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# Impact de l'ouverture H24 du laboratoire du C.H.U. de Nice sur la prise en charge des bactériémies

David Chirio

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FACULTE DE MEDECINE

THESE D'EXERCICE DE MEDECINE

POUR L'OBTENTION DU

DIPLÔME D'ETAT DE DOCTEUR EN MEDECINE

**IMPACT DE L'OUVERTURE H24 DU LABORATOIRE  
DE BACTERIOLOGIE DU C.H.U. DE NICE SUR LA  
PRISE EN CHARGE DES BACTERIEMIES**

**CHIRIO David**

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Devant le jury composé de :

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## LISTE DES ABREVIATIONS

AST: antibiotic susceptibility testing

ATB: antibiotic

BC: blood culture

BSI: blood stream infection

CAT: change in antibiotic therapy

ESBL: extended spectrum beta-lactamase

ICU: intensive care unit

IQR: interquartile range

IS: immunosuppressive

LOS: length of stay

Maldi-ToF MS: Matrix assisted laser desorption ionization time-of-flight mass spectrometry

MRSA: methicillin-resistant *staphylococcus aureus*

PREI: pre-intervention period

POSTI: post-intervention period

**CLINICAL IMPACT OF AROUND THE CLOCK  
PROCESSING OF BLOOD CULTURES**

## ABSTRACT

Background: Rapid microbial identification is pivotal in order to adapt antibiotic treatment and ensure its efficacy in bloodstream infections. We aimed to evaluate the clinical impact of an uninterrupted around the clock processing of blood cultures on antibiotic prescription and patient outcome.

Methods: Monomicrobial episodes of bacteremia were retrospectively evaluated over two four-month periods (pre and post-intervention), before and after a continuous 24/7 workflow system was implemented in our clinical microbiology laboratory. Species identification was performed by mass spectrometry directly on positive blood cultures. Primary outcome was the time from specimen collection to the first change in antibiotic therapy (CAT), defined as initiation, discontinuation, addition or switch occurring after detection of bacterial growth. Secondary outcomes were the time from specimen collection to efficient antibiotic therapy (defined as at least one molecule with in vitro activity on the causative pathogen), the time from collection to bacterial growth detection, to pathogen identification, and to antibiotic susceptibility testing results. Hospital length of stay and all-cause mortality at 30 days following bloodstream infection onset were also evaluated.

Results: 548 episodes of bacteremia in 515 patients were included in the final analysis. Mean time to CAT was reduced by 10.4 hours in the post-intervention group (POSTI,  $p < 0.001$ ). Mean time until efficient antibiotic therapy was reduced by 4.8h in POSTI ( $p < 0.001$ ) when empirical treatment was lacking or ineffective. The time from specimen collection to bacterial growth detection was reduced by 3.4h ( $p < 0.001$ ), the time to pathogen identification by 6.9h ( $p < 0.001$ ), and the time to susceptibility testing results by 5.1h ( $p = 0.006$ ) in POSTI. There was no difference in hospital length of stay between the two groups. At 30 days, 30 patients had died in PREI vs 23 in POSTI ( $p = 0.5$ ).

Conclusion: Around the clock processing of blood cultures allows for a faster change in antibiotic therapy and hastens the time to efficient antibiotic therapy prescription.

## INTRODUCTION

Bloodstream infections (BSI) represent a significant healthcare burden, with nearly 2 million episodes annually in North America and Europe combined (1), and are associated with high mortality rates, ranging from 20% to over 50% in case of septic shock (2,3). One of the main risk factors for mortality in BSI is the delay between sepsis onset and first administration of an effective antibiotic, with a suggested 7.6% mortality increase per hour without appropriate antibiotic therapy (4,5). While most clinical presentations of BSI will warrant the initiation of an empirical antibiotic therapy, optimal antibiotic prescription remains dependent on microbiological findings. The gold standard for microbial identification is the incubation of blood cultures, which allows bacterial growth detection; then, Gram staining represents the first clue towards definitive pathogen identification. Historically, conventional identification techniques subsequently implied overnight subculture, followed by antibiotic sensibility testing, resulting at best in a 48-hour timeframe until complete results were available (6). In order to ensure the fastest effective antibiotic treatment, rapid and efficient identification methods are required, especially considering the added ecological impact of maintaining broad-spectrum empirical antibiotic therapy for longer than necessary (7).

