

# UNDERSTANDING YOUR DATA: THE EXPERT RULES

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# WHAT WE WILL COVER:

- Define expert rule and describe how they are applied to AST
- Describe strategies for evaluating and developing expert rules
- Discuss examples of expert rules and the downstream implications for use
- Disclaimer – different systems use different terminology (alert, trigger, comment, etc.)

# AST EXPERT RULES

- **Definition: action to be taken given a specific AST result**
- **Based on current clinical breakpoints and knowledge of resistance mechanisms**
- **Instrument generated**
- **Ability to modify, customize, create rules**
- **Clinical decision support system**

# AST EXPERT RULES

- Expert rules are designed to automatically detect:
  - Technical errors – mixed cultures, over inoculation, etc
  - Result abnormalities – 3<sup>rd</sup> gen cephalosporins are resistant but 1<sup>st</sup> gen cephalosporins are sensitive
  - Intrinsic resistance patterns – *C. freundii* should be resistant to ampicillin

# WHAT'S IN AN EXPERT RULE

- Based on boolean operators
- Consist of multiple conditions

If (condition a)

**and** (condition b)

**or** (condition c)

 **then** (action)

# TYPES OF RULES

## 1. Inherent resistance

- Isolate tests susceptible, do you want to call it resistant
  - Activity of agent insufficient for success
  - Resistance innate
  - May test susceptible in vitro, therefore testing and reporting of (susceptible) results should be avoided
- Example is nitrofurantoin against *P. mirabilis*

# HANDLING OF IR EXCEPTION

- Instrument automatically makes agent resistant irrelevant of MIC
  - No hands-on time by technologist, decision made by instrument
- Instrument alerts technologist to verify result and/or identification
  - Hands-on time and expertise provided by technologist

# CLSI GUIDANCE

## B1. Enterobacteriaceae

Antimicrobial Agent \ Organism	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporin I: Cefazolin, Cephalothin	Cephamycins: Cefoxitin, Cefotetan	Cephalosporin II: Cefuroxime	Imipenem
<i>Citrobacter freundii</i>	R	R	R			R	R	R	
<i>Citrobacter koseri</i>	R			R	R				
<i>Enterobacter aerogenes</i>	R	R	R			R	R	R	
<i>Enterobacter cloacae</i> complex	R	R	R			R	R	R	
<i>Escherichia coli</i>	There is no intrinsic resistance to $\beta$ -lactams in this organism.								
<i>Escherichia hermannii</i>	R				R				
<i>Hafnia alvei</i>	R	R	R			R	R		
<i>Klebsiella pneumoniae</i>	R				R				
<i>Morganella morganii</i>	R	R				R		R	'
<i>Proteus mirabilis</i>	There is no intrinsic resistance to penicillins and cephalosporins in this organism.								
<i>Proteus penneri</i>	R					R		R	'



# EUCAST GUIDANCE

Rule no.	Organisms	Ampicillin	Amoxicillin-clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin
I.1	<i>Citrobacter koseri</i>	R	–	R	R	–	–
I.2	<i>Citrobacter freundii</i>	R	R	–	–	R	R
I.3	<i>Enterobacter cloacae</i>	R	R	–	–	R	R
I.4	<i>Enterobacter aerogenes</i>	R	R	–	–	R	R
I.5	<i>Escherichia hermannii</i>	R	–	R	–	–	–
I.6	<i>Hafnia alvei</i>	R	R	–	–	R	–
I.7	<i>Klebsiella</i> spp.	R	–	R	–	–	–
I.8	<i>Morganella morganii</i>	R	R	–	–	R	–
I.9	<i>Proteus mirabilis</i>	–	–	–	–	–	–
I.10	<i>Proteus vulgaris</i>	R	–	–	–	R	–
I.11	<i>Proteus penneri</i>	R	–	–	–	R	–
I.12	<i>Providencia rettgeri</i>	R	R	–	–	R	–
I.13	<i>Providencia stuartii</i>	R	R	–	–	R	–
I.14	<i>Serratia marcescens</i>	R	R	–	–	R	–
I.15	<i>Yersinia enterocolitica</i>	R	R	R	–	R	R
I.16	<i>Yersinia pseudotuberculosis</i>	–	–	–	–	–	–

