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Making Antibacterial Susceptibility Available in Clinical Practice

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Disclosures

- Employee: Mayo Clinic
- Grants: CD Diagnostics, BioFire, Check-Points, Curetis, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, Allergan, The Medicines Company, EnBiotix
- Consultant: Curetis (paid to Mayo Clinic), Specific Technologies
- Patents: *Bordetella pertussis/parapertussis* PCR issued, device/method for sonication with royalties (paid by Samsung to Mayo Clinic), anti-biofilm substance issued
- Data safety monitoring board: Actelion
- Travel reimbursement/editor's stipends: ASM & IDSA
- Honoraria: NBME, Up-to-Date, Infectious Diseases Board Review Course

Why Do We Need Susceptibility Testing (AST) Available in the Clinic?

Antimicrobial resistance (AMR)

- Patient safety
  - Patients infected with…
    - resistant organisms get treated appropriately
    - susceptible organisms don't get over-treated
- Infection prevention and control
  - Patients infected with resistant organisms appropriately isolated
- Public health
  - Avoid using overly broad spectrum treatment → resistance

➢ <u>Accurate & timely AST must be performed in clinical labs</u>

- Requires method(s) and breakpoints

Challenges in Making Susceptibility Testing (AST) Available in the Clinic

- This is new!
  - Evolving mechanisms of AMR & local epidemiology thereof
    - Changes in testing recommendations & breakpoints
    - MICs straddling breakpoints
    - Absence of up-to-date performance data on commercial AST (cAST) systems
  - Rare need off-label use cAST systems before ~2010
  - Delays in availability of FDA-cleared tests for new antimicrobial agents & existing agents with updated breakpoints
  - Limitation on use of FDA breakpoints with cAST systems (circa 2007)
- Divergent recommendations from different breakpoint-setting organizations

Humphries and Hindler. Clin Infect Dis 2016;63:83–8

AST Methods

- Commercial automated systems (bioMérieux Vitek2; Beckman Coulter MicroScan; BD Phoenix; Thermo Scientific Sensititre)
  - Streamlined workflow, objective results measurement, interpretive software
- Gradient strips (Etest, Liofilchem MIC Test Strips)
- Disk diffusion (Kirby Bauer)
- Broth microdilution
- Agar dilution
- Molecular susceptibility testing (commercial, laboratory-developed)

Challenges Associated With Use of cAST Systems (United States)

Challenge	Examples	Impact
Updated breakpoints unavailable on cAST devices	*Enterobacteriaceae* and carbapenems, cephalosporins	• Patient safety issue (laboratories may not detect resistance) Public health issue (resistance may be undetected)
Tests for new drugs not available on cAST devices in a timely manner	Ceftazidime-avibactam Ceftolozane-tazobactam	• Patient safety issue (may miss being treated with an active drug or be treated with an inactive drug) • Public health issue (resistance may be undetected) • Pharmaceutical company issue (new compounds may not be used)
FDA does not provide breakpoints for organisms that were not included in or did not perform reliably during pharmaceutical company's clinical trial	Daptomycin and *Enterococcus faecium* Meropenem and *Acinetobacter* species	• Patient safety issue (antimicrobial agents often used off label but AST may be unavailable)
Lack of FDA-cleared tests for antimicrobial agents that do not have FDA breakpoints	Colistin	• Patient safety issue (laboratories may not detect resistance) • Public health issue (resistance may be undetected)

https://clsi.org/media/1699/ast_newsletter_june2017.pdf
Humphries and Hindler. Clin Infect Dis 2016;63:83–8

AST Breakpoints

- MIC and disk zones - interpreted using breakpoints
- Breakpoints set by breakpoint-setting organizations
- **US FDA** establishes breakpoints with new drug application/on request of pharma company (older agents)
  - Package insert
  - Breakpoints: www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm275763.htm
  - Cannot compel drug manufacturers to revise breakpoints
    - Problematic for older generic drugs - takes time & $$$ to update breakpoints
- **CLSI** - multidisciplinary, volunteer organization, sets consensus standards
  - Updates breakpoints for older agents according to criteria outlined in M23 guideline
    - New resistance mechanism, new pharmacokinetic/pharmacodynamic data, simplification of laboratory testing, harmonization of breakpoints with FDA, **EUCAST**, **USCAST**
  - New drugs
    - Publishes
      - FDA breakpoints
      - Alternative breakpoints (2 years after drug's initial FDA approval)
    - May reevaluate breakpoints *independent* of requests made by drug manufacturers, if M23 criteria met
  - M100S standard, updated annually, available free: www.clsi.org/m100/

