What do you mean you can't give me a result?

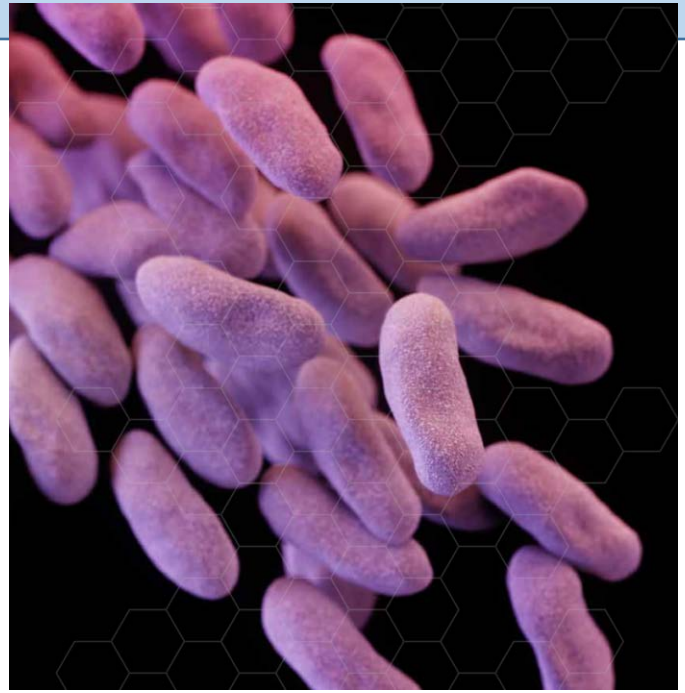
AST challenges from the clinicians perspective

Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices Workshop

September 29th, 2016

Amy Mathers, MD

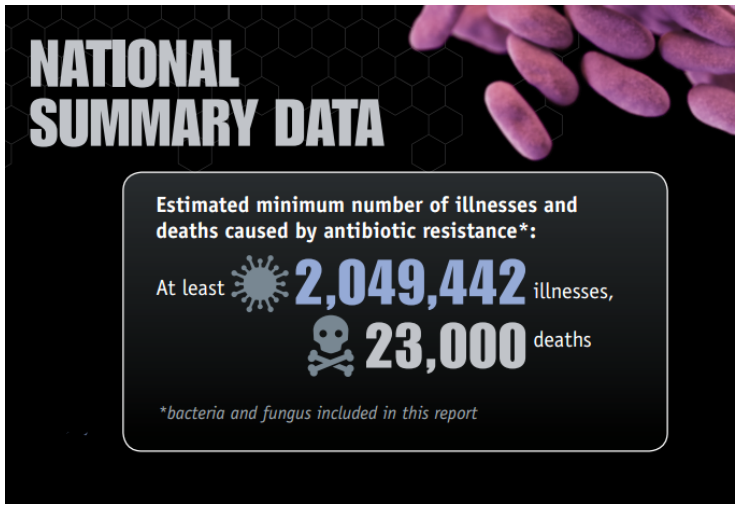
University of Virginia



Declarations

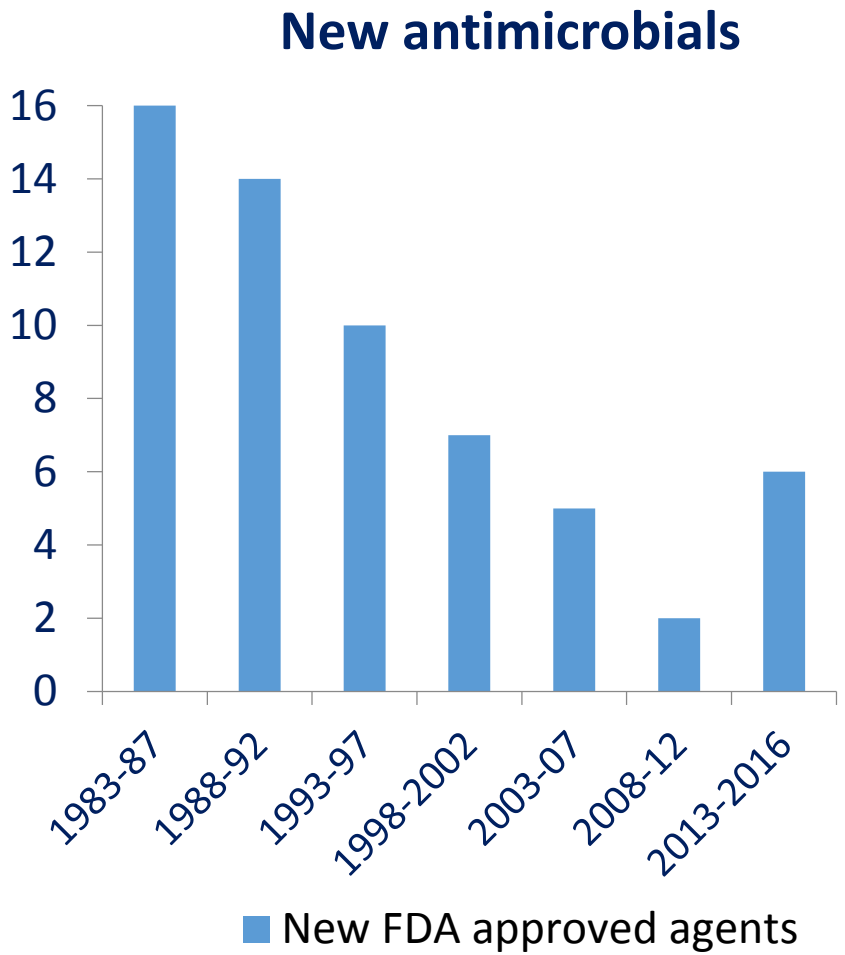
- I have acted as a paid consultant to the Medicines Company (formerly Rempex) and Accelerate Diagnostics

- I have past and ongoing paid clinical research in the form of a clinical trail site with the Medicines Company



Fischbach, *et al.* Science (2009)325:1089-93
Clin Infect Dis 2004;38:1279-86
www.idsociety.org
CDC 2013 Antibiotic Threat Report

We are seeing new agents available for use but…



Adapted from Deak D et al. *Ann Intern Med.* 2016;165(5):363-372.

Some of the most urgent challenges around susceptibility relate to new antimicrobials

- Focus of my slides on new Gram negative agents where susceptibility has not been available as an example of the issue
- There appears to be more antidotal resistance to new agents than originally thought which makes empiric use difficult
- Urgency felt when susceptibility gets delayed
- Gap in understanding of the clinicians about the challenges—is getting some potentially incorrect data better than no data?

Example Case

Patient in early 20's with cystic fibrosis admitted with respiratory failure and septic shock and most recent sputum shown

- Initially placed on intravenous colistin, meropenem and tobramycin
- Developed neurologic toxicity attributed to colistin as evidenced by weakness, paresthesia and myoclonic jerks
- Stopped intravenous colistin and meropenem, then started intravenous ceftolozane/tazobactam, ciprofloxacin and continued tobramycin without any susceptibility data as the reference lab will not assess bacteria from non-urinary or non-abdominal specimens

Patient not improving what should I do?

Pseudomonas aeruginosa mucoid

Tested	Interpretation
AZTREONAM	RESISTANT
CIPROFLOXACIN	INTERMEDIATE
GENTAMICIN	RESISTANT
PIPERACILLIN/TAZO	RESISTANT
AMIKACIN	INTERMEDIATE
CEFEPIME	RESISTANT
IMIPENEM	RESISTANT
MEROPENEM	RESISTANT
TOBRAMYCIN	SUSCEPTIBLE
COLISTIN*	SUSCEPTIBLE

*Disk Diffusion

Weighing the risk benefit while trying to treat patients

In favor of use of a new agent

- Apparent decreased toxicity
- There is biological, *in vitro* and mouse data demonstrating that it might be superior to comparators
- Anything must be better than an aminoglycoside, colistin and/or an antibiotic with *in vitro* resistance

Against use of a new agent

- Little data for the current infection
- With older agents there is a much better sense of use and failure
- PK/PD for certain infections and patients may not be clear
- **No (timely) susceptibilities**

Disconnect between the way antibiotics are studied and used

- Physicians are largely trained to use an effective antimicrobial based on the *in vitro* susceptibility and not necessarily the source of infection