EUCAST: [www.eucast.org](http://www.eucast.org)

Leclercq R et. al., CMI, 2011

# TYPES OF RULES




## 2. Unlikely or exceptional resistance

- Isolate tests non-susceptible to agent in which this phenotype is rare
- Isolate resistance pattern amongst antibiotic class is inconsistent (resistant to doripenem but susceptible to erta, mero, and imi)

# EXCEPTIONAL RESISTANCE

## ■ Changes over time

- Example is VRE – once rare, now common
- Now daptomycin is exceptional (but may be moving the same direction)

Biotype	---
Organism	E. faecium VRE <span style="float: right;"><b>VREFCM+</b></span>
Alerts	<ul style="list-style-type: none"><li>▷  Daptomycin-nonsusceptible enterococcus</li><li>▷  DAPTOMYCIN-NONSUSCEPTIBLE ENTEROCOCCUS</li><li>▷  Vancomycin-resistant enterococcus</li></ul>

# ENTEROCOCCUS EXPERT RULES V1

## ■ Vancomycin

### ■ Vancomycin-resistant Enterococcus

Check infection control policy

## ■ Daptomycin (x2)

### ■ Daptomycin-nonsusceptible Enterococcus

Unusual resistance

Verify isolate results by repeat testing unless patient had isolate previously

Save isolate

Infectious Disease consult suggested

### ■ DAPTOMYCIN-NONSUSCEPTIBLE ENTEROCOCCUS

Unusual resistance

Freeze isolate

- ▷ ❌ Daptomycin-nonsusceptible enterococcus
- ▷ ❌ DAPTOMYCIN-NONSUSCEPTIBLE ENTEROCOCCUS
- ▷ ⚠️ Vancomycin-resistant enterococcus

# ENTEROCOCCUS IMPROVED EXPERT RULES

- Vancomycin-resistant Enterococcus
  - Add ICPR comment
    - (ICPR internal code for “Infection control precautions recommended”)
  - OR – Could build logic in LIS
  - If organism ID is (all *Enterococcus* codes) and vancomycin MIC  $\geq 8$ , then add ICPR comment
    - Limitation – depending upon where you set MIC, may not capture all isolates or may capture too many

# ENTEROCOCCUS LIS-BASED VRE RULES

	VanA	VanB	VanM	VanD	VanE	VanC
Vancomycin	≥64	≥4	>256	64-128	8-32	2-32
Teicoplanin	R	S	S-R	S-R	S	S
Transferable	Yes	Yes	Yes	No	No	No
Notable	<b>VRE</b>	<b>VRE</b>	<b>VRE</b>			<i>E. gallinarum</i> <i>E. casseliflavus</i>

- If set threshold to capture I/R (MIC ≥8) then will capture other mechanisms (e.g. vanC) that do not pose infection control transmission risk
  - Exclude *E. gallinarum* and *E. casseliflavus* from rule one
  - Second rule : *E. gallinarum* and *E. casseliflavus* must have vancomycin MIC ≥32

# ENTEROCOCCUS IMPROVED EXPERT RULES

- **Daptomycin-nonsusceptible Enterococcus**
  - **Confirm resistance by Etest unless previously isolated. If confirmed, release result, add ICPR comment. Freeze all isolates.**
    - **Limitations - doesn't say what to do if doesn't confirm**
      - **Could add that info, refer isolate to antibiotic bench, or simply state to refer to procedure**
    - **Requires management of method changes**

# EXCEPTIONAL RESISTANCE

- Changes over time
- Geographical differences
- May indicate incorrect ID, contamination, error
  - Example is VRSA – would be truly exceptional resistance
  - Confirmation of result and identification required
  - Happen very infrequently, almost always errors



