Étude interventionnelle prospective de 3 approches RAST sur 200 hémocultures patients à bacilles à Gram négatif :

performances microbiologiques et impact sur la prescription antibiotique.

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CORATA– 19 septembre 2024

- **1.2-1.4 million** bloodstream infections in Europe each year with an associated mortality rate of **13.2 – 19.7%**
- **30%** off all patients receive an inappropriate empirical treatment
- A retrospective cohort study on 10 628 bloodstream infections in Sweden concluded that
  - No association in favor of a protective effect between appropriate therapy and mortality was found at 1, 3 and 6 hours after blood culture collection

  BUT

  - At **12 hours** the risk of death increased with inappropriate treatment and continued to increase gradually at 24, 48 and 72 hours.

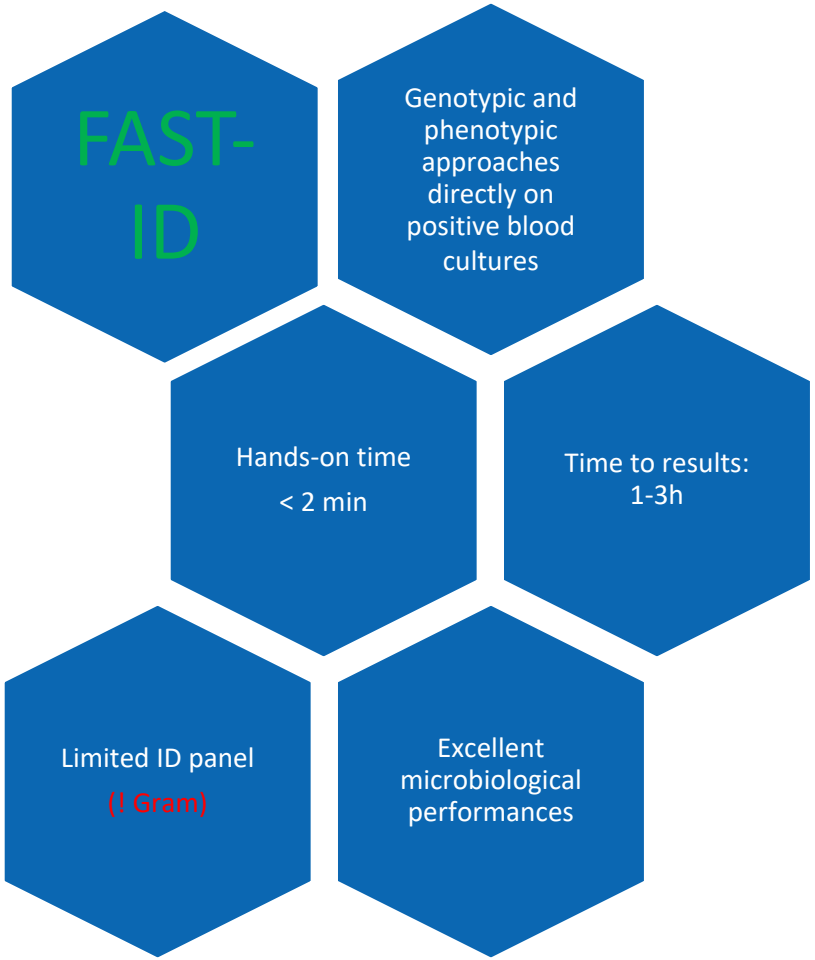
→URGENT NEED for rapid diagnostic tests

Fleischmann-Struzek et al., Lancet Resp Med 2018 – Cassini et al., Lancet 2019 – Van Heuverswyn et al., CID 2023

TABLE 2 | Select genotypic tests that are approved for rapid detection of resistance markers in positive blood cultures.