In recent years, clinical microbiology laboratories have managed to optimize their performance in this regard through the widespread use of new identification techniques (8). Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Maldi-ToF MS) has notably emerged as one of the essential tools in micro-organism identification, with a high degree of specificity and sensitivity (9). Moreover, direct use of Maldi-ToF MS on positive blood cultures has been repeatedly evaluated, showing a success rate of up to 90%, with an accuracy of over 99%, especially for gram-negative pathogens (10–13). This rapid identification technique decreases the turnaround time compared to traditional procedures, foregoing altogether the subculture-induced 24-hour delay, which in turn may allow for a reduction in the time to efficient and optimal antibiotic prescription. Indeed, Vlek et al. found an 11.3% increase in effective antibiotic therapy in the first 24 hours after blood culture collection, following a 28.8-hour reduction in turnaround time ( $p=0.01$ ) thanks to early pathogen identification (14). Additionally, Clerc et al. found in a prospective study that direct Maldi-ToF identification led to a modification of empirical therapy in 35.1% of cases, versus 20.8% after Gram staining without species identification (15). Decreased costs and hospital length of stay can also be expected, as Perez et al. showed an estimated 2.4-million-dollar annual reduction following a 5.3 days' decrease in hospital stay ( $p=0.002$  and  $0.008$ , respectively) with batch-wise direct Maldi-ToF MS

identification (16). Their study also showed a reduction in mortality in case of gram-negative bacteremia (8.9 vs 21.0%,  $p=0.01$ ).

Still, as most clinical microbiology laboratories operate on a scheduled timeline, only specific and limited samples are processed during night-time or on weekends. Typically, blood cultures are loaded in the incubators during “working hours”, and positive samples are processed during the same period. This can lead to a prolonged delay through every step of the identification technique, with possible consequences on patient care or even on mortality. Indeed, Schneiderhan et al. found that 60% of blood cultures turned positive outside regular duty hours (17). After specimen collection, time to positivity during incubation can already be reduced by continuous loading of incubators, as was shown by Kerremans et al., with an overall 10.1-hour reduction in turnaround time ( $p<0.001$ ) (18). Around-the-clock processing of blood cultures therefore seems to be the next step in improving laboratory efficiency, with a reduced timeframe for microbial growth detection and full identification (19). There are however limited data on the clinical impact of continuous processing of blood cultures.

In this study, we aimed to evaluate the impact of around-the clock sample processing of blood cultures on antibiotic prescription, patient mortality and hospital length of stay.

## METHODS

### *Study design*

This study was a single-center retrospective analysis of two identical periods of time, in a 1600-bed tertiary care teaching hospital in Nice, France: first, from July 1<sup>st</sup> to October 31<sup>st</sup> 2016, before the laboratory was opened 24 hours a day, hereafter referred to as the *pre-intervention* period (PREI); then, from July 1<sup>st</sup> to October 31<sup>st</sup> 2017, after the practice change was implemented, hereafter referred to as the *post-intervention* period (POSTI).

During PREI, the laboratory was fully staffed between 8 a.m. and 6.5 p.m.; then, after 6.5 p.m., the reduced on-call staff only processed cerebrospinal fluid samples and malaria tests in a dedicated area close to the emergency room. The laboratory itself was technically closed from 6.5 p.m. to 8 p.m.; blood cultures were not loaded in the incubators (BACT/alert® automated system) during this timeframe and positive samples (as per the BACT/alert® notifications) were only processed in the morning. During POSTI, following an increase in on-call personnel, the laboratory was opened non-stop. Regarding blood cultures, loading in incubators was performed continuously, and Gram staining of positive samples was immediately realized following growth detection through incubator alerts. As for species identification, an in-house method for direct same-day use of Maldi-ToF MS (Bruker®) on positive incubating blood cultures was locally evaluated, approved and defined as standard procedure in June 2016. Consequently, after the 24-hour workflow was implemented in 2017, batch-wise identification via Maldi-ToF MS was performed during the nightshift in addition the dayshift series. Likewise, antibiotic susceptibility testing was performed directly from the index positive sample in both periods. Finally, the first available information regarding pathogen species identification was given by the microbiologist to the caregiver, by phone, along with advice regarding antibiotic therapy and infection source investigation, either between 8 a.m. and 6.5 p.m. in PREI or 24 hours a day in POSTI. There was an on-call physician on every ward, who could prescribe or change antibiotic therapy if necessary.

### *Data collection*

All positive blood cultures drawn on a date that fell within either one of the study periods were evaluated. Only first episodes of monomicrobial bloodstream infections in patients aged over 18 were included. First episodes referred to bacteremia occurring in a patient without any previous positive blood culture in the past seven days. Polymicrobial bacteremia was defined as the isolation of two or more micro-organisms during the same episode. Coagulase-negative staphylococci as well as environmental contaminants were not included, nor were all fungi-associated bloodstream infections, blood cultures referred from outside facilities, or false-positive signals from BACT/alert®

notifications (absence of micro-organism upon culture). Patients were ultimately excluded if they were transferred to another hospital after specimen sampling, if they were treated as outpatients or if they died before the first results of the index blood culture were available. Absence of comprehensive data regarding timing of antibiotic prescription and/or of blood culture sampling (*i.e.* absence of evaluable timeframe) also led to an exclusion from the final analysis.