Humphries and Hindler. Clin Infect Dis 2016;63:83–8

Select Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa*

	CLSI MIC (µg/mL) Breakpoint			FDA MIC (µg/mL) Breakpoint			EUCAST MIC (µg/mL) Breakpoint			USCAST MIC (µg/mL) Breakpoint		
	S	I	R	S	I	R	S	I	R	S	I	R
Enterobacteriaceae												
Cefepime	**≤2**	**4–8 (SDD)**	**≥16**	**≤2**	**4–8**	**≥16**	**≤1**	**2-4**	**≥8**			
Cefotaxime	≤1	2	≥4	≤1	2	≥4	≤1	2	≥4	≤1	2	≥4
Ceftazidime	**≤4**	**8**	**≥16**	**≤4**	**8**	**≥16**	**≤1**	**2-4**	**≥8**			
Ceftriaxone	≤1	2	≥4	≤1	2	≥4	≤1	2	≥4	≤1	2	≥4
Ertapenem	≤0.5	1	≥2	≤0.5	1	≥2	≤0.5	1	≥2			
Imipenem	**≤1**	**2**	**≥4**	**≤1**	**2**	**≥4**	**≤2**	**4-8**	**≥16**			
Meropenem	**≤1**	**2**	**≥4**	**≤1**	**2**	**≥4**	**≤2**	**4-8**	**≥16**			
Pseudomonas aeruginosa												
Cefepime	**≤8**	**16**	**≥32**	**≤8**	**…**	**≥16**	**≤8**	**…**	**≥16**	**≤8**	**…**	**≥16**
Ceftazidime	**≤8**	**16**	**≥32**	**≤8**	**…**	**≥16**	**≤8**	**…**	**≥16**	**≤8**	**…**	**≥16**
Imipenem	**≤2**	**4**	**≥8**	**≤2**	**4**	**≥8**	**≤4**	**…**	**≥16**	**≤2**	**…**	**≥16**
Meropenem	**≤2**	**4**	**≥8**	**≤2**	**4**	**≥8**	**≤2**	**…**	**≥16**	**≤2**	**…**	**≥16**

If Package Inserts Not Updated, Breakpoints May Be Antiquated

MEROPENEM- meropenem injection, powder, for solution Sandoz Inc

Table 2. Susceptibility Interpretive Criteria for Meropenem

	Susceptibility Test Result Interpretive Criteria					
	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤ 1	2	≥ 4	≥ 23	20-22	≤ 19
Pseudomonasaeruginosa	≤ 4	8	≥ 16	≥ 16	14-15	≤ 13

MERREM IV- meropenem injection AstraZeneca Pharmaceuticals LP

Table 7: Susceptibility Interpretive Criteria for Meropenem

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤ 1	2	≥ 4	≥ 23	20-22	≤ 19
*Pseudomonas aeruginosa**	≤ 2	4	≥ 8	≥ 19	16-18	≤ 15

https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=meropenem accessed September 3, 2017

Commercial AST Devices

- cAST devices (US) must be cleared by FDA as *in vitro* diagnostic (IVD) devices & used by laboratories according to manufacturers' instructions listed in FDA-cleared product insert
- Class II devices
  - FDA clearance achieved through premarket notification or 510(k) process - manufacturer documents cAST performs comparable to reference broth microdilution (BMD)
  - For devices that yield MICs, categorical agreement (same susceptible, intermediate, or resistant interpretation) and essential agreement (MICs within +1 $\log_2$ dilution reference BMD results) required (acceptance criteria set by FDA)
- Major *changes* require FDA re-review and clearance

Laboratory Requirements CLIA Standard 493.1253(b)(1)

- ***Verification of Performance Specifications***
  - Unmodified, FDA-cleared or -approved test system
    - Show that test yields performance specifications comparable to those established by manufacturer
- ***Establishment of Performance Specifications***
  - Modified FDA cleared or -approved test system, test system not subject to FDA clearance or approval (e.g., in-house developed) or test system for which the performance characteristics not provided by manufacturer
    - *Extensive* study to establish relevant performance characteristics of test system
    - Ideally, meet same requirements for FDA clearance of cAST system…
      - …not easy for clinical laboratories

Patel J, Sharp S & Novak-Weekley S. Clin Microbiol Newsletter 2013;35:103-109

Implementing FDA-Approved Test or Reference Method

- FDA-approved test or reference method - test performance reviewed and approved by FDA and/or CLSI
- CLIA verification requirements
  - Determine whether method produces results consistent with reported accuracy, precision and reportable range
  - Test in parallel by new method and method being replaced or alternative method established in laboratory
- Typically at least 30 (ideally ≥100) fresh clinical isolates representing various species, various susceptibility profiles (some around breakpoints and including resistant isolates from laboratories' patient population)
- CLIA does not specify what level of agreement constitutes an acceptable result, but ≥90% essential agreement and categorical agreement reasonable
- Precision or reproducibility assessed by QC testing