Test	Organisms identified	Resistance genes	References
Biofire BCID2 (Biofire, Salt Lake City, UT)	9 Gram-positive bacterial targets 14 Gram-negative bacterial targets 7 yeast targets	Carbapenemases bla_{IMP} bla_{KPC} $bla_{OXA-48-like}$ bla_{NDM} bla_{VIM} Colistin resistance *mcr-1* ESBL bla_{CTX-M} Methicillin *mecA/C* MREJ Vancomycin *vanA/B*	(59)
Verigene BC-GN (Luminex, Austin, TX)	9 Gram-negative bacterial targets	Carbapenemases bla_{IMP} bla_{KPC} $bla_{OXA-48-like}$ bla_{NDM} bla_{VIM} ESBL bla_{CTX-M}	(60)
Verigene BC-GP (Luminex)	13 Gram-positive bacterial targets	Methicillin *mecA* MREJ Vancomycin *vanA/B*	(61)
ePlex® BCID-GP (GenMark, Carlsbad, CA)	20 Gram-positive bacterial targets "pan" Gram-negative target "pan" Candida target	Methicillin *mecA* MREJ Vancomycin *vanA/B*	(62)
ePlex® BCID-GN (GenMark)	21 Gram-negative targets "pan" Gram-positive target "pan" Candida target	Carbapenemases bla_{IMP} bla_{KPC} $bla_{OXA-48/OXA-23}$ bla_{NDM} bla_{VIM} ESBL bla_{CTX-M}	(63)
ePlex® BCID-FP (GenMark)	15 Fungal targets	None	(64)
Xpert® MRSA/SA BC (Cepheid, Sunnydale CA)	1 Gram-positive target	Methicillin *mecA*	(65)

Banerjee and Humphries, Frontiers in Medecine 2021



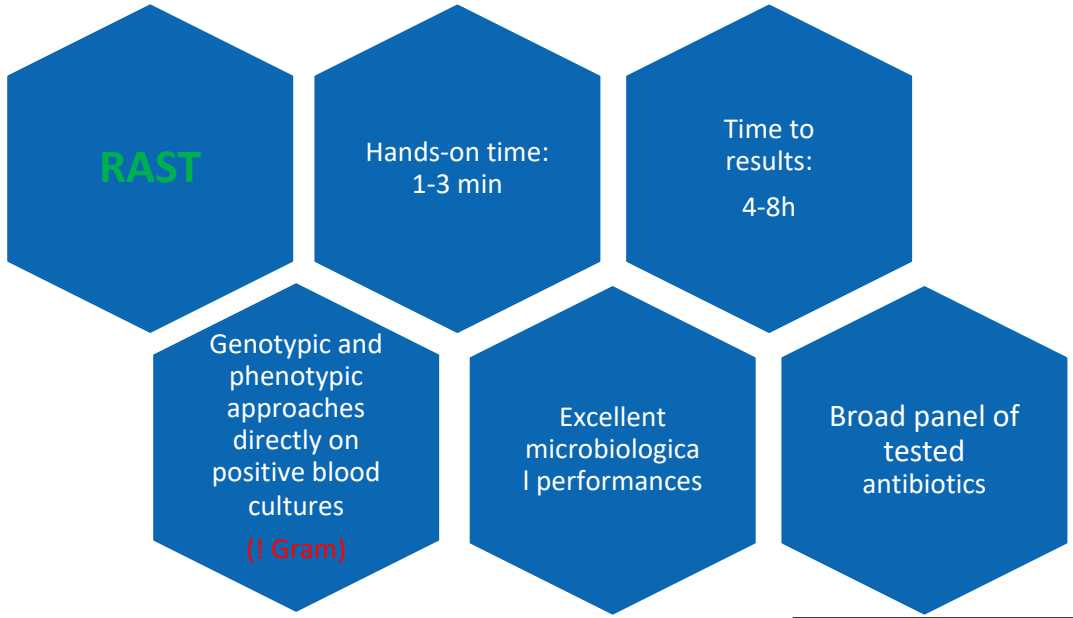


TABLE 1 | Select rapid phenotypic AST methods that are approved for testing positive blood cultures.

Test	AST technology	TTR	Regulatory status	References
PhenoTest BC (Accelerate Diagnostics)	Time-lapse imaging of bacterial cells under dark-field microscopy. Morphological and kinetic changes analyzed.	7 h	US FDA cleared, CE-IVD	(46)
Alfred (AliFAX)	Light scattering to detect bacterial growth in liquid culture broth.	3–5 h	CE-IVD	(47)
dRAST (QuantaMatrix)	Time-lapse imaging of bacterial cells on micropatterned plastic microchips.	6 h	CE-IVD	(48)
Reveal AST (Specific Diagnostics)	Sensor array for volatile organic compounds emitted during microorganism growth.	4.5 h	CE-IVD	[1]
ASTar (Q-linea)	Time-lapse imaging of bacterial growth in broth.	3–6 h	CE-IVD	[2]
Fastinov	Flow cytometry applying fluorescent dyes that reveal cell damage during treatment.	80 min	CE-IVD	[3]
LifeScale (Affinity Biosensors)	Mass measurement using a microcantilever.	4 h	CE-IVD	[4]

