Members of the bureau of the National Antibiotic Susceptibility Committee (NAC)

- Olivier Denis (ULB- Chirec, BAPCOC, BVIKM-SBIMC)
- Stefanie Desmet (UZ Leuven)
- Youri Glupczynski (CHU UCL Namur, Godinne)
- Te-Din Daniel Huang (CHU UCL Namur, Godinne)
- Bénédicte Lissoir (GHdC – Charleroi)
- Koen Magerman (Jessa Ziekenhuis, Hasselt - BAPCOC)
- Pierrette Melin (CHU Liège)
- Hector Rodriguez-Villalobos (St Luc Bruxelles, UCL, BVIKM-SBIMC)
- Anne-Marie Van den Abeele (AZ St Lucas Gent)
- Kris Vernelen (Sciensano, Brussel)

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Redefining susceptibility testing categories **S**, **I** and **R**.

TD Daniel Huang
For the Belgian National Antibiogram Committee
The presentation in its original form can be found at www.eucast.org
Gunnar Kahlmeter and the EUCAST Steering Committee

SBIMC-BVIKM Symposium
04/04/2019

The EUCAST Steering Committee (SC) has decided to change the definitions of susceptibility testing categories but to retain the abbreviations S, I and R.

This decision was taken in June, 2018, following three general consultations (2015, 2017 and 2018). The results of the consultations are available on the EUCAST website (see Consultations)

New definitions are valid from 2019-01-01 (EUCAST breakpoint table v.9.0)

The 2002 – 2018 definitions of S, I and R
”The old definition”.

Since 2002, EUCAST has used the following definitions to categorise the microorganisms as treatable or not treatable with the agent in question.

Breakpoints in breakpoint tables are clinical, i.e. are meant to predict the clinical outcome in the infected patient.