# EXCEPTION

- AST results that just don't make sense
- Reproducible; thoroughly validated scenario where the cause of error has been determined to be the instrument/panel/limitation of system
  - Example: Doripenem MIC is elevated, all other carbapenems susceptible for *Pseudomonas*
  - Current protocol: alert triggers based on exceptional resistance profile
  - Technologist manually reads doripenem MIC and changes to susceptible

# RESOLVING THE EXPERT RULE

- Look at all times alert fired in X time-frame
- Document number of times MIC was changed
- Document other relevant data
  - Organism type, any other resistance
- Compare to known mechanisms (literature) to demonstrate it simply is a system issue
- Determine agent usage

# RESOLVING THE EXPERT RULE

- Remove alert, routinely hide result
  - If a physician requests agent, cannot report without confirming
  - Isolate may not be available when asked
  - List as limitation to your system
- Cannot take this approach with agents commonly used or commonly requested

# HANDLING OF EXCEPTIONAL RESISTANCE EXCEPTION

- Instrument makes the determination for reporting
  - No hands-on time by technologist, decision made by instrument
- Instrument alerts technologist to verify result and/or identification
  - Hands-on time and expertise provided by technologist

# EXCEPTIONAL RESISTANCE RESOURCES

- Instruments typically have CLSI examples pre-loaded as expert rules
- EUCAST provides examples for GN, GP, and anaerobes
- Routinely evaluate your system

Rule no.	Organisms	Exceptional phenotypes
5.1	Any <i>Enterobacteriaceae</i> (except <i>Proteae</i> )	Resistant to meropenem and/or imipenem <sup>2</sup>
5.2	<i>Serratia marcescens</i> and <i>Proteae</i>	Susceptible to colistin
5.3	<i>Pseudomonas aeruginosa</i> and <i>Acinetobacter</i> spp.	Resistant to colistin
5.4	<i>Haemophilus influenzae</i>	Resistant to any third-generation cephalosporin, carbapenems, and fluoroquinolones
5.5	<i>Moraxella catarrhalis</i>	Resistant to ciprofloxacin and any third-generation cephalosporin
5.6	<i>Neisseria meningitidis</i>	Resistant to any third-generation cephalosporin and fluoroquinolones
5.7	<i>Neisseria gonorrhoeae</i>	Resistant to third-generation cephalosporin and spectinomycin

<sup>2</sup>Except in countries in which carbapenemase-producing *Enterobacteriaceae* are not rare.

# TYPES OF RULES

## 3. Interpretative rules

- Reading of resistance to drug reported by using another agent
- Inference of mechanism based on susceptibility test results

# INTERPRETIVE RULE

## ■ MRSA

- If organism identification is *S. aureus* and cefoxitin is resistant then result as resistant to methicillin and other (define) beta-lactams

## ■ Aminoglycoside resistance in *Enterobacteriaceae*

- If organism is *Enterobacteriaceae* and intermediate to tobramycin, resistant to gentamicin, and susceptible to amikacin, then report tobramycin as resistant (derived from EUCAST)

# INTERPRETIVE RULE

- Based on clinical evidence that reporting interpretation other than resistant may lead to clinical failure
- Typically controversial without tremendous amounts of supportive data
- Based primarily on microbiological data



# TYPES OF RULES

## 4. Stewardship or pharmacy-based rules

- Hide result or only report under specific circumstances
- Hide agents not on formulary
- Tier reporting to promote preferential use utilization of targeted agents

# STEWARDSHIP RULES

- Based on bioavailability of agent
  - Hide daptomycin on respiratory specimens
  - Hide clindamycin on CSF specimen
- Based on inadequacy of monotherapy
  - Only release rifampin on *S. aureus* by request
- Promote formulary options
  - Panel contains four carbapenems, but meropenem is carbapenem of choice (price)
    - If all susceptible, only release meropenem

