Nuovi metodi e nuove tecniche di diagnosi rapida a disposizione del clinico

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Conflicts of interest

- Investigator-initiated grants (Pfizer, Gilead Italia, Shionogi)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma)

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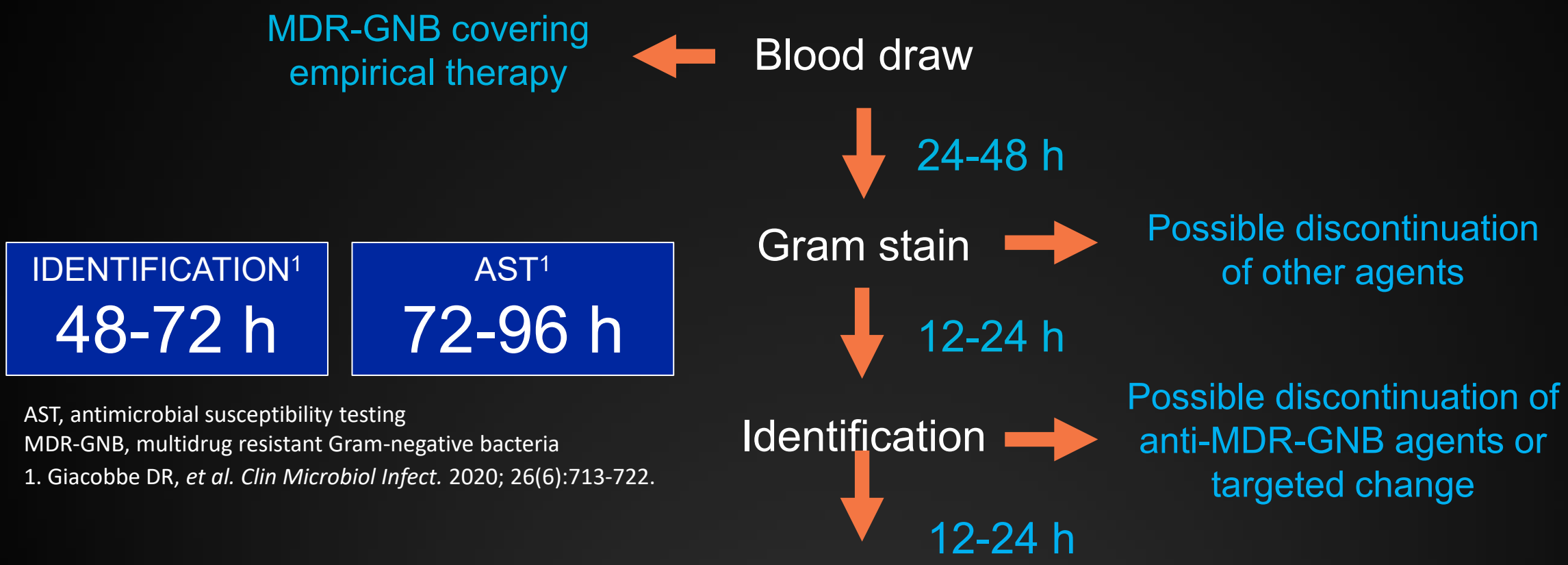
Conventional methods in patients with suspected MDR-GNB BSI[1]



AST, antimicrobial susceptibility testing
MDR-GNB, multidrug resistant Gram-negative bacteria