S = Susceptible

I = Intermediate

R = Resistant

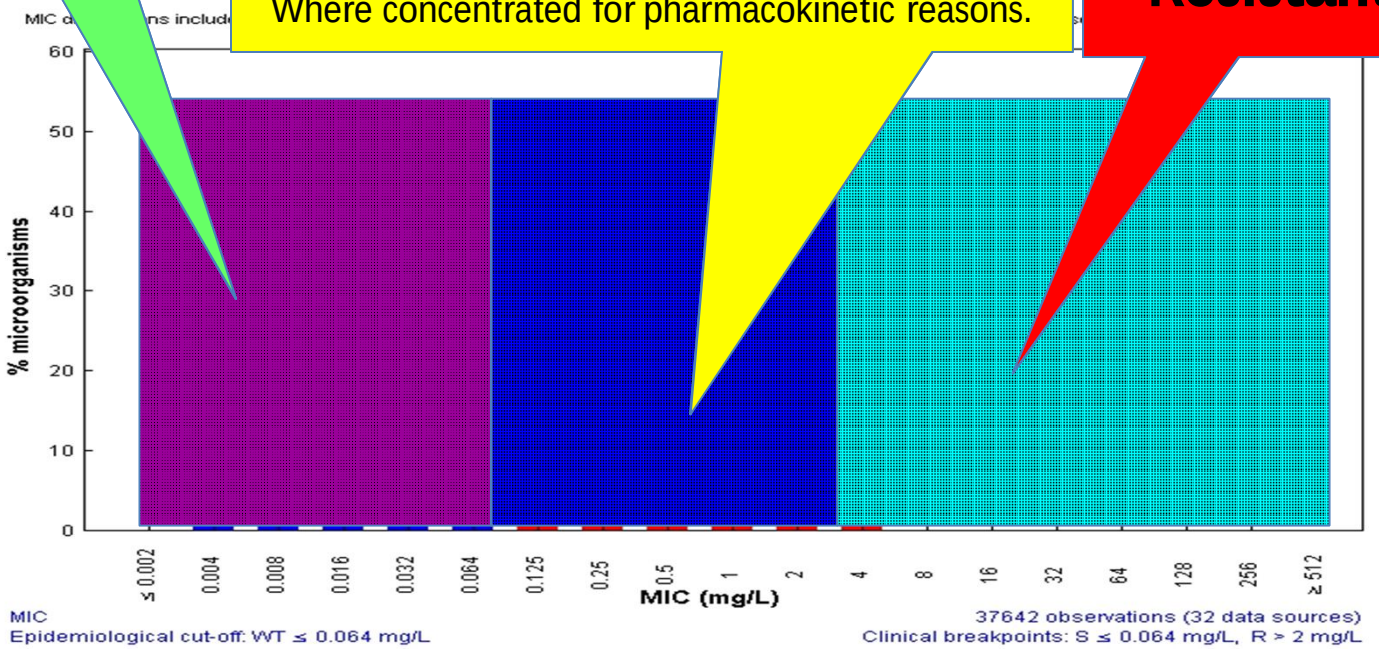
SIR – the old definitions

Susceptible

Intermediate

Uncertain effect.
Buffer zone for technical variation.
For a high dose.
Where concentrated for pharmacokinetic reasons.

Resistant



The new definitions of S, I and R

The new definitions reflect the need for correct exposure and for laboratories to take responsibility for technical difficulties and solve them prior to finalising AST reports.

The **dosing strategies relevant to EUCAST breakpoints** are available in the **breakpoint table, "Dosing" tab**.

These are the new definitions:

Susceptible, standard dosing regimen (S)

S - Susceptible, standard dosing regimen: A microorganism is categorised as *Susceptible, standard dosing regimen*,* when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

* Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution, metabolism and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Susceptible, increased exposure (I)

I – Susceptible, increased exposure: A microorganism is categorised as *Susceptible, Increased exposure** when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

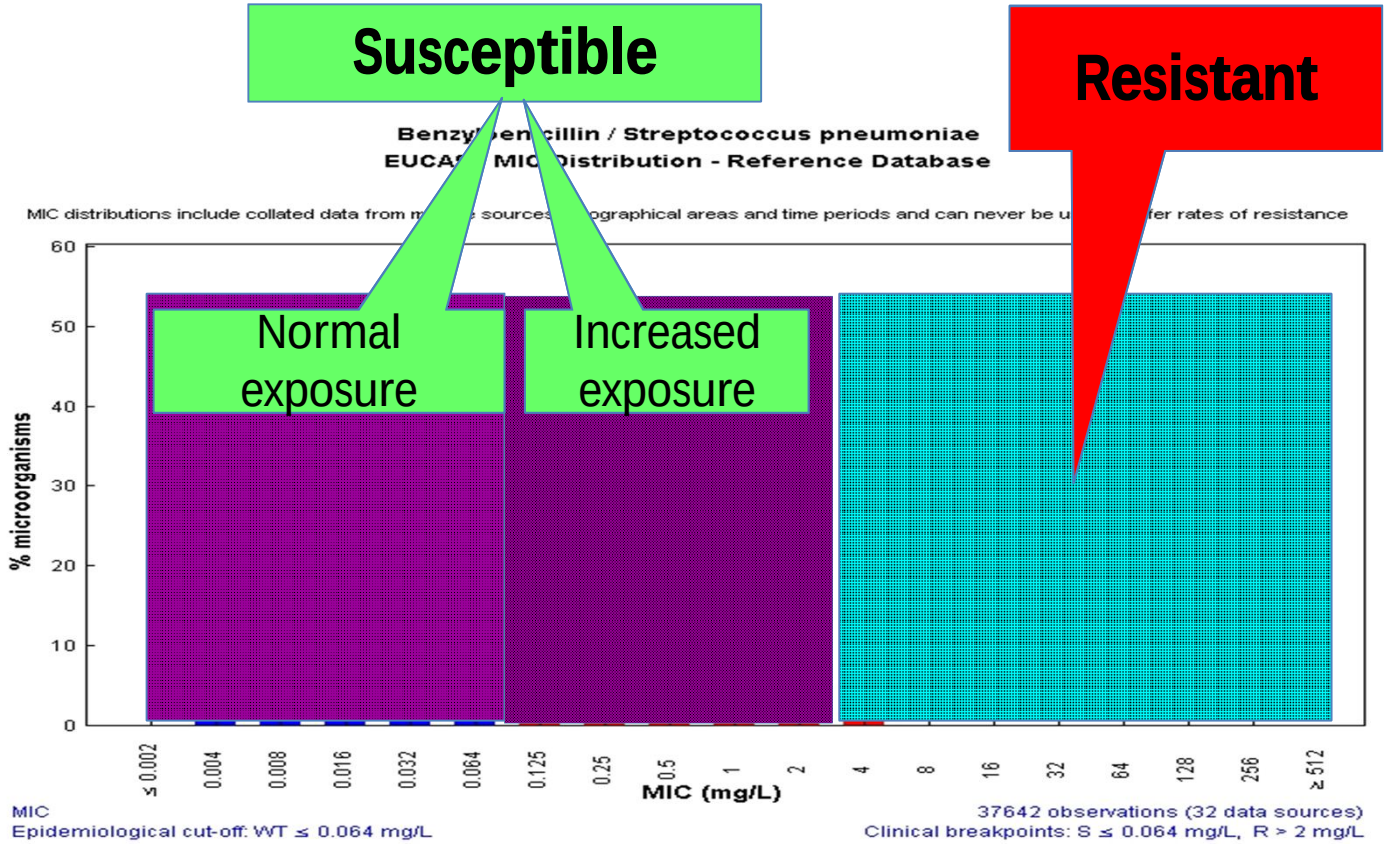
* Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution, metabolism and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Resistant (R)

