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BacteREVEAL : étude monocentrique interventionnelle de type avant/après évaluant l'impact de l'apport des solutions diagnostiques BacT/Alert ® VIRTUO ®, BioFire® Blood Culture Identification 2-BCID2 et VITEK® REVEAL™ (bioMérieux) sur l'optimisation de l'antibiothérapie des bactériémies à bacilles à Gram négatif chez le patient de réanimation

Louis Oudiane

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Louis Oudiane. BacteREVEAL : étude monocentrique interventionnelle de type avant/après évaluant l'impact de l'apport des solutions diagnostiques BacT/Alert ® VIRTUO ®, BioFire® Blood Culture Identification 2-BCID2 et VITEK® REVEAL™ (bioMérieux) sur l'optimisation de l'antibiothérapie des bactériémies à bacilles à Gram négatif chez le patient de réanimation. Human health and pathology. 2024. dumas-04646220

HAL Id: dumas-04646220

<https://dumas.ccsd.cnrs.fr/dumas-04646220>

Submitted on 12 Jul 2024

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UNIVERSITÉ DE MONTPELLIER
FACULTÉ DE MÉDECINE MONTPELLIER-NÎMES

THESE

Pour obtenir le titre de
DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement
Par
Louis OUDIANE

le 28 mars 2024

TITRE

« BacteREVEAL »

Étude monocentrique interventionnelle de type avant/après évaluant l'impact de l'apport des solutions diagnostiques BacT/Alert® VIRTUO®, BioFire® Blood Culture Identification 2-BCID2 et VITEK® REVEAL™ (bioMérieux) sur l'optimisation de l'antibiothérapie des bactériémies à bacilles à Gram négatif chez le patient de Réanimation

Directeur de thèse : Pr Claire ROGER

JURY

Président : Pr Jean-Philippe LAVIGNE

Assesseurs : Pr Pierre-François PERRIGAULT, Pr Claire ROGER, Dr Flora DJANIKIAN

UNIVERSITÉ DE MONTPELLIER
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Directeur de thèse : Pr Claire ROGER

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Acknowledgments

Au Pr Claire Roger, ma directrice de thèse, je te remercie de m'avoir fait confiance en me permettant de participer à ce projet et pour tes conseils tout au long de sa réalisation. Merci pour ton importante implication dans notre formation.

Au Pr Jean-Philippe Lavigne, merci de l'honneur que vous me faites de présider ce jury.

Au Pr Pierre-François Perrigault et au Dr Flora Djanikian, je vous remercie également d'avoir accepté de faire partie de mon jury. Je conserve d'excellents souvenirs du DAR C en votre compagnie, notamment celui de votre bienveillance, une source d'inspiration pour la suite.

À mes parents adorés, merci pour les coups de pied aux fesses lorsque j'étais trop paresseux au lycée ou timoré plus jeune. Ils m'ont permis de prendre des risques et d'arriver là où j'en suis aujourd'hui. Avec un brin d'auto-dérision, je constate qu'il me reste encore un soupçon de paresse, mais certains aiment à rappeler qu'elle est le propre de l'anesthésiste. Quelques lignes sont insuffisantes pour témoigner de ma gratitude, on oublie parfois les sacrifices et l'énergie que vous mettez pour nous accompagner tous les 3 mais plus le temps passe, plus j'en prends conscience. Merci pour tout, continuez de profiter de votre nouvelle liberté ! Je vous aime.

À Camille, ma grande sœur et consoeur, on a fait un bout de parcours ensemble, 6 ans de collocation (c'est plus qu'avec JB pour l'instant ^^). J'en garde les souvenirs de beaucoup de travail, de ta chambre dans tous ses états, de tes mélanges culinaires récurrents (Albane s'en souvient aussi), de nos engueulades sur le ménage ou les courses ou encore de la moisissure dans la loggia. Je me souviens de te faire réviser tes cours avant les partiels, cours auxquels moi je ne comprenais rien avec l'année qui nous séparait. Je me souviens de t'entendre partir à la BU ou en stage le matin quand je cuvais des soirées P2, D1. Bref, des souvenirs qu'il est toujours nostalgique de se remémorer. Nous nous sommes suivis (encore une fois) dans le sud et dans certaines villes et c'est avec joie de constater que tout le monde a suivi par la suite. Merci Camille pour tout et bravo pour ton parcours avec JB.

À Éloïse, ma petite sœur, tu as fait ton bonhomme de chemin en parallèle à Paris et j'ai hâte qu'on puisse passer plus de temps ensemble maintenant que tu es dans le sud. On pourrait par exemple mettre à profit notre "grande" expérience en plongée pour explorer les récifs des calanques. Je me souviens encore de la plongée en Sardaigne et surtout de la douche froide à l'île d'Yeu lorsque je me retrouve d'un coup inondé dans mon masque avec heureusement ton sauvetage inespéré. N'oublie pas de vivre tes rêves de liberté et d'indépendance que tu évoques souvent.

À JB, mon beau-frère, bravo pour tout ce que vous avez entrepris avec Camille et bravo pour ta détermination dans tes projets professionnels ! L'apparente facilité avec laquelle tu les réalises est rageante mais en fait elle

cache une impressionnante capacité de travail dont tu peux être fier ! Merci pour l'inspiration que tu nous donnes !

À Isabelle et Thierry, mes beaux-parents, merci pour votre accueil dans la famille. Je me souviens des WE passés à Jargeau, de la convivialité passée autour d'un plateau pizza télé, d'une bonne bière avec Thierry, des nombreuses petites attentions (les chaussons), du jacuzzi dans le jardin (qui est bien différent maintenant)... Finalement de toutes ces choses qui nous donnent envie de revenir vous voir malgré la distance.

Merci aussi à Didier pour ton accueil simultané, tes conseils avisés et ta bienveillance vis à vis de notre avenir commun avec Albane.

A mes amis rencontrés au cours de ce parcours,

À Corentin, encore aujourd'hui je n'ai pas réussi à me mettre à la muscu. Je te revois me montrer des répétitions sur les triceps avec une chaise où j'en alignais au maximum 5, ou encore les séances de plongée à la piscine avec la monitrice qui pétait un câble de nous voir autant dissipés. Des très bons moments qui se font plus rares avec la distance maintenant, mais j'espère qu'on puisse changer ça comme on se l'était dit après l'ECN.

À la team DAR C, Nicolas, Simon et Rémy. Je pense que vous avez aussi un super souvenir de l'ambiance qu'il y avait dans ce bureau ! Les collègues c'est bien mais des copains au boulot c'est mieux et on a eu une belle preuve ! A suivre avec plaisir !