AST, antimicrobial susceptibility testing; TTR, time to result.
[1]*https://specificdx.com/reveal-ast (accessed November 30, 2020).*
[2]*https://www.qlinea.com/our-products/astar/astar-instrument/ (accessed November 30, 2020).*
[3]*http://www.fastinov.com/ (accessed November 30, 2020).*
[4]*http://www.lifescaleinstruments.com/Products/Clinical (accessed November 30, 2020).*

Banerjee and Humphries, Frontiers in Medecine 2021

ASTar
Q-linea

- ✓ Bacterial concentration + Broth microdilution + time lapse microscopy → MIC values
- ✓ 14 Gram negative bacteria
- ✓ 25 antibiotics + AmpC screen
- ✓ TAT 6h
- ✓ Random access – 12 sample capacity

dRAST™
QuantaMatrix

- ✓ Bacterial concentration + Broth microdilution + time lapse microscopy → MIC values
- ✓ > 100 Gram negative bacteria
- ✓ 16 antibiotics + ESBL screen
- ✓ TAT 4-6h
- ✓ Random access - 12 sample capacity

Vitek Reveal®
bioMérieux

- ✓ Microdilution followed by measure of volatile metabolites → MIC values
- ✓ 9 Gram negative bacteria
- ✓ 21 antibiotics + ESBL/AmpC screen
- ✓ TAT 4.5-6.5h
- ✓ Random access - 4/8/12 sample capacity

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Prospective interventional study of the 3 RAST approaches on 200 patient Gram-negative blood cultures:

Impact on antimicrobial prescription and time savings

A. Verroken, A. Brochier, I. El Achab, A. Anantharajah, H. Rodriguez, X. Wittebole, J-C Yombi

Objectives

1. Microbiological performances of the 3 RAST approaches

- Reference method: subculture broth microdilution: NMDRM2 panel (Analis - MicroScan, Beckman Coulter)

- EUCAST 2021 breakpoints
  - CA, VME, ME, mE
  - For all antibiotics for which an S category is missing, VME an ME were calculated as if all I results were interpreted as S
  - EA on categorical discordances
  - ATU results were excluded from analysis

- Time savings towards AST results

Objectives

2. Clinical outcomes of the 3 RAST approaches

- Impact of communicated RAST results on antibiotic tailoring
- Time savings towards administration targeted treatment in included bacteremic patients