Patel J, Sharp S & Novak-Weekley S. Clin Microbiol Newsletter 2013;35:103-109

Clinical Laboratory Verification of Updated Breakpoints

- **Joint Commission & College of American Pathologists allow labs to use FDA or CLSI breakpoints**
- Clinical laboratories that implement CLSI breakpoints on FDA-approved cAST devices implementing modifications or off-label use of their FDA-approved devices and must **establish performance specifications** of cAST devices for non-FDA breakpoints [CLIA standard 493.1253(b)(2)]
- cAST systems must have **requisite antimicrobial concentrations** – FDA-approved for essential agreement
  - Laboratory must determine if antibiotic susceptibility panel will obtain correct categorical agreement
  - Compare with standard reference method using either disk diffusion or broth microdilution
  - Isolates tested should be appropriate for evaluating new breakpoints

Patel J, Sharp S & Novak-Weekley S. Clin Microbiol Newsletter 2013;35:103-109

Gold Standard *versus* New MIC Methods for Drug X Breakpoints - 1, 2 and 4 µg/ml

MIC Results (µg/ml) for New Method	MIC (µg/ml) Results for Gold Standard Method							
	0.06	0.12	0.25	0.5	1	2	4	8
0.06								
0.12			4	1				
0.25			8	11	1			
0.5			3	21	5			
1			2	4	11	1		1
2				1	1	6		1
4						2	7	5
8						1	2	1

Numbers in squares are numbers of isolates tested with corresponding MIC.
Results shaded in light grey are minor errors.
Result shaded in dark grey is a very major error

Categorical Agreement (92%)

Error type	Gold standard method result	New method result	# Isolates	Total # Isolates
Minor	Susceptible	Intermediate	2	7 (7%)
	Intermediate	Susceptible	1	
	Resistant	Intermediate	1	
	Intermediate	Resistant	3	
Major	Susceptible	Resistant	0	0
Very Major	Resistant	Susceptible	1	1 (1%)

Essential Agreement (92%)

Doubling dilution difference	-3	-2	-1	0	1	2	3	Total
# Isolates	0	4	12	54	26	3	1	100

What's Acceptable? (Cumitech 31A. ASM Press, 2009)	
Error Type	**Acceptable Error Rate**
Very major	≤3%
Major	≤3%
Major and minor	≤7%
Essential agreement	≥90%
Categorical agreement	≥90%

Patel J, Sharp S & Novak-Weekley S. Clin Microbiol Newsletter 2013;35:103-109

Select Breakpoints for *Enterobacteriaceae* and *Pseudomonas aeruginosa* Updated Sin

	CLSI MIC (µg/mL) Breakpoint			FDA MIC (µg/mL) Breakpoint			Year CLSI Breakpoint Updated		Current cAST Systems with Updated Breakpoints (bioMérieux Vitek2, BD Phoenix, Beckman Coulter MicroScan, Thermo Scientific Sensititre)
	S	I	R	S	I	R			
Enterobacteriaceae									
Cefepime	≤2	4–8 (SDD)	≥16	≤2				2014/2016	2
Cefotaxime	≤1	2	≥4					2015	1
Ceftazidime	≤4	8	≥1				2010	2014/2015	0
Ceftriaxone	≤1	2				4	2010	2013/2015	4
Ertapenem	≤0.5	1				≥2	2010, 2012	2012	4
Imipenem	≤1				2	≥4	2010	2012	2
Meropenem				≤1	2	≥4	2010	2013	2
Pseudomonas aeruginos									
Cefepime			32	≤8	…	**≥16**	No update	2014/2016	
Ceftazidim			≥32	≤8	…	**≥16**	No update	2014/2015	
Imip			≥8	≤2	4	≥8	2012	2012	2
		4	≥8	≤2	4	≥8	2012	2013	1

"Manufacturers have indicated that considerable resources are required to reformulate cAST devices to accommodate revised breakpoints, hampering progress and innovation in other areas." Humphries and Hindler. Clin Infect Dis 2016;63:83–8

*As list under "Date of Most Recent FDA Review of Microbiology Susceptibility Interpretive Criteria" at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm275763.htm (accessed August 29, 2017); date the specific FDA breakpoint was updated occurred at or prior to the date listed here; multiple years are listed as included on this website.