1. Giacobbe DR, *et al. Clin Microbiol Infect.* 2020; 26(6):713-722.

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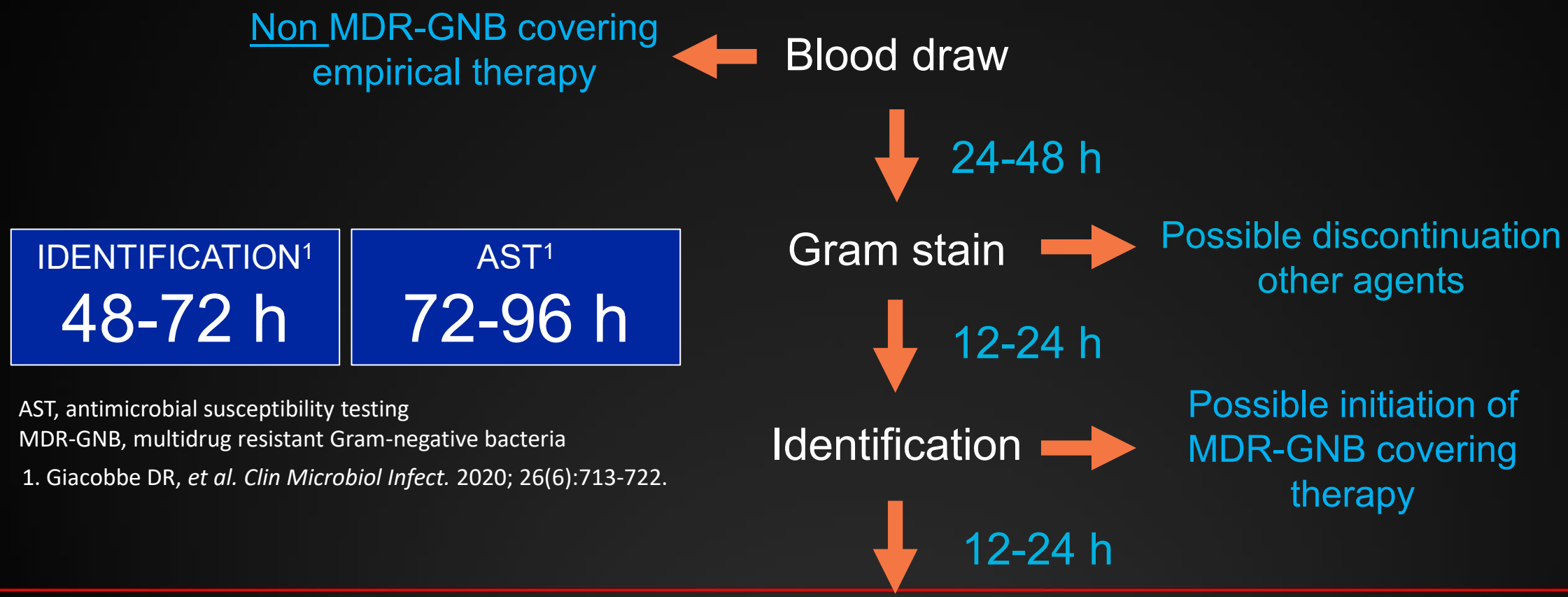
Potential advantages of rapid tests for therapy of patients with suspected MDR-GNB infection

- More rapid discontinuation of toxic agents
- More rapid administration of an appropriate therapy

MDR-GNB, multidrug resistant Gram-negative bacteria

Giacobbe DR, personal opinion

Conventional methods in patients without suspected MDR-GNB BSI



IDENTIFICATION[1]	AST[1]
48-72 h	72-96 h

AST, antimicrobial susceptibility testing
MDR-GNB, multidrug resistant Gram-negative bacteria

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Potential advantages of rapid tests for therapy of patients without suspected MDR-GNB infection

- More rapid administration of an appropriate therapy
- Identification and more rapid isolation of an unknown carrier

MDR-GNB, multidrug resistant Gram-negative bacteria

Giacobbe DR, personal opinion

Management of KPC-producing *Klebsiella pneumoniae* infections[1]

on behalf of the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID), Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA)

- **Question:** How can the laboratory speed up KPC-KP identification and susceptibility testing?

- **Answer:** diagnostic technologies could speed up the diagnosis of KPC-KP infections and potentially improve patient outcomes. However, whether they should be introduced into the laboratory workflow remain a choice to be carefully balanced locally, according to the available resources and personnel in each hospital.

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1. Bassetti M, *et al. Clin Microbiol Infect.* 2018; 24(2):133-144.

Examples of tests for (more) rapid diagnosis of MDR-GNB BSI[1]

- **MALDI-TOF** (Identification: 0.5-6 h after blood culture positivity)
- **PNA-FISH/Quick-FISH** (Identification: 0.5-3 h after blood culture positivity)
- **ALFRED60** (Phenotypic antibiogram: 3-5 h after blood culture positivity)
- **Accelerate Pheno system** (Identification and phenotypic antibiogram: 1.5-3 h and 7-9 h after blood culture positivity, respectively)
- **Verigene BC-GN** (Identification and molecular antibiogram: <2 h and <2 h after blood culture positivity, respectively)
- **FilmArray BCID** (Identification and molecular antibiogram: 1 h and 1 h after blood culture positivity, respectively)
- **Unyvero system** (Identification and molecular antibiogram: 4-5 h and 4.5 h after blood culture positivity, respectively)
- **LightCycler SeptiFast** (Identification: 4-5 h after blood draw)
- **Magicplex Sepsis** (Identification: 3-6 h after blood draw)
- **VYOO** (Identification: 7 h after blood draw)
- **SepsiTest** (Identification: 8 h after blood draw)
- **T2Bacteria panel** (Identification: 5-6 h after blood draw)
- **T2Resistance panel** (Molecular antibiogram: 3-5 h after blood draw)

