

# Automated ID/AST Systems

ID: 5-18 h  
AST: overnight

## Sensititre ARIS 2X



ID: Gram positive and Gram negative (2-12h), Yeast (4-15h)  
AST: 6-16 h (Ave: 12.1 +/-2.7h): full range

## BD Phoenix



96-well plate



136-well polystyrene tray



## bM Vitek 2



## Siemens Microscan



64-well card



96-well plate

ID: GN ID (2 to <10h), GP ID (2 to <8h), NH ID (6h), ANC ID (6h), YST ID (18h), BCL (14 h)  
AST: Ave: 8.4 +/- 2h: GN AST (2 to 18h), GP AST (2 to 18h), AST-YS01 (6h)

ID: 2-2.5h on rapid panel, synergies plus  
AST: Conventional panels: Overnight 15-18h, can be read visually; Rapid panels: 4.5-16 to 18h, finalized within 18h; Synergies plus panels: read-when-ready, flagged in as few as 4.5h, ON for drugs required longer incubation

# Automated ID/AST Systems

- ID

- Correct to genus >95%
- Correct to species >90%
- Difficulties with difficult organisms; non-fermenters: *Burkholderia*, viridans streptococci, *S. suis* –enterococci, *Capnocytophaga* – *Brevundimonas*, *Cryptococcus neoformans-gattii*
- *Candida auris* - *C. haemulonii* (BD Phoenix, Vitek2 and some MS), *C. sake* by API20C, *C. catenulata* by BD Phoenix, *C. catenulata*, *C. famata*, *C. guilliermondii*, *C. lusitaniae* by Microscan, *Rhodotorula glutinis* by API20C

**\*\* the backbone of accuracy is database \*\***

- AST

- Concordant with other methods >95%
  - For FDA clearance: agreement >90%, VME < 1.5%, ME <3%
- **Need to be updated with CLSI**
- Specific issues with specific drug-bug combinations & certain instruments: vancomycin & *S. aureus*, beta-lactams eg. piperacillin & *Pseudomonas*, Colistin

Chazigeorgio KS et al. JCM 2011; 49:3284-91.

Rhoads S et al. JCM 1995;33:3044-6.

