EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

RUHR-UNIVERSITÄT BOCHUM

RUB

# Expert Rules in Antimicrobial Susceptibility Testing. Finally There!

Sören Gatermann

Bochum, Germany
soeren.gatermann@rub.de

# Utility of the Rules

- Intrinsic resistance or unusual phenotype
  - validity of identification and/or susceptibility test
- expert rules
  - based on clinical data on the usefulness of a drug in a given species or in a particular phenotype
  - avoid inappropriate use of a drug
  - suggest further actions

# Unusual phenotypes

- Resistance to penicillin G in group A streptococci
- Susceptibility to linezolid in *E. coli*

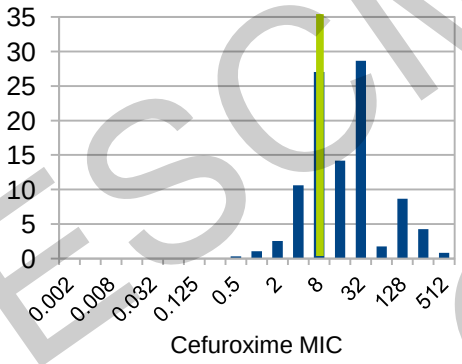
# Recognition of the unusual

- using the tables
  - intrinsinc resistances
    - a dash in the breakpoint table
  - exceptional phenotypes

**IF instrinsic resistance is absent**
**OR an exceptional phenotype (R/S) is found**
**THEN**
**check identification/susceptibility tests**

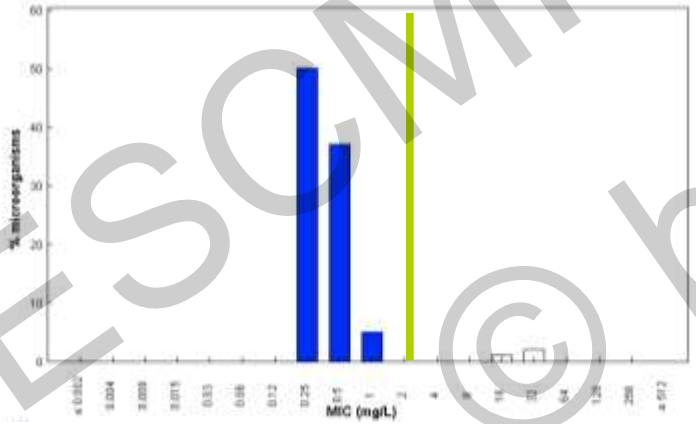
# Implicit Expert Rules

- a dash „-“ in the table says „do not use this drug on this organism“
- regardless of the testing result report as resistant (or not at all)
- this does not imply that all strains appear resistant in susceptibility tests



# Salmonella

- therapy with aminoglycosides (or some cephalosporins) is not recommended
- *in vitro* MICs are often below the breakpoints for other *Enterobacteriaceae*
- this is an expert rule, not intrinsic resistance