Recently Approved Antibacterial Agents and Availability on Commercial AST Systems

Antimicrobial	Year Drug Approved by FDA	FDA-Cleared Test Available
Meropenem-vaborbactam	2017	
Delafloxacin	2017	Sensititre
Ceftazidime-avibactam	2015	BD Phoenix Sensititre
Ceftolozane-tazobactam	2014	Sensititre Vitek2
Dalbavancin	2014	Sensititre
Oritavancin	2014	Sensititre
Telavancin	2014	Sensititre
Tedizolid	2014	Sensititre
Ceftaroline	2013	BD Phoenix MicroScan Sensititre Vitek2

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)
Advisory Council, Incentives Working Group

- 1st report, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria*
  - "current economic model…insufficient to ensure availability of products and resources to fight AMR"
- Ideas for incentivizing diagnostics development
  - **DRAFT:** Vote upcoming (September 2017 meeting)

www.hhs.gov/sites/default/files/paccarb-incentives-working-group-issue-statements.pdf

PACCARB Advisory Council, Incentives Working Group

"Diagnostics…**inform appropriate antibiotic prescribing**…**can reduce hospital lengths of stay, prevent hospital admissions, reduce antibiotic use & benefit society by curtailing AMR**

- …tests do not…match…clinical needs of inpatient and outpatient settings…stems from problems related to…development & limited use of diagnostics
- Barriers to development
  - **Cost of development**, **lack of clinical implementation of approved tests**, **inadequate reimbursement**, **expensive and complex regulatory process**

1. **AST devices for new antibiotics**
2. Rapid tests that distinguish between bacterial and viral infections
3. Tests that quickly identify bacteria & provide rapid susceptibility testing

www.hhs.gov/sites/default/files/paccarb-incentives-working-group-issue-statements.pdf

PACCARB Advisory Council, Incentives Working Group: Economic Issue 1 "There is a delay in availability of ASTs for newly approved antibiotics"

- "As…number of infections from multidrug resistant bacteria increases, clinicians …relying on new antibiotics that…target these bacteria to provide lifesaving treatment
- Prior to prescribing, clinicians need results from AST, but…tests are often not made available at time antibiotic is approved by FDA
- Lack of AST…major impediment to use of that drug
  - Neither laboratorians nor clinicians comfortable recommending an antibiotic without some direct data of drug susceptibility of organism, so antibiotic is not prescribed in situations where it may be useful
  - Under current regulatory system, it may take 2–3 years for automated, updated AST devices to become available for use in clinical laboratories
  - Thus, use of new drugs limited because drug susceptibility cannot be confirmed
  - **Availability…an Etest or an antibiotic disc, when…antibiotic is approved would greatly improve…ability of laboratories to provide critical information"**

www.hhs.gov/sites/default/files/paccarb-incentives-working-group-issue-statements.pdf

PACCARB Advisory Council, Incentives Working Group

- **Economic Issue 2:** Because there is no method to determine the value of a diagnostic test, reimbursement is not aligned with the value of the diagnostic test.
- **Economic Issue 3:** There is a lack of clinical and economic outcome studies showing that diagnostic tests prevent the emergence of antibiotic-resistant bacteria and are cost-effective.
- **Economic Issue 4:** The high cost of development of diagnostics is a disincentive for diagnostics companies.
- **R&D Issue 3:** Tests are needed that rapidly identify or quantify pathogens directly from the clinical specimen and provide rapid susceptibility results.
- **R&D Issue 4:** Collaboration between diagnostics companies and other stakeholders is limited and inconsistent.
- **Regulatory Issue 1:** The regulatory approval clearance process for modifying and improving existing diagnostic tests is complex and expensive.
- **Regulatory Issue 2:** The current regulatory process for new diagnostics is time-consuming and costly, posing a disincentive for developers.
- **Regulatory Issue 3:** There are no requirements for hospitals to update their microbiology laboratories with newer technologies.
- **Behavioral Issue 1:** Clinicians do not always use diagnostic tests, believe the results, and act on them.

www.hhs.gov/sites/default/files/paccarb-incentives-working-group-issue-statements.pdf

Coordinated Development of Antimicrobial Drugs and cAST Devices
Draft Guidance for Industry and FDA Staff (9/21/16)