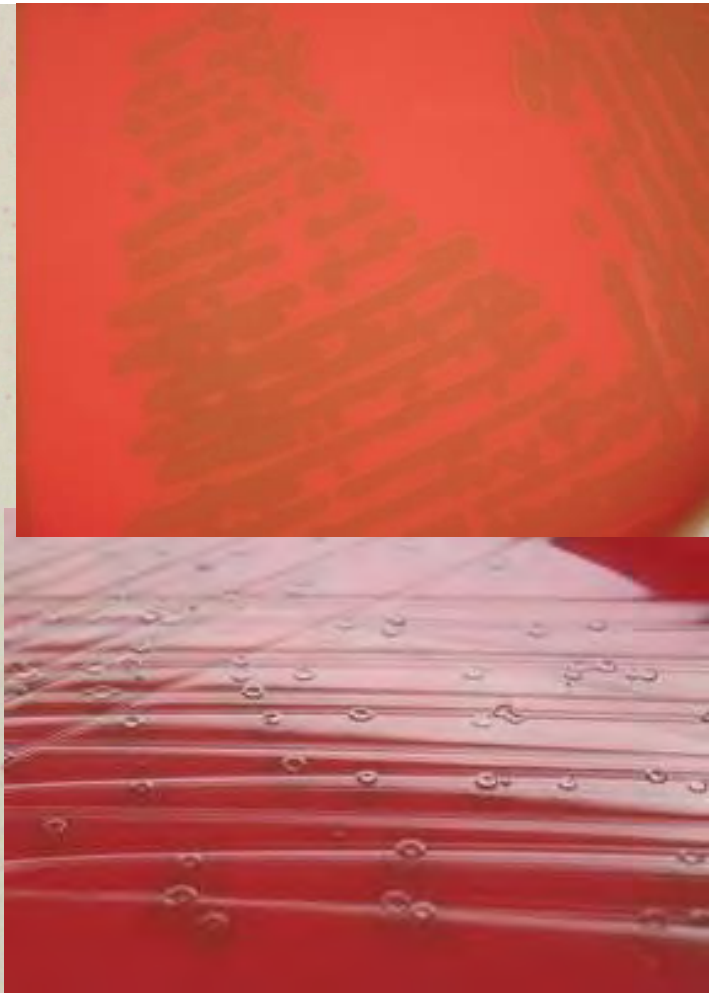
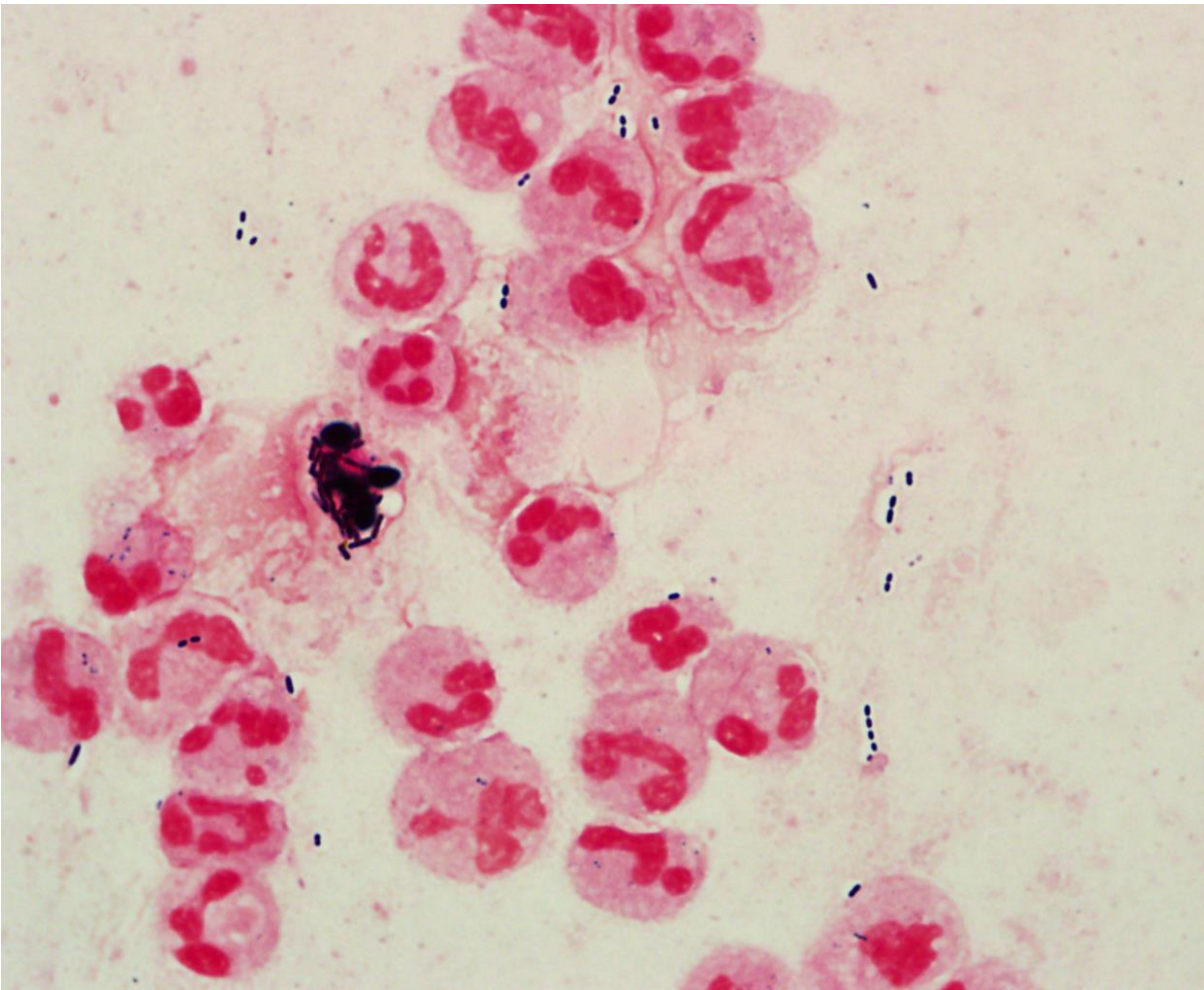
Jin WY et al. DMID 2011;70:442-7.