- Although the drug may not have been studied for an indication it is general practice to use antibiotics based on *in vitro* susceptibility, available literature, PK/PD, knowledge of tissue penetration

Example meropenem

- Package insert for meropenem only lists skin/soft tissue, intra-abdominal and meningitis as indications
- Use is widely accepted for complicated urinary tract and nosocomial pneumonia against susceptible bacteria from these sources
- Has been used in comparison trials for these infection sites

Merrem (meropenem) i.v package insert. NDA 50-706/S-022
http://www.accessdata.fda.gov/

Where do clinicians turn when susceptibility testing not available from the clinical microbiology lab

- Population resistance rates higher than 5-10% (or not available) challenging especially when individual pathogen already multi-drug resistant

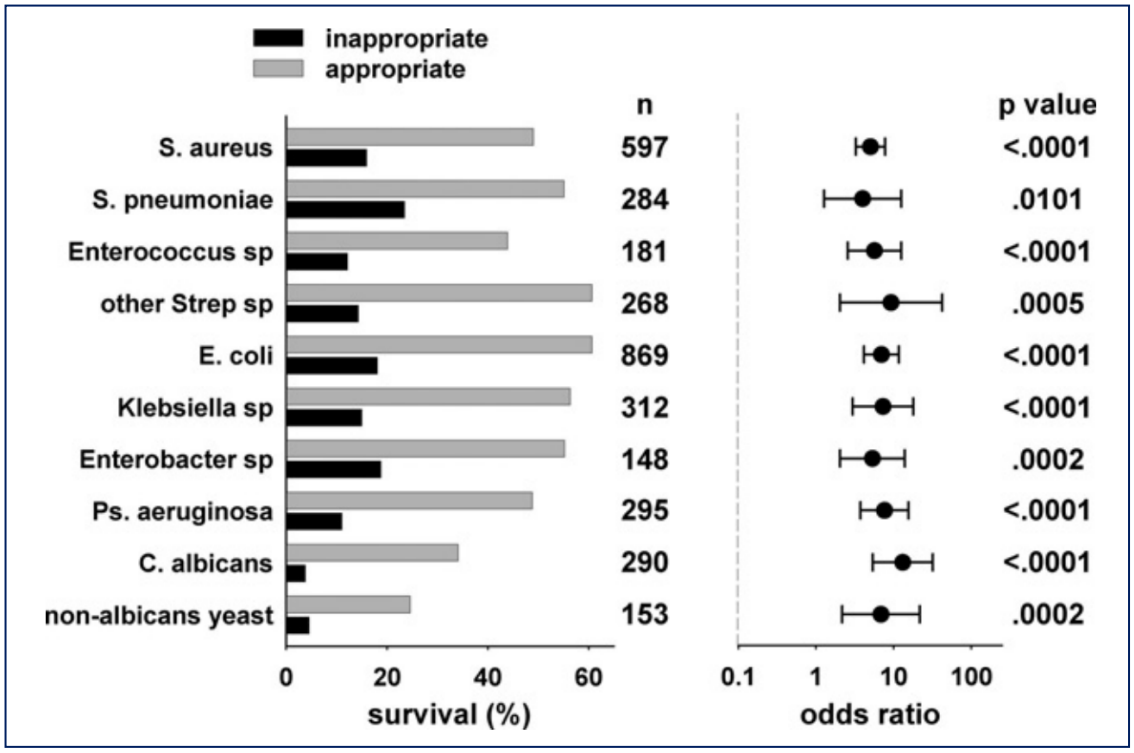
- Difficult to use an agent with very little clinical data or experience AND no susceptibility data over one where at least there is a generally known effect even if resistant

- Will resistance appear in my patient?
  - Recent retrospective review of 37 patients with carbapenem resistant Enterobacteriaceae infection found 3/10 microbiologic failure developed resistance to ceftazidime/avibactam on therapy

Shields RK *et al*. Clin Infect Dis. 2016 Sep 13. pii: ciw636. [Epub ahead of print]

In the setting of septic shock early administration of antimicrobials with *in vitro* activity changes patient outcomes

Odds Ratio of survival for culture proven infection in appropriate* versus inappropriate

