Expert Rules and their impact on interpretation

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Traditional approach

- Consider the results of ASTs as if each result were independent of other results
- Resistances to multiple related antimicrobial agents often depend on single mechanisms

Interpretive Reading

- Analyses susceptibility *patterns* rather than results for individual antimicrobials
- Makes use of surrogate markers of resistance
- Predicts underlying resistance mechanisms
- Edits as necessary

Requirements

- Organisms be identified (generally to species level)
- A battery of appropriate antimicrobial agents is tested
  - marker antimicrobials may be tested
- One is able to apply the necessary expert knowledge

Journal of Antimicrobial Chemotherapy (2001) **48**, *Suppl. S1*, 87–102

JAC

Interpretative reading: recognizing the unusual and inferring resistance mechanisms from resistance phenotypes

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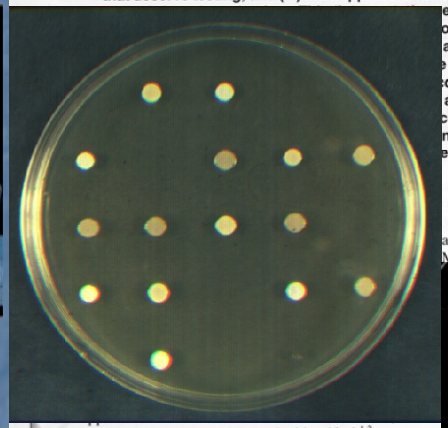
If isolates are speciated and if a sufficient range of antibiotics is tested, underlying resistance mechanisms can often be inferred from the antibiogram data. This allows: (i) anomalous combinations of phenotype and organism to be reconsidered; (ii) prediction of further antibiotics that deserve testing; and (iii) the suppression of susceptibilities that are anomalous in the light eading' is widely undertaken in France but is on and the testing of narrow ranges of anti- aware of: (i) grossly anomalous combinations e laboratory confirmation; (ii) useful indicator conferring other resistances that may be less are prone to select resistant mutants of par- combinations of organism and resistance are nd mechanism are also presented to allow full els of drugs versus speciated isolates.



and their implications for antibiotic choice, are outlined. Most UK laboratories presently test too few drugs for

further drugs that merit testing can be identified.[1,2]

To exploit its full potential, interpretative reading requires that isolates are speciated accurately and tested with large batteries of different antibiotics. This is done in France, where panels of 16 antibiotics are routinely tested against most isolates, and in some commercial systems, such as the VITEK 2, which tests panels of up to 20 antibiotics.[1–3] Interpretative reading with such comprehensive data is discussed in the second part of this paper, where the resistance patterns associated with different mechanisms,

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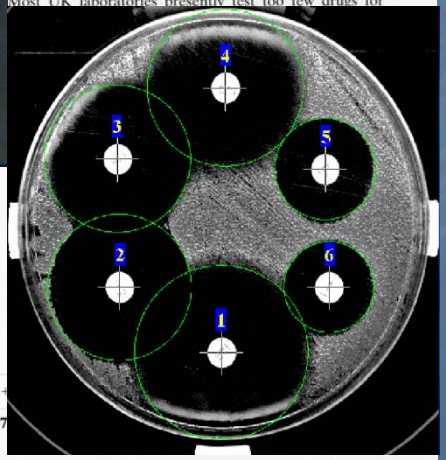