À Albane, après 7 ans de vie commune, tu es sans doute la personne qui me connaît le mieux. Tu as appris à m'appivoiser et dieu sait que je ne suis pas facile tous les jours ! (je sais que tu confirmes en lisant cette phrase). Merci d'être là pour le meilleur et quelquefois pour le "pire". Nous passons notre thèse le même jour ce 28 Mars 2024 et c'est un très beau symbole de notre progression côte à côte tout le long de ces études. Je suis immensément fier de toi ! Tu es maintenant Dr Girel pour tes patients mais tu restes pour moi, mon Albane ou tous les petits noms que je te donne. Je t'aime.

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1 Introduction

Bloodstream infection (BSI) refers to positive blood cultures associated with systemic signs of infection and may be either secondary to an identified source of infection or the primary source, i.e. when no other source could be identified. It represents a life-threatening infection occurring in 5% of critically ill patients with a length of stay (LOS) > 3 days and is associated with significant mortality ranging from 12% to 38% (1–4).

Among patients with suspected BSI and sepsis, initial empirical broad-spectrum antibiotics must be promptly administered as any delay in early adequate therapy is associated with worse outcomes (5–7). The rising prevalence of multidrug resistant (MDR) Gram negative bacilli (GNB) may compromise adequate empirical antimicrobial coverage. On the other hand, the unnecessary use of broad-spectrum antibiotics may be harmful as reported in a large cohort of culture proven sepsis (8).

In recent years, genotypic and phenotypic rapid diagnostic tools (RDT) together with rapid antimicrobial susceptibility testing (rAST) have emerged as a means to decrease the time to adequate antimicrobial therapy in bloodstream infections (BSI). These new tools come into play at different stages of the blood culture management process and have demonstrated excellent analytical performance. First, new blood culture incubation systems have improved sensitivity in detecting bacteremic episodes and led to an average 3-hour time saving for blood culture positivity (9).

Secondly, the implementation of molecular RDTs such as multiplex PCR has allowed for substantial time and effort savings in directly identifying both pathogens and antimicrobial resistance (AMR) genes from positive blood cultures (10,11).

Finally, rAST that can be performed directly from a blood culture bottle, such as the new VITEK[®] REVEAL[™] system (bioMérieux, Marcy l'Étoile, France), may provide AST results for a broad panel of antibiotics targeting GNB within 4.6 hours (12).

However, the clinical impact of these combined RDTs has not been studied, and their costs remain high, necessitating evidence of their cost-effectiveness before widespread implementation in microbiological laboratories. To establish effective and optimal antibiotic therapy as quickly as possible for bacteremic patients in the Intensive Care Unit (ICU), the time for blood culture analyses (microbial culture, identification, and susceptibility testing) should be minimized. The unjustified use of broad-spectrum antibiotic agents promotes selection pressure and the emergence of bacterial resistance. Providing clinicians with rAST results could help in tailoring initial antimicrobial therapy and accelerating de-escalation.

The aim of this research was to assess the clinical impact of the implementation of innovative diagnostic solutions, namely BacT/Alert[®] VIRTUO[®], BioFire[®] Blood Culture Identification 2-BCID2[®], and VITEK[®] REVEAL[™] (bioMérieux) on antimicrobial therapy in critically ill patients with BSI.

2 Method

2.1 Setting

This single center quasi-experimental pre/post interventional study was conducted in the three ICUs of the Nimes University Hospital. The ethics committee approved the study and informed consent was obtained from the patient prior to enrolment for the post-interventional period. An information letter was sent to participating patients from the pre-interventional period. The study was registered in ClinicalTrials.gov (NCT 05741424).

2.2 Study Population

All adult patients admitted to the ICU with a diagnosis of GNB BSI were enrolled. Patients with polymicrobial blood cultures, those with out-of-panel GNB (Table S1), those experiencing a second episode of BSI, and moribund patients were excluded.

2.3 Study Design

This study was conducted retrospectively from June 2021 to May 2022, and prospectively from January 2023 to October 2023. The innovative diagnostic technologies (bioMérieux) including the BacT/Alert® VIRTUO® blood culture instrument, the BioFire® Blood Culture Identification 2 (BCID2) molecular assay, and the VITEK® REVEAL™ rapid antibiotic susceptibility testing (AST) system were implemented in December 2022.

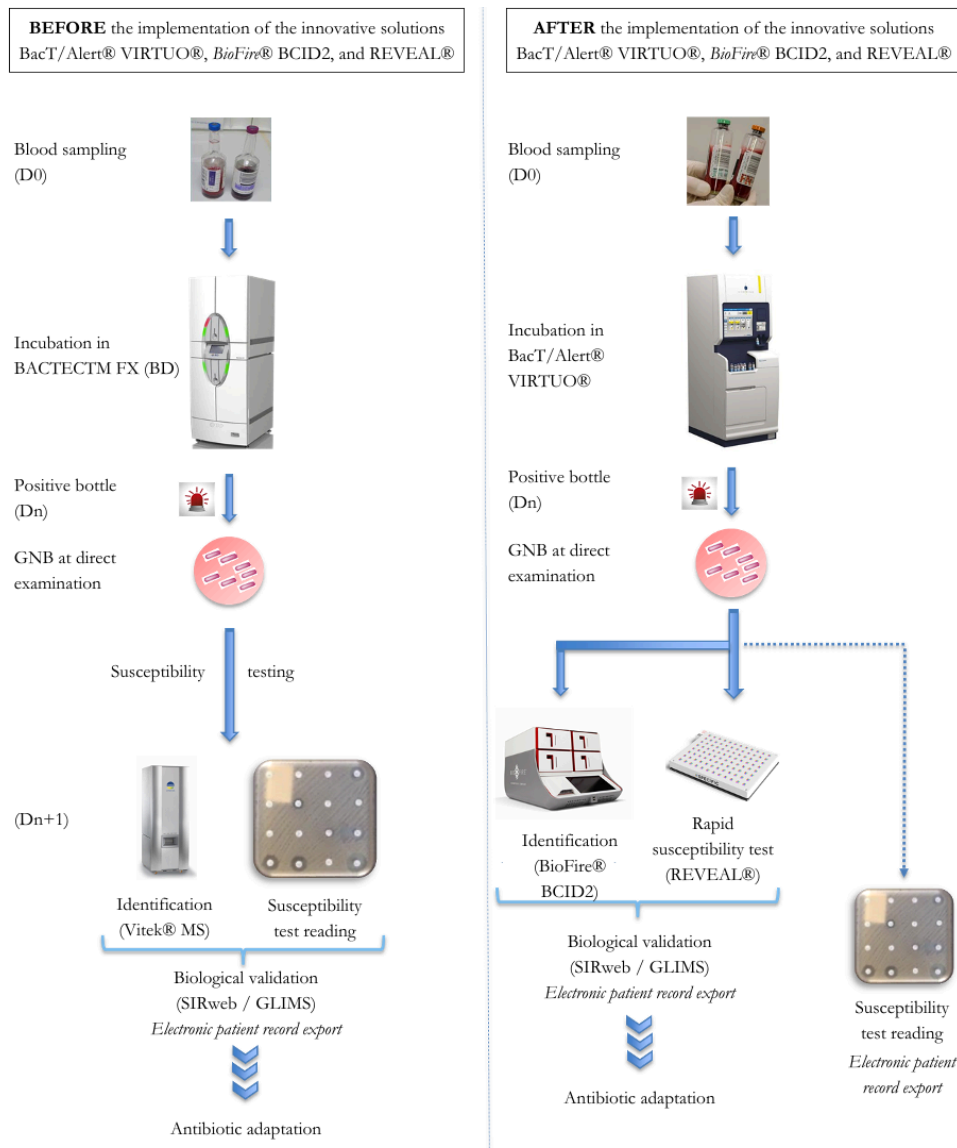


Figure 1 :

Flowchart comparing the management of blood cultures before and after implementation of innovative techniques.

