Tufts Medical Center

Current Constraints in Antibacterial Drug Development: Clinician's Perspective

Helen Whamond Boucher MD FACP FIDSA

Chief, Division of Geographic Medicine and Infectious Diseases

Professor of Medicine

Tufts | CENTER FOR INTEGRATED MANAGEMENT OF ANTIMICROBIAL RESISTANCE

Disclosures

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
- Treasurer, Infectious Diseases Society of America
- Member, ID Board, American Board of Internal Medicine
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Case 1

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 1 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 38.7C, 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**

Case 2

- 60-year-old lady with leukemia s/p chemotherapy, in remission
- Developed fever, cough
- Chest x-ray showed pneumonia
- Labs showed pancytopenia
- The hematologists were optimistic about her prognosis
- Meropenem and vancomycin were started as empirical therapy

Blood culture results

Elizabethkingia meningoseptica

- ID consult recommended
- Multi-drug resistant organism

- Plazomicin result >=512 ug/mL NIS
- Piperacillin/tazobac >=128 R
- Ceftazidime >=64 R
- Ceftriaxone >=64 R
- Cefepime >=64 R
- Meropenem >=16 R
- Amikacin >=64 R
- Gentamicin >=16 R
- Tobramycin >=16 R
- Ciprofloxacin >=4 R
- Trimethoprim/Sulfa 80 R
- Ceftazidime/avibacta 32 NIS
- Ceftolozane/tazobact 32 NIS

NIS = no interpretive standards

Case 2 (continued)

- When I sat to deliver this news, my patient said, “how can this be?…surely you’ll find something to treat this”

- Ceftazidime-avibactam and aztreonam were added
- The organism was rushed to Dr. Bonomo’s lab for further testing
- Compassionate use cefiderocol was obtained under IND
  - Arrived 4 days later
- Antibiotic background was changed based on results of testing
  - Minocycline added
- She deteriorated, required ventilatory support, died 10 days later

Messages from these cases

- Crisis of AMR is here
- Resistant infections can affect you and me, threaten modern medical care, require urgent action
- Physicians make decisions with limited/no data
- 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

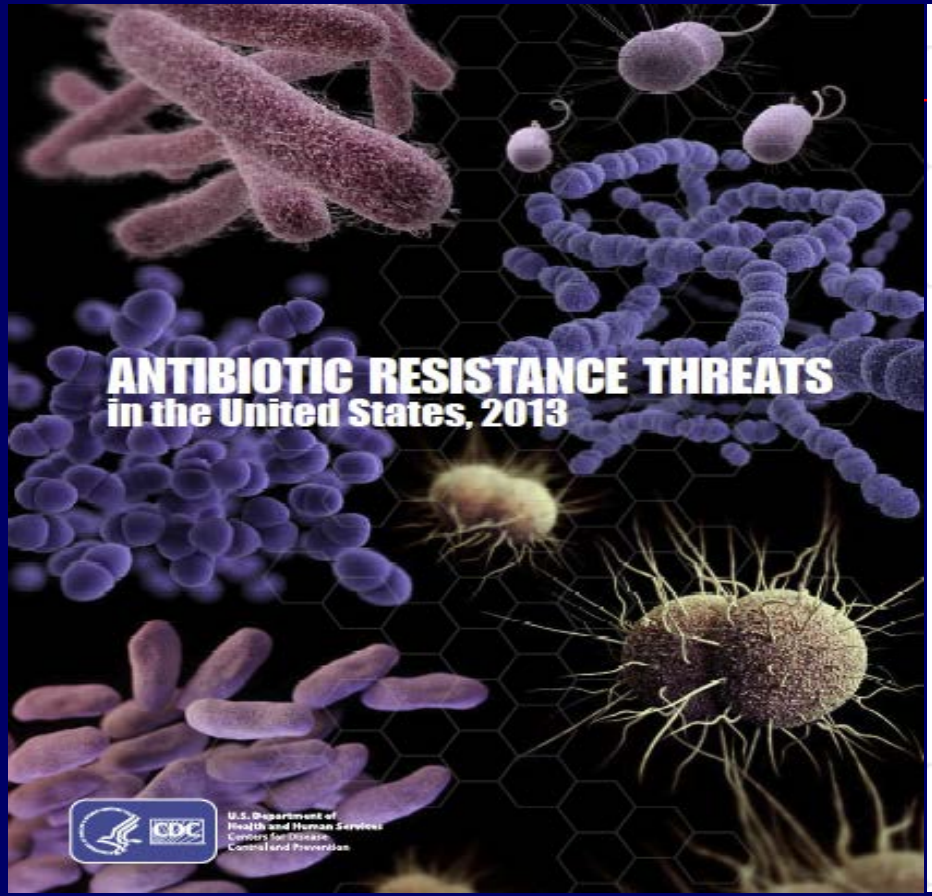
Clinician's Perspective

- ID physicians can and do work with incomplete data EVERY DAY
- We routinely extrapolate from available data
  - pK data
  - In vitro and surveillance studies
  - Different indications (some less serious), case reports
  - Pediatricians rarely have any clinical data
    - Extrapolate from adult and pK data

Antibiotics and Medical Progress

Ability to control infection is critical to other advances in medicine including:

- Neonatal care
- Transplantation
- Chemotherapy
- Immunosuppression
- Complex and routine surgery
  - Joint replacement
- Obstetric care
- Intensive care interventions



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 β-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*