An example

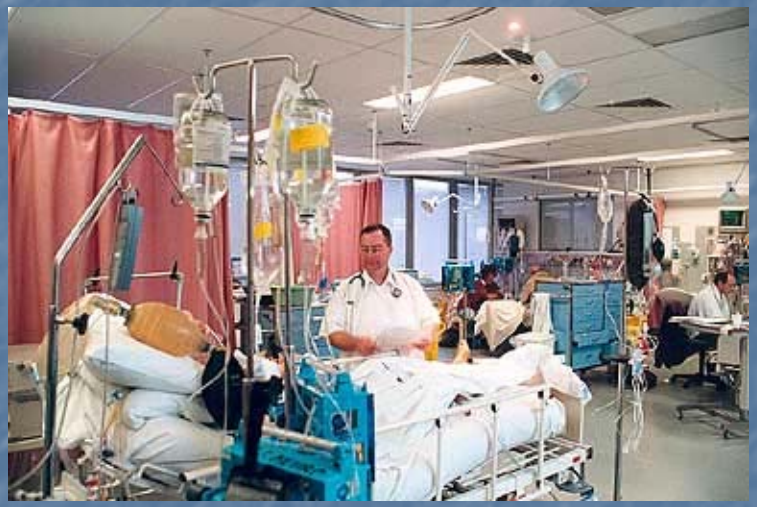
- UKNEQAS 2082 *Pseudomonas aeruginosa*

mg/L	BSAC		CLSI	Expected result
	1	2		
Amikacin	8	8	16	S
Ceftazidime	4	4	8	S
Ciprofloxacin	64	32	64	R
Gentamicin	16	32	128	R
Imipenem	16	16	>16	R
Meropenem	16	16	>16	R
Pip-tazobactam	>128	>128	>128	R
Tobramycin	16	16	128	R

mg/L	BSAC	CLSI	Expected Result
Amikacin	8	16	S
	S<8 R>16	S<=16 R>=32	
Concordance	32.7%	11.7%	

Ceftazidime	4	8	S
	S<=8 R>8	S<=8 R>=32	
Concordance	84.3%	78.5%	
Vitek2 “high-level resistance”			→ I

What does the breakpoint conceal?



Ceftazidime and amikacin have borderline susceptibility

The organism is resistant to all other agents tested

Probably derepressed AmpC and/or up-regulated efflux

Pseudomonas bacteraemia or pneumonia is life-threatening

The "correct" results may lead to ceftazidime been used as monotherapy

If used at all, ceftazidime should be used in high dosage, in combination with amikacin

European Committees

BSAC
United Kingdom

CA-SFM
France

DIN
Germany

SRGA
Sweden

CRG
Netherlands

NWGA
Norway

CLSI (NCCLS) USA

European Union

European Committee on Antimicrobial Susceptibility Testing

Expert Rules in Antimicrobial Susceptibility Testing

- Intrinsic resistance
  - susceptible results should be viewed with caution
  - anomalous combinations of phenotype and organism should be reconsidered

Intrinsic resistance

- Enterobacteriaceae
  - penicillin G; glycopeptides; fusidic acid; macrolides; linezolid; clindamycin; rifampicin…
- *Haemophilus, Moraxella, Neisseria*
  - glycopeptides; fusidic acid; linezolid; lincosamides…
- Gram positives
  - aztreonam; colistin; temocillin; nalidixic acid…
- *Proteus* spp.
  - nitrofurantoin; colistin; tetracycline
- *Campylobacter* spp.
  - glycopeptides; fusidic acid; linezolid; lincosamides; trimethoprim
- *Enterobacter* spp.
  - cefazolin; cefoxitin
- *S.maltophilia*
  - aminoglycosides; co-amoxyclav; meropenem

etc.

Expert rules in Antimicrobial Susceptibility Testing

- Exceptional resistance phenotypes
  - resistance has not been reported or is very rare
  - anomalous combinations of phenotype and organism should be reconsidered

Exceptional resistance

- Enterobacteriaceae
  - meropenem
- *Pseudomonas aeruginosa*
  - colistin
- *Neisseria meningitidis*
  - cefotaxime
- *Staphylococcus aureus*
  - glycopeptides; linezolid
- *N.gonorrhoeae*
  - cefixime; spectinomycin
- *Bacteroides* spp.
  - metronidazole, carbapenems
- *Clostridium difficile*
  - metronidazole; vancomycin
- β-haemolytic streptococci
  - penicillin

etc.