2.3.1 Pre interventional period

During this period, the diagnosis of BSI relied on the following steps:

- Incubation of blood culture bottles in a BACTECTM FX (BD) automated system.

The bottles were manually introduced into the machine. If microorganisms were present in the sample being tested, their growth resulted in the production of CO₂. The BACTECTM FX system measured the CO₂ generated by microbial growth using fluorometry. In case of a positive result, an audible signal was emitted.

- Direct examination Gram stain analysis

Direct examination Gram stain analysis was performed for each positive bottle. The ICU staff was notified of the positivity of the blood culture and direct examination by phone call.

- Agar-based susceptibility testing and cultures incubation

Direct AST by disc diffusion method (BIO-RAD) from positively flagged blood culture bottles was performed following the recommendations of the current CASFM/EUCAST guidelines. The inoculated agar plates were incubated in an incubator at 37 ± 2 °C until the next day (12-24 hours of incubation).

- Bacterial identification and susceptibility testing interpretation
 - The bacteria isolated the following day was identified using Matrix Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) mass spectrometry with the VITEK[®] MS system (bioMérieux).
 - AST results were interpreted by the SIRweb software (i2a) and the microbiologist. If the susceptibility test was not readable (non-confluent culture indicating a too low inoculum), it was restarted from a subculture and read the next day.
- Transmission of results and therapeutic adjustment

The identification and AST results were exported to the electronic patient record. Empirical antibiotic therapy was adjusted based on the susceptibility test results (effective antibiotic therapy and, if clinically indicated, optimized).

2.3.2 Post interventional period

During this period, the diagnosis of BSI was based on:

- Incubation of blood culture bottles in a BacT/Alert[®] VIRTUO[®] automated system.

The BacT/Alert[®] VIRTUO[®] system allowed for automatic loading and unloading of bottles, saving time for the technical teams and ensuring thermal stability of the incubation modules, thus promoting optimal growth of potentially present microorganisms in the bottles. Microorganism multiplication led to CO₂ production, which lowered the pH and caused a colorimetric indicator on the bottle's base to change. The color change was measured by reflectometry, and an audible signal was emitted by the machine.

- Direct examination

Gram staining was performed for each positive bottle, like the first study period.

- Molecular-based identification and susceptibility testing
 - If a GNB was observed during the direct examination, identification was performed using the BioFire® FilmArray® BCID2 system. This innovative molecular approach allowed for the detection of 43 targets, including 14 GNB commonly involved in BSI, within a closed system that integrated sample preparation, nested PCR amplification, and pathogen detection in 1 hour.
 - In parallel with BCID2, rapid susceptibility testing (rAST) was initiated from the GNB broth using the VITEK® REVEAL™ instrument. This new system enabled the measurement of minimum inhibitory concentrations (MICs) for a wide range of antibiotics and was based on a unique metabolomic signature technology that detected volatile organic compounds emitted by growing bacilli. The susceptibility test results were typically available within an average of 4.6 hours, depending on the bacterial species and the antibiotic tested (12).
 - During the second period, the conventional routine techniques used in the first period (inoculation and incubation of agar plates, identification by VITEK® MS, and direct AST by disc diffusion method) were conducted in parallel.
- Transmission of results and therapeutic adjustment

The clinician was informed by phone-call and fax of the identification (BCID2) and rAST data (VITEK® REVEAL™). The results of both innovative and conventional approaches were exported to the electronic patient record after biological validation.

Empirical antibiotic therapy was adjusted based on the rapid susceptibility testing results upon receipt (effective antibiotic therapy and, if clinically indicated, optimization).

2.4 Study Outcomes

The primary objective was to measure the real clinical impact of innovative diagnostic technologies, including BacT/Alert® VIRTUO®, BioFire® BCID2, and VITEK® REVEAL™, on optimizing antibiotic therapy for ICU patients with GNB BSI within 24 hours of blood culture handling.

Optimized antibiotic therapy was defined as an antibiotic therapy covering the causative pathogen(s) i.e, effective and with the narrowest spectrum, according to Weiss and al. (13) modified ranking (Table S2) and was assessed within 24 hours of blood culture handling, both before and after the implementation of the new diagnostic solutions.

The secondary objectives included evaluating the theoretical impact of innovative diagnostic technologies—BacT/Alert® VIRTUO®, BioFire® BCID2, and VITEK® REVEAL™—on antibiotic optimization, the time required to optimize antibiotic therapy, the turnaround times for positive blood cultures, BCID2 and VITEK® REVEAL™ results, the assessment of the performance of the VITEK®

REVEAL™ rAST (categorical agreement) compared to the reference agar dilution method, and their effects on clinical outcomes, such as length of stay (LOS) and mortality. The data collected are displayed in Table S3.

2.5 Statistical Analysis

The normality of the distribution of quantitative variables was assessed using a Henry plot (or Q-Q plot) and Kurtosis and Skewness coefficients. Quantitative variables were expressed as means and standard deviations or as medians and quartiles. Qualitative variables were expressed as frequency and percentage.

Given the study design (pre-interventional/post-interventional interventional study before/after), it was essential to verify the comparability of the "Before" and "After" groups as closely as possible because various biases could come into play (different time periods, epidemics, other practice changes, etc.). A comparison between the two groups was conducted for each study variable. For quantitative variables, Student's t-tests or Mann-Whitney tests (depending on the distribution's normality) were performed. For qualitative variables, Fisher's exact tests or Chi-square tests were used to compare the groups. In cases where some of the tested variables showed significant differences between the groups, multivariate models were employed to adjust for these variables across all criteria evaluated in the study.

The proportions of patients with optimized antibiotic therapy were calculated for each group and accompanied by confidence intervals. A Chi-square test was used to determine if these rates were significantly different. In cases where certain variables showed differences between the groups, a multivariate logistic regression model was used, with the binary variable explaining the status of optimized antibiotic therapy (Yes/No) and the predictive variables being the group ("Before" vs. "After") and potential confounding factors.