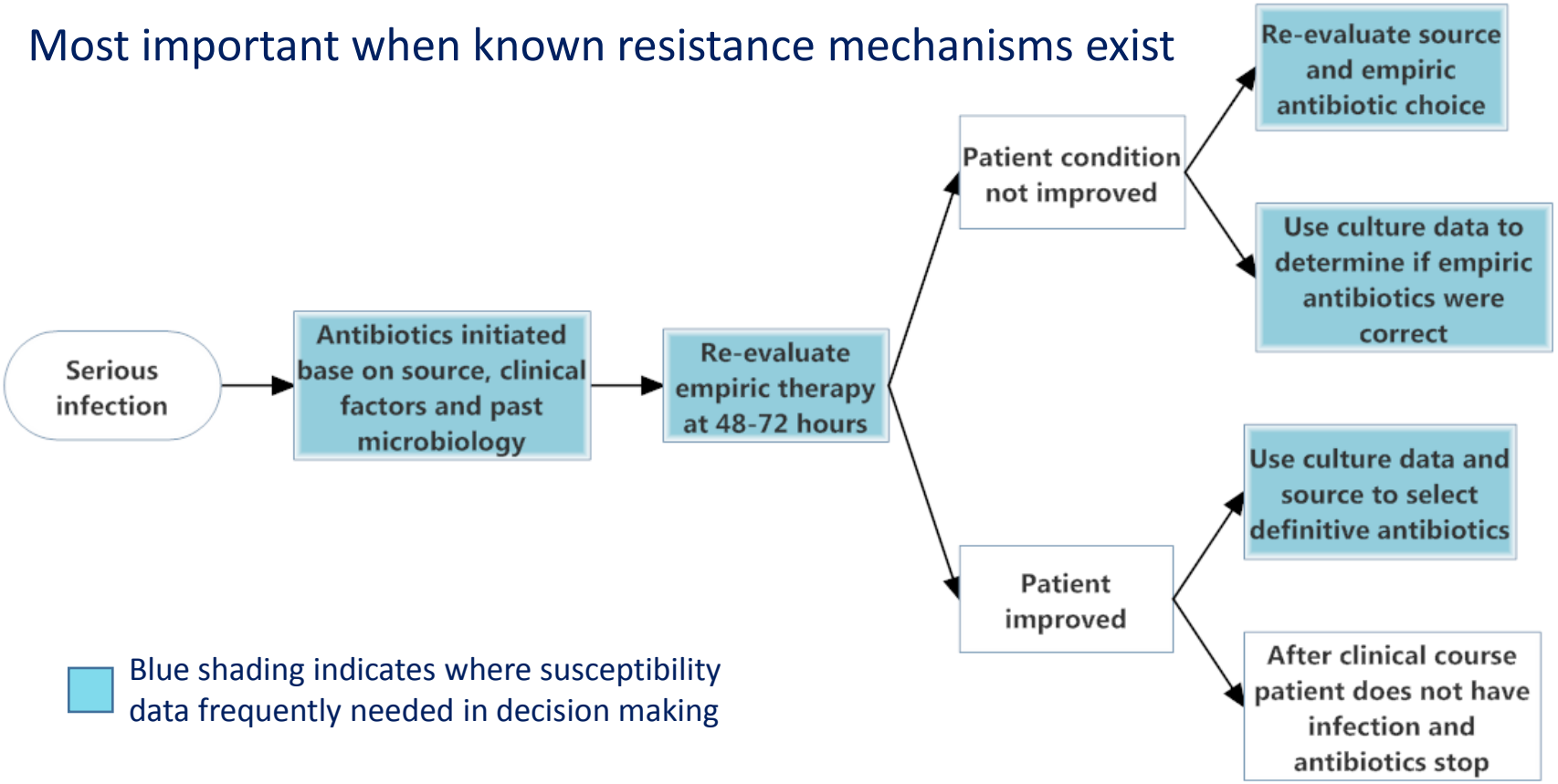


Kumar A *et al*. Chest. 2009;136(5):1237-48.