R - Resistant: A microorganism is categorised as *Resistant* when there is a high likelihood of therapeutic failure even when there is increased exposure*.

* Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution, metabolism and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

SIR - new definitions 2019



Dosages

EUCAST Clinical Breakpoint Tables v. 9.0, valid from 2019-01-01

Cephalosporins	Standard dose	High dose	Special situations
Cefaclor	0.25-1 g x 3 oral depending on species and/or infection type	None	*Staphylococcus* **spp.:** Minimum dose 0.5 g x 3
Cefadroxil	0.5-1 g x 2 oral depending on species and/or infection type	None	
Cefalexin	0.25-1 g x 2-3 oral depending on species and/or infection type	None	
Cefazolin	1 g x 3-4 (or 2 g x 3) iv depending on species and/or infection type	None	
Cefepime	1 g x 3 or 2 g x 2 iv	2 g x 3 iv	*Pseudomonas* **spp.:** High dose only
Cefixime	0.2-0.4 g x 2 oral	None	**Gonorrhoea:** 0.4 g oral as a single dose
Cefotaxime	1 g x 3 iv	2 g x 3 iv	**Meningitis:** 2 g x 4 iv *S. aureus:* High dose only ~~**Gonorrhoea:** 0.5 g im as a single dose~~
Cefpodoxime	0.1-0.2 g x 2 oral depending on species and/or infection type	None	
Ceftaroline	0.6 g x 2 iv over 1 hour	0.6 g x 3 iv over 2 hours	*S. aureus* **in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv	*Pseudomonas* **spp.:** High dose only
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g avibactam) x 3 over 2 hours	None	
Ceftibuten	0.4 g x 1 oral	None	
Ceftobiprole	0.5 g x 3 iv over 2 hours	None	
Ceftolozane-tazobactam	(1 g ceftolozane + 0.5 g tazobactam) x 3 iv over 1 hour	Under evaluation	
Ceftriaxone	1 g x 1 iv	2 g x 2 iv	**Meningitis:** 4 g x 1 iv *S. aureus:* High dose only ~~**Gonorrhoea:** 0.5 g im as a single dose~~
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv	*E. coli, Klebsiella* **spp. (except** *K. aerogenes*), *Raoultella* **spp. and** *P. mirabilis:* High dose only
Cefuroxime oral	0.25-0.5 g x 2 oral depending on species and/or infection type	None	