Analysis of Secondary Outcomes involved comparing the therapy adaptation times between the "Before" and "After" groups. A shorter time was favorable for patient survival. Patients who had not undergone therapy changes were divided into two categories: those for whom antibiotic therapy was optimized from the start (time 0) and those for whom antibiotic therapy had never been optimized (maximum time of 28 days). Patients who died during the study resulted in a shortening of the time, which was a non-beneficial event, and the maximum time was also assigned to them. The times obtained were compared using a suitable mean comparison test (Student's t-test or Mann-Whitney).

Analysis of LOS used a competitive risk survival model, with the event being hospital discharge and the competitive risk being patient death during hospitalization. Cumulative incidence functions (CIF) and Gray tests were performed. In the event of group non-comparability, potential confounding factors were incorporated into a Fine & Gray model.

A difference was considered statistically significant when the significance level of the test was less than or equal to 0.05.

3 Results

Of the 175 patients assessed for eligibility, 50 patients were included in the pre-interventional period from June 2021 to May 2022 and 50 were included in the post-interventional period from February 2023 to October 2023 (Figure 2).

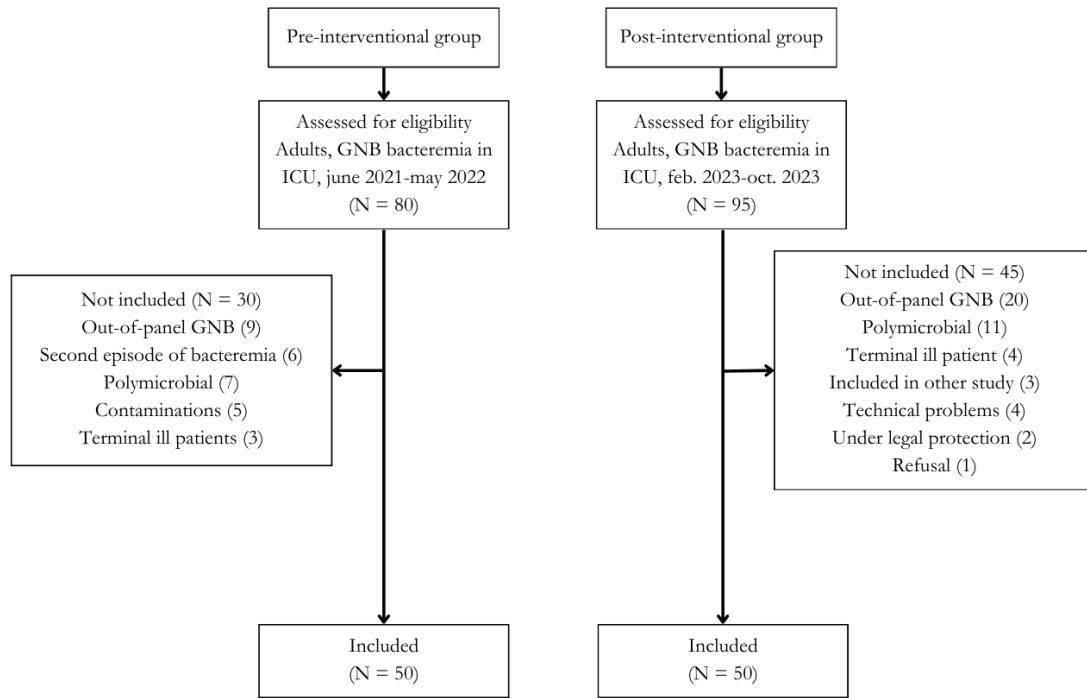


Figure 2 :
Flowchart.

3.1 Demographics data

Demographics data are displayed in Table 1. The median age was 69 years old in the pre-interventional group and 71 years old in the post-interventional group ($p=0.3$). There was no difference in sex ratio ($p=0.7$) or comorbidities between the groups. Additionally, there was no difference in SOFA severity scores upon admission ($p=0.7$) and at Day 7 ($p>0.9$). IGS2 score at admission was statistically different, with a score of 46 in the pre-interventional group and 53 in the post-interventional group ($p=0.019$). Hospitalizations related to COVID-19 were more common in the pre-interventional group ($p<0.001$), and there was an overrepresentation of pulmonary origin of bacteremia in the pre-interventional group ($p=0.028$).

Table 1 :
Demographics data

	Pre-interventional group (n = 50) ¹	Post-interventional group (n = 50) ¹	p value ²
Demographics			
Age	69 (62, 74)	71 (62, 76)	0.3
Sex			0.7
Male	32 (64%)	34 (68%)	
Female	18 (36%)	16 (32%)	
BMI	26 (23, 29)	26 (23, 30)	>0.9
COVID related hospitalizations	10 (20%)	0 (0%)	<0.001
Comorbidities			
Ischemic cardiomyopathy	3 (6%)	3 (6%)	>0.9
COPD	8 (16%)	7 (14%)	>0.9
Chronic kidney disease	6 (12%)	8 (16%)	0.8
Hepatic cirrhosis	3 (6.0%)	1 (2.0%)	0.6
Immunocompromised	9 (18%)	7 (14%)	0.8
Antibiotic therapy allergy	0 (0%)	3 (6.0%)	0.2
Severity scores			
IGS2 score at admission	46 (33, 57)	53 (40, 66)	0.019
SOFA score at inclusion	6.0 (5.0, 8.0)	7.0 (4.0, 9.0)	0.7
SOFA score 7 days after inclusion	3.0 (0.0, 6.8)	2.0 (1.0, 5.0)	>0.9
Bacteremia sources			
Pulmonary	16 (32%)	6 (12%)	0.028
Urinary	13 (26%)	19 (38%)	0.28
Abdominal	12 (24%)	17 (34%)	0.38
Intravascular catheter	4 (8%)	2 (4%)	0.7
Skin and soft tissue	4 (8%)	1 (2%)	0.4
Endocarditis	0 (0%)	1 (2%)	>0.9
Other	1 (2%)	4 (8%)	0.4

¹Data are expressed as Median (IQR) and proportion (n, %)

²Fisher's exact test

BMI (body mass index), COPD (chronic obstructive pulmonary disease), IGS2 (index de gravité simplifié 2), SOFA (sepsis-related organ failure assessment)

3.2 Study outcomes

Study outcomes are displayed in Table 2. The proportion of patients with optimized antibiotic therapy at 24 hours from sample handling was 20% (CI 95% 11-34%) in the pre-interventional group compared to 28% (CI 95% 17-43%) in the post-interventional group (p=0.3). The time to first antibiotic optimization was not significantly different between the two groups (p=0.2). The ICU LOS was 8 days shorter in the post-interventional group (p=0.049). There was no significant difference between the two groups in terms of the MDR bacteria prevalence and mortality at Day 28 (p=0.6 and 0.3 respectively).