Data regarding patients' age, sex, ward of care, intensive care requirement, immune competence, hospital length of stay, underlying infection, setting of infection (community acquired or nosocomial), as well as the nature and timing of systemic antimicrobial agents prescribed, were extracted from patients' medical records and the hospital common prescription software (Clinicom<sup>®</sup>, Metavision<sup>®</sup> and Orbis<sup>®</sup>). Immunodeficiency included HIV infection, ongoing chemotherapy, cytotoxic agents, corticosteroids (at a dosage of 7.5 mg or more of prednisolone daily), or any other immunosuppressive agents prescribed within 1 month of infection onset. Underlying infections were classified as genito-urinary, respiratory, catheter-related, endocarditis, bone and joint infection following surgery, intra-abdominal or cutaneous. Infections were considered nosocomial if they were hospital-acquired (bacteremia occurring over 48 hours after admission, with no prior sign of infection) or healthcare-related (bacteremia following any kind of medical or surgical procedure or treatment). Empirical therapy referred to any systemic anti-infective agent prescribed prior to the first available microbiological result. Bloodstream infection onset was considered as the collection time of the index positive blood culture.

Data regarding causative pathogen, antibiotic susceptibility, the time of specimen collection, the time of arrival at the laboratory and loading in the incubator, the time of bacterial growth detection, the time of species identification, and of complete antibiotic susceptibility testing results, were extracted from the laboratory information software (Glims<sup>®</sup>).

### *Outcomes*

Primary outcome was the time from specimen collection to the first change in antibiotic therapy occurring after detection of bacterial growth. Changes included antibiotic initiation, or, in case of empirical therapy, addition of a new drug, switch to a different regimen, discontinuation of one or more drugs (if multiple antibiotics were initially prescribed), or complete antibiotic discontinuation.

Secondary outcomes included all-cause in-hospital patient mortality at 30 days following bloodstream infection onset, hospital length of stay, and the time from collection to effective antibiotic therapy. Treatment was considered effective when the causative pathogen was susceptible in vitro to at least one prescribed antimicrobial agent, as per the antibiotic susceptibility testing results. Additionally, the laboratory's performance in regard to pathogen identification was



evaluated, through several time intervals: the time from blood culture draw to sample loading into the incubator; the time to positivity, defined as the time from specimen collection to bacterial growth detection through BACT/alert® notification; the time to pathogen species identification by Maldi-ToF MS; and finally the turnaround time, defined as the time from specimen collection to antibiotic susceptibility testing results.