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Examples of tests for (more) rapid diagnosis of MDR-GNB VAP[1]

- **MALDI-TOF** (Identification: 0.5-6 h after respiratory sample positivity)
- **FilmArray Pneumonia Panel Plus** (Identification and molecular antibiogram: 1 h after collection of respiratory sample)
- **Unyvero Hospitalized Pneumonia panel** (Identification and molecular antibiogram: 4-5 h after collection of respiratory sample)
- **Accelerate Pheno system** (FDA approved and CE-IVD marked for bacteremia, preliminary results on respiratory samples but still needing development for respiratory infections[1,2])

1. Riccobono E, *et al. Expert Rev Mol Diagn* 2022;22(1):49-60;
2. Douglas IS, *et al. Am J Respir Crit Care Med* 2015;191(5):566–573.

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Is it only a matter of time and resources/personnel?

TIME TO IDENTIFICATION

TIME TO ANTIBIOGRAM

IDENTIFIED ORGANISMS

IDENTIFIED RESISTANCE DETERMINANTS

COSTS

PERSONNEL AND 24/7 LABORATORY SERVICE

EXPERTISE FOR INTERPRETATION

LOCAL EPIDEMIOLOGY OF MDR-GNB AND RESISTANCE DETERMINANTS

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Example of implementation of rapid testing

- Retrospective quasi-experimental study
- Verigene BC-GN
- 832 patients included
- In presence of IDS consultation, both post-RDT/pre-AMS (aHR, 1.34; 95% CI, 1.04-1.72) and post-RDT/AMS (aHR, 1.28; 95% CI, 1.01-1.64), improved time to optimal therapy

aHR, adjusted hazard ratio; ID, infectious diseases specialist
AMS, antimicrobial stewardship; RDT, rapid diagnostic test

1. Claeys KC, *et al. Open Forum Infect Dis.* 2020; 7(10):ofaa427.

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Rapid tests to guide rapid targeted treatment according to resistance determinants

	ESBL	AmpC	KPC	OXA-48	MBL
Ceftazidime-avibactam	+	+	+	+	-
Ceftolozane-tazobactam	+	+	-	-	-
Meropenem-vaborbactam	+	+	+	-	-
Imipenem-relebactam	+	+	+	-	-
Cefiderocol	+	+	+	+	+

Lagace-Wiens et al. Infect Drug Res 2014;9:13-25
Castanheira et al. AAC 2012;56:4779-85
Livermore et al. AAC 2011; 55:390-4
Hong et al. Infect Drug Res 2013;6:215-23
Livermore et al. JAC 2013;68:2286-90
Shortridge et al. Microbiol Spectr 2022;9;e0271221