Expert rules in Antimicrobial Susceptibility Testing

- Interpretive rules
  - predict further antimicrobials that merit testing
  - promote / suppress antibiotic results
  - add footnotes and warnings from standard guidelines

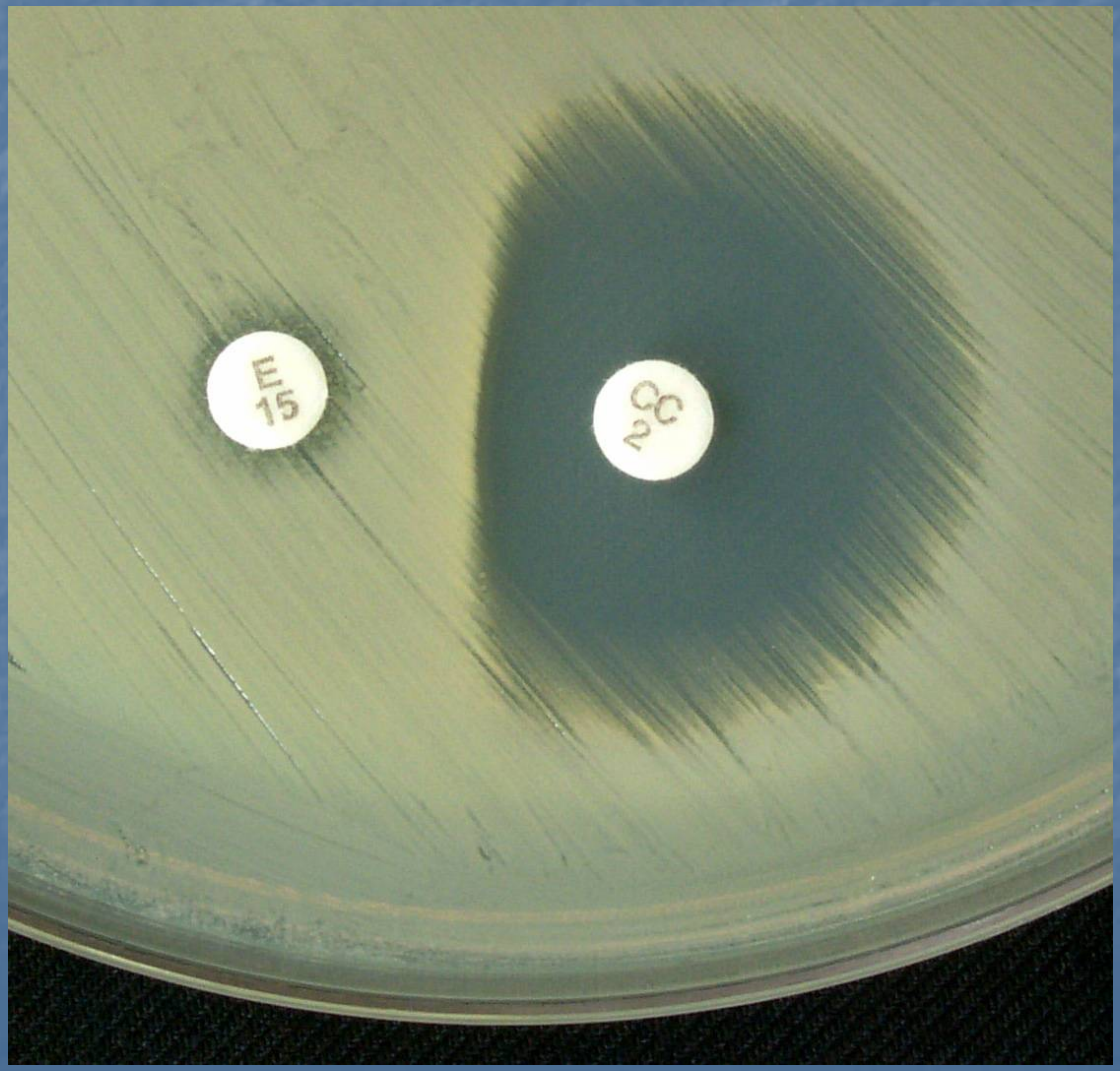
Expert rules in Antimicrobial Susceptibility Testing