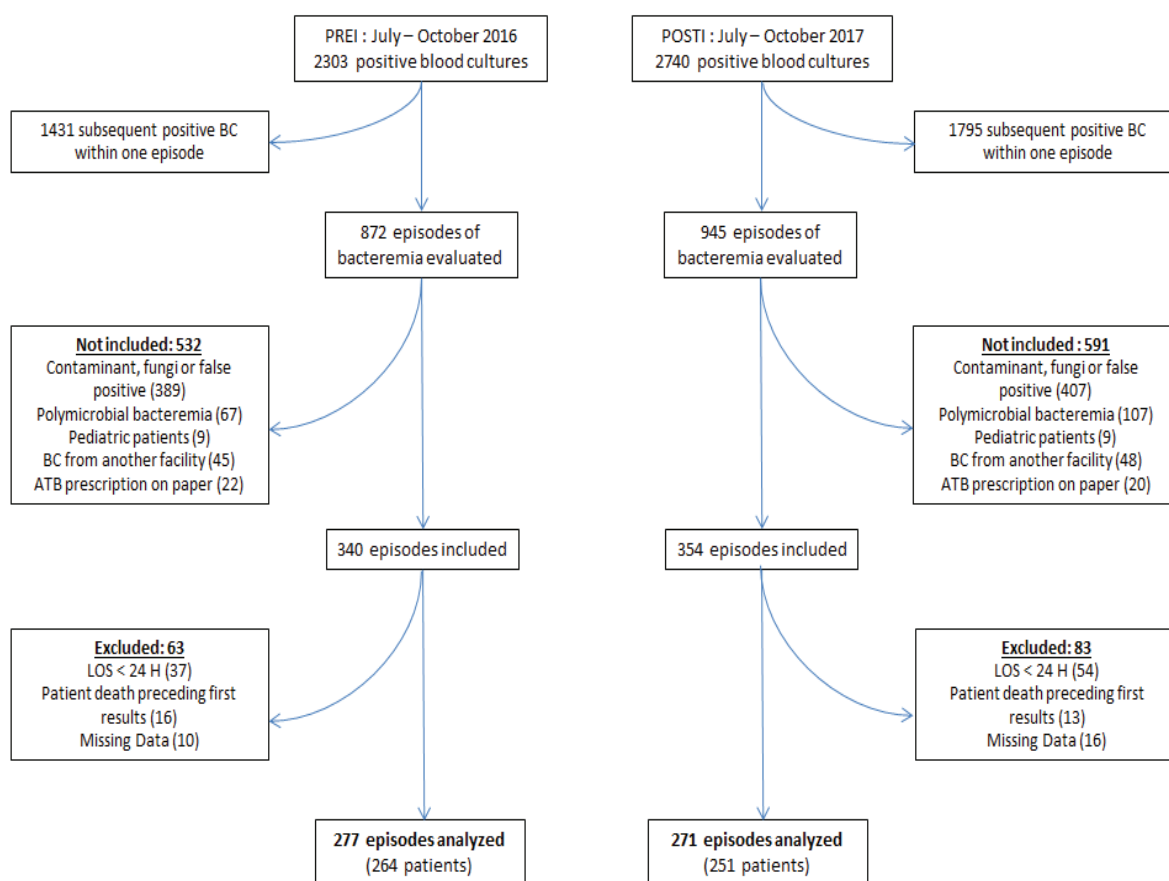
### *Statistical analysis*

Results for continuous variables are expressed as means with standard deviation or as medians with interquartile range (IQR) when not normally distributed, and for categorical variables as absolute number with percentages between brackets. Summary data were calculated using a Student's t test (normal distribution) or Mann-Whitney U test (skewed distribution) for continuous variables and by chi-square or Fisher test for categorical variables. Analyses were performed with use of the R® software (R foundation for Statistical Computing).

## RESULTS

### Study population

The flowchart illustrating the evaluation and inclusion process is presented in **Figure 1**. A total of 1817 positive index blood cultures were evaluated. Eventually, 548 bloodstream infection episodes were included in the final analysis: 277 in PREI and 271 in POSTI, representing 264 and 251 patients in each study period. There was no difference between the two groups regarding patient characteristics. Overall, patients were mostly male (54.0%), with a mean age of  $70.7 \pm 17.7$  years, and were treated in majority on medical wards (83.4%). Immunodeficiency was present in 22.1% of patients and 53.6% of episodes were community-acquired. The most frequent underlying infection involved the urinary tract, accounting for 36.1% of episodes. Patient and episode characteristics are summarized in **Table 1**.



**Figure 1. Flowchart of bloodstream infections included in both study periods**

ATB: antibiotic; BC: blood culture; LOS: length of stay; PREI: pre-intervention period; POSTI: post-intervention period

**Table 1. Patient and episode characteristics**

Characteristic	Value		p-value
	Pre-intervention	Post-intervention	
<u>Patient demographics</u>	n = 264 (%)	n = 251 (%)	
Mean age	71.7 ± 17.4	70.2 ± 18.1	0.585
Male Sex	138 (52.3)	140 (55.8)	0.478
Immunodeficiency	53 (20.1)	56 (22.3)	0.608
Ongoing chemotherapy	29 (11.0)	37 (14.7)	0.31
Anti-rejection medication	14 (5.3)	10 (4.0)	0.397
Corticosteroids	3 (1.1)	2 (0.8)	0.95
Other IS agent	3 (1.1)	3 (1.2)	1
HIV	2 (0.8)	3 (1.2)	1
Other	2 (0.8)	1 (0.4)	0.611
<u>Episode characteristics</u>	n = 277 (%)	n = 271 (%)	
Ward of care			
Medical	228 (82.3)	229 (84.5)	0.566
Surgical	49 (17.7)	42 (15.5)	0.567
Intensive care unit admission <sup>a</sup>	30 (10.8)	33 (12.2)	0.719
Acquisition setting			
Community acquired	154 (55.6)	140 (51.7)	0.402
Nosocomial	123 (44.4)	131 (48.3)	0.388
Underlying infection			
Genito-urinary	107 (38.6)	91 (33.6)	0.254
Intra-abdominal	61 (22.0)	57 (21.0)	0.859
Catheter related	31 (11.2)	32 (11.8)	0.926
Cutaneous <sup>b</sup>	15 (5.4)	30 (11.1)	0.024
Respiratory	16 (5.8)	11 (4.1)	0.465
Endocarditis	12 (4.3)	14 (5.2)	0.796
Bone and joint	7 (2.5)	3 (1.1)	0.34
Other <sup>c</sup>	4 (1.4)	2 (0.7)	0.689
Unknown <sup>d</sup>	24 (8.7)	31 (11.4)	0.348

IS: immunosuppressive

<sup>a</sup> refers to patients who required intensive care at bloodstream infection onset.

<sup>b</sup> including non-organ related surgical site infections, skin and soft tissue infections and bacteremia from wounds and bed sores.

<sup>c</sup> includes bacteremia following dental infections (three and two episodes in each group, respectively) or meningitis (one patient in the pre-intervention group).

<sup>d</sup> refers to bacteremia without evidence for any underlying infection or apparent source.

The most common causative pathogen isolated was *Escherichia coli* (38.1%). There was no difference between the two groups regarding micro-organisms. The complete detail can be found in **Table 2**.