Table 2 :
Antibiotic therapy modification according to time from sampling

	Pre-interventional group (n = 50) ¹	Post-interventional group (n = 50) ¹	p value ²
Primary outcome			
Antibiotic optimization at 24h from blood culture incubation	10 (20%)	14 (28%)	0.3
Secondary outcomes			
Antibiotic optimization at 24h from positive blood culture	13 (26%)	23 (46%)	0.037
Antibiotic adaptation			
Adequate initial empirical treatment	45 (90%)	47 (94%)	0.71
Time to effective treatment	11 (4, 24)	2.1 (0, 10)	<0.001
Escalation	3 (6%)	2 (4%)	>0.9
Time to escalation	19 (15, 41)	49 (39, 85)	0.03
De-escalation	26 (52%)	27 (54%)	>0.9
After direct examination	16 (32%)	10 (20%)	0.25
Time to change	24 (21, 28)	17 (15, 22)	0.047
After first available AST result	30 (60%)	14 (28%)	0.002
Time to change	58 (44, 71)	29 (24, 31)	<0.001
Optimization			
Overall	29 (58%)	38 (76%)	0.056
Time to first antibiotic optimization	39.7 (19.2, 63)	30.9 (16.9, 52.3)	0.2
After first available AST result	18 (62%)	9 (24%)	0.014
Time to change	46 (43, 70)	27 (22, 31)	<0.001
Unchanged treatment	22 (44%)	21 (42%)	>0.9
ICU length of stay (days)	13 (3.9, 23.7)	5 (3.4, 11.3)	0.049
28-day mortality	13 (26%)	8 (17%)	0.3
MDR bacterias	9 (18%)	7 (14%)	0.6

¹Data are expressed as Median (IQR) and proportion (n , %)

²Fisher's exact test; Kruskal-Wallis rank sum test

Empirical antibiotic therapy was effective in 90% of cases in the pre-interventional group compared to 94% in the post-interventional group ($p=0.71$). From this empirical antibiotic therapy, in the pre-interventional and post-interventional group respectively, escalation represented 6% and 4% of cases, de-escalation 52% and 54% of cases, and unchanged treatment 44% and 42%.

Antibiotic therapy optimization was achieved for 58% of patients in the pre-interventional group compared to 76% of patients in the post-interventional group ($p=0.056$). In the post-interventional group, 24% of the patients were optimized thanks to rAST results. Most were optimized either before the AST results (29%) or after the results of conventional AST (47%). Among rAST-based optimized patients, the median time to antibiotic optimization was 27h compared to 46h in the group of patients optimized after conventional AST ($p<0.001$).

The prescribed ranks of antibiotic therapy, both actual and theoretical, are represented in Figures 3a and 3b. The most commonly prescribed empirical antibiotic therapy was ranked ≥ 4 according to the modified Weiss et al. classification, accounting for 86% in the pre-interventional group and 80% in the post-interventional one. After final adaptation of the antibiotic therapy, there was a sparing of ranks ≥ 4 by 38% in the pre-interventional group and 42% in the post-interventional group. If the narrowest spectrum antibiotic had been chosen based on conventional AST (pre interventional period) or rAST (post interventional period), the sparing of ranks ≥ 4 would have been 46% in the pre-interventional group and 50% in the post-interventional group.

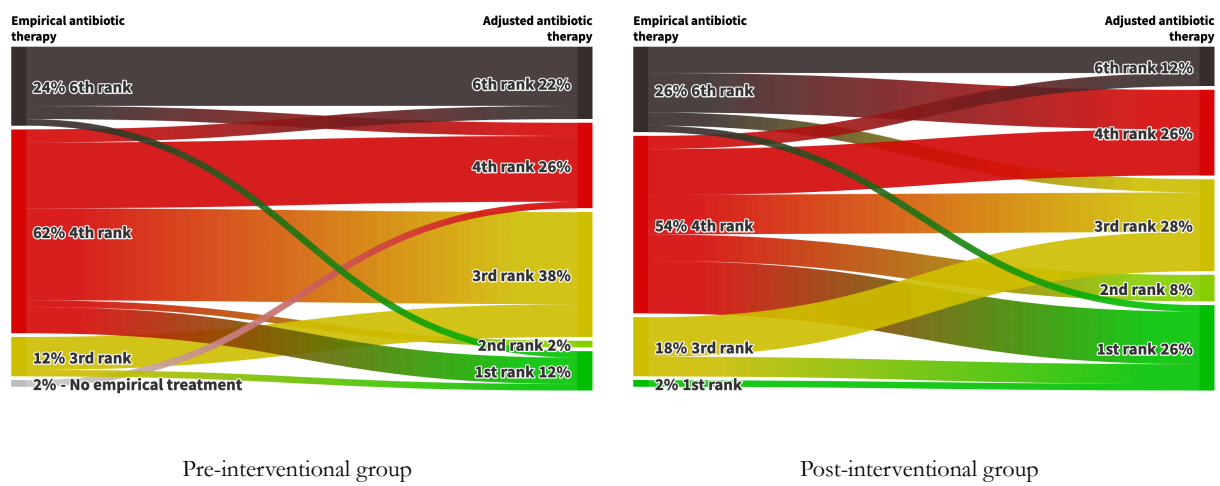


Figure 3a :
Representation of real antibiotic modification in each group.

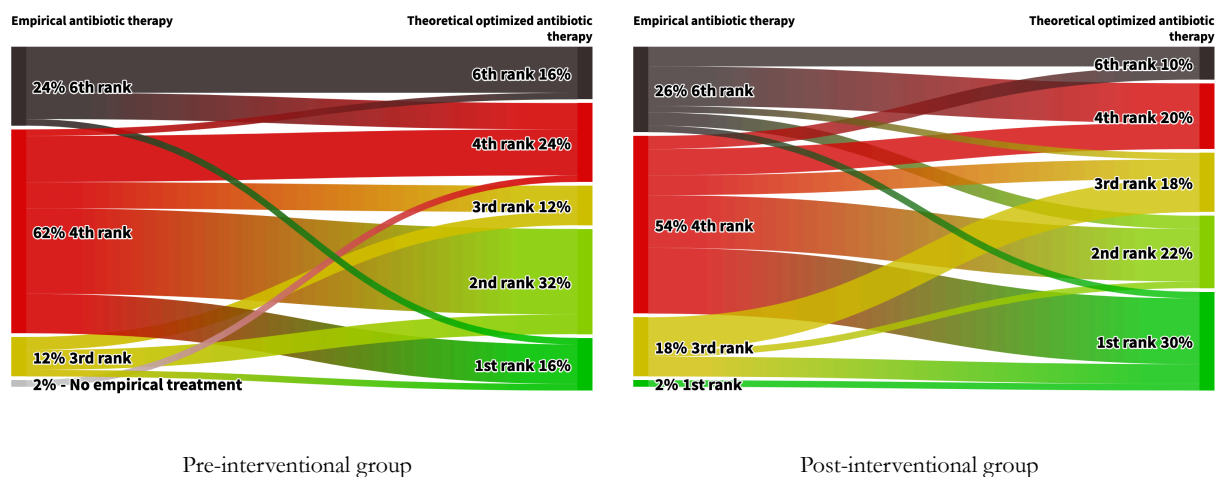


Figure 3b :
Representation of theoretical antibiotic modification in each group.