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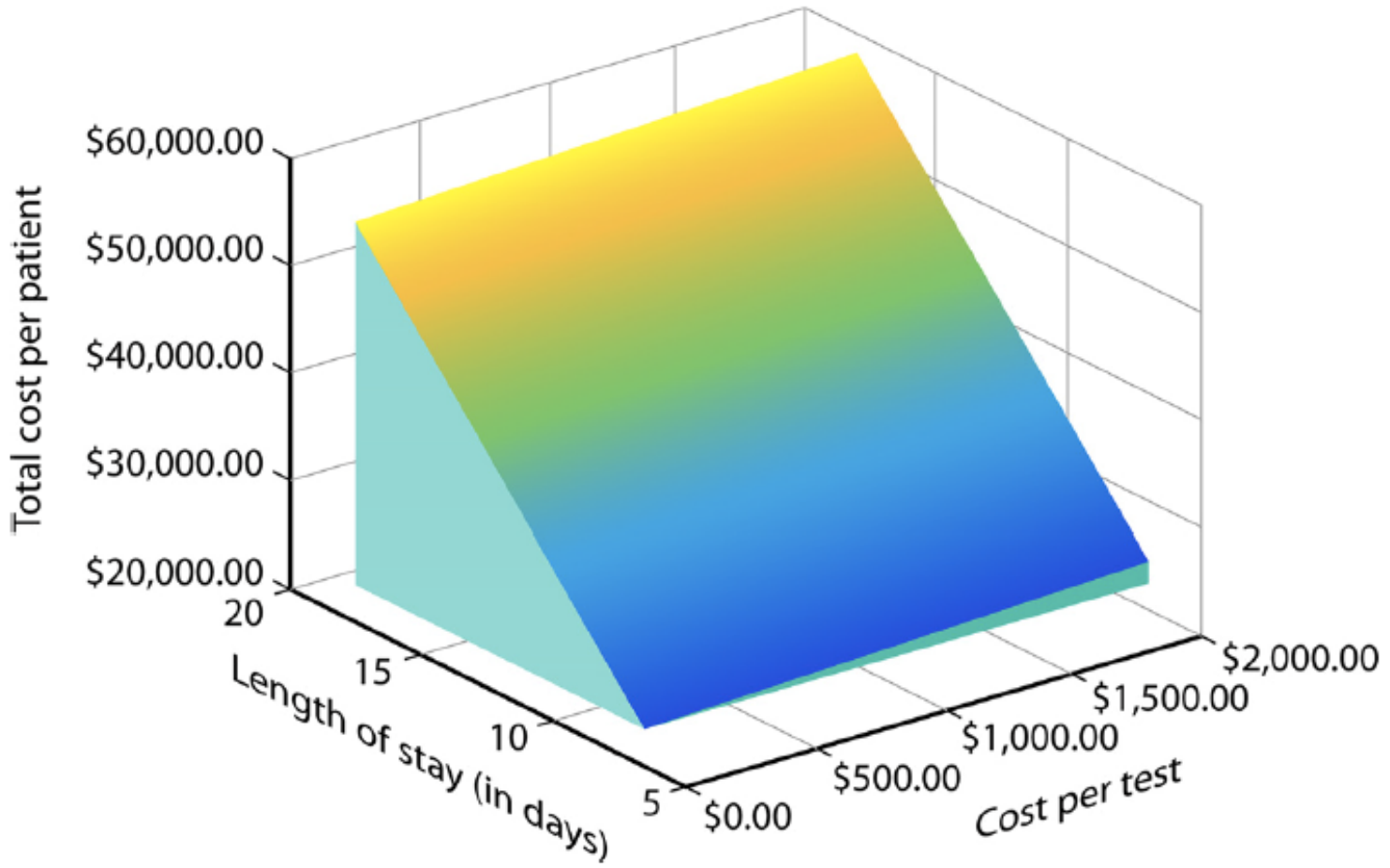

FIG 5 Three-dimensional plane showing the relationship between length of stay (*x* axis) (ranging from 6 to 18 days), total cost per patient (*y* axis) (ranging from $22,322.04 to $58,167.84), and cost per test per patient (*z* axis) (ranging from $43 to $2,000).

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Pliakos et al. ***Clin Microbiol Rev*** 2018

Clinical Case: Patient Presentation

- **October 2021**
- Request of IDS consultation for fever
- Presence of pneumonia at chest X-ray
- PCT 9.02 ng/mL; CRP 292 mg/L
- Collection of deep respiratory specimens for culture
- Collection of different sets of blood cultures from peripheral veins and CVC
- T2Bacteria panel and T2Resistance panel on blood

Giacobbe DR, personal case

Clinical Case: T2Bacteria and T2Resistance results

- **T2Bacteria**
- *Enterococcus faecium*: not detected
- *Staphylococcus aureus*: not detected
- *Klebsiella pneumoniae*: not detected
- *Acinetobacter baumannii*: not detected
- ***Pseudomonas aeruginosa*: detected**
- *Escherichia coli:* not detected

- **T2Resistance**
- *mecA, mecC*: not detected
- *VanA, VanB*: not detected
- *KPC*: not detected
- *CMY, DHA*: not detected
- *OXA-48*: not detected
- *NDM, VIM, IMP*: not detected
- *CTX-M*: not detected

Clinical Case: Patient Presentation

- Very rapid availability of T2Bacteria and T2Resistance results
- Therapy was decided based on rapid test results (early diagnostic-driven therapy)

Clinical Case: Patient Presentation

- Recent isolation of ceftazidime/avibactam-susceptible and ceftolozane/tazobactam-susceptible CRPA from other patients in the same ward (information on resistance determinants unavailable)
- Initiation of ceftazidime/avibactam was considered
- ceftolozane/tazobactam was not available at that time

Clinical Case: Patient Presentation

- Carbapenem resistance in CRPA may be also mediated by efflux systems/alterations to outer membrane permeability[1]
- Ceftazidime/avibactam was started
- An improvement of clinical conditions was registered in the subsequent days