CDC 2019 Threat Report

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

***C. auris* not in 2013 Threat Report**

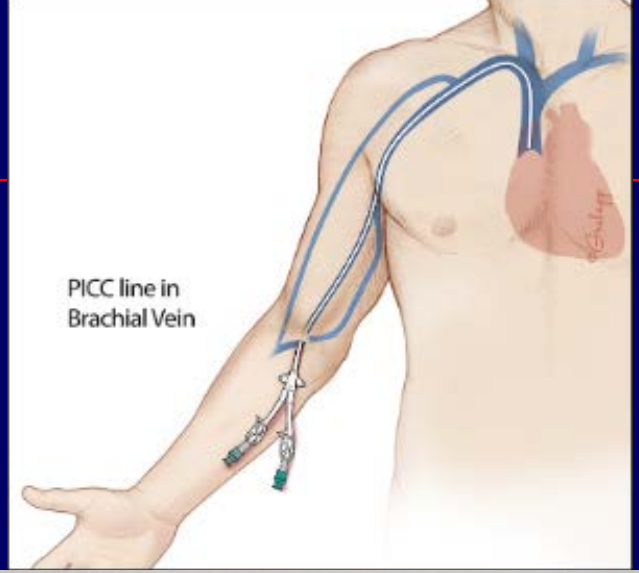
We need to prepare for threats we can predict and those that emerge

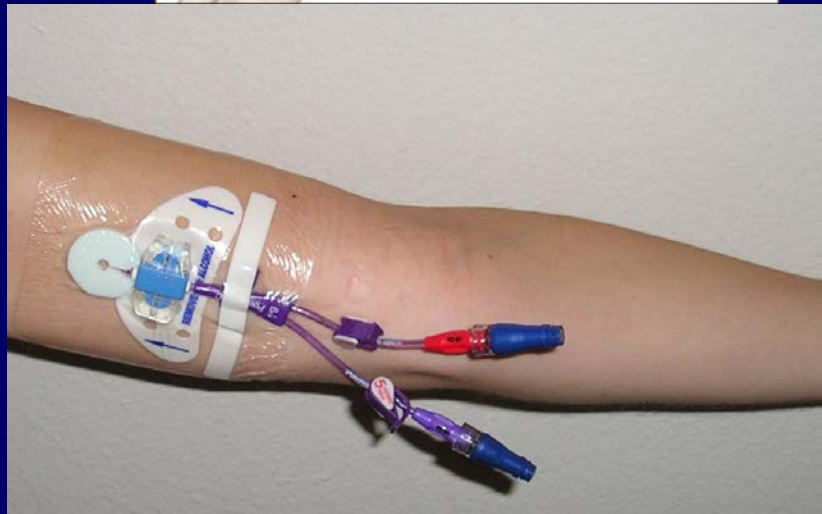
--- Robust, renewable pipeline of antibacterial drugs

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf;
GH Talbot, A Jezek, BE Murray, RN Jones, RH Ebright, GJ Nau, KA Rodvold, JG Newland, HW Boucher. Clin Infect Dis 2019

Why consider oral antibiotics?

- Less intravenous access complications
- Reduced frequency of hospital follow-up appointments
- Fewer restrictions in activities of daily living and return to work





US Patients

Ceftazidime-Avibactam
REPROVE Study Nosocomial Pneumonia

	Caz-avi N = 356	Mero N = 370	Tx Diff (95% CI)
	N (%)		
VABP	118 (33)	128 (35)	
No prior abx	122 (34)	117 (32)	
Cure MITT	245 (69)	270 (73)	-4.2 (-10.76, 2.46)
Mortality day 28	30 (8.4)	27 (7.3)	1.1 (-2.84, 5.18)
Mortality d 28 caz NS*	8.2%	8.5%	

- NO US patients (China 33%, Eastern Europe 26%), Prior abx <= 48 hrs
- 355 (44%) micro MITT pop – K. pneumo, *P. aeruginosa* most freq GNB
- 100 (28%) + ceftaz NS GNB
- Overall mortality LOWER than expected
- SAEs: 19% caz-avi (N=4 drug-related) vs 13% meropenem

Torres et al. Lancet ID 2017. *www.FDA.gov

AMR 2019 - Clinicians Need

- Diverse, novel, renewable pipeline of parenteral and oral antibacterial agents
- At least some efficacy and safety data
  - Data from US patients
  - Surveillance data to inform empirical therapy
- Susceptibility testing to guide therapy
- Data re: various sites of infection, populations/patient types
  - Skin, bloodstream infection, bone, urinary tract, lung
  - Old, young, obese, pregnant, organ dysfunction (liver, kidney, etc.)
  - pK data helps

AMR 2019 - Clinicians Need

- Availability of data in as close to real-time as is feasible
  - FDA labeling
    - Used by physicians, pharmacy committees, payors
    - CRE data should be in labels, even when imperfect, to make LPAD approvals work
    - Limitations can be clearly stated
  - Publications
    - Is it possible to publish pivotal trials faster, when data becomes public via FDA process?
  - Updating Guidelines takes up to 10 years
    - Can we expedite the process?
    - Should we consider Guidance as with Hepatitis C?

https://www.idsociety.org/practiceguidelines#/name_na_str/ASC/0/+/; https://www.hcvguidelines.org/

Clinician's Perspective

- ID physicians can and do work with incomplete data EVERY DAY
- We are unable to care for patients without new drugs
  - Can't insist on or wait for perfect data
  - Need every piece of information about new drugs, susceptibility testing, good stewardship, to optimally use and preserve new drugs

Thank You!

- Sara Cosgrove
- Vance Fowler
- Amanda Jezek
- Sumathi Nambiar
- John H. Rex
- George H. Talbot

- Our patients and their families