3.3 Turnaround times

The different turnaround times from blood culture sampling to conventional susceptibility testing are displayed in Table 3 and Figure 4. The median time saving was 17h for ID ($p < 0.001$) and 13h for AST in the post interventional period ($p < 0.001$). The overnight reporting of results between 00:00 and 06:00 affected 32% of rAST results, while no conventional AST results were reported during the night.

Table 3 :
Turnaround times between the two groups

	Pre-interventional group (n = 50) ¹	Post-interventional group (n = 50) ¹	p value ²
Sampling - Handling (hours)	3.0 (2.2, 4.6)	3.5 (2.7, 5.1)	0.14
Handling - Incubation (hours)	0.18 (0.07, 0.5)	0.07 (0.05, 0.08)	<0.001
Sampling - Positivity (hours)	15 (12, 17)	17 (13, 20)	0.3
Incubation - Positivity (hours)	11 (7, 13)	11 (9, 15)	0.2
Positivity - Direct Examination (hours)	1.4 (0.6, 3.4)	1.2 (0.5, 5.6)	0.15
Positivity - Identification (hours)	21 (16, 28)	4 (2, 9)	<0.001
Positivity - AST (hours)	24 (18, 29)	11 (9, 16)	<0.001

¹Data are expressed as Median (IQR)

²Wilcoxon rank sum test

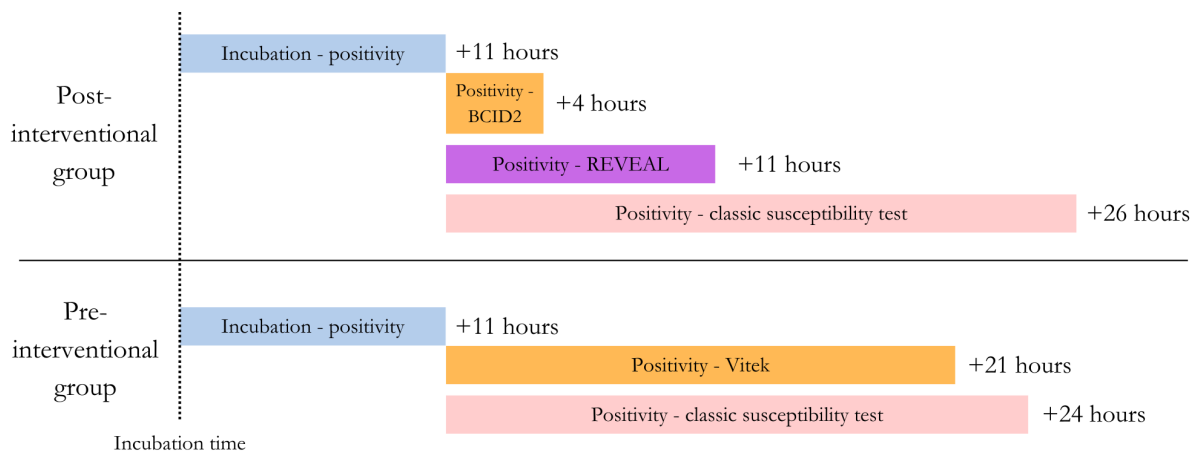


Figure 4 :
Representation of main turnaround times between the two groups.

3.4 Microbiological data

The predominant pathogens were E. Coli and K. Pneumoniae in the pre-interventional group and E. Coli (60%) in the post-interventional group. MDR pathogens were identified in 9 (18%) patients in the pre-interventional group and 7 (14%) in the post-interventional group ($p = 0.6$). The main mechanisms of

antimicrobial resistance were extended-spectrum beta lactamase (ESBL) and hyperproduced cephalosporinase (HCase) (Table 4 and S4).

Table 4 :
Pathogens identified

	Overall (n = 100) ¹	Pre-interventional group (n = 50) ¹	Post-interventional group (n = 50) ¹	p value ²
Escherichia coli	43 (43%)	13 (26%)	30 (60%)	0.001
Proteus mirabilis	6 (6.0%)	4 (8.0%)	2 (4.0%)	0.7
Enterobacter cloacae complex	11 (11%)	7 (14%)	4 (8.0%)	0.5
Klebsiella aerogenes	4 (4.0%)	2 (4.0%)	2 (4.0%)	>0.9
Klebsiella pneumoniae	16 (16%)	13 (26%)	3 (6.0%)	0.01
Klebsiella oxytoca	3 (3.0%)	1 (2.0%)	2 (4.0%)	> 0.9
Pseudomonas aeruginosa	16 (16%)	9 (18%)	7 (14%)	0.8
Acinetobacter-baumannii/calcoaceticus complex	1 (1.0%)	1 (2.0%)	0 (0%)	>0.9

¹Data are expressed as proportion (n, %)

²Fisher's exact test

3.5 VITEK[®] REVEAL[™] overall analytical performance

The categorical agreement between VITEK[®] REVEAL[™] rAST and conventional AST is displayed in Table 5. The VITEK[®] REVEAL[™] rAST results were 93.73% concordant with conventional AST. Among the discrepancies, five VME (2 on piperacillin/tazobactam, 1 on piperacillin, 1 on tobramycin and 1 on cefotaxime) and 6 major errors (2 on piperacillin, 2 on ertapenem, 1 on amoxicillin and 1 on aztreonam) were observed. The concordance of results could only be evaluated in 68.4% of cases due to the lack of antibiotic sensitivity evaluation in one or both techniques.

Table 5 :
Overall performance of VITEK[®] REVEAL[™]

Performance of VITEK [®] REVEAL [™] against conventional AST	
CA	93.73% (733/782)
mE	0.90% (7/782)
ME	0.88% (6/679)
VME	5.26% (5/95)

Total organisms tested = 782

Total susceptible organisms by reference method = 679

Total resistant organisms by reference method = 95

4 Discussion

In this quasi-experimental study investigating for the first time the clinical impact of the VITEK[®] REVEAL[™] rAST combined with BacT/Alert[®] VIRTUO[®], BioFire[®] Blood Culture Identification 2-BCID2 (bioMérieux, Marcy l'Etoile, France), the implementation of these innovative diagnostic solutions did not increase the proportion of bacteremic patients receiving optimized antibiotic therapy within 24 hours of blood culture handling despite good overall performance and 17-hour and 13-hour time reduction in pathogen identification and AST results respectively.

