?

- How do we develop X-1 before infections caused by resistant *P. aeruginosa* become prevalent enough to allow conduct of a focused clinical trial for specific indications?
  - We never want to see so many cases of MDR *P. aeruginosa* infection that conduct of a standard phase 3 trial is possible
- Tension between desire for a volume of quality data and the challenges in generating these data
- Can we interpret murky data?
  - Studies likely to include small #s of patients with MDR pathogens
  - Limited inferential testing/results

What is the best path forward for X-1?

- All include adequate, well controlled studies
- Continuum of datasets provided from standard RCT with statistical testing to smaller datasets based on externally controlled or even uncontrolled data
  - Well controlled RCTs focusing on a single indication provide meaningful effectiveness data
  - Externally controlled (even external historical controls), especially in the most severe infections with high, predictable mortality
  - All + good preclinical PK, PK/PD and adequate safety data
  - All benefit from
    - Sites with clinical trials expertise
      - Goal: clinical trials networks
    - Diagnostics – help enroll patients with disease
- Clinicians prepared to use drugs developed based on any of these approaches

Caliendo et al. CID 2013;57(S3):S139–70; McDonnell et al. CID 2016, *in press*

Randomized, Active Control NI studies, Standard Indications (cIAI, HABP/VABP, cUTI) – Tier B

- Strengths
  - Inferential testing possible
  - Patients included with proven infection
  - PK at a key site of infection
  - Population studied can be well characterized
  - Safety data
- Challenges
  - Enrollment – large # of patients
    - Time, $
    - Empirical vs. targeted enrollment
  - Small #s of patients, especially with pathogen of interest
  - Comparator choice (efficacy, harmonization)
  - NI margins may be wide

Small Studies of X-1 for *P. aeruginosa* Infection at Multiple Body Sites - Tier C

- Design
  - Randomized vs. best available therapy? external controls?
    - Superiority testing
  - Non-randomized?
  - Include most seriously ill patients with highest mortality
  - Rigorous diagnosis (strict definitions, severity of illness scores, etc.)
- Strengths
  - Patients included have proven infection
  - Treatment course, outcome carefully described
    - PK at key sites (blood, bone, brain), safety data
  - Perhaps less resource intensive
- Challenges
  - Lack of randomization, statistical rigor
  - Assuring adherence to strict diagnostic criteria
    - Potential role for adjudication committee
  - Need for additional safety (and other?) data

Clinical Trials for Single Species Tier B or C

- Challenges:
  - Small numbers of patients with pathogen of interest treated with X-1
    - Smaller dataset
  - Resource intensity – time, $
  - Limited statistical power/support
  - Other factors may impact outcome (e.g., critical illness, surgery)

- Risks with either approach (and with status quo)!

Pathogen-Specific Studies Academic Perspective (revisited)

In a perfect world? Perfection, of course

What we can work with when perfection not possible:

- **Well conducted preclinical PK/PD & animal studies**
- **Understanding of needed exposure and how to dose**
- **Even small amount of clinical efficacy data**
- **Reasonable safety database**

So, what does this mean for X-1?

If X-1 Approved, The Minimum Data Clinicians Need to Be Able to Use It

Primary label

- **Data from a well-controlled study**
- **Pharmacology and dosing, including PK data**
  - **At as many body sites as possible**
  - **In patients with organ dysfunction, critical illness**
  - **Age, gender, and drug-drug interaction studies**

Secondary data that is easy to find (appendix to label?)

- **Less controlled or even uncontrolled data**
- **Anecdotes in patients with really severe syndromes**
- **Diversity in data would help inform practice**

New Antibiotics: The PATH Forward

- **Bipartisan PATH Act, S. 185, would make these programs feasible by establishing a new Limited Population Antibacterial Drug FDA approval pathway (Similar legislation already approved by the House with overwhelming bipartisan support)**
  - **LPAD applicable to limited population most at risk**
  - **Creates options for development pathways where only limited data are possible**
- **Many safeguards (in PATH and other policy initiatives) to ensure these drugs are safe and effective and used appropriately**
  - **Clear, prominent limited population labeling**
  - **FDA pre-review of promotional material**
  - **Monitoring of drug use**

Stewardship Protects the Effectiveness of Antibiotics and Improves Patient Care

- Antibiotic stewardship programs in every hospital/LTC facility as a condition of Medicare/Medicaid participation
- Enhanced antibiotic use and resistance data collection to help us better assess scope of the problem and evaluate interventions
- Improved surveillance to rapidly identify and respond to emerging threats
- Better infection prevention practices
- Increased research on the optimal ways to use current antibiotics to improve patient care and protect the drugs' utility

Final Thoughts

- Have We Returned to the Pre-antibiotic Era?
  - Maybe…
  - Current cases highlight need for IV and oral agents
  - *mcr*-1 – transmissible (plasmid) colistin resistance
  - We should be scared
- Forced to use drugs with extremely limited/negative data – e.g.,
  - Inhaled/parenteral colistin
  - Fosfomycin for ESBL infections
  - Tigecycline for MDR infections (despite warning re: death)
- Infection prevention, stewardship, surveillance of paramount importance

McGann P, Snesrud E, Maybank R , et al. Antimicrob. Agents Chemother 2016

Final Thoughts
Pathogen Focused Indications for X-1

- Adequate, well controlled data can emerge from either small RCTs with wide NI margins or really small (Tier C) studies with external controls
  - Must ensure strong case definitions and (if possible) include more severe infections
  - Data quality key
  - Trial networks
- Including multiple body sites and infection types provides useful data for clinicians
- LPAD mechanism ensures use in limited population with needed safeguards
- ID physician led stewardship ensures expert management of all patients in whom these medicines are used

McGann P, Snesrud E, Maybank R , et al. Antimicrob. Agents Chemother 2016

Thank You!

- S. Nambiar
- M. Cavaleri
- E. Cox
- A. Jezek
- J. Rex
- J. Tomayko