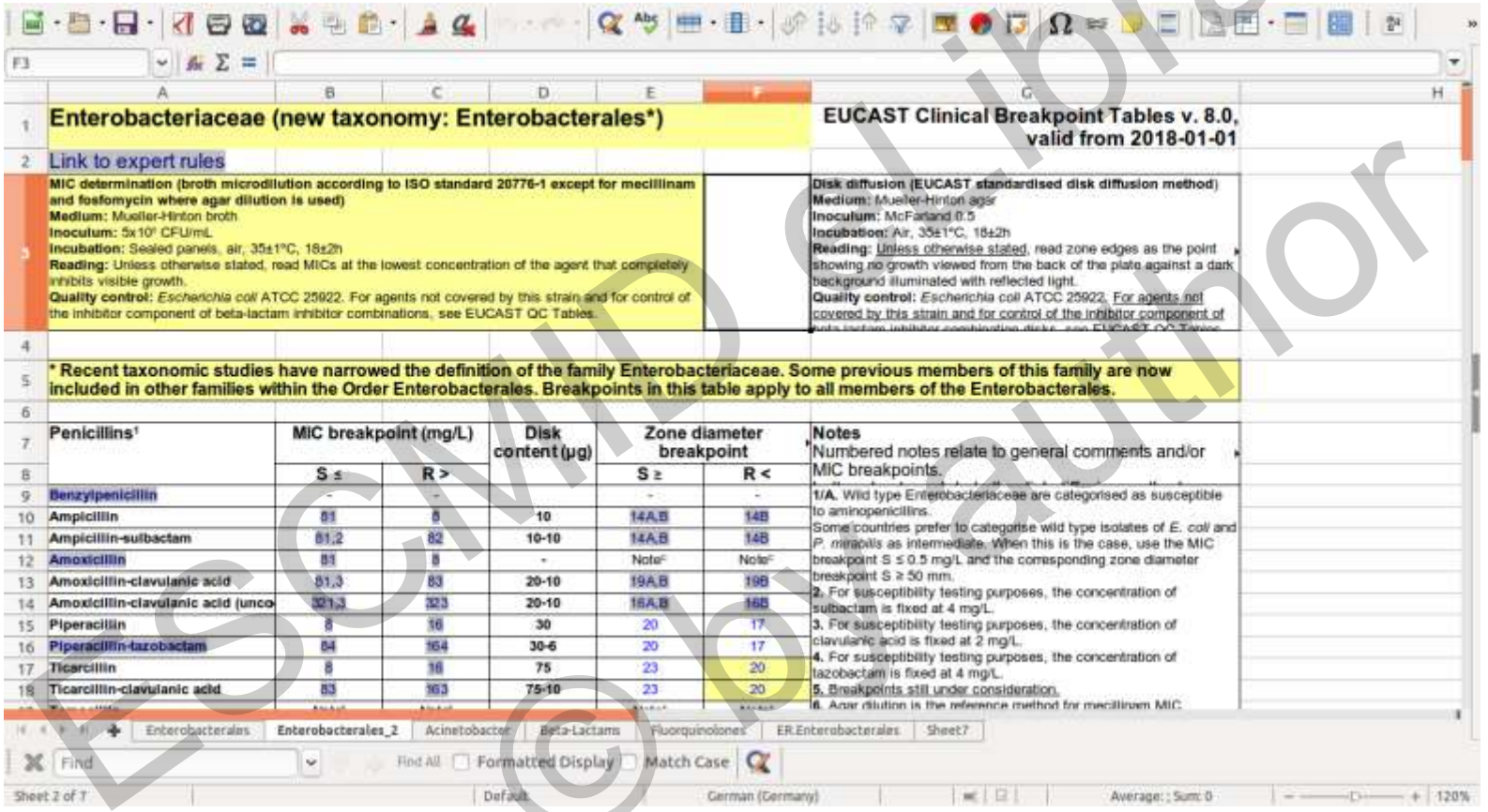
# New Format

- Outline similar to breakpoint tables
- Links from breakpoint tables to expert rules
- Rules for one organism/group of organisms  together

# Tables for

- *Enterobacterales*
- Staphylococci
- *S. pneumoniae*
- Streptococci
- Enterococci

# Integration Into Breakpoint Tables



**Enterobacteriaceae (new taxonomy: Enterobacterales*)**

**EUCAST Clinical Breakpoint Tables v. 8.0, valid from 2018-01-01**

Link to expert rules

**MIC determination (broth microdilution according to ISO standard 20776-1 except for mecillinam and fosfomycin where agar dilution is used)**
**Medium:** Mueller-Hinton broth
**Inoculum:** 5x10⁵ CFU/mL
**Incubation:** Sealed panels, air, 35±1°C, 18±2h
**Reading:** Unless otherwise stated, read MICs at the lowest concentration of the agent that completely inhibits visible growth.
**Quality control:** *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of beta-lactam inhibitor combinations, see EUCAST QC Tables.