3. Ease of use (hands-on time, reagents, system failures)

Material & methods

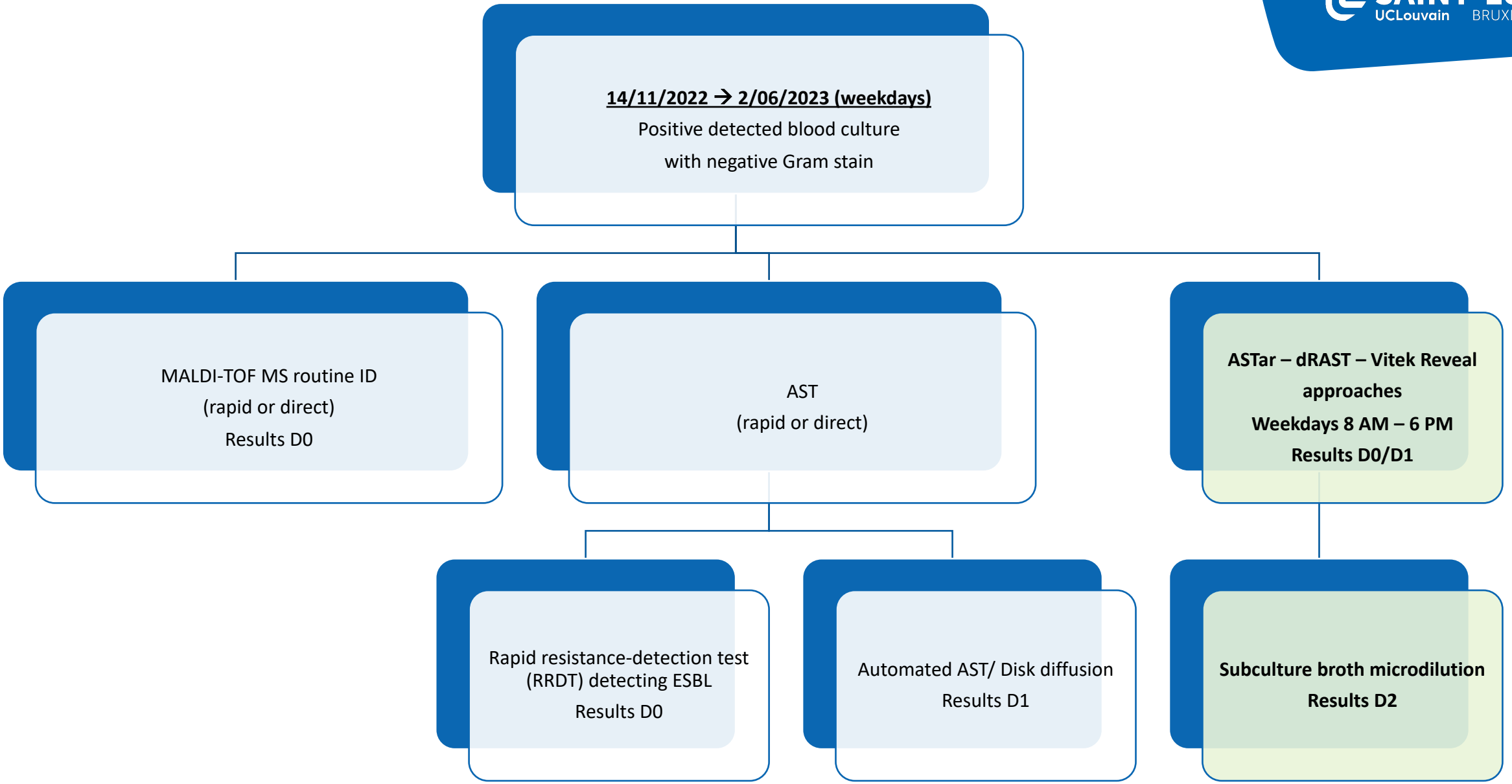
- Monocentric : Cliniques universitaires Saint-Luc – 960 beds

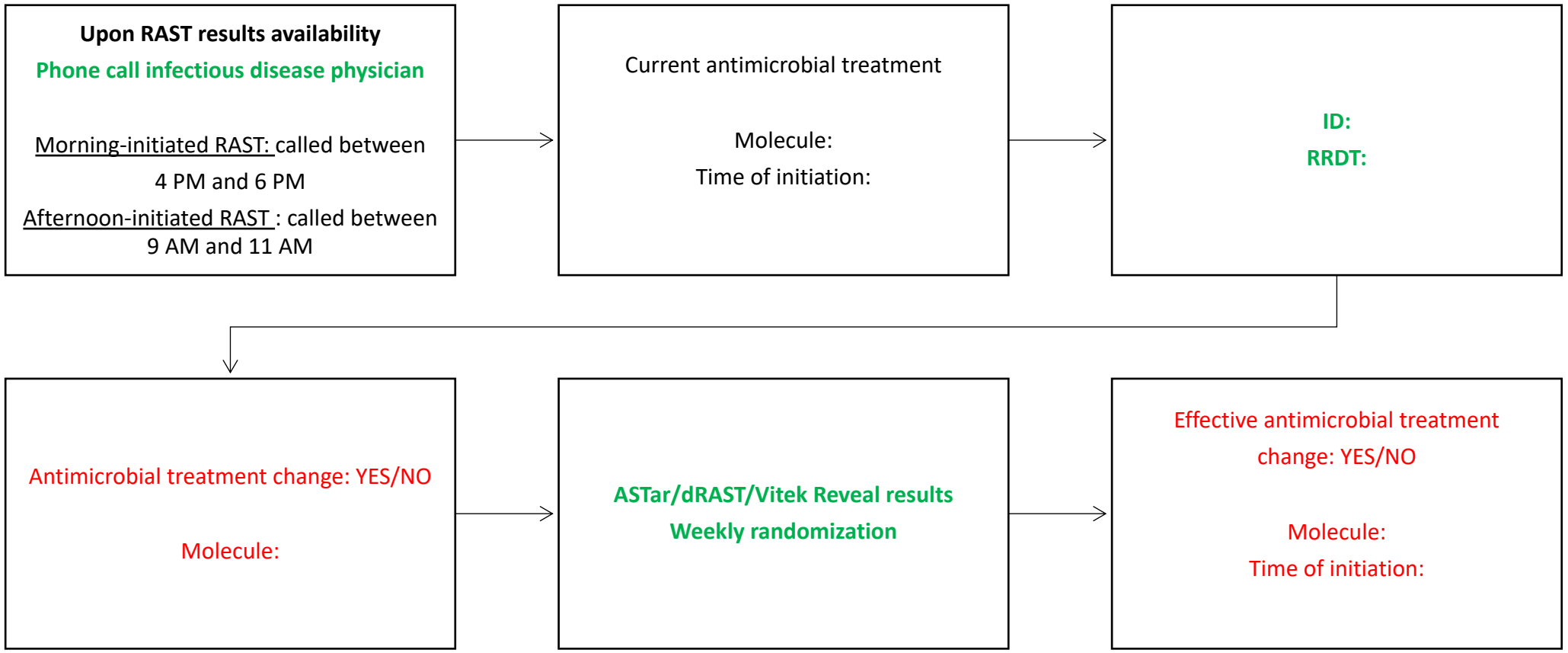
- Microbiology laboratory
    - blood culture incubation 24h/24
    - positive blood culture management: 7d/7 : 7h → 21h