Carbapenems	Standard dose	High dose	Special situations
~~Doripenem~~			
Ertapenem	1 g x 1 iv over 30 minutes	None	
Imipenem	0.5 g x 4 iv over 30 minutes	1 g x 4 iv over 30 minutes	*Pseudomonas* **spp.:** High dose only ~~*Acinetobacter* **spp.:** High dose only~~
Meropenem	1 g x 3 iv over 30 minutes	2 g x 3 iv over 3 hours	**Meningitis:** 2 g x 3 iv over 30 minutes (or 3 hours)
Meropenem-vaborbactam	(2 g meropenem + 2 g vaborbactam) x 3 iv over 3 hours	None	

Monobactams	Standard dose	High dose	Special situations
Aztreonam	1 g x 3 iv	2 g x 4 iv	*Pseudomonas* **spp.:** High dose only

EUCAST decision 2018

- To change the definition of **S**, **I** and **R**.
- To retain the abbreviations **S**, **I** and **R**.
- To emphasise the relationship between the exposure of the microorganism at the site of infections and the breakpoint and to task National AST Committees (NAC) with informing colleagues about the relationship between dosing practices and breakpoints.
- To task laboratories with taking the responsibility for and deal with ”technical variation and errors”.

Summary of new terminology

- An organism can still be reported ”Susceptible (**S**)” and ”Resistant (**R**)” but can no longer be reported using the word ”intermediate” to an agent. It should instead be reported using the words ”**Susceptible, increased exposure**” but **still with the abbreviation ”I”**.

- EUCAST suggests that during 2019 to include **a comment in laboratory reports**:

Susceptible, increased exposure (abbreviated “**I**”) category: high likelihood of therapeutic success because exposure to the agent can be increased at the site of infection by adjusting the dosing regimen, mode of administration or because the concentration is naturally high at the site of infection (see http://www.eucast.org/clinical_breakpoints/).

WHAT SHOULD BE DONE IN A ROUTINE MICROBIOLOGY LABORATORY FOR AST OF ANAEROBES IN 2019?

Question (Y.Glupczynski)-Answers (D. Pierard)

Universitair Ziekenhuis Brussel

VUB

WHY TO TEST AND REPORT ANTIBIOGRAMS FOR ANAEROBES ?

Lack of appropriate coverage of anaerobes is associated with bad clinical evolution (at least in some settings)

Failure of empirical therapy -> higher morbidity and higher hospitalisation costs.

Antibiotic resistance of anerobes increases over time (resistance profile not easily predictible (for some species/groups); scarce timely surveillance studies.

Usefulness of establishing epidemiology of AB susceptibility of anaerobes for probabilistic treatment of other patients in the future

Important in case of failure of treatment (documentation of antimicrobial resistance vs. inappropriate drainage of collections !!)

SHOULD ALL ANAEROBES BE TESTED ?

Is it really needed to perform AST on species/organism combinations with very predictible susceptibility ?

BUT:

- It demands a good knowledge of susceptibility/resistance patterns by microbiologist and/or infectiologist. (which is most often time not the case for both categories)
- Risk of not recognizing/detecting resistances or risk to select for resistance.
  - *e.g. Systematic treatment of mixed abdominal infections with carbapenems in the USA without any laboratory testing for anaerobes*

CLINICAL INFECTIOUS DISEASES® 2018;67(2):221–8

Eggerthella lenta Bloodstream Infections Are Associated With Increased Mortality Following Empiric Piperacillin-Tazobactam (TZP) Monotherapy: A Population-based Cohort Study

Alejandra Ugarte-Torres,[1,a] Mark R. Gillrie,[2,a] Thomas P. Griener,[3,a] and Deirdre L. Church[4]