The added value of a novel RDT should be evaluated in various aspects, including analytical performance, the ability to shorten turnaround times in a clinically significant way, and the impact on antimicrobial optimization.

The overall performance reported in the present study are in agreement with previously published studies showing categorical agreement > 95% with Vitek 2 for a large panel of GNB and for *P. Aeruginosa* (12). However, the VME was slightly higher (5.26%) in our study compared to the study conducted by Tibbetts et al. (1.3%) (12) and Couchot et al. (1.6%) (14) and mainly concerned piperacillin-tazobactam accounting for 2 strains. The turnaround times observed in our study are also close to the ones reported in previously published studies with VITEK[®] REVEAL[™] and other rAST techniques. For example, Couchot et al. (14) found a 6h22 mean time to VITEK[®] REVEAL[™] results, and the evaluation of the accelerate PhenoTest[®] BC system in GNB BSI found a median time from sampling to pathogen identification of 8.8 hours and to AST of 16.8 hours (15). Despite shortened turnaround times, rAST results at 24 hours from blood culture handling were available in only half of the patients. This may have contributed to the absence of significant difference between the two groups on the primary outcome. These findings imply that for an rAST result to promptly lead to an earlier treatment modification, blood culture workflow needs to be optimized, clinicians need to be informed in a timely manner and need to be able to interpret the results (16).

In our setting of low MDR prevalence and the use of broad-spectrum empirical therapy, de-escalation was the main antibiotic adaptation whereas escalation was uncommon due to seldom ineffective empirical treatment. Although rAST results were available for clinicians 13 hours earlier than conventional AST results, de-escalation or optimization based on rAST results was applied to less than one third of patients. This study highlights the difference between antibiotic adaptation in a real-world setting and the antibiotic adaptation achievable with rAST. Similar to our results, in a study by Lee et al., in cases where the accelerate PhenoTest[®] BC system revealed an inappropriate empiric treatment, escalation followed in most cases. In contrast, more than half of the opportunities to de-escalate treatment were missed (17). The main explanations for these discrepancies likely stem from the poor implementation of de-escalation in critically ill patients, despite international recommendations. For example, the DIANA study showed a de-escalation rate of 16% in a large international cohort of critically ill patients although no deleterious effect of antimicrobial de-escalation was reported (18). This issue is compounded by the need for clinicians to have sufficient confidence in RDTs and

to feel comfortable with early de-escalation of treatment in bacteremic critically ill patients, even when clinical signs of improvement may not yet be evident. In ICU patients, the main barriers to apply antimicrobial de-escalation are driven by illness severity, the uncertainty regarding the safety of de-escalation and cognitive biases (19–21). Therefore, it is likely necessary to implement antimicrobial stewardship programs to enhance the clinical impact of these RDTs (11,22). These findings are in line with previous studies showing that rAST could theoretically lead to faster antimicrobial optimization in two thirds of the patients. In a study involving 27 patients, the Accelerate Pheno™ System showed potential for optimizing antimicrobial therapy in 67% of patients with an average reduction of 18.1 hours (23) and could significantly decrease time to antimicrobial de-escalation for GNB BSI (15,24). In RCTs comparing the Accelerate Pheno™ System to standard care, the greatest improvement in time occurred when rAST was combined with antimicrobial stewardship, even with limited support (23,25,26). In the present study, the lack of decision support and antimicrobial stewardship-oriented change may have contributed to the limited number of antimicrobial adaptations based on rAST. As such, antimicrobial stewardship teams may facilitate de-escalation in accordance with rAST results.

However, emotional, cognitive and social factors influence antimicrobial prescribing and should be considered while implementing antimicrobial stewardship interventions (20). Regarding de-escalation cognitive biases such as the commission or present bias may occur frequently. The omission bias relates to the regret associated with an omission error outweighing that of a commission error and may be enhanced by patient or family demand. The present bias is defined by the tendency to favor smaller more immediate benefits over larger benefits in the future. As an example, antimicrobial stewardship recommendations are more likely to be accepted if they expand antibiotic spectrum compared with reducing spectrum as concerns about not covering MDR pathogens outweigh concerns about serious antibiotic harms and later outcomes such as emergence of antimicrobial resistance. As such debiasing strategies may be incorporated as a novel way to further support antimicrobial stewardship endeavors.

4.1 Limitations

We acknowledge some limitations to the present study. First, this study was not randomized, leading to imperfect comparability between the two groups, which may have influenced certain results. For example the over-representation of COVID-19 related hospital stays in the pre-interventional period, could have influenced outcomes such as ICU LOS and mortality. Second, we chose a strict primary outcome, as antibiotic therapy was considered optimized if the the narrowest antibiotic was chosen according to modified Weiss et al. classification. This choice likely contributed to the lower proportion of optimized antibiotic therapy than expected. This low proportion should also be considered within the context of evaluating this primary outcome at 24 hours post-laboratory handling, whereas an assessment at 24 hours post-positivity could have been more relevant.

5 Conclusion and future perspectives

Although rAST may be theoretically valuable for shortening antibiotic therapy optimization, the real-world implementation of rapid diagnostic solutions such as BacT/Alert® VIRTUO®, BioFire® Blood Culture Identification 2-BCID2, and VITEK® REVEAL™ (bioMérieux) has failed to improve antibiotic therapy optimization within 24 hours of blood culture handling. The reluctance of physicians to de-escalate antibiotic therapy based on rAST alone limits its clinical impact. A stringent antimicrobial stewardship program integrating the psychosocial factors of antimicrobial prescribing could help enhance the clinical impact of rAST.

6 Abbreviations and glossary

Abbreviation	Signification
BSI	Bloodstream Infection
LOS	Length of Stay
MDR	Multidrug Resistant
GNB	Gram-negative Bacilli
RDT	Rapid Diagnostic Tools
rAST	Rapid Antimicrobial Susceptibility Testing
ICU	Intensive Care Unit
PCR	Polymerase Chain Reaction
MALDI-TOF	Matrix Assisted Laser Desorption Ionization - Time of Flight
MIC	Minimum Inhibitory Concentration
SAS	Statistical Analysis System
IQR	Interquartile Range
SOFA	Sepsis-related Organ Failure Assessment
COPD	Chronic Obstructive Pulmonary Disease
AST	Antimicrobial Susceptibility Testing
NA	Not Available
CASFM	Comité de l'Antibiogramme de la Société Française de Microbiologie
EUCAST	European Committee on Antimicrobial Susceptibility Testing
BCID2	Blood Culture Identification 2
BMI	Body Mass Index
IGS2	Index de gravité simplifié 2

7 Supplemental

Table S1 :

Validated GNB species on VITEK[®] REVEAL[™]

Escherichia coli
 Klebsiella pneumoniae
 Klebsiella oxytoca
 Klebsiella aerogenes
 Enterobacter cloacae
 Citrobacter koseri
 Citrobacter freundii
 Proteus mirabilis
 Pseudomonas aeruginosa
 Acinetobacter baumannii