**Table 2. Micro-organisms isolated from the index blood culture in each episode**

Causative pathogen	Value		p-value
	Pre-intervention n = 277 (%)	Post-intervention n = 271 (%)	
Gram-negative bacteremia	193 (69.7)	185 (68.3)	0.792
<i>Escherichia coli</i>	108 (39.0)	101 (37.3)	0.744
<i>Klebsiella</i> spp	29 (10.5)	39 (14.4)	0.207
<i>Enterobacter</i> spp	20 (7.2)	10 (3.7)	0.103
<i>Proteus</i> spp	5 (1.8)	4 (1.5)	1
<i>Morganella</i> spp	3 (1.1)	1 (0.4)	0.624
Other enterobacteriaceae	2 (0.7)	7 (2.6)	0.103
<i>Pseudomonas</i> spp	12 (4.3)	8 (3.0)	0.526
Anaerobic bacteria	13 (4.7)	12 (4.4)	1
Other gram-negative organisms	1 (0.4)	3 (1.1)	0.368
Gram-positive bacteremia	84 (30.3)	86 (31.7)	0.792
<i>Staphylococcus aureus</i>	36 (13)	47 (17.3)	0.194
<i>Streptococcus</i> spp	31 (11.2)	24 (8.9)	0.443
<i>Enterococcus</i> spp	14 (5.1)	11 (4.0)	0.723
Other gram-positive organisms	3 (1.1)	4 (1.5)	1

The rates of cephalosporin-resistant gram-negative bacteremia were similar in both study periods (11.2% ESBL-producing bacteria each; 1.7% and 0% amp-C producing bacteria, respectively,  $p=0.854$ ). Carbapenem-resistant enterobacteriaceae were found in 3 episodes in PREI, versus none in POSTI ( $p=0.337$ ). There were more MRSA-associated infections in the post-intervention group (2.8% vs 17.0% of *Staphylococcus aureus*-associated bacteremia,  $p=0.029$ ). Nosocomial bacteremia were significantly associated with *Enterobacter* spp ( $p<0.001$ ), *Klebsiella* spp ( $p=0.002$ ) and *Pseudomonas* spp ( $p<0.001$ ).

Finally, we found that 52.0% of all evaluated blood cultures were drawn between 6.5 p.m. and 8 a.m., while 67.3% were detected positive in the same timeframe, leading to a combined 89.2% of samples that were either drawn or found positive between 6.5 p.m. and 8 a.m.

### Outcomes

Antibiotic prescription was either initiated or changed after pathogen identification and oral result communication in 227 episodes in PREI and 236 in POSTI (82.0 vs 87.0%,  $p=0.123$ ; **Table 3**). Mean

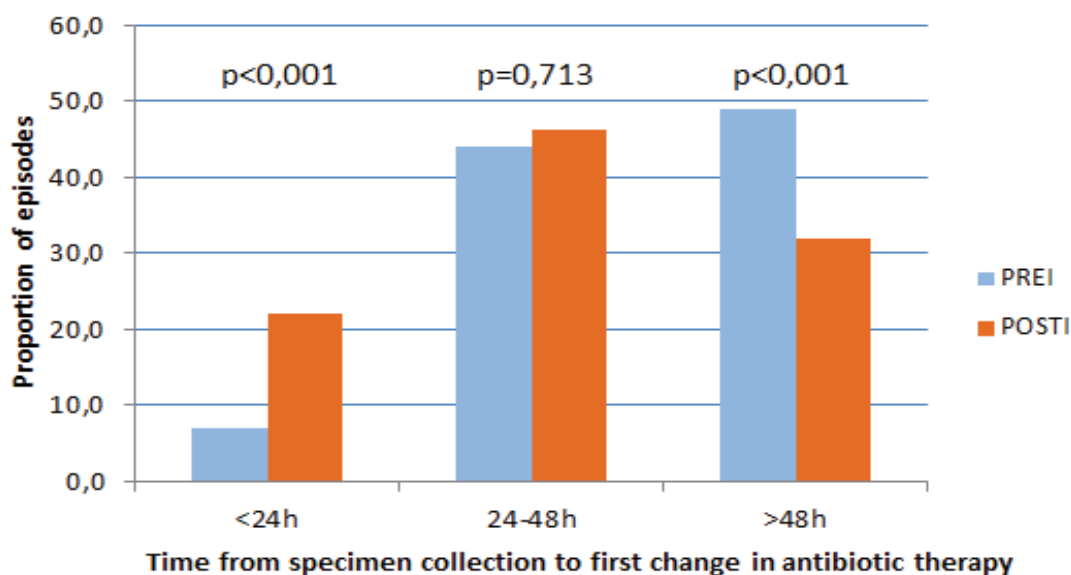
time from sample collection to the first change in antibiotic therapy (CAT) was reduced by 10.4 hours in POSTI ( $56.0 \pm 35.5$  vs  $45.6 \pm 30.2$  hours,  $p < 0.001$ ).