# Antimicrobial Susceptibility

# Culture and Susceptibility

- Physicians **should not demand that the laboratory report “everything that grows.”**  
This can provide irrelevant information that could result in inaccurate diagnosis and inappropriate therapy
- Susceptibility testing should be done only on clinically significant isolates, not on all microorganisms recovered in culture

# A 45-year-old male with a long-standing history of alcoholic cirrhosis and diabetes with meningitis



# CSF Culture

## *Streptococcus pneumoniae*

- |               |   |                   |   |
|---------------|---|-------------------|---|
| • Penicillin  | R | • Erythromycin    | S |
| • Ceftriaxone | S | • Clindamycin     | S |
| • Cefepime    | S | • TMP-SMX         | S |
| • Cefuroxime  | S | • Chloramphenicol | S |
| • Meropenem   | S | • Rifampicin      | S |
| • Vancomycin  | S | • Levofloxacin    | S |
|               |   | • Linezolid       | S |

# Warning Comments

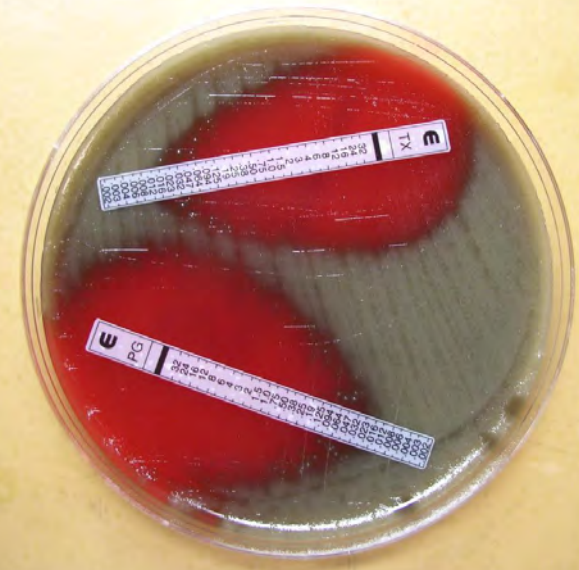
- The following antimicrobial agents should **NOT** be routinely reported for **bacteria isolated from CSF**. These antimicrobial agents are not the drug of choice and may not be effective for treating CSF infections caused by these organisms

Organism	Antimicrobial Agents
Bacteria isolated form CSF	<ul style="list-style-type: none"><li>• Agents administered by oral route only</li><li>• 1<sup>st</sup>- and 2<sup>nd</sup>-generation cephalosporins</li><li>• Cephameycins</li><li>• Clindamycin</li><li>• Macrolides</li><li>• Tetracyclines</li><li>• Fluoroquinolones</li></ul>



# Streptococcus pneumoniae interpretative breakpoint

- For *S. pneumoniae* isolated from CSF, penicillin and cefotaxime, ceftriaxone, or meropenem should be tested by a reliable MIC method
- With isolates from the other sites, oxacillin disk may be used



	MIC (µg/mL)			Zone (mm)			Note
BREAKPOINTS	S	I	R	S	I	R	
Penicillin (use oxacillin 1 µg disc)	-	-	-	≥20	-	-	≥20→susceptible (MIC ≤0.06), ≤19→MIC
Penicillin (nonmeningitis)	≤2	4	≥8	-	-	-	
Penicillin (meningitis)	≤0.06	-	≥0.12	-	-	-	
Cefotaxime/ ceftriaxone (nonmeningitis)	≤1	2	≥4	-	-	-	
Cefotaxime/ ceftriaxone (meningitis)	≤0.5	1	≥2	-	-	-	
Meropenem	≤0.25	0.5	≥1	-	-	-	
Vancomycin	≤1	-	-	≥17	-	-	CLSI M100-S27



# CSF Culture

## *Streptococcus pneumoniae*

	MIC	
• Penicillin	0.12 mg/L	R (meningitis)
•		S (nonmeningitis)
• Ceftriaxone	0.25 mg/L	S (meningitis)
•		S (nonmeningitis)
• [Meropenem	MIC 0.12	S]
• [Vancomycin		S]