Table S2 :

Modified Weiss and al ranking including non β -lactams according to both their spectrum and their resistance-promoting potential

Rank	Molecule(s)
1	Amoxicillin Trimethoprim-Sulfamethoxazole
2	Amoxicillin + Clavulanic Acid
3	Third-generation cephalosporin Ureido/carboxy-penicillin
4	Piperacillin + Tazobactam Ticarcillin + Clavulanic Acid Fourth generation cephalosporin Antipseudomonal third-generation cephalosporin
5	Ertapenem
6	Imipenem Meropenem Doripenem Cefiderocol

Table S3

Data collected

Demographic data

Medical history (infection source, IGS2 score, SOFA score at drain time and 7 days)

Microbiological data

 Turnaround times (sampling, handling, introduction, positivity, direct examination, pathogen identification, AST)

 Pathogens

 Susceptibility

Antibiotic therapy

Vital status at 28 days

Hospital length of stay (LOS)

MDR bacterias

Table S4 :
Resistance profiles.

	Other	CRAB	ESBL	ESAC	Hcase	Hcase, ESAC	HYPERSHV-1 Klebsiella pneumoniae	Ceftazidime-R Pseudomonas
<i>Acinetobacter-baumannii/calcoaceticus</i> complex	0	1	0	0	0	0	0	0
<i>Enterobacter cloacae</i> complexe	0	0	1	1	2	1	0	0
<i>Escherichia coli</i>	0	0	1	0	2	0	0	0
<i>Klebsiella aerogenes</i>	0	0	0	1	2	0	0	0
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	0	0
<i>Klebsiella pneumoniae</i>	0	0	4	0	0	0	1	0
<i>Proteus mirabilis</i>	1	0	0	0	0	0	0	0
<i>Pseudomonas aeruginosa</i>	0	0	1	0	0	0	0	2

CRAB (carbapenem resistant *Acinetobacter Baumannii*); ESBL (extended-spectrum beta lactamase); ESAC (Extended Spectrum AmpC); Hcase (hyperproduced cephalosporinase)

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SERMENT

- En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.
- Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.
- Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.
- Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.
- Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.

9 Abstract

Background Rapid diagnostic tools together with rapid antimicrobial susceptibility testing (rAST) have emerged as a means to shorten the time to pathogen identification and AST for bloodstream infections (BSI). We assessed the clinical impact of the new diagnostic solutions BacT/Alert® VIRTUO®, BioFire® Blood Culture Identification 2-BCID2, and VITEK® REVEAL™ (bioMérieux) on the antibiotic therapy optimization of Gram-negative bacilli (GNB) BSI in intensive care unit (ICU) patients.

Methods A single-center quasi-experimental study comparing antibiotic optimization before and after the implementation of the new diagnostic solutions. Adult patients with a first episode of GNB BSI admitted to the ICU were included in the study. The primary outcome was antibiotic therapy optimization (according to the modified Weiss et al. classification) within 24 hours of blood culture handling in the laboratory.

Results A total of 100 patients, 50 in each group, were included. The proportion of patients receiving optimized antibiotic therapy at 24 hours was not significantly different in the post-interventional group compared to the pre-interventional group, 28% vs. 20%, respectively ($p=0.3$). The length of stay (LOS) in the ICU was shorter by 8 days in the post-interventional group ($p=0.049$). There were no significant differences in the overall time to optimization, prevalence of multidrug-resistant (MDR) bacteria, or 28-day mortality. The time to optimization in VITEK® REVEAL™ rAST-based optimized patients was shorter than in conventional AST-based optimized patients, 27 hours vs. 46 hours, respectively ($p<0.001$).

Conclusions The real-world implementation of RDT combined with VITEK® REVEAL™ rAST (bioMérieux) did not improve antibiotic therapy optimization within 24 hours of blood culture handling. Physician reluctance to de-escalate antibiotic therapy based on rAST alone limits its clinical impact. A rigorous antimicrobial stewardship program integrating the psychosocial factors of antimicrobial prescribing could help enhance the clinical impact of rAST.

Keywords Anti-bacterial agents, Antimicrobial susceptibility testing, Rapid identification, Gram negative bacteremia, Intensive Care Unit

10 Résumé

Contexte Les solutions de diagnostic et d'antibiogramme rapide ont émergé comme un moyen de raccourcir le délai d'identification et d'évaluation de la sensibilité aux antibiotiques des agents pathogènes dans les bactériémies. Nous avons évalué l'impact des nouvelles solutions de diagnostic BacT/Alert® VIRTUO®, BioFire® Blood Culture Identification 2-BCID2 et VITEK® REVEAL™ (bioMérieux) sur l'optimisation de l'antibiothérapie des bactériémies à bacilles Gram négatif (BGN) chez les patients hospitalisés en réanimation.

Méthode Une étude monocentrique quasi expérimentale comparant l'optimisation de l'antibiothérapie avant et après l'implémentation de nouvelles solutions diagnostiques. Les patients adultes admis en réanimation avec un premier épisode de bactériémie à BGN étaient inclus dans cette étude. Le critère de jugement principal était l'optimisation de l'antibiothérapie (selon la classification modifiée de Weiss et al.) à 24h de la prise en charge de l'hémoculture au laboratoire.

Résultats Un total de 100 patients, 50 patients dans chaque groupe, ont été inclus. La proportion de patients ayant reçu une antibiothérapie optimisée à 24h n'était pas significativement améliorée dans le groupe post-interventionnel comparé au groupe pré-interventionnel, 28% vs. 20%, respectivement ($p=0.3$). La durée de séjour en réanimation était raccourcie de 8 jours dans le groupe post-interventionnel ($p=0.049$). Il n'y avait pas de différence significative sur le délai d'optimisation global, la prévalence de bactéries multi-résistantes (BMR) et la mortalité à J28. Le délai d'optimisation était significativement raccourci de 19 heures chez les patients optimisés grâce au VITEK® REVEAL™ comparé aux patients optimisés selon l'antibiogramme conventionnel ($p<0.001$).

Conclusion L'implémentation des solutions de diagnostic rapide associée à l'antibiogramme rapide VITEK® REVEAL™ n'a pas amélioré l'optimisation de l'antibiothérapie à 24h de la prise en charge de l'hémoculture au laboratoire. La réticence des médecins à désescalader l'antibiothérapie uniquement sur la base de l'antibiogramme rapide limite son impact clinique. Un programme rigoureux de gestion des antimicrobiens intégrant les facteurs psychosociaux de la prescription des antibiotiques pourrait aider à améliorer l'impact clinique des solutions de diagnostic rapide.

Mots clés Antibiotique, Antibiogramme rapide, Optimisation, Bactériémie à BGN, Réanimation

Spécialité : Anesthésie-Réanimation