# PHYSICIAN-DRIVEN RULE

- Urologist that wants quinolones released on all isolates from his patients
- Currently, it is a manual process
  - Technologists know about physician request, attempt to capture his specimens
  - Physician (unhappily) requests antibiotic to be released every time one is missed

# CONDITIONS OR PARAMETERS VARY BY AST SYSTEM

- Most systems allow for customized rules that can be trigger off of a number of conditions:
  - Location
  - Patient
  - Source
  - Culture type
  - Organism
  - Antibiotic result
- Bi-directional interface may be required

# PHYSICIAN-DRIVEN EXPERT RULE – OPTION 1

- If ordering physician is Dr. P and organism is *Enterobacteriaceae* and ciprofloxacin is susceptible and levofloxacin is susceptible, then release levofloxacin

AND

- If ordering physician is Dr. P and organism is *Enterobacteriaceae* and ciprofloxacin is resistant and levofloxacin if resistant, then release result

AND

- If ordering physician is Dr. P and organism is *Enterobacteriaceae* and ciprofloxacin is resistant and levofloxacin is susceptible, then release result and comment

AND

- If ordering physician is Dr. P and organism is *Enterobacteriaceae* and ciprofloxacin is susceptible and levofloxacin is resistant then manually read panel

# PHYSICIAN-DRIVEN EXPERT RULE – OPTION 2

- If ordering physician is Dr. P and organism is *Enterobacteriaceae* and levofloxacin is resistant, then release levofloxacin
- Limitations:
  - Only releasing resistance, so physician will need to assume if not present, the isolate is susceptible
  - Could be an issue if release other drugs but panel has problem with that agent and additional testing needed
    - Consider adding new interpretation of Pending

**STRATEGIES FOR  
EVALUATING AND  
DEVELOPING EXPERT  
RULES**

# THE SYSTEMS

<b>System</b>	<b>Expert System</b>
Vitek 2, Biomerieux	Advanced Expert System (AES)
MicroScan Walkaway, Beckman Coulter	Lab Pro Alert System
Phoenix, BD	BDXpert
Sensititre ARIS, Thermo Fisher	SWIN

\*Others not covered



# INSTRUMENTATION

- Expert rules in commercially available AST systems are based on
  - FDA-approved breakpoints (manufacturer's are required to use FDA-breakpoints)
  - CLSI standards
- Customizable by user

# INSTRUMENTATION

- Generally speaking, the interpretation may be altered, but the underlying MIC remains the same
- Enabled or disabled to fire automatically
- Updated annually (if not more frequently)

# DESIGNING RULES

REVIEW

BACTERIOLOGY

## **EUCAST expert rules in antimicrobial susceptibility testing**

**R. Leclercq<sup>1,2</sup>, R. Cantón<sup>2,3,4</sup>, D. F. J. Brown<sup>4</sup>, C. G. Giske<sup>2,4,5</sup>, P. Heisig<sup>2,6</sup>, A. P. MacGowan<sup>4,7</sup>, J. W. Mouton<sup>4,8</sup>, P. Nordmann<sup>2,9</sup>, A. C. Rodloff<sup>4,10</sup>, G. M. Rossolini<sup>2,11</sup>, C.-J. Soussy<sup>4,12</sup>, M. Steinbakk<sup>4,13</sup>, T. G. Winstanley<sup>2,14</sup> and G. Kahlmeter<sup>4,15</sup>**

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# ASSISTING YOUR RULES

- Provide written descriptions of each rule
  - Rule
  - Description
  - What is performed
  - How discrepancies are resolved
  - Why created
  - Validation data
  - Clinical validation data
  - Issues, exceptions, or alterations required