# Specimen Source Reporting -Urine

Do not report on urine isolates	Only report on urine isolates
<ul style="list-style-type: none"><li>• Chloramphenicol</li></ul>	<ul style="list-style-type: none"><li>• [Fosfomycin]</li></ul>
<ul style="list-style-type: none"><li>• Clindamycin</li></ul>	<ul style="list-style-type: none"><li>• Nalidixic acid</li></ul>
<ul style="list-style-type: none"><li>• Erythromycin</li></ul>	<ul style="list-style-type: none"><li>• Nitrofurantoin</li></ul>
<ul style="list-style-type: none"><li>• Tigecycline</li></ul>	
<ul style="list-style-type: none"><li>• Moxifloxacin</li></ul>	
<ul style="list-style-type: none"><li>• Minocycline</li></ul>	

## Specimen Source Reporting –Respiratory

- Do not report daptomycin

# Warning Comments

- The following antimicrobial agent/organism combinations may appear active *in vitro*, but are not effective clinically and must not be reported as susceptible

Organism	Antimicrobial Agents
<i>Salmonella</i> spp., <i>Shigella</i> spp.	<ul style="list-style-type: none"><li>• 1<sup>st</sup>- and 2<sup>nd</sup>-generation cephalosporins</li><li>• Cephameycins</li><li>• Aminoglycosides</li></ul>
<i>Enterococcus</i> spp.	<ul style="list-style-type: none"><li>• Aminoglycosides (except for high-level resistance testing)</li><li>• Cephalosporins</li><li>• Clindamycin</li><li>• Trimethoprim-sulfamethoxazole</li></ul>
MRSA	<ul style="list-style-type: none"><li>• All beta-lactams, except ceftaroline</li></ul>

# Therapy-Related Comments

- Comments relate to therapy concerns
- Example
  - when rifampicin is being reported stating that **“Rifampicin should not be used alone for antimicrobial therapy”**
  - For staphylococci that test susceptible: “Gentamicin is use only in combination with other active agents that test susceptible”

## Development of Resistance and Testing of Repeat Isolates

- 3<sup>rd</sup>-generation cephalosporins and ***Enterobacter*, *Citrobacter* and *Serratia* spp.**
- All antimicrobial agents and ***P. aeruginosa***
- Fluoroquinolones and **staphylococci**
- Vancomycin and ***S. aureus*** with prolonged therapy

# Colistin Susceptibility

- **CLSI M100, 29<sup>th</sup> ed:** The only approved MIC method for testing is **broth microdilution**.
- Disk diffusion and gradient diffusion methods should not be performed
  - Disc diffusion: 23% very major errors in one study; poor diffusion in the agar

Colistin Etest Studies (select)					
Organism	N	vs.	Results		Reference
			VME	ME	
<i>A. baumannii</i>	115 (22-R)	BMD	1.7%	0.0%	Arroyo, JCM 2005;43:903.
<i>A. baumannii</i> <i>P. aeruginosa</i>	58 (0-R) 47 (15-R)	AD	0.0% 11%	1.9% 30%	Tan, CMI 2007;14:539.
<i>P. aeruginosa</i>	64 (12-R)	AD	8.3%	50%	Goldstein, JAC 2007;59:1039
<i>A. baumannii</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i>	27 (8-R) 60 (9-R) 20 (8-R)	BMD	50% 0% 25%	7.8%	Hindler, JCM 2013;51:1678

# Breakpoints and ECVs: CLSI/EUCAST Joint Working Group

	MIC (µg/mL)			Zone (mm)		
BREAKPOINTS	S	I	R	S	I	R
• <i>P. aeruginosa</i>	≤2	-	≥4	None		
• <i>A. baumannii</i> complex	≤2	-	≥4	None		
• <i>Enterobacteriaceae</i>	Insufficient clinical and PK/PD data					