- Interpretive rules
  - resistance mechanisms may be inferred
  - resistance to other agents may be predicted
  - Resistance Marker Rules edit S or I to R
    - resistance may not be fully expressed *in vitro*

Expert rules in Antimicrobial Susceptibility Testing

- Erythromycin resistance in staphylococci, streptococci, *Peptococcus, Bacteroides*
  - Efflux pumps
  - Erm ribosomal methylases
    - inducible MLS_B phenotype
    - constitutively resistant mutants can be selected
      - associated with diminished bactericidal activity of Quinupristin-Dalfopristin

Dissociated resistance



Staphylococci

- Penicillinase producers are resistant to all penicillins
  - except isoxazolyl penicillins and β-lactamase inhibitor combinations
    - Penicillinase-producing *Neisseria gonorrhoeae* and *Haemophilus influenzae* are resistant to all other penicillins
    - *Moraxella catarrhalis* virtually always produces penicillinase

Staphylococci

- Those resistant to isoxazolyl penicillins
  - oxacillin or cefoxitin resistant
  - detection of *mec* A or PBP2a
- Resistant to all β-lactams except ceftaroline and ceftobiprole

MICs (mg/L) for ESBL +ve *E.coli*

	R-	*TEM-1+*	*TEM-3+*	*TEM-10+*
Ampicillin	2	1024	256	1024
Piperacillin	1	128	64	64
Pip + 4 mg/L taz	0.5	1	2	1
Ceftriaxone	0.03	0.03	64	2
Ceftazidime	0.12	0.12	32	128
Cefoxitin	4	4	8	4
Imipenem	0.12	0.12	0.12	0.12
Meropenem	0.03	0.03	0.03	0.03

Inoculum effects

		CTX		*CAZ*		*FEP*		*PTZ*	
		10^5	10^7	10^5	10^7	10^5	10^7	10^5	10^7
TEM-10	PRM	0.12	1	4	256	2	64	2	8
SHV-10	ECO	≤0.06	≤0.06	≤0.25	4	0.12	0.25	4	8
TEM-12	KPN	0.5	8	128	1024	8	>128	8	16
SHV-3	ENC	8	1024	4	512	1	>128	2	1024
SHV-4	MMO	2	64	2	128	0.06	4	0.5	64

Thomson & Moland Ant.Agents Chemother. 2001 45:12; Bedenic *et al* Clin.Microbiol.Infect. 2001 7:626; Queenan *et al* J.Clin.Microbiol. 2004 42: 269

In vitro vs *in vivo*

- Prospective study of *K.pneumoniae* bacteraemia & literature review
- 32 evaluable patients with cephalosporin S / I ESBL producers

- 19/32 failed cephalosporin therapy

Paterson *et al JCM* 2001 39 2206

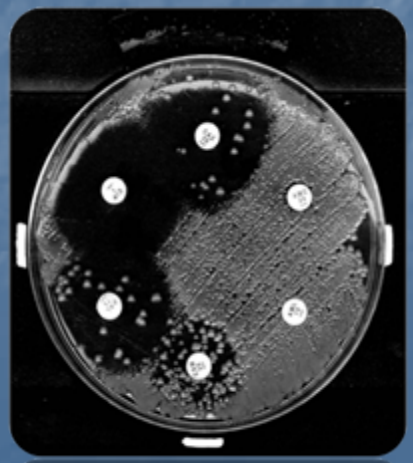
Enterobacteriaceae

- If I or R to any 3rd or 4th generation cephalosporin or aztreonam – perform an ESBL test
- If positive – edit all S to I and all I to R
  - use of β-lactam combinations is contentious
  - as is cephalosporin therapy of ESBL-producers with MICs < 2 mg/L

