

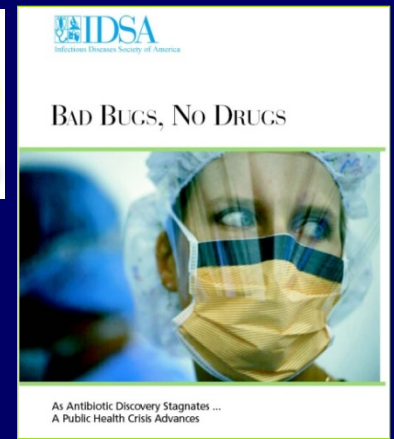


# Current State and Further Development of Animal Models of Serious Infections Caused by *A. baumannii* and *P. aeruginosa*: A Clinician's Perspective

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# Disclosures

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- **Adjudication Committee – NIH**
- **Data Monitoring Committee**
  - **Actelion**
- **Editor**
  - **ID Clinics of North America**
  - **Antimicrobial Agents and Chemotherapy**
- **Treasurer, Infectious Diseases Society of America**
- **Member, ID Board and ID Test Writing Committee, American Board of Internal Medicine**
- **Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)**

# Have we returned to the pre-antibiotic era?

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Maybe so...

- **mcr-1/mcr-2**
  - Transmissible (plasmid) colistin resistance
  - Already associated with KPC; true MDR/XDR possible
- 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
  - Progress is being made through CARB

McGann, et al. Antimicrob. Agents Chemother 2016; DiPlato et al. Antimicrob. Agents Chemother 2016



# ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

## Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

## Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum  $\beta$ -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

## Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

# 2017 WHO Priority List of Bacteria For Which New Antibiotics are Urgently Needed

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Three categories according to urgent need for new antibiotics:

## Critical priority

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

## High priority

- *Enterococcus faecium*, VRE
- *Staphylococcus aureus*, MRSA, VISA/VRSA
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

## Medium priority

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

# Status of IDSA 10 x '20 Initiative



Progress, but unmet needs remain, all of these drugs have gaps, and we remain at high risk

# Clinical Impact of Antibiotic Resistant Infection

## Recent Case

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71 year old lady with laryngeal cancer post laryngectomy, 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

# Recent Case

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## 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



# Recent Case

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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  $\geq 100,000$  CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, MDR organism

# Recent Case

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Culture Urine  $\geq 100,000$  CFU/mL *Klebsiella pneumoniae*,  
+ Carbapenem resistance, multidrug resistant (MDR) organism

## Resistant to:

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

# Recent Case (continued)

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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

## Case 2

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**46 year old man with endstage cardiomyopathy,  
diabetes, obesity**

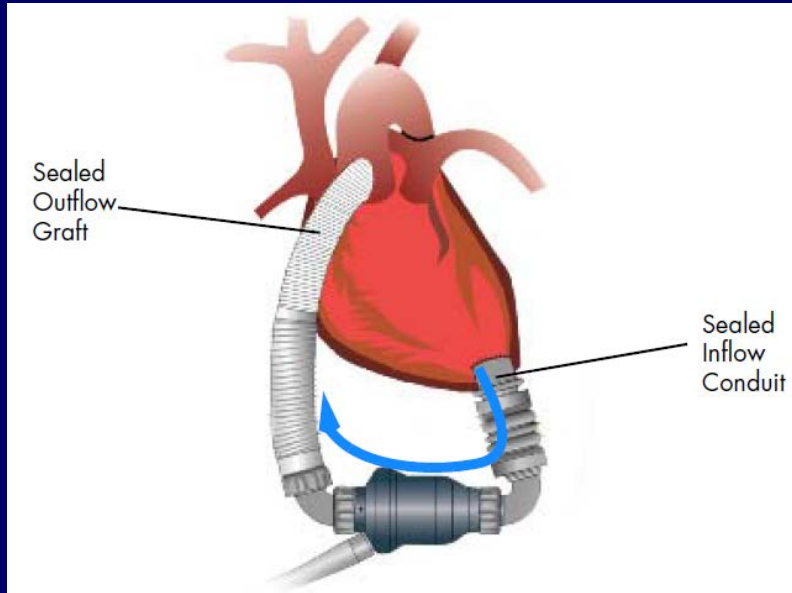
- **Cardiogenic shock**
- **HM II LVAD heart pump placed**
- **Works full time**
- **Married, 2 young sons**

## Few months after VAD placement

- irritation followed by local infection
  - oral antibiotics for *Corynebacterium* spp.
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- One month later – new brown foul smelling discharge
  - Cx + *E. aerogenes*, *H. paraflu*
- Managed with wound care and oral antibiotics