- Prospective inclusion of **200 adult patients**

    - with routine Gram-negative detected blood culture(s)
    - detected during weekdays
    - 1 blood culture bottle inclusion/bacteremic episode

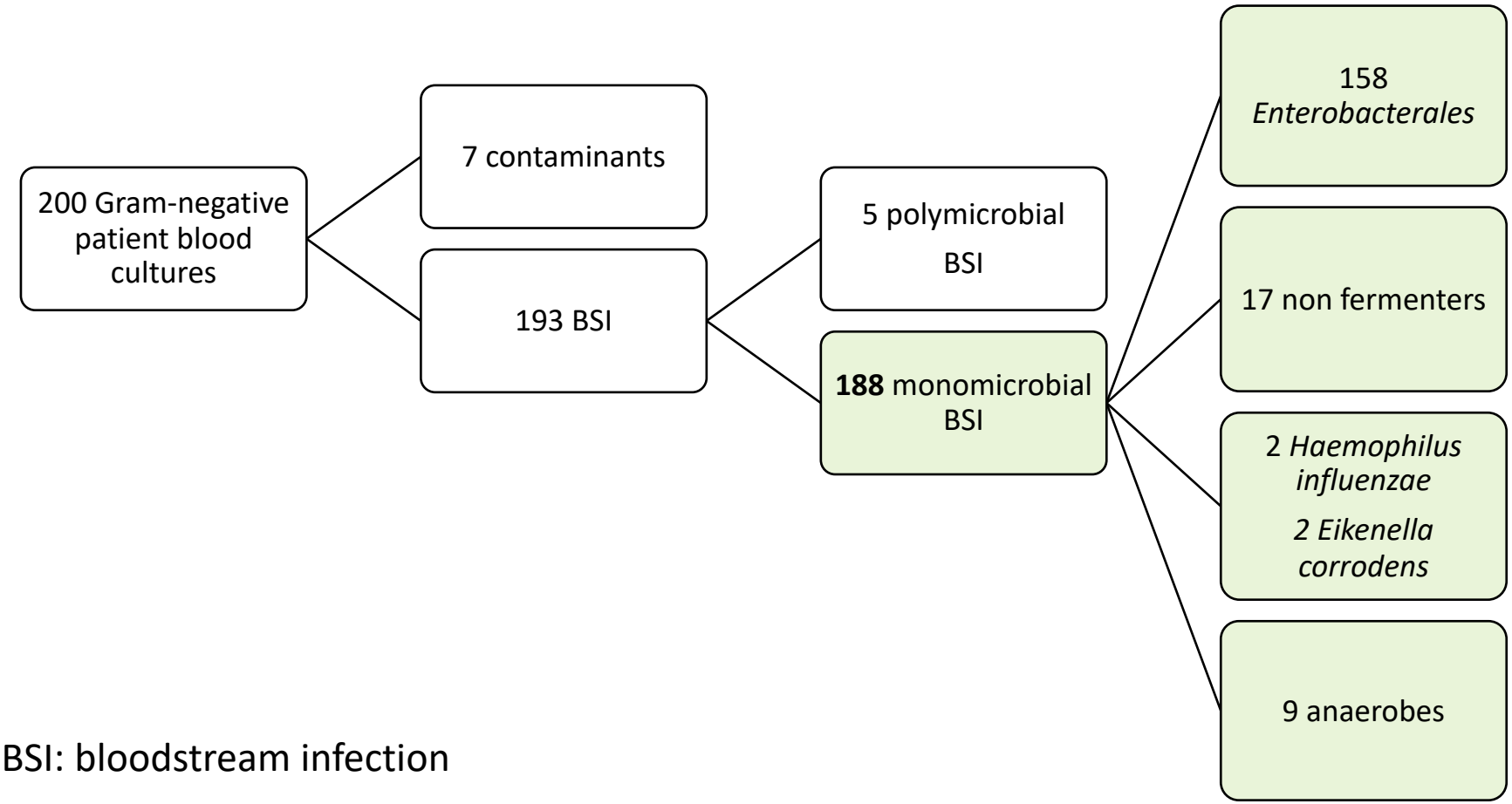
    - Exclusion criteria
        - at positive blood culture detection
            - patient deceased
            - patient transferred
            - patient on palliative care