1. Poole K. *Front Microbiol 2011;* 2:65.
CRPA, carbapenem-resistant *Pseudomonas aeruginosa*

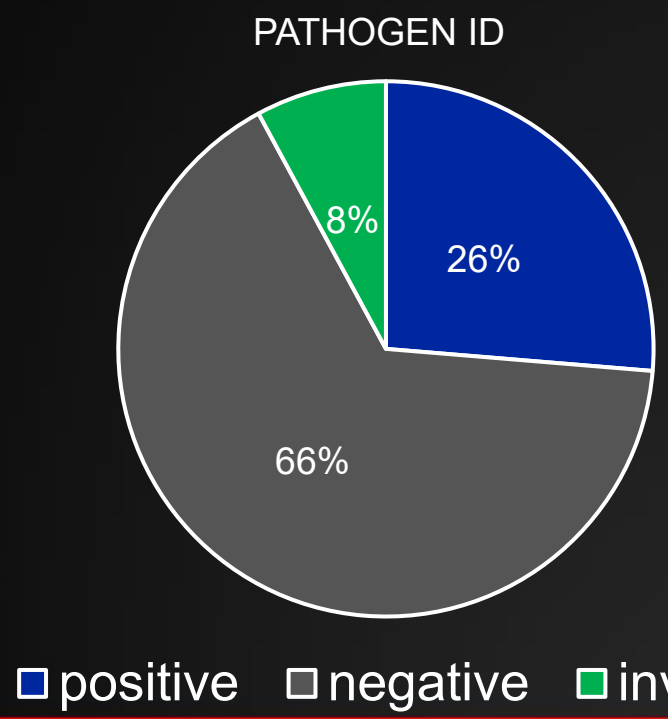
Clinical Case: Patient Presentation

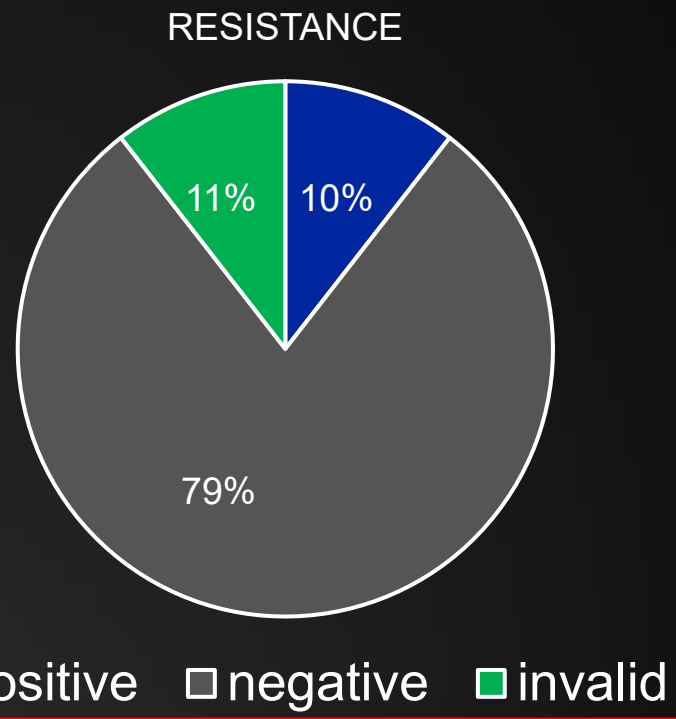
- After a few days blood cultures turned out positive for ceftazidime/avibactam-susceptible, meropenem-susceptible, but third/fourth generation cephalosporins-resistant *Pseudomonas aeruginosa*
- No bacteria grew from respiratory cultures

Giacobbe DR, personal case

T2Bacteria/T2Resistance ®

- 37 tests over April-December 2021





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Discussion

- The potential impact on prognosis of rapid tests is mediated by reduction of turnaround time for identification/antibiogram and by direct targeted treatment on occasions
- Crucial role of resistance determinants in guiding treatment choices
- Role of local resources and microbiological epidemiology in building local diagnostic algorithms

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Discussion

- Need for clinicians' expertise in interpreting results (including negative ones)
- Molecular rapid tests generally identify a limited spectrum of microorganisms and of resistance mechanisms
- Molecular antibiogram provides qualitative but not quantitative results
- Consider prioritization of specific patients' categories and wards of patients at risk to maximize cost-effectiveness

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Discussion

- Differential activity of novel agents according to resistance determinants is becoming essential for both empirical and diagnostic-driven therapeutic choices
- Need for large studies assessing the impact of rapid diagnostics on the outcome of MDR-GNB infections in the ICU
- Importance of generalization of results and between-center heterogeneity

Thank you

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