# ASSISTING YOUR RULES

## ■ Develop a high quality reporting scheme

Antibiotic	<i>Enterobacteriaceae</i> (not <i>Salmonella</i> or <i>Shigella</i> ) <sup>1</sup>	<i>Salmonella</i> species/ <i>Shigella</i> species	<i>Aeromonas</i> species/ <i>Plesiomonas</i> <i>shigelloides</i>	<i>Vibrio</i> species (not <i>V. cholerae</i> )	<i>Pseudomonas</i> <i>Aeruginosa</i> <sup>6</sup>	<i>Acinetobacter</i> Species <sup>6</sup>	<i>Burkholderia</i> <i>Cepacia</i> (non-CF isolates)	Other Non- <i>Enterobacteriaceae</i> species		
Amikacin	7				✓	✓		✓	Reporting Key:	
Ampicillin	✓	✓		✓						✓
Ampicillin/Sulbactam	✓		✓	✓		✓ <sup>5</sup>			✓	Report only on isolates recovered from the urinary tract.
Aztreonam	✓		✓						✓	Do not report on isolates recovered from cerebrospinal fluid (CSF).
Cefazolin	✓		✓	✓					✓	Hidden from reporting
Cefepime	✓		✓	✓	✓	✓		✓	✓	<sup>1</sup> Add AmpC comment {AMPC3} to the following except when isolated from urine cultures: <i>Aeromonas</i> species
Cefotaxime	✓		✓	✓					✓	
Cefotetan <sup>9</sup>	✓								✓	
Ceftazidime	✓	✓ <sup>4</sup>	✓	✓	✓	✓	✓	✓	✓	
Ceftriaxone	✓	✓ <sup>4</sup>	✓						✓	
Ciprofloxacin	✓	✓	✓	✓	✓	✓		✓	✓	

# EXAMPLE 2

- Display for given organism per source/site
- Provide footnotes (e.g. 1 = Daptomycin can never be released on a lower respiratory specimen.)

Staphylococcus Reporting Guidelines				
Antibiotic	SAUR			
	Blood	Other	Urine	CNS
Ampicillin				
Cefazolin				
Ceftroline		2		
Ceftriaxone				
Chloramphenicol				
Ciprofloxacin				
Clindamycin				
Daptomycin		1		
Erythromycin				
Gentamicin				
Gentamicin Synergy				
Levofloxacin				
Linezolid				
Moxifloxacin				
Nitrofurantoin				
Oxacillin				
Penicillin				
Rifampin		3		
Streptomycin Synergy				
Quin/dalfopristin				
Tetracycline				
Tigecycline				
Trimethoprim/Sulfa				
Vancomycin				

Reporting Key	
	Report on all isolates
	Report by physician request
	Report only with Lead approval
	Never report
	Selective reporting, see comment
	Intrinsic resistance

# ASSISTING YOUR RULES

- Interpretation tables
- Document rules for interpretation, for example: instrument generated, SOP (tech-driven), interpreted by LIS, etc.

Drug	Conc.	<i>Enterobacteriaceae (non-Salmonella/ Shigella)</i>
Amikacin	≤16	SN
	32	INT
	>32	R
Ampicillin	≤8	SN
	16	INT
	>16	R
Ampicillin/Sulbactam	≤8/4	SN
	16/8	INT
	>16/8	R
Aztreonam	≤1	SN
	2	SN
	4	SN
	8	INT
	>8	R

# AST EXPERT RULES

## PROS

Contribute to quality assurance

Highlight unusual results

Prompt user

Customizable

Increase efficiency in the lab

Promote stewardship

Contribute to better patient care

## CONS

Require management

Limited by situational knowledge

“alert fatigue”

Requires trial and error



# RESOURCES

- CLSI guidelines and standards
- EUCAST
- Instrument manuals and technical experts
- Literature
- The “experts” – pharmacy, stewardship, technologists, directors, etc.

# CONCLUSIONS

- Expert rules are designed to detect and alert laboratorians to:
  - Potential technical errors
  - Inconsistent results
  - Intrinsic resistant patterns
- Intended to provide unbiased interpretations
- Successful implementation of expert rules can benefit in clinical decisions regarding antibiotic prescribing and antibiotic stewardship efforts