- Assist drug sponsors and device manufacturers planning to develop new antimicrobial drugs and cAST devices and who seek to **coordinate development of products** such that **cAST device could be cleared upon new drug approval or shortly thereafter**
  - Minimize time between approval of an antimicrobial drug and clearance of cAST device
  - *Possible* benefits to drug sponsor and device manufacturer during drug & device development
    - Drug sponsor - access to AST device technology may be valuable during clinical studies
    - Device manufacturer - access to clinical samples and isolates may aid in device validation
- Goals
  - Describe interactions between drug sponsors and device manufacturers for coordinated development of a new antimicrobial drug and an AST device; and
  - Explain considerations for submitting separate applications when seeking clearance of an AST device coincident with, or soon following, antimicrobial drug approval; and
  - Clarify that review of new antimicrobial drug product and AST device(s) will remain independent, and that coordinated development does not influence review timelines for either product.
- **"FDA has traditionally not considered microbiology diagnostics to be companion diagnostic devices, i.e., "as an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product" (emphasis added)."**

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM521421.pdf

Coordinated Development of Antimicrobial Drugs and AST Devices
Draft Guidance for Industry and FDA Staff (9/21/16)

- **Agreement between antimicrobial drug sponsor and AST device manufacturer**
- **Drug sponsor and AST device manufacturer submit coordinated development plans to CDER and CDRH, respectively, for review and comment**
  - FDA welcomes joint meetings with drug sponsor and device manufacturer and personnel from both CDER and CDRH to address issues that affect coordinated development
- In general, an **investigational device exemption (IDE) not needed** for investigation of AST devices
  - If AST device under development (e.g., a rapid susceptibility testing device) is to be used for clinical trial enrollment, an IDE may be needed
- If coordinated development of drug and AST device pursued, **CDRH can communicate with CDER and review 510(k) submission during NDA review process**, to maximize likelihood that AST device clearance can occur either coincident with or shortly after drug approval
- For device clearance to occur either contemporaneously or shortly after drug approval, AST device 510(k) submission should be submitted early enough to allow sufficient time for FDA to review. In 510(k) submission, appropriate permissions to FDA from drug sponsor to cross-reference information from NDA should be provided
- FDA will make decisions for antimicrobial drug product and AST device independently

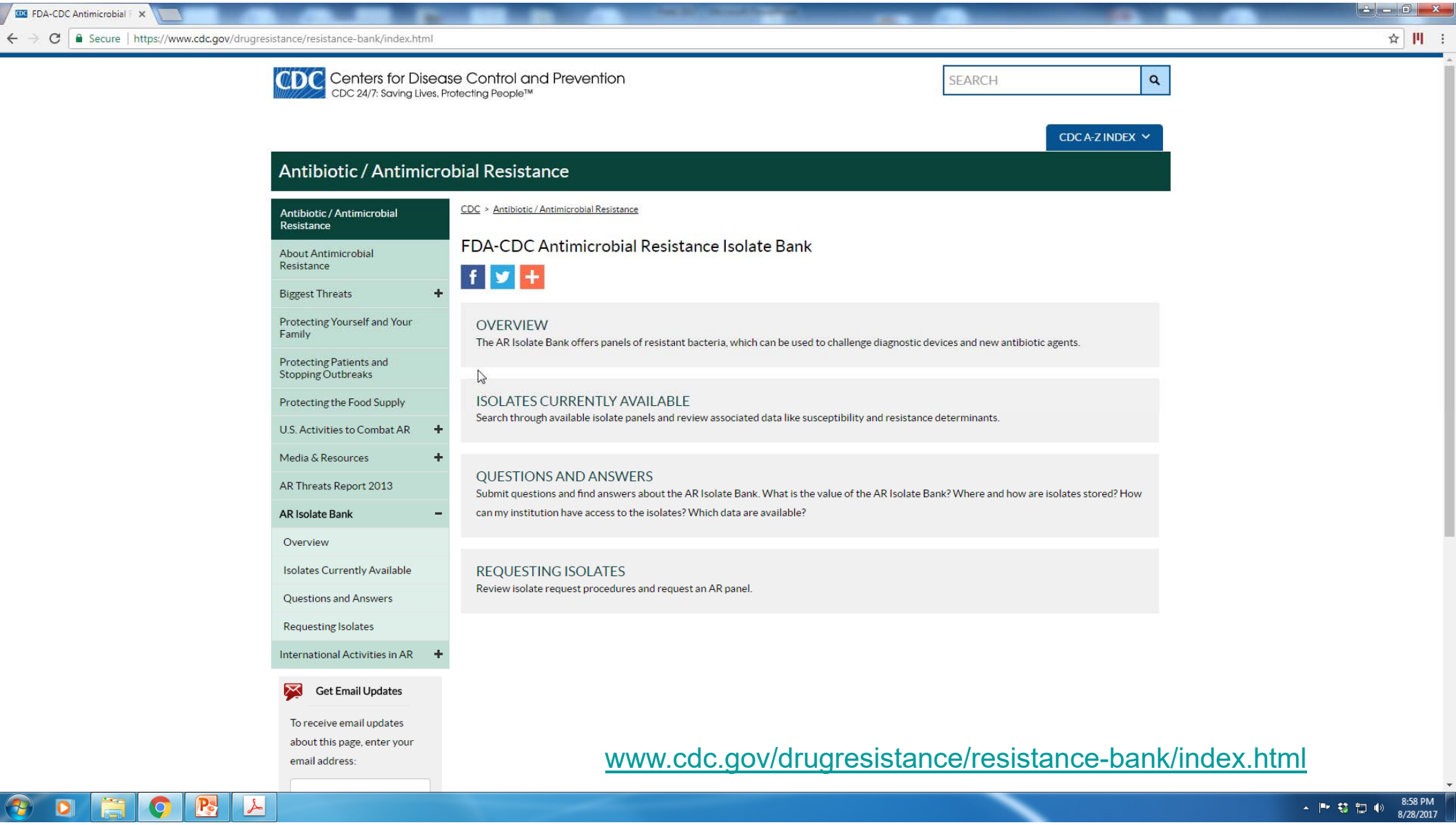
www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM521421.pdf