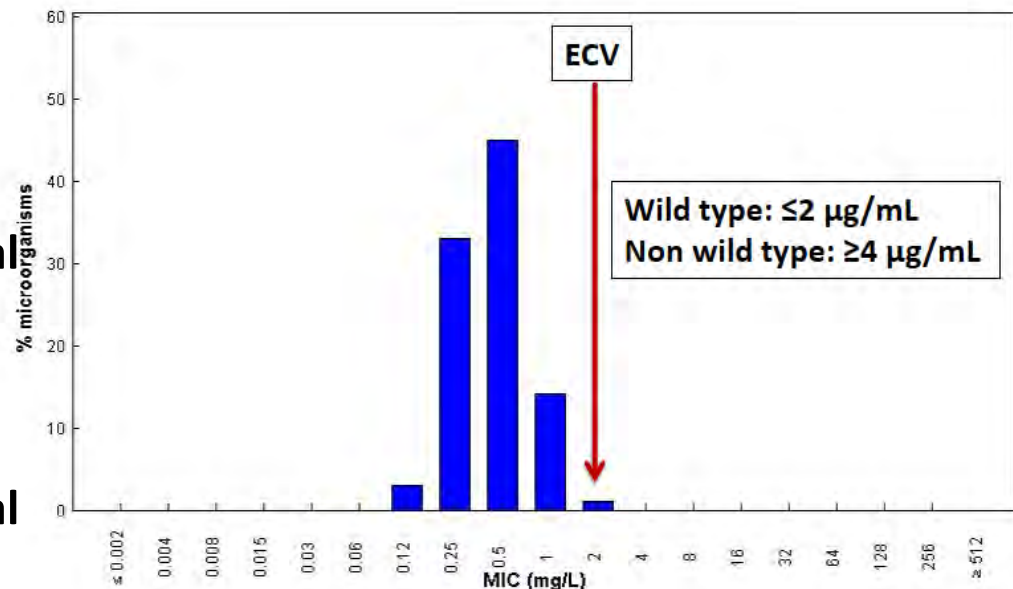
EPIDEMIOLOGICAL CUTOFF VALUE (ECV)	Wild-type	Non-wild-type	
• <i>E. coli</i>			None
• <i>K. pneumoniae</i>			None
• <i>Enterobacter cloacae</i>	≤2	≥4	None
• <i>R (E.) aerogenes</i>			None
• <i>Raoultella ornithinolytica</i>			None

# Epidemiological cutoff value

## ECVs or ECOFFs

- The MIC or zone diameter value that separates microbial populations into those with and without phenotypically detectable resistance (non-wild-type [NWT] or wild-type [WT])
- ECV defines the highest MIC or smallest zone diameter of WT population of isolates
- ECV interpretive categories
  - **WT**: an ECV that describes isolated with no detectable resistance or reduced susceptibility of antimicrobial agent being evaluated
  - **NWT**: an ECV that describes isolated with detectable resistance and reduced susceptibility of antimicrobial agent being evaluated

Colistin ECV and *E.coli*





# Epidemiological cutoff value

ECVs	CLINICAL BREAKPOINTS
Interpretation is wild type (WT) versus non wild type (NWT)	Interpretation is S/SDD/I/R
Only MIC distribution is needed to establish an ECV <b>Not for predicting clinical outcome</b>	MIC distributions, PK/PD data, and clinical outcome data are used to establish clinical breakpoints
Tool to monitor emergence of resistance	Tool to aid in predicting clinical outcome of infection

- ECVs **are not** clinical breakpoints and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency
- Can be reported when clinical breakpoints are not available

**“Caution”:** Zone diameter (disk diffusion) and MIC values for which ECVs are defined are not to be interpreted or reported as susceptible, intermediate, or resistant, but rather as WT or NWT. The ECVs should not be used as clinical breakpoints.

# Minimum inhibitory concentration (MIC)

- Lowest concentration that will inhibit **visible growth** of a test organism over a defined interval related to the organism's growth rate



The first clear tube

# To know or not to know MIC

- Although quantitative tests have an aura of increased sophistication, and attempts are commonly made to correlate the MIC results with achievable concentrations of the antibiotic at the site of infection, the existing studies demonstrate that **the clinical predictive values of qualitative test results are equivalent for virtually all organisms and antibiotics**

# To know or not to know MIC

- **Why not always report?**
  - **Too much information**
    - May be reported directly to clinician for patient care purpose, but not without and interpretive category results
  - **The drug with the ‘lowest MIC’ **does not** mean it is the most effective drug for treatment of the patient**
    - MIC is specific for drug-bug combination can't compared

