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 – 3rd gen cephalosporins are resistant but 1st gen cephalosporins are sensitive
  - Intrinsic resistance patterns – *K. pneumoniae* 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*

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

Appendix B

EUCAST GUIDANCE

Rule no.	Organisms	Ampicillin	Amoxycillin–clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin
1.1	*Citrobacter koseri*	R	–	R	R	–	–
1.2	*Citrobacter freundii*	R	R	–	–	R	R
1.3	*Enterobacter cloacae*	R	R	–	–	R	R
1.4	*Enterobacter aerogenes*	R	R	–	–	R	R
1.5	*Escherichia hermannii*	R	–	R	–	–	–
1.6	*Hafnia alvei*	R	R	–	–	R	–
1.7	*Klebsiella spp.*	R	–	R	–	–	–
1.8	*Morganella morganii*	R	R	–	–	R	–
1.9	*Proteus mirabilis*	–	–	–	–	–	–
1.10	*Proteus vulgaris*	R	–	–	–	R	–
1.11	*Proteus penneri*	R	–	–	–	R	–
1.12	*Providencia rettgeri*	R	R	–	–	R	–
1.13	*Providencia stuartii*	R	R	–	–	R	–
1.14	*Serratia marcescens*	R	R	–	–	R	–
1.15	*Yersinia enterocolitica*	R	R	R	–	R	R
1.16	*Yersinia pseudotuberculosis*	–	–	–	–	–	–

EUCAST: www.eucast.org

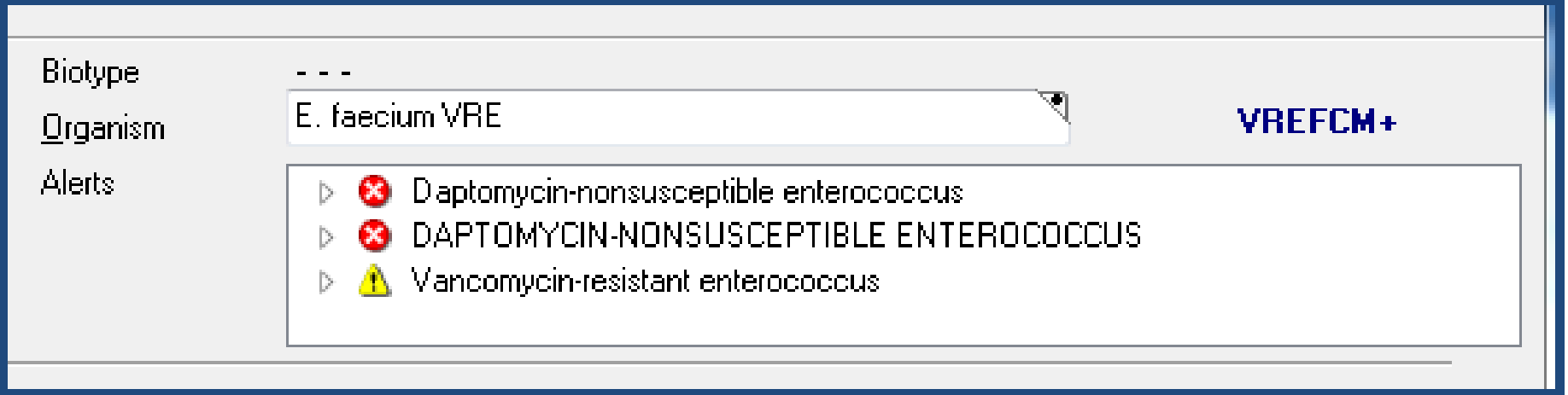
Leclercq R et. al., CMI, 2011

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)

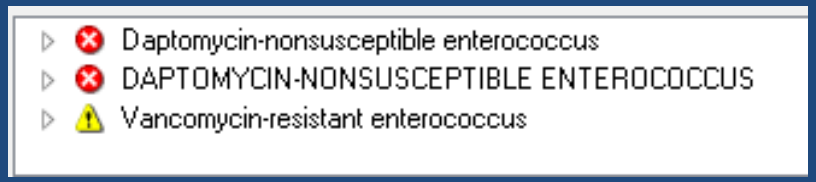
EXCEPTIONAL RESISTANCE

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



ENTEROCOCCUS EXPERT RULES V1

- Vancomycin
  - Vacomycin-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

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 *E. faecalis* or *E. faecium* and vancomycin MIC ≥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	VRE	VRE	VRE			*E. gallinarum* *E. casseliflavus*

- If set threshold at MIC ≥8 for all enterococci then will capture other mechanisms (e.g. vanC) that do not pose infection control transmission risk
  - Need separate rule for organisms containing vanC
  - 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 *Enterobacteriaceae* (except *Proteae*)	Resistant to meropenem and/or imipenem[a]
5.2	*Serratia marcescens* and *Proteae*	Susceptible to colistin
5.3	*Pseudomonas aeruginosa* and *Acinetobacter* spp.	Resistant to colistin
5.4	*Haemophilus influenze*	Resistant to any third-generation cephalosporin, carbapenems, and fluoroquinolones
5.5	*Moraxella catarrhalis*	Resistant to ciprofloxacin and any third-generation cephalosporin
5.6	*Neisseria meningitidis*	Resistant to any third-generation cephalosporin and fluoroquinolones
5.7	*Neisseria gonorrhoeae*	Resistant to third-generation cephalosporin and spectinomycin

[a]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
    - Most panels have both oxacillin and cefoxitin, so need rule to handle discrepant results
    - If either R, report as MRSA

INTERPRETIVE RULE

- Based on clinical evidence that reporting interpretation other than resistant may lead to clinical failure
- May be controversial without tremendous amounts of supportive data
- May be 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 lower 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 cabapenems, 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

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

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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	*Enterobacteriaceae* (not *Salmonella* or *Shigella*)[1]	*Salmonella* species/ *Shigella* species	*Aeromonas* species[1]/ *Plesiomonas shigelloides*	Vibrio species (not *V. cholerae*)	*Pseudomonas Aeruginosa*[6]	*Acinetobacter* Species[6]	*Burkholderia Cepacia* (non-CF isolates)	Other Non-*Enterobacteriaceae* species
Amikacin	[7]				✓	✓		✓
Ampicillin	✓	✓		✓				
Ampicillin/Sulbactam	✓		✓	✓		✓[5]		
Aztreonam	✓		✓					
Cefazolin	✓		✓	✓				
Cefepime	✓		✓	✓	✓	✓		✓
Cefotaxime	✓		✓	✓				
Cefotetan[9]	✓							
Ceftazidime	✓	✓[4]	✓	✓	✓	✓	✓	✓
Ceftriaxone	✓	✓[4]	✓					
Ciprofloxacin	✓	✓	✓	✓	✓	✓		✓

Reporting Key:

✓	Report on all isolates.
✓	Report only on isolates recovered from the urinary tract.
✓	Do not report on isolates recovered from cerebrospinal fluid (CSF).
✓	Hidden from reporting

[1] Add AmpC comment {AMPC3} to the following except when isolated from urine cultures:
Aeromonas species

Jean Houk, HMC, Seattle, WA

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

	SAUR			
Antibiotic	**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.	*Enterobacteriaceae (non-Salmonella/ Shigella)*
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

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AST EXPERT RULES

PROS	CONS
Contribute to quality assurance	Require management
Highlight unusual results	Limited by situational knowledge
Prompt user	“alert fatigue”
Customizable	Requires trial and error
Increase efficiency in the lab	
Promote stewardship	
Contribute to better patient care	

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