**Table 3. Distribution of antibiotic therapy in both study groups**

Antibiotic prescription	Value		p-value
	Pre-intervention n = 277 (%)	Post-intervention n = 271 (%)	
Empirical antibiotic treatment	220 (79.4)	197 (72.7)	0.081
Antibiotic change after BC results	227 (82.0)	236 (87.0)	0.123
Antibiotic initiation	52 (18.8)	73 (26.9)	0.03
Switch to a different antibiotic	156 (56.3)	140 (51.7)	0.582
Discontinuation of $\geq$ one drug	8 (2.9)	10 (3.7)	0.545
Addition of a new antibiotic	11 (4.0)	13 (4.8)	0.591
No change	50 (18.1)	35 (12.9)	0.123

BC : blood culture

“Antibiotic initiation” was more frequent in POSTI than in PREI (26.9% vs 18.8%,  $p = 0.03$ ), as opposed to the modification of an empirical treatment. If the evaluation timeframe was limited to the first 48 hours after blood culture collection, there were 16 CAT in PREI vs 52 in POSTI in the first 24 hours and a total of 116 vs 161 in under 48 hours, respectively ( $p < 0.001$ , **figure 2**).



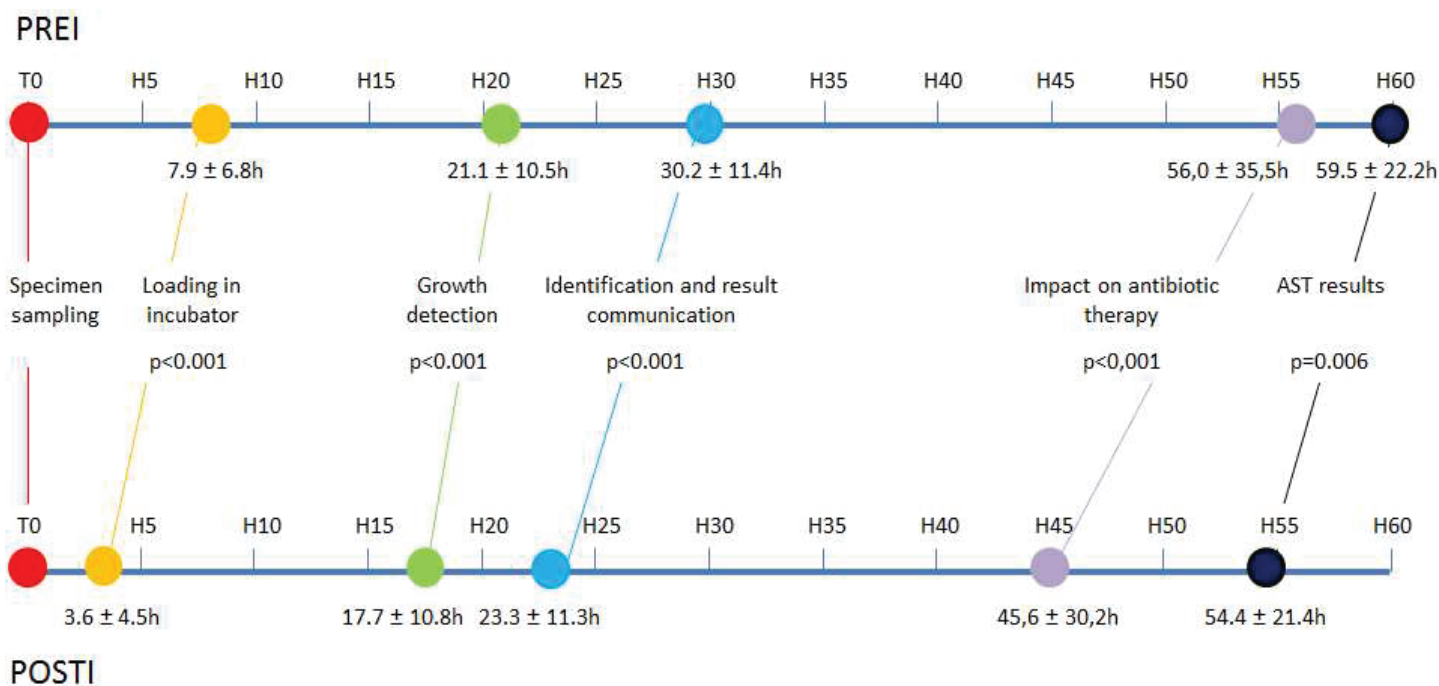
**Figure 2. Distribution of episodes according to the time from specimen collection to the first change in antibiotic therapy**

PREI: pre-intervention period; POSTI: post-intervention period

There were 220 episodes in PREI and 197 in POSTI that benefited from an empirical antibiotic treatment. Beta-lactams were the most frequently used antibiotic, as they were present in 85.5% and 84.8% of regimens, respectively. Empirical treatment was ineffective in 51 episodes in each group (23.2% and 25.9%, respectively,  $p=0.148$ ). Regarding patients with either ineffective empirical treatment or without any altogether, the time to effective treatment was reduced by 4.8 hours in POSTI ( $p<0.001$ ).