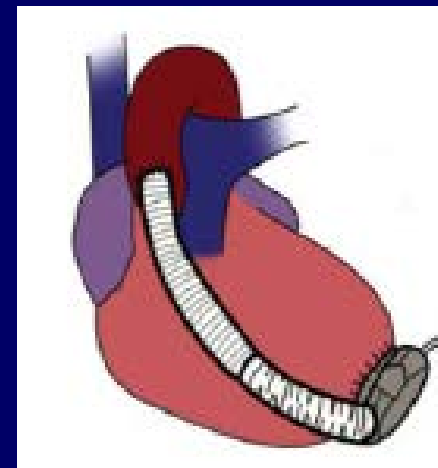


# Continuous Flow Rotary Pump Left Ventricular Assist Device (LVAD)



**HeartMate II (Thoratec)**

**Pump resides in pre-peritoneal or  
intraabdominal space**



**HeartWare**

**Pump resides in the  
pericardial space**

# **Case (continued)**

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- **Nearly 2 years later – VAD thrombosis/device malfunction**
- **HeartWare VAD exchange**
  - **Complicated post-op course**

**Three months later...**

- **Pain and drainage from LVAD driveline exit site**
- **Cultures + *S. aureus*, MSSA**
- **Admitted**
  - **empirical vancomycin and ertapenem started**
- **VAD wound culture + MSSA**
- **Therapy narrowed to cefazolin, then cephalexin**

# Case (continued)

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- Several further admissions with infection
- Last admission – presented with pain, increased drainage, abnormal imaging
- Admitted, IV ABX
- *P. aeruginosa* –
  - Resistant to ciprofloxacin, meropenem, susceptible to tobramycin, amikacin
  - Increased pain and drainage despite ongoing parenteral therapy
  - Not a candidate for aminoglycosides
  - Not a candidate for VAD exchange
  - Not a candidate for transplant
- Discharged to hospice



# Lessons from these cases

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- Infections caused by resistant pathogens are serious
  - This could happen to you or your children
- Having drugs targeting single pathogens will be useful to clinicians and patients
- 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 of Narrow-spectrum Drugs are Hard

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- Developing narrow-spectrum drugs is surprisingly hard outside of a few specific areas:
  - Tractable: *S. aureus* (cSSTI), GC (STD), *C. difficile*, and *P. aeruginosa* in CF
- But, a path is desperately needed for narrow-spectrum agents for other infections
  - Biggest gaps: *Pseudomonas*, *Acinetobacter* spp. Plausible candidates are emerging
- For these relatively uncommon but life-threatening organisms:
  - The needed patients are rare (and this is a good thing!)
  - Neither NI nor superiority approaches are routinely feasible
  - Diagnostics aren't a fix as they don't create the patients – they only help spot them
- 19 July 16 workshop underscored challenges and need for new options – more next with J. Rex et al.

# So, what do we do?

## *Ideas that have emerged*

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1. PK-PD-based dose selection and validation
2. **Validated animal models**
  - **Validation after the fashion of the Animal Rule**
3. Validated external controls
  - Paired with open-label data with the test agent
4. Very small clinical datasets
  - Perhaps also pooling data from multiple body sites

### **Possible development plans:**

- Fully validated Animal Rule animal models + ZERO clinical efficacy data (Tier D)
- Good animal models (? Multiple, exploring different things today) + SOME clinical efficacy data

# Animal Models as Basis for Development

## Clinical Considerations

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For development of drugs in which fully powered clinical trials are not feasible, consider major contribution from animal studies and potentially the Animal Rule

- Study infections with reasonable human correlates
- Optimize PKPD to understand and predict efficacy at a variety of body sites, e.g.,
  - Lungs
  - Bloodstream
  - Intra-abdominal infection

# Final Thoughts - Clinician's Perspective on Pathogen Focused Indications

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**Current status 2017 - forced to use drugs with extremely limited or negative data**

- **Inhaled/parenteral colistin**
- **Fosfomycin for ESBL infections**
- **Tigecycline for MDR infections despite warning re: death**

**Looking ahead:**

- **Traditional clinical development plans, NI or superiority studies may not be feasible**
  - **Small clinical studies**
    - **Data quality key**
    - **Safety data**
    - **Trial networks**
    - **Including multiple body sites and infection types provides useful data for clinicians**

# Final Thoughts - Clinician's Perspective on Pathogen Focused Indications

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- Animal studies, perhaps with use of the Animal Rule, in addition to robust PKPD studies can provide foundation for development
  - Fully validated Animal Rule studies + ZERO clinical efficacy data
  - Good animal models + SOME clinical efficacy data
- 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

## 2017 WHO Critical priority pathogens:

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
  - *P. aeruginosa* and *A. baumannii* have moved from serious to critical in last 3 years

# We Need to Act Now!

## Premature Death



**Rebecca Lohsen  
(17 yr)--Dead**



**Mariana Bridi da Costa  
(22 yr)--Dead**



**Carlos Don  
(12 yr)--Dead**



**Ricky Lannetti  
(21 yr)--Dead**

## Life-altering Disability



**Tom Dukes: colostomy, lost 8" colon**



**Addie Rereich, 11yo  
Double lung transplant  
Stroke, nearly blind  
\$6 million hospital bill**



# Thank You!

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- **K. Beaulac**
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- **A. Jezek**
- **S. Nambiar**
- **J. Rex**