Coordinated Development of Antimicrobial Drugs and AST Devices
Advanced Medical Technology Association (AvaMed) Comments

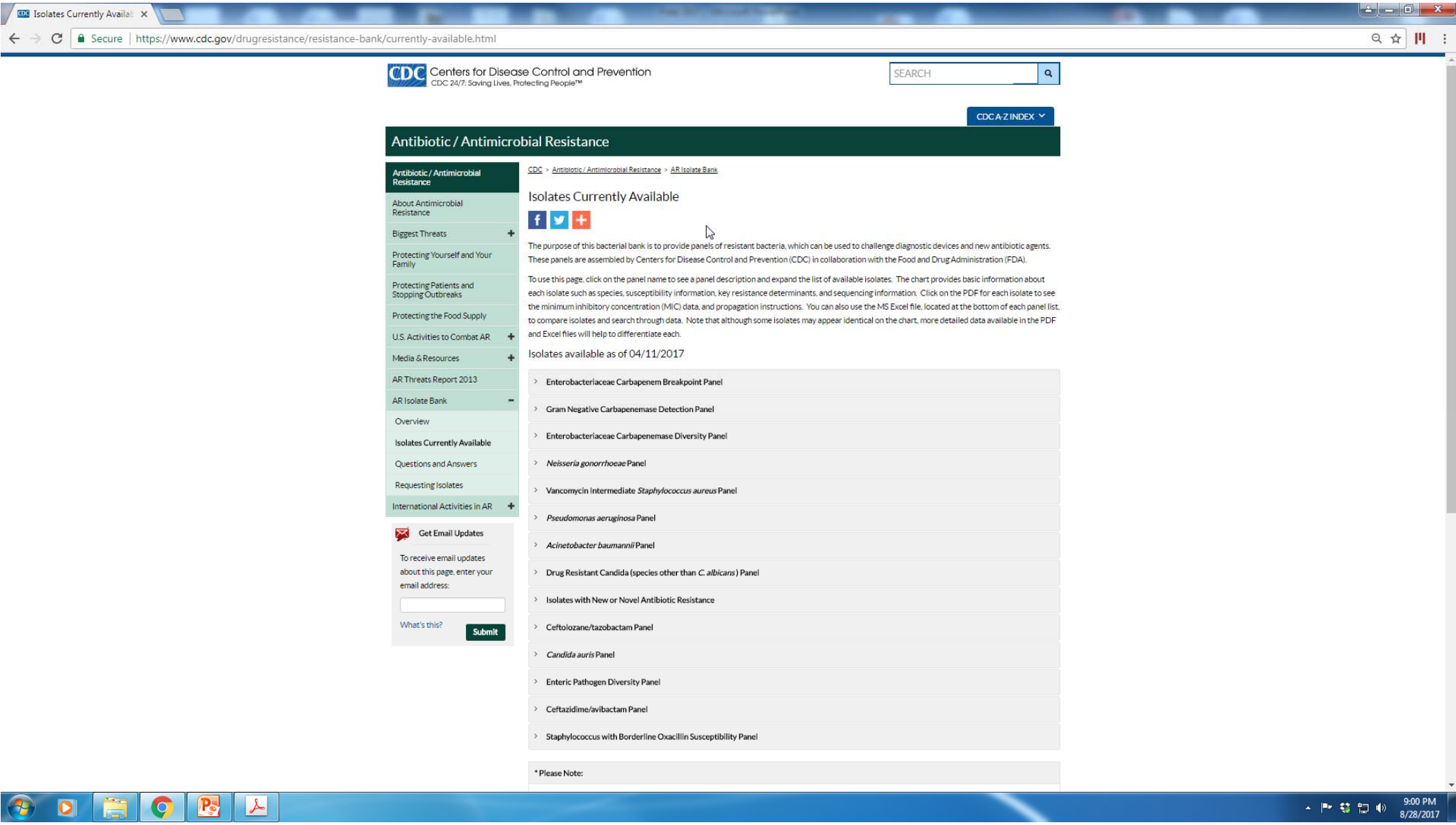
Addressing Changes to Breakpoints/Claimed Organisms during FDA NDA Review