**Disk diffusion (EUCAST standardised disk diffusion method)**
**Medium:** Mueller-Hinton agar
**Inoculum:** McFarland 0.5
**Incubation:** Air, 35±1°C, 18±2h
**Reading:** Unless otherwise stated, read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
**Quality control:** *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of

*** Recent taxonomic studies have narrowed the definition of the family Enterobacteriaceae. Some previous members of this family are now included in other families within the Order Enterobacterales. Breakpoints in this table apply to all members of the Enterobacterales.**

| Penicillins[1] | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint | | Notes |
|---|---|---|---|---|---|---|
| | S ≤ | R > | | S ≥ | R < | Numbered notes relate to general comments and/or MIC breakpoints. |
| Benzylpenicillin | - | - | | - | - | **1/A.** Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm. **2.** For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L. **3.** For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L. **4.** For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L. **5.** Breakpoints still under consideration. **6.** Agar dilution is the reference method for mecillinam MIC |
| Ampicillin | 8[1] | 8 | 10 | 14[A,B] | 14[B] | |
| Ampicillin-sulbactam | 8[1,2] | 8[2] | 10-10 | 14[A,B] | 14[B] | |
| Amoxicillin | 8[1] | 8 | - | Note[5] | Note[5] | |
| Amoxicillin-clavulanic acid | 8[1,3] | 8[3] | 20-10 | 19[A,B] | 19[B] | |
| Amoxicillin-clavulanic acid (unco | 32[1,3] | 32[3] | 20-10 | 18[A,B] | 16[B] | |
| Piperacillin | 8 | 16 | 30 | 20 | 17 | |
| Piperacillin-tazobactam | 8[4] | 16[4] | 30-6 | 20 | 17 | |
| Ticarcillin | 8 | 16 | 75 | 23 | 20 | |
| Ticarcillin-clavulanic acid | 8[3] | 16[3] | 75-10 | 23 | 20 | |

r_enterobacteral | Organism(s)

| | A | B | C | D | E |
|---|---|---|---|---|---|
| 2 | **Organism(s)** | **Indicator Antibiotic** | **Antibiotic Affected** | **Rule** | **Remarks** |
| 3 | *E. coli, P. mirabilis* | ampicillin | Piperacillin | IF ampicillin resistant THEN report piperacillin resistant regardless of test result | |
| 4 | *Klebsiella spp., Raoultella spp.* | piperacillin | Piperacillin | Report all Klebsiella spp. and Raoultella spp. piperacillin resistant | |
| 5 | *Enterobacter* spp., *Citrobacter freundii, Hafnia alvei* | cefotaxime, ceftriaxone, ceftazidime | cefotaxime, ceftriaxone and ceftazidime | IF susceptible *in vitro* to cefotaxime, ceftriaxone or ceftazidime, THEN note that monotherapy with cefotaxime, ceftriaxone or ceftazidime as well as combination therapy of these agents with an aminoglycoside should be discouraged owing to risk of selecting resistance, or suppress the susceptibility testing results for these agents. | Selection of AmpC derepressed cephalosporin resis occur during therapy. The risk is high in Enterobact and low in Morganella and Serratia.<br>The use of a 3rd generation cephalosporin in combin aminoglycoside may also lead to failure by selectior Combination with quinolones has, however, been fo The selection risk is absent or much diminished for |
| 6 | *Serratia* spp., *Morganella morganii, Providencia* spp | cefotaxime, ceftriaxone, ceftazidime | cefotaxime, ceftriaxone and ceftazidime | IF susceptible *in vitro* to cefotaxime, ceftriaxone or ceftazidime, THEN note that monotherapy with cefotaxime, ceftriaxone or ceftazidime in rare cases my select resistant mutans. | |
| 7 | *Enterobacter* spp., *Citrobacter freundii, Serratia* spp., *Morganella morganii, Hafnia alvei* | cefuroxime, | cefuroxime, | IF susceptible *in vitro* to cefuroxime THEN report cefuroxime or any other second generation cephalosporin as resistant | Although strains may appear susceptible *in vitro* the higher than with *E. coli* and *Klebsiella* spp. and thera recommended. In addition, derepressed mutants ma with cef. III, see 9.2). |
| 8 | *E. coli, Klebsiella spp., Raoultella spp.* | Cefotaxime, ceftriaxone, ceftazidime, cefepime, | cefotaxime, ceftriaxone, ceftazidime, cefepime | IF intermediate or resistant to any 3rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4th generation (cefepime) oxyimino-cephalosporin, AND susceptible to another 3rd or 4th generation cephalosporin THEN report as tested and enclose a warning on uncertain therapeutic outcome for infections other than urinary tract infections. | This phenotype is most often caused by ESBL prod producers are sometimes categorized as susceptib cephalosporins. With the exception of urinary tract i stream infections secondary to this origin, the use o in infections caused by ESBL producers remains cc should be approached with caution. There is less ex AmpC or OXA.-1 producers |
| | *E. coli, Klebsiella spp., Raoultella spp.* | Cefotaxime, ceftriaxone, ceftazidime, cefepime, | piperacillin.tazobactam, amoxicillin.clavulanic acid | IF intermediate or resistant to any 3rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4th generation (cefepime) oxyimino- | This phenotype is most often caused by ESBL prod producers are sometimes categorized as susceptib |