14/11/2022 → 2/06/2023 (weekdays)
Positive detected blood culture
with negative Gram stain
MALDI-TOF MS routine ID
(rapid or direct)
Results D0
AST
(rapid or direct)
ASTar – dRAST – Vitek Reveal approaches
Weekdays 8 AM – 6 PM
Results D0/D1
Rapid resistance-detection test (RRDT) detecting ESBL
Results D0
Automated AST/ Disk diffusion
Results D1
Subculture broth microdilution
Results D2


Upon RAST results availability
Phone call infectious disease physician
Morning-initiated RAST: called between 4 PM and 6 PM
Afternoon-initiated RAST : called between 9 AM and 11 AM
Current antimicrobial treatment
Molecule:
Time of initiation:
ID:
RRDT:
Antimicrobial treatment change: YES/NO
Molecule:
ASTar/dRAST/Vitek Reveal results
Weekly randomization
Effective antimicrobial treatment change: YES/NO
Molecule:
Time of initiation:

Results

Microbiological performances



BSI: bloodstream infection

			Derepressed cephalosporinase	ESBL	Carbapenemase
Monomicrobial GNB bacteremia	**188**		**12**	**15**	**2**
Enterobacterales	**158**				
C. freundii		1			
C. koseri		2			
E. cloacae complex		12	3		1 (NDM)
E. coli		94	4	10	1 (VIM)
H. alvei		2	1		
K. aerogenes		3	3		
K. oxytoca		6			
K. pneumoniae		22		4	
K. variicola		1			
M. morganii		3	1	1	
P. agglomerans		1			
P. mirabilis		3			
P. rettgeri		1			
S. marcescens		5			
Salmonella sp.		2			
Non-fermenters	**17**				
P. aeruginosa		14			
P. stuzeri		1			
P. mosselii		1			
A. baumannii complex		1			
H. influenzae	**2**				
Others	**11**				
Anaerobes		9			
Eikenella corrodens		2			
Polymicrobial GNB bacteremia	**5**				
Contaminants	**7**				

Time analysis

Median time measurements start upon blood culture positivity detection.