[1]Department of Medicine, Division of Infectious Diseases, Alberta Health Services, University of Calgary, [2]Department of Microbiology, Immunology and Infectious Diseases, and [3]Department of Pathology & Laboratory Medicine, Cumming School of Medicine, University of Calgary, and [4]Department of Medicine, Division of Infectious Diseases, Department of Pathology & Laboratory Medicine and Medicine, University of Calgary, Section of Microbiology, Calgary Laboratory Services, Alberta, Canada

Background. *Eggerthella lenta* is a anaerobic gram-positive bacilli associated with polymicrobial intraabdominal infections. Recently, *E. lenta* was recognized as an important cause of anaerobic bloodstream infections (BSIs) associated with high mortality. *Eggerthella lenta* has been reported to have high minimal inhibitory concentrations (MICs) to piperacillin-tazobactam (TZP), a broad-spectrum antibiotic with anaerobic coverage commonly used in multiple centers for empiric treatment of abdominal sepsis.

Methods. We describe a retrospective population-based analysis of invasive *E. lenta* infections from 2009 through 2015. A logistic regression analysis for 30-day mortality risk factors was conducted.

Results. We identified 107 *E. lenta* infections, 95 (89%) were BSIs, 11 (10%) skin and soft tissue infections, and 1 intraabdominal abscess. Polymicrobial infections were found in 40%; 72% of isolates were from a gastrointestinal source, most commonly appendicitis (33%) of which two-thirds were perforated. TZP MIC50 and MIC90 for *E. lenta* isolates were 32 µg/mL and 64 µg/mL, respectively. The overall 30-day mortality for BSI was 23% and was independently associated with empiric TZP monotherapy (odds ratio [OR], 4.4; 95% confidence interval [CI], 1.2–16; $P = .02$) and intensive care unit stay (OR, 6.2; 95% CI, 1.4–27.3; $P = .01$). Thirty-day mortality rates were significantly influenced by the use of different TZP MIC breakpoints.

Conclusions. Our results demonstrate the increased recognition of *E. lenta* as an anaerobic opportunistic pathogen and highlight the need for improved empiric antimicrobial guidelines and TZP MIC breakpoints with better correlation to clinical outcomes to guide appropriate management of invasive *E. lenta* infections.

SHOULD ALL ANAEROBES BE TESTED ?

Nearly always active:

Metronidazole

- Bactericidal vs most Gram-neg. anaerobic strains (*Bacteroides* spp.: 0-<2 % resistant)
- Inactive versus microaerophilic streptococci, *Propionibacterium/Cutibacterium* and *Actinomyces* spp.

Carbapenems

Resistant to most *Bacteroides* spp. beta-lactamases (cephalosporinases). Excellent activity against all anaerobes, but increasing incidence of Group II *B. fragilis* (identification by MALDI)

- *B. fragilis* group: 0-7% resistance (but minority of *cfi*A + strains (group II *B. fragilis;*)
- cfiA+ -> not necessarily Carba-R (silent gene); Carbapenem-R linked to other resistance mechs (cephalosporinases + Porin impermeability)

β-lactam/ β-lactamase inhibitors

- Some increase of resistance over time (*B. fragilis* group, especially species other than *B. fragilis*)
- Overproduction of chromosomal cephalosporinase (CepA) + porin impermeability
- *B. fragilis group (other than B. fragilis)* > *B. fragilis*: 10-15% (I+R) Amoxy-clav
  15-20% (I+R) Pip/tazo
  (validity of Etest questionnable)

SHOULD ALL ANAEROBES BE TESTED ?

Variable activity :

Clindamycin

Increasing resistance over time (bimodal distribution)

- *Bacteroides fragilis* (B. fragilis group > B. fragilis): 30-40%
- *Prevotella* spp.: 30%

CAVE: inducible resistance, incubation at least 48 hours (even if strain well grown!)