Median hospital length of stay was 16.0 days in PREI and 15.0 days in POSTI (IQR [9.0-33.0] and [9.0-26.5],  $p=0.83$ ). At 30 days following bloodstream infection onset, a non-significant difference in mortality was found, as 30 patients had died in PREI vs 23 in POSTI (10.8% vs 8.5%,  $p=0.511$ ).

The continuous workflow implemented in POSTI allowed for a reduction in the mean time from blood culture collection to sample loading in incubators:  $7.9 \pm 6.8\text{h}$  vs  $3.6 \pm 4.5\text{h}$  ( $p<0.001$ ). Consequently, the average time to positivity was reduced by 3.4 hours in POSTI ( $p<0.001$ ) and subsequently, all timeframes regarding laboratory performance were also significantly reduced in POSTI, as is illustrated in **Figure 3**.



**Figure 3. Timeline comparison of both study periods regarding sample processing and impact on treatment**

AST: antibiotic susceptibility testing; PREI: pre-intervention period; POSTI: post-intervention period.

Results are presented as means  $\pm$  standard deviation of the time from specimen collection to loading incubators, bacterial growth detection, species identification by Maldi-ToF MS, first change in antibiotic therapy, and AST results.

## DISCUSSION

In this retrospective study of 548 monomicrobial episodes of bacteremia, we found a significant 10.4-hour reduction in the time to the first change in antibiotic therapy after around the clock sample processing was implemented. Likewise, the time from blood culture (BC) collection to specimen loading in incubators, to bacterial growth detection, to pathogen identification and to antibiotic susceptibility testing results were all reduced through the continuous workflow. These improvements allowed for a significant 4.8-hour reduction in the time to effective antibiotic therapy.

Data regarding the clinical impact of a 24-hour workflow for BC is limited. Two studies evaluated a partial aspect of around the clock sample processing: first, in a prospective randomized controlled clinical trial, Kerremans et al. showed a 10.1h reduction in turnaround time thanks to uninterrupted loading in incubators ( $p < 0.001$ ), which in turn led to a 21-hour decrease in the time to empirical antibiotic treatment modification ( $p = 0.024$ ) (18). Second, Barenfanger et al. showed that by adding an evening shift in order to process more blood cultures, mean turnaround time was reduced by 5.2 hours ( $p = 0.001$ ) which allowed for a reduction in the time to appropriate antibiotic therapy ( $p = 0.006$ ) (20). These results were mirrored in studies conducted in laboratories with a 24/7 workflow: Perez et al. showed in 2013 that rapid pathogen identification in a 24-hour workflow setting was associated with a 36.7-hour reduction in the time to active antibiotic treatment ( $p = 0.0001$ ) compared to conventional techniques (21). However, only gram-negative bacteremia were included in this before/after study, and the 24/7 setting was not the evaluated variable. Eveillard et al. showed that appropriate antibiotic therapy was started sooner in 22.7% of patients if bacterial identification and antibiotic susceptibility testing were performed 24 hours a day, but their study was not limited to blood cultures, and did not use direct same-day identification (22). On the other hand, in a prospective randomized controlled study, Bruins et al. found that extending the usual workday was not associated with an increase in antibiotic change or a reduction in the time to effective treatment, but they only added one hour to their schedule (23).

We found a higher rate of antibiotic initiation following BC results in the post-intervention group, which suggests that the earlier communication of pathogen identification allowed for an immediate *targeted* treatment, when it would have remained *empirical* in the pre-intervention group in the same timeframe, as the clinician would still be waiting for the first result. This led to the reduction in the time to effective therapy in the post-intervention group, and highlights the considerable impact rapid microbial identification can have in a 24-hour setting (24).

Our study population consisted mostly of elderly male patients hospitalized on medical wards, with a total of 63 intensive care units (ICU) admissions (11.5%) following infection onset, and 53.6% community-acquired episodes. Comparing demographics from one study to another remains difficult owing to the discrepancies in inclusion criteria between them. Indeed, ICU requirement and acquisition setting of bloodstream infection show somewhat variable rates in most studies: from 10 to 61% for ICU admissions and from 59 to 79% for healthcare-associated infections (9,15,21,25,26).