<i>E. coli</i>	MIC (breakpoint)	Interpretation
Ampicillin	2 ( $\leq 8$ )	S
Ceftriaxone	0.5 ( $\leq 1$ )	S
Ciprofloxacin	0.06 ( $\leq 1$ )	S
Meropenem	0.5 ( $\leq 1$ )	S
Nitrofurantoin	16 ( $\leq 32$ )	S

# To know or not to know MIC

- **No disc diffusion breakpoint or is not reliable:**

Organism	MIC Needed for Antimicrobial Agents
<i>Staphylococcus</i> spp.	vancomycin; daptomycin oritavancin, televancin
<i>Enterococcus</i> spp.	vancomycin “Int” results; daptomycin oritavancin, televancin
<i>Burkholderia cepacia</i> , <i>S. maltophilia</i>	several agents (see M100S)
Non-Enterobacteriaceae (other than those above and <i>Acinetobacter</i> and <i>P. aeruginosa</i> )	all agents
<i>Acinetobacter</i> spp. <i>Pseudomonas aeruginosa</i>	colistin polymyxin B
<i>Streptococcus pneumoniae</i>	penicillin (if not “S” by oxacillin disk) cefotaxime/ceftriaxone + some other $\beta$ -lactams
<i>Streptococcus viridans</i> Group	penicillin
<i>Streptococcus beta</i> Group	daptomycin

# To know or not to know MIC

- To compare the in vitro activity of similar antibiotics
  - e.g., various aminoglycosides or carbapenems tested against *Pseudomonas*
- To optimized PK/PD target: MDROs, piperacillin/tazobactam in ESC, vancomycin in MRSA

<i>P. aeruginosa</i>	Interpretation	MIC (Resistant breakpoint)
Doripenem	R	8 ( $\geq 8$ )
Meropenem	R	32 ( $\geq 8$ )
Imipenem	R	128 ( $\geq 8$ )

**Can we just do PCR?**



# Pros and Cons of Syndromic Panels

## Pros

- **Rapid TAT**
- **No influence of antibiotics and isolation**
- **High sensitivity**
- **Semi-automated or automated system**
- **Less labor-intensive**
- **Appropriate for highly fastidious microorganisms**
- **Identify outbreak and epidemiologic studies**

## Cons

- **Lack of a gold standard**
- **No susceptibility data**
- **Not tailored to the individual (syndromic panel)**
- **Detect nucleic acids instead of viable organisms**
- **Detect asymptomatic carrier prolonged shedding or latent/reactivated virus**
- **Restricted availability**
- **Presence of contamination**
- **Cost-effectiveness?**

**Test selection and interpretation always correlate with clinical context**

# Targeted approach to panel testing

## Diagnostic Stewardship

- Just because a new test is FDA approved does not necessarily mean it is the right test for all patients
- Multiplex reagents and instrumentation is expensive and the pretest probability for infection differs significantly according to patient age, host immunocompetence, time of year, and geographic region

In the absence of cost-effectiveness data, recommend the following targeted approach to panel testing:

### • RV panels

- Immunocompromised patients
- Critically ill patients
- Hospitalized children

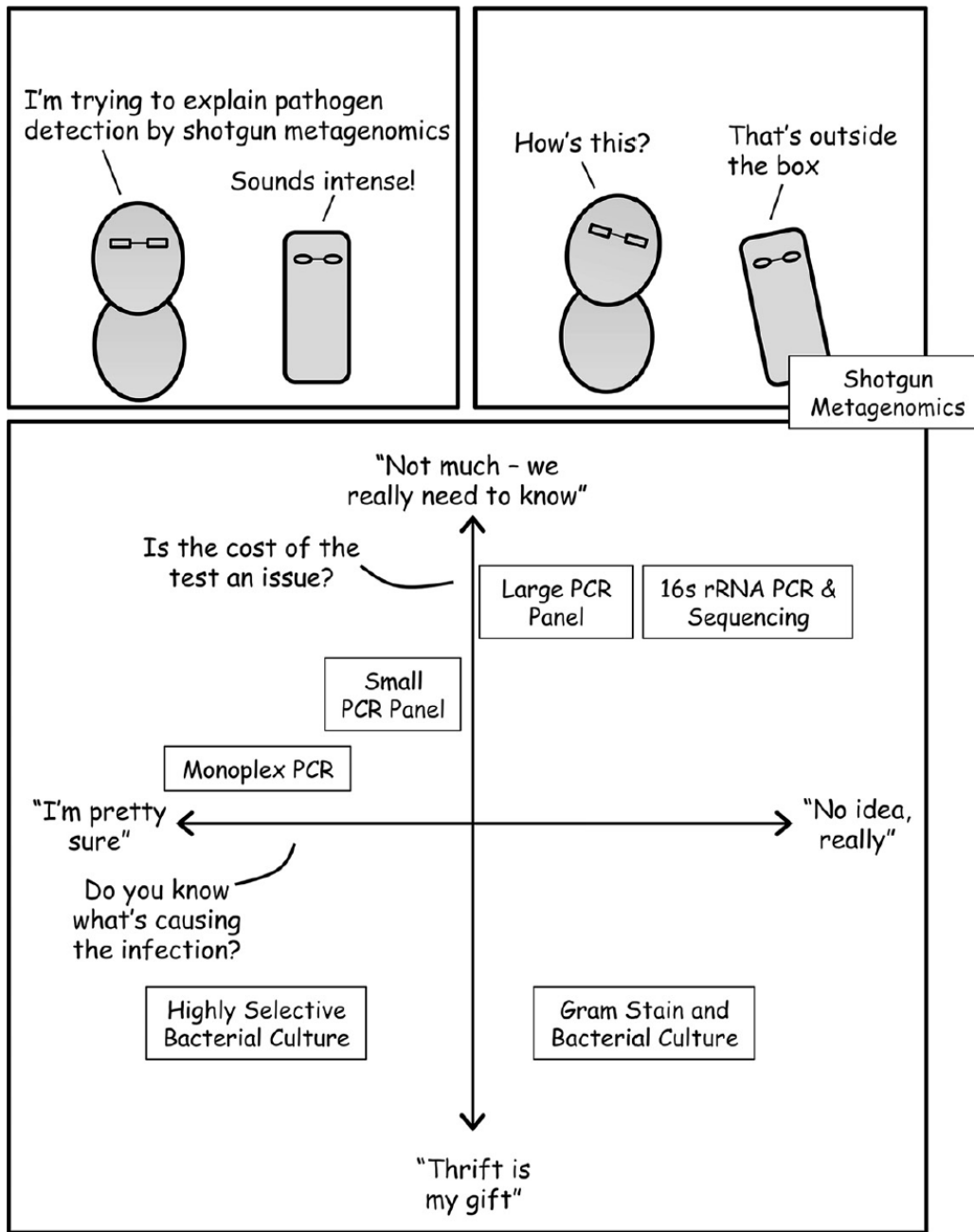
### • GI panels

- Dysentery
- Moderate or severe disease
- Symptoms lasting more than a week
- Immunocompromised host with community- onset symptoms

### • ME panel

- Immunocompromised patients.
- Testing may also speed time to diagnosis when the clinical suspicion for bacterial meningitis is high
- When the patient has already received antibiotics

### • Laboratory consultation with acceptance



# Antibiotic Stewardship Statement for Antibiotic Guidelines – Recommendations of the Healthcare Infection Control Practices Advisory Committee

- **Principles of Testing**

- Diagnostic tests should be used wisely to avoid unnecessary antibiotic therapy or therapy that is unnecessarily broad-spectrum, with consideration of healthcare value
- Rapid diagnostic tests, biomarkers, and decision rules that have acceptable performance characteristics to differentiate bacterial vs. non bacterial infection should be used to avoid
- Bacterial cultures with susceptibility testing should be collected, handled and processed promptly and appropriately to identify specific bacteria causing infection and facilitate use of narrow-spectrum antibiotics whenever possible
- When available and appropriate for the infection and the bacterial isolate, molecular testing to identify specific resistance genes or novel non-culture based phenotypic assays of susceptibility may be used to target antibiotic therapy toward susceptibility or resistant isolates
- **Avoid diagnostic testing without an appropriate indication when the results may have unintended consequences. For instance , a urine culture, rapid strep test, or *C. difficile* testing should not be performed unless the patient meets criteria for testing**

## Test Selection

**“Remember ordering a diagnostic laboratory test is like picking your nose in public. You must first consider what you will do if you find something.”**

**Catherine D. DeAngelis, MD MPH (1994)**

**Thank You**