# Rules Integrated Into Table - Examples

- *E. coli*, *P. mirabilis*
  - **IF** ampicillin resistant **THEN** report piperacillin resistant
- *K. pneumoniae, Raoultella* spp.
  - report piperacillin resistant
- *Enterobacter* spp., *Citrobacter freundii*
  - report cefuroxime resistant (or not at all)

# ESBL Rule: *E.coli*, *P. mirabilis*, *Klebsiella pneumoniae*, *Raoultella* spp.

**IF** intermediate **OR** resistant to any 3rd generation or 4th generation cephalosporin **AND** susceptible to amoxicillin-clavulanate and/or piperacillin-tazobactam

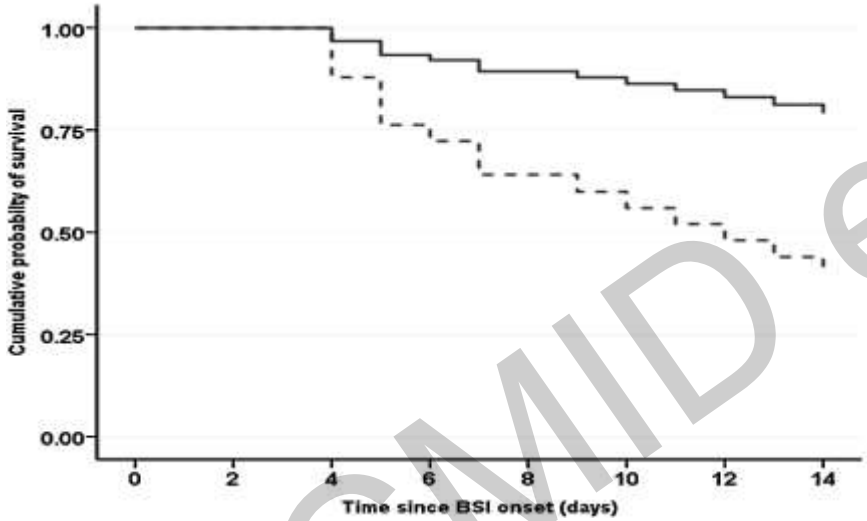
**THEN**

add a comment such as: The therapeutic outcome of treatment with amoxicillin-clavulanate or piperacillin-tazobactam is uncertain in some infection types; consideration should be given to a higher dosing regimen if these agents are used.