  - UKNEQAS 8623 *E.coli* 19 November 2007

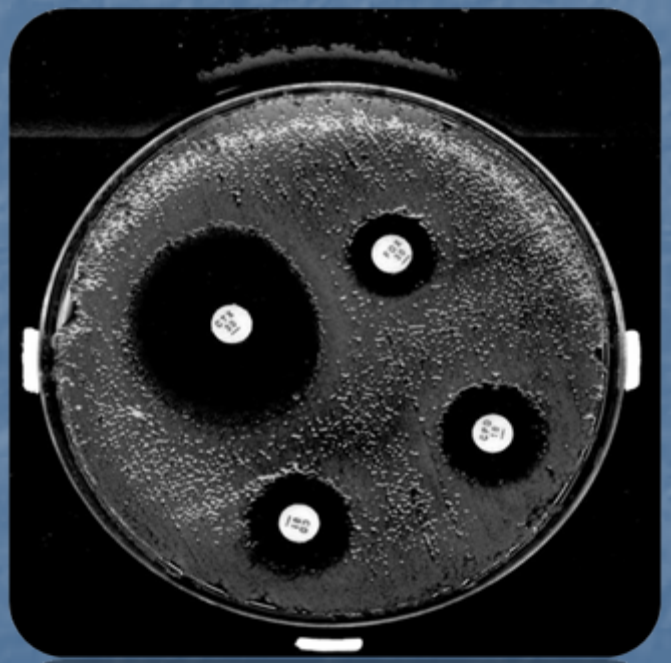
Enterobacteriaceae

- No editing required for:
  - those derepressed for AmpC or with plasmid-mediated AmpC
  - *Klebsiella oxytoca* and *Citrobacter koseri* hyperproducing chromosomal β-lactamase



Enterobacter spp., *Citrobacter freundii*, *Serratia* spp., *Morganella morganii*

- Cefotaxime, ceftriaxone, ceftazidime can select derepressed mutants
  - add comments or suppress results
  - "Avoid penicillins, cephalosporins and β-lactamase inhibitor combinations"



Enterobacteriaceae

- If R to ticarcillin, edit piperacillin to R also
  - ticarcillin-hydrolysing β-lactamases also attack piperacillin but are not expressed as well *in vitro*

BSAC Table 10: MIC and zone diameter for *Streptococcus pneumoniae*

Antibiotic	MIC Bpt. mg/L			Disc content µg	Interpretation mm		
	R>	I	S≤		R≤	I	S≥
Penicillin	1	0.12 - 1	0.06	Oxacillin 1	19	-	20

Footnote 1: Organisms with an MIC ≤ 1 mg/L are considered susceptible to β-lactam agents except in infections of the central nervous system.

If oxacillin resistant, perform penicillin, ampicillin (or amoxicillin), cefotaxime (or ceftriaxone) MICs – patterns of susceptibility are not predictable

Aminoglycosides

- *e.g.* staphylococci

GEN	TOB	KAN	APH(3')1-3	ANT(4')(4")-1	APH(2')-AAC(6)	GEN	KAN	AMI	TOB	STR
		R	√		√		R	R		
	R			√	√		R	R	R	
R					√	R	R	R	R	S

Fluoroquinolones

- *e.g. Str.pneumoniae*
  - OFL R or CIP R but MOX S and LEV S
    - target mutation in *parC (parE)*
    - "may lead to resistance under therapy"
  - MOX R or LEV R
    - combined mutation in *parC* and *gyrA*
    - resistant to all fluoroquinolones

Development of UKNEQAS

- Raw results
- Clinical comment
- Effect of Expert rules
  - EUCAST
  - Reported result
- Effect on patient management