- Add language to the Guidance for AST developers in event that **breakpoints and/or claimed organisms change during FDA review of NDA**.
- Special Controls Guidance calls for **Category Agreement for clinically relevant organisms as criteria for clearance of AST devices**. As a result, **CDRH cannot grant clearance of an AST until FDA has approved antimicrobial drug indications, specifically clinically relevant organisms and breakpoints**. Breakpoints and claimed organisms can change very late in drug approval cycle as labeling is one of the last items in NDA to be negotiated between drug sponsor and FDA.
- These potential changes raise uncertainty for AST developers, and act as disincentive for coordinated development. AST development performed based on input from the drug company, which provides its best educated guess at the time that it submits the NDA as to what breakpoints/claimed organisms will be. If drug company's best guess for breakpoints is close, but not exact, data for AST 510(k) submission would need to be repackaged and reanalyzed. If drug company is "off" in its guess, then AST developer would need to re-conduct analytical and clinical testing, wasting time and money.
- **We recommend that FDA consider granting clearance to AST based on Essential Agreement instead of Categorical Agreement.**
- **As an alternative, we recommend that breakpoints and claimed organisms are reviewed earlier in the drug approval process.**

www.advamed.org/sites/default/files/resource/11_21_2016_advamed_comments_on_dkt_no_fda-2016-d-2561_ast_devices.pdf



www.cdc.gov/drugresistance/resistance-bank/index.html


Isolates Currently Availa
Secure | https://www.cdc.gov/drugresistance/resistance-bank/currently-available.html
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
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Protecting the Food Supply
U.S. Activities to Combat AR
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AR Threats Report 2013
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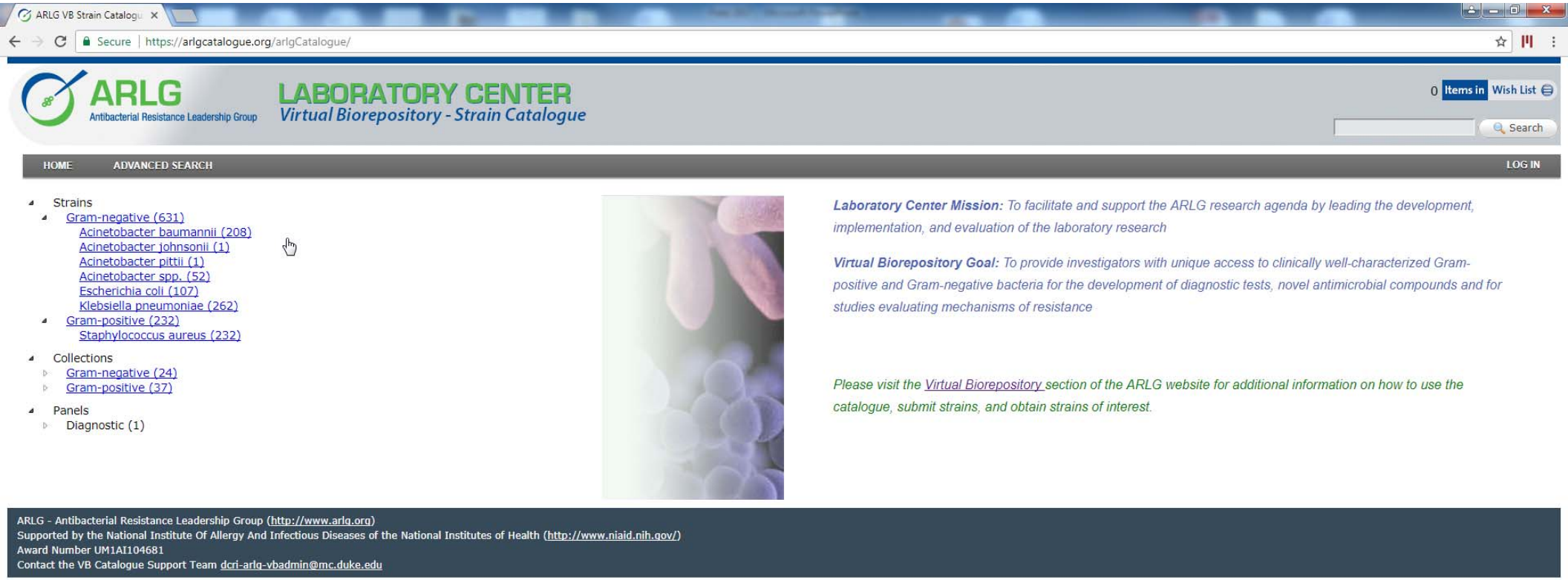
Questions and Answers
Requesting Isolates
International Activities in AR
Get Email Updates
To receive email updates about this page, enter your email address:
What's this?
Submit
CDC > Antibiotic / Antimicrobial Resistance > AR Isolate Bank
Isolates Currently Available
The purpose of this bacterial bank is to provide panels of resistant bacteria, which can be used to challenge diagnostic devices and new antibiotic agents. These panels are assembled by Centers for Disease Control and Prevention (CDC) in collaboration with the Food and Drug Administration (FDA).
To use this page, click on the panel name to see a panel description and expand the list of available isolates. The chart provides basic information about each isolate such as species, susceptibility information, key resistance determinants, and sequencing information. Click on the PDF for each isolate to see the minimum inhibitory concentration (MIC) data, and propagation instructions. You can also use the MS Excel file, located at the bottom of each panel list, to compare isolates and search through data. Note that although some isolates may appear identical on the chart, more detailed data available in the PDF and Excel files will help to differentiate each.
Isolates available as of 04/11/2017
Enterobacteriaceae Carbapenem Breakpoint Panel
Gram Negative Carbapenemase Detection Panel
Enterobacteriaceae Carbapenemase Diversity Panel
Neisseria gonorrhoeae Panel
Vancomycin Intermediate Staphylococcus aureus Panel
Pseudomonas aeruginosa Panel
Acinetobacter baumannii Panel
Drug Resistant Candida (species other than C. albicans) Panel
Isolates with New or Novel Antibiotic Resistance
Ceftolozane/tazobactam Panel
Candida auris Panel
Enteric Pathogen Diversity Panel
Ceftazidime/avibactam Panel
Staphylococcus with Borderline Oxacillin Susceptibility Panel
* Please Note:
9:00 PM
8/28/2017