# Recognize Carbapenemases

- if the MIC is low, then this drug – even a carbapenem – may be used
- therapy with carbapenems is less effective if carbapenemase is present
  Hagihara et al JAC 68:161 (2013)
- efficacy depends on carbapenemase and dosing
  Wiskirchen et al AAC 57:3936 (2013), AAC 58:1671 (2014)

# Combination Therapy Better Than Single Agent

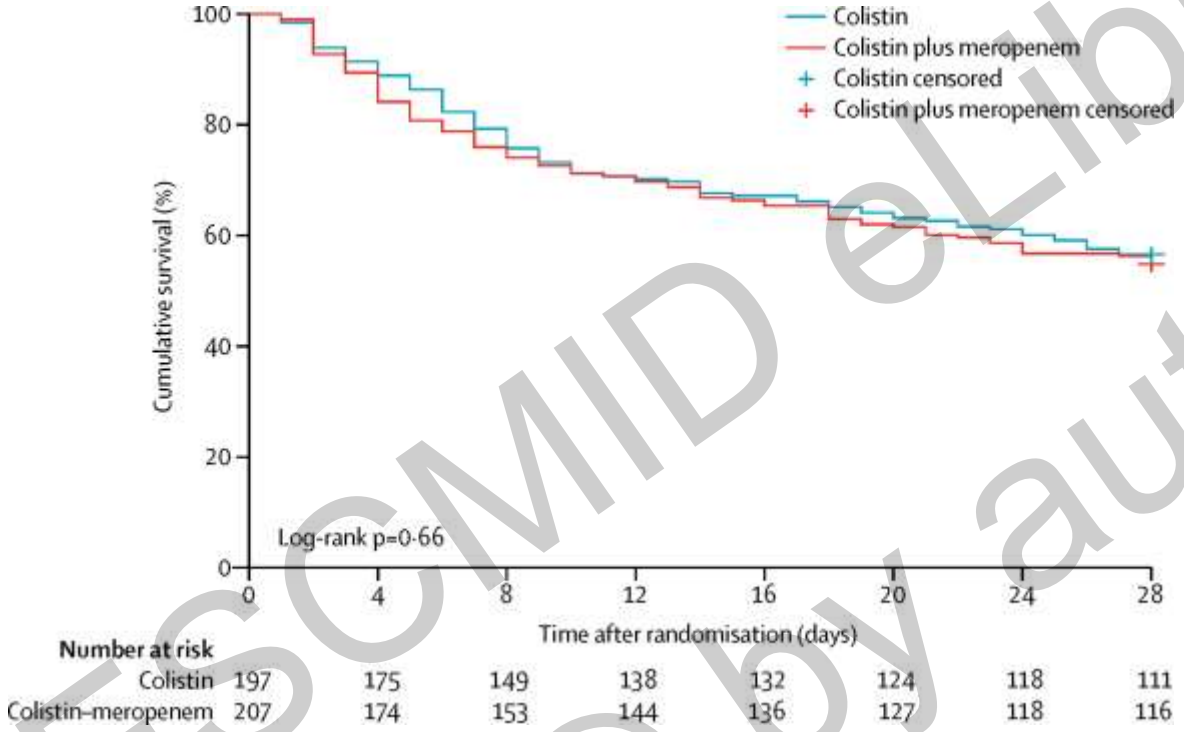



Combination therapy

Single agent

Tofas IJAA (2016) 47:335

# Meropenem-Colistin Not Superior to Colistin Alone in Acinetobacter




Paul Lancet Infect Dis. 2018 Apr;18(4):391-400.

Vardakas International Journal of Antimicrobial Agents 51 (2018) 535–547

# Expert Rule for Carbapenemases

**IF** carbapenemase is detected **AND** a carbapenem is tested susceptible

**THEN**

add a comment that significance of the result for therapy is not known