Fluoroquinolones

'Third-generation' (i.e. moxifloxacin) show good in-vitro activity; limited published data

- *B. fragilis* group moxifloxacin 29% with CLSI breakpoints

NB: no specific EUCAST breakpoints for Moxifloxacin (="IE") document for anaerobes (lowering PK/PD breakpoint of down to MIC of 0.25 mg/L since 2017)

Tigecycline

- Active against nearly all anaerobes including strains of *B. fragilis* that are resistant to b-lactams, clindamycin and quinolones. MIC values are somewhat higher for clostridia

Note: warning about lack of clinical activity in intra-abdominal infections

Variable activity but often predictable :

Penicillin

Effective (>95% susceptibility) against *Peptostreptococcus* spp., most *Clostridium* spp. and nonsporulating anaerobic bacilli

Inactive versus some or most penicillinase-producing anaerobes (>95% *Bacteroides* spp. and 70-75% *Prevotella* spp. are beta-lactamase positive; *Fusobacterium* spp.; 5-10% (low numbers) *Clostridium* spp. 5% (low numbers)

WHAT AST METHOD IS RECOMMENDED FOR ANAEROBES?

Adapted from E. Nagy et al. / Clinical Microbiology and Infection 2018

Method	Pro	Contra	
Agar dilution	Validated method	Labour intensive	Reference standard
Broth microdilution	Commercial assays available, multiple antibiotics, inexpensive	Only suitable for the *Bacteroides fragilis* group	Limited number of studies
Gradient strips	Easy and flexible	Expensive	Concerns about performance and warnings on specific agents
Disc diffusion	Inexpensive, easy, flexible	No validated method, studied mainly fast-growing anaerobic species	EUCAST development project disbanded

Anaerobe 31 (2015) 65–71

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Development of EUCAST disk diffusion method for susceptibility testing of the *Bacteroides fragilis* group isolates☆

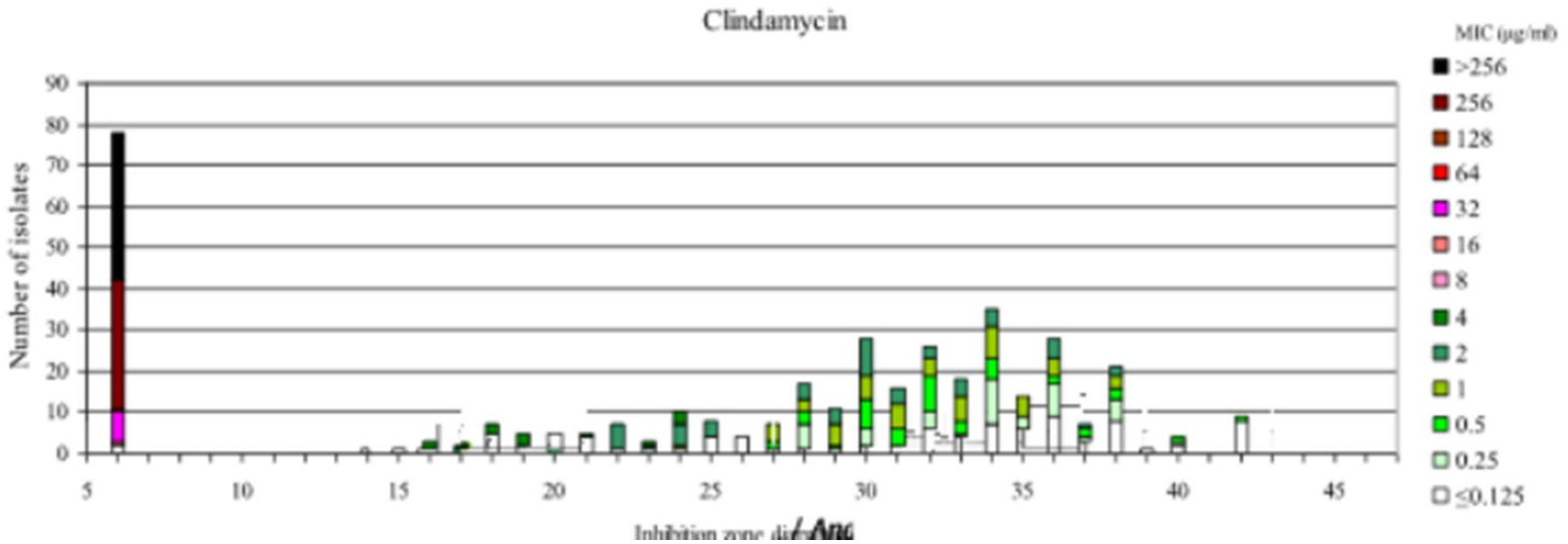
Elisabeth Nagy [a, *], Ulrik Stenz Justesen [b], Zsuzsa Eitel [a], Edit Urbán [a], on behalf of ESCMID Study Group on Anaerobic Infection