https://arlgcatalogue.org/arlgCatalogue/

21st Century Cures Act

- Passed November 2016, signed into law by former President Obama on December 13th, 2016
- Sec 3044 includes updates to Sec. 511 of Federal Food, Drug and Cosmetic Act (21 USC 360a), to **allow FDA to recognize breakpoints established by breakpoint-setting organization(s)**, providing they uphold certain standards to mitigate potential conflicts of interest and maintain transparency in decision making processes
- **Breakpoints** to be **listed on website established by FDA (to be established by November 2017)**
  - Updated at minimum every 6 months
- **Breakpoints** will be **removed from drug prescribing information (by November 2018)**
  - Diagnostics manufacturers can submit data to FDA to have their AST system cleared using breakpoints listed on website
- Allows a streamlined process for FDA to recognize breakpoints established by breakpoint-setting organization(s)
- Provides transparency regarding which breakpoints must be used by diagnostic manufacturers
- Manufacturers able to request FDA clearance for drugs that currently lack FDA breakpoints (e.g., colistin)
- **Because breakpoints no longer be associated with 'indications for use' listed in drug package insert, ASTs for drug/bug combinations without FDA indication for use could be cleared by FDA**

https://clsi.org/media/1699/ast_newsletter_june2017.pdf

Pharmaceutical Company–Supported Reference Laboratories

- Some pharmaceutical companies offer reference laboratory service to test isolates against their agent
  - Reporting delays
  - May only be performed if resistance is suspected, and often only for isolates recovered from specimens consistent with FDA indications (e.g., urine or intra-abdominal sources for a drug approved for infections of these sites only)
  - Concerns regarding compliance with Sunshine Act
    - Free-of-charge susceptibility testing construed as kickback to prescribing company's drug

Humphries and Hindler. Clin Infect Dis 2016;63:83–8

Conclusions

- Accurate & timely AST must be performed in clinical labs
  - Requires reliable method(s) and breakpoints
- Challenges:
  - Financial, scientific, regulatory, variation between breakpoint-setting organizations
  - Fast-tracking available to pharmaceutical companies but not AST device manufacturers dealing with same antimicrobial agents
- Initiatives:
  - PACCARB Advisory Council, Incentives Working Group
  - Coordinated Development of Antimicrobial Drugs and AST Devices
  - Isolate banks/collections
  - 21st Century Cures Act