Results

Clinical outcomes

- ✓ RAST results enabled 27 antibiotic modifications
- ✓ <u>ALL but 1 modifications = targeted treatment</u>
- ✓ Impact on 27/188 monomicrobial Gram-negative BSI = **14.4%**
  - ✓ Narrowing : 33.3% (9/27)
  - ✓ Broadening : 55.5% (15/27)
  - ✓ Switch : 11.1% (3/27)
- ✓ Reduced time towards administration optimal treatment = **19 hours 53 minutes**

Results/ discussion

Clinical outcomes

✓ **Impact on 27/188 included patients = 14.4% … can we do better?**

- ✓ Bias of “weak” local resistance epidemiology with efficient antimicrobial stewardship guidelines for empirical treatments
- ✓ Added value of RRDT test
- ✓ Suboptimal study workflow

✓ **Necessity of optimized integration of RAST testing in positive blood culture workflow of our SETTING**

- ✓ Selection of time slots for RAST testing (between 8AM and 1PM)
- ✓ Result transmission towards patient files prior to medical validation
- ✓ Speeded-up identification

→ Hypothetical application of these criteria on study population : Impact of 27 RAST results / 114 included patients = **23.7% = > 1 patient/4**

Microbiological performances of the 3 RAST approaches on blood cultures spiked with multi-resistant Gram-negative bacilli

A. Brochier, A. Anantharajah, H. Rodriguez, A. Verroken

ASTar®, Q-linea

dRAST™, Quantamatrix

Vitek Reveal®, bioMérieux

Material & methods

- Spiking of 42 blood culture bottles with human blood + defined concentration of multi-resistant Gram-negative bacteria

- RAST testing within 6 hours following positivity detection

- Evaluation of the microbiological performances identical to the the prospective study

	ESBL	Carbapenemase				
		OXA-48	NDM	VIM	OXA-23	OXA-58
Enterobacterales (32)						
Escherichia coli	5	2	1	1		
Klebsiella pneumoniae	3	3	2			
Enterobacter cloacae complex	4	2	2	1		
Klebsiella aerogenes	1					
Proteus mirabilis	1					
Citrobacter koseri	1					
Citrobacter freundii		1	2			
Gram negative non fermenters (10)						
Pseudomonas aeruginosa				5		
Acientobacter baumannii complex					3	2

WHAT'S NEXT?

- How about impact on mortality? On length of stay?

Clinical Infectious Diseases
MAJOR ARTICLE

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

Tristan T. Timbrook,[1,4] Jacob B. Morton,[1,4] Kevin W. McConeghy,[2] Aisling R. Caffrey,[1,2,4] Eleftherios Mylonakis,[3] and Kerry L. LaPlante[1,2,4]

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- Review in 2017 of 31 studies with 5920 patients

- ✓ Applying rapid (ID) testing with ASP allowed to prevent 1 death within 30 days
- ✓ Applying rapid (ID) testing reduced total length-of-stay with 2.57 days

- What about the cost and QALY ?

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REVIEW

The Cost-Effectiveness of Rapid Diagnostic Testing for the Diagnosis of Bloodstream Infections with or without Antimicrobial Stewardship

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- Review and meta-analysis in 2021 US data + HEOR Lifetime study

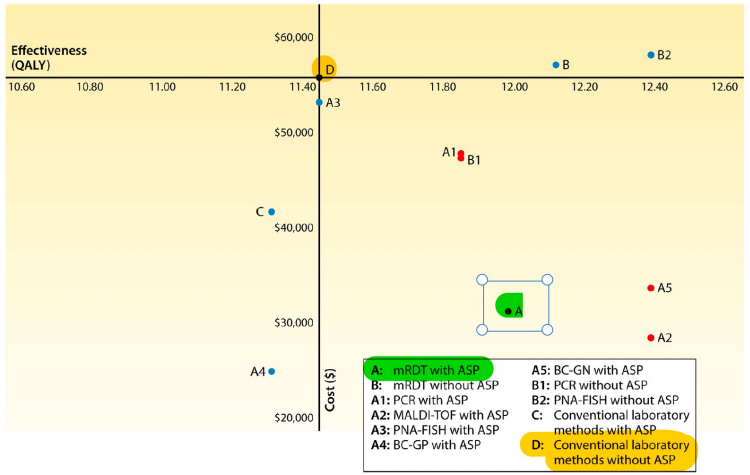

FIG 3 Cost-effectiveness plane for all of the strategies. The *y* axis represents the average cost of a strategy, while the *x* axis represents the average effectiveness of a strategy. Cost-effective strategies are depicted with red markers, the baseline strategy is depicted with a black marker, and the remaining strategies that are suboptimal or not cost-effective are indicated with blue markers.

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Merci pour votre attention !

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