[a] Institute of Clinical Microbiology, University of Szeged, Szeged, Hungary
[b] Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark

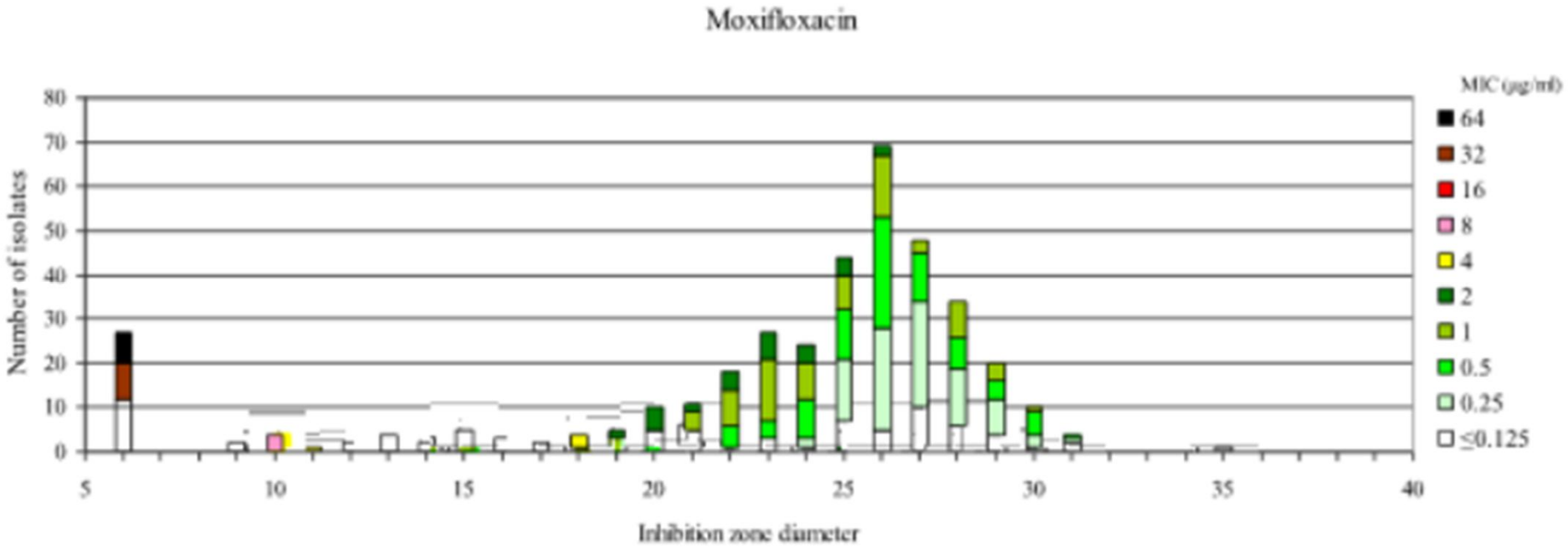
- good agreement between the inhibition zone diameters and the MICs for meropenem, metronidazole, moxifloxacin and tigecyclin
- amoxicillin/clav & pip/tazo: overlap of the zone diameter determination
- the 10 mg clindamycin disc clearly separated the resistant and the susceptible population