*Appropriate was an antibiotic initiated which had in vitro activity within 6 hours of onset of septic shock

Current clinical management of invasive bacterial infections is reliant on susceptibility testing

Most important when known resistance mechanisms exist



Blue shading indicates where susceptibility data frequently needed in decision making

Dellinger et al. IDSA Sepsis Guidelines. Crit Care Med 2012
Ferrer R et al Am J Respir Crit Care Med 2009; 180:861–866
Kumar A et al. Crit Care Med 2006; 34:1589– 1596

Clinical impact of not having AST to new agents from non-random query of physicians (6 of 8 responded)

Practice type	Patient care effects	Impact on use of new agent	Stewardship effects	Delay	Comments
University	Not using potentially effective agent when susceptibility not available or delayed	Seldom use rare to use empirically	Cannot change to appropriate agent until susceptibility returns	Yes 3-5 days	Difficult to explain to other clinicians issues of the availability of susceptibility testing
University	Adds to already difficult decision making with management of MDRO	Using widely	Getting susceptibility with E-strips on all available isolates to compare to other agents	No Use of in-house RUO	Have seen resistance at base line and then development of resistance after exposure [The situation is] "HORRIBLE!"
University	Can't really use new agents without susceptibility	Not using	More rapid diagnostics would help stewardship efforts	N/A	[Inability to get susceptibility testing].. "has become a critical management issue"
University	Have to use more toxic drugs until susceptibility comes back	Avoid empiric use until AST back	Yes but with additional TAT makes use difficult in practice	Yes~ 3-5 days	Very frustrated that the lab took away the E-test.
Community	"it may lead to overtreatment, or under treatment, or incorrect treatment"	We use but variably	Very difficult for antibiogram and detection of resistance*	Yes 3-5 days	Thankfully our MDR rate is relatively low
Community	Unfortunately susceptibility testing of little use in patient management because of TAT	Missed opportunities	Having testing would help promote judicious use of antibiotics	Yes 3-4 weeks	With such a delayed result makes it difficult to use the agent

*Relates to the inability to get revised CLSI breakpoints for resistance detection
Most responses referred to the impact of ceftazidime/avibactam and ceftolozane/tazobactam

Clinicians generally do not understand the nuisances of susceptibility testing

- Clinical microbiology/devices/FDA has done a good job providing reliable, accurate and relatively rapid susceptibility data
- Average clinician does not understand the differences between platforms and techniques or FDA cleared versus lab developed test
- Polled clinicians that I personally knew regarding use of non-validated E-tests and disks for new agents
  - n=3 of 6 who responded
  - All three reported that they or their colleagues felt the result was reliable and were using for clinical decision making
  - Two reported that the lab stopped performing because of misuse for clinical decision making (which resulted in frustration)

Impression of availability of AST to new agents from query of physicians (6 of 8 responded)

Practice type	Does the lab report non-valid RUO?	Can get send out results	Delay	Comments
University	Did and then stopped	1) Initially no (RUO only) 2) only for certain infections 3) now with delay	Yes-3-5 days	Very difficult to control the issue of the use and interpretation of RUO
University	Yes-widely but not into chart intentionally	N/A	No (~1 day)	Feeling that many clinicians using the information do not understand the limitations of non-validated RUO
University	No	No	N/A	where we are using a 'last resort' antibiotic ideally we would not be guessing that the drug *might* work-ideally we would know, and rapidly
University	Yes—but recently lab stopped and now sending out much to the everyone's frustration	Yes, but with additional TAT makes use difficult in practice	Yes~ 3-5 days	Feel RUO results pretty reliable and gets used in practice.
Community	No- A university lab will run an E-test and leave to us to interpret but we usually send out	Yes	3-7 days	Not having in the clinical lab is not a big issue because available as send-out (although there is a delay)
Community	No (but we are trying to get them to do so)	Initially could not get regional lab to do so	One month	Now can but turn around time ridiculously long unable to use result

Most responses referred to the impact of ceftazidime/avibactam and ceftolozane/tazobactam

Summary—We need timely AST for clinical use antimicrobials

- Management of serious bacterial infections with antibiotic resistant bacteria is challenging even when susceptibility is available
- Lack of susceptibility testing may result in varied practice between groups
- Time to susceptibility testing is critical to management
- There does not appear to be wide understanding from clinicians about the limitations of results by non-FDA cleared methods

Thank you for your attention and discussion of this important issue

ajm5b@virginia.edu