B. FRAGILIS GROUP / CLINDAMYCIN
CAVE INDUCTIBLE RESISTANCE (ALWAYS 48 H INCUB)

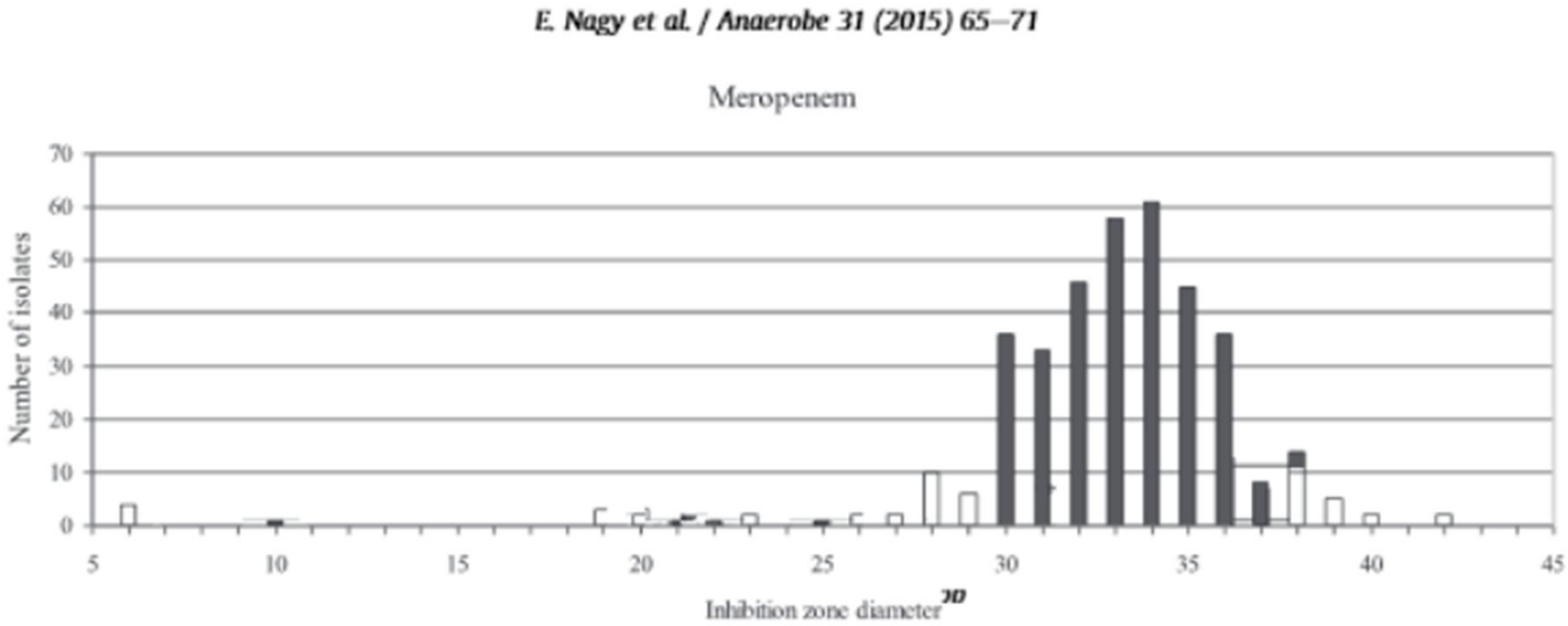
E. Nagy et al. / Anaerobe 31 (2015) 65–71



B. FRAGILIS GROUP / MOXIFLOXACIN



B. FRAGILIS GROUP / MEROPENEM



WHICH ANTIBIOTICS SHOULD BE TESTED ?

UZ Brussel (=NAC):

- **Gram positive:**
  - Penicillin
  - Clindamycin
  - Metronidazole (not for *Cutibacterium*)

- **Gram negative:**
  - ~~Penicillin~~ always reported as R
  - Amoxi/clav
  - Clindamycin
  - Metronidazole
  - Meropenem

In specific settings (diabetic foot, osteo-articular, PJI)
- Moxifloxacin
- Tigecycline
- (Minocycline)

DANK U

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