The reduction in turnaround times and the earlier antibiotic treatment modification were not significantly associated with decreased length of stay (LOS) or mortality in our study. Regarding the former, a possible explanation might stem from the fact that LOS data extracted from our hospital information database included in-hospital recovery units, leading to a prolonged LOS that was possibly not caused by the bloodstream infection (BSI), therefore not influenced by a faster approach to patient care in this regard. Regarding mortality, while statistically not significant, there were seven less patients in the post-intervention group that had passed away at 30 days following BSI onset. Had our study population been larger, the difference in mortality rates might have been more significant. However, establishing a relevant chronological limit like the 30-day mark used in most BSI studies (16,21,27) suggesting association between mortality and BSI management is hazardous at best, and any conclusions should be carefully made. Data in published studies focusing on rapid microbial identification are conflicted regarding both LOS and mortality. Vardakas et al. found in their review that one of the factors associated with mortality in BSI was the time to efficient antibiotic therapy. The aforementioned studies by Barenfanger et al. and Kerremans et al. found a non-significant difference in mortality (7.9% vs 9.6%) and a 48-hour reduction in LOS ( $p=0.006$ ) for the former, and no statistically significant difference regarding both parameters for the latter (18,20,27). Perez and colleagues found a statistically significant reduction in LOS (11.9 vs 9.3 days,  $p=0.01$ ) and a non-significant reduction in mortality (10.7% vs 5.6%,  $p=0.19$ )(21); while in their study on antibiotic-resistant gram-negative bacteremia, both results were significant: 10.7 vs 16 days ( $p=0.008$ ) and 8.9 vs 21.0 % ( $p=0.01$ ), respectively (16). There are several confounding variables when one evaluates mortality and length of stay alike, even in seemingly comparable populations, as any complication can lead to patient death or increase LOS, with no relation whatsoever to antibiotic efficiency or laboratory performance, which could explain the non-significant results found in our study.

Regarding laboratory performance, continuous managing of blood cultures, from loading in incubators to antibiotic susceptibility testing, appears to be mandatory in order to ensure the best possible results, as we showed that 89.2% of samples were either drawn or detected positive during “off-hours”, which is *on par* with the 90% rates found by Schneiderhan et al (17). This information alone should be an incentive to standardize the uninterrupted workflow system in all clinical



microbial laboratories. Additionally, delays in processing BC upon arrival can hinder micro-organism recovery, which can be avoided by continuous loading in incubators and non-stop monitoring alike (28,29). However, the time from collection to arrival remains out of the laboratory's control, no matter the "working hours", and should be of concern when evaluating turnaround times. A point could also be made regarding *continuous* species identification through immediate Maldi-ToF MS following Gram staining, as opposed to *batch-wise* series. In the study by Schneiderhan et al., immediate identification by Maldi-ToF MS allowed for an extra 5-hour reduction in turnaround time compared to batch-wise series; however, only two series were performed every night in their evaluation, while there were at least three in our study (17). Finally, the success rate of direct Maldi-ToF identification on positive BC was not systematically available in our study; in case of dubious results, Gram staining would thus have constituted the first information communicated by phone to the clinician, which could increase the delay until antibiotic modification, as was shown by Clerc et al (15).

To our knowledge, standard of care and hospital ecology were similar in both evaluated periods. A sporadic variation remains however possible, as illustrated by the difference in rates of MRSA-associated bloodstream infections, which probably explains the increased proportion of underlying "cutaneous infections" found in POSTI. We selected two identical calendar periods in an effort to avoid seasonal pathogen variation and any bias pertaining to changes in staff experience and training, as the study center was a teaching hospital. We voluntarily excluded any potential contaminant, which led us to disregard all coagulase negative staphylococcus-associated (CoNS) bacteremia, aside from a handful of *Staphylococcus lugdunensis*. The inclusion of these CoNS-related infections would have allowed us to evaluate the timing of antibiotic discontinuation in case of actual contamination, as was done by French et al, and evidently, a fraction of them is bound to have had clinical significance indeed (30).

Our evaluation of antibiotic therapy only concerned inpatients. Any treatment received prior to admission was not recorded, and patients treated outside our facility following blood culture draw were not included. Moreover, antibiotic prescription changes, or lack thereof, might have been influenced by other microbiological results, or by clinical incidents such as allergic reactions or acute kidney failures. On the other hand, physicians are often likely to maintain the same treatment in case of clinical improvement, thus leading to a longer delay until antibiotic prescription change following apparently efficient empirical treatment (31). This can be viewed as an illustration of real-life practice, as clinical patient evolution can remain the primal motivation for prescription changes, or lack thereof, often leading to antibiotic escalation or, on the opposite, to the absence of streamlining

even in light of microbiological findings. Still, we found a significant difference regarding the proportion of episodes that benefited from antibiotic therapy modification - or initiation - in the first 48 hours following blood culture collection. It seems reasonable to assume that these early modifications resulted from blood culture findings, and it is precisely the patients with no empirical antibiotic therapy that would benefit the most from the reduction in turnaround times.

We did not evaluate cost changes that followed the implementation of a continuous workflow. Our monocentric setting in a large referral center may not be representative of all facilities, especially regarding the actual possibility of enabling the laboratory to function 24/7, in terms of personnel and material alike. Indeed, increased expenses associated with the extra staff and procedures need to be balanced by the reduction in overall hospitalization costs, ideally through reduced LOS and antibiotic use. Berild et al. were among several teams that showed decreased LOS, antibiotic use and overall costs following early appropriate antibiotic treatment changes, sometimes up to several thousands of dollars per patient (20,21,32–34). Aside from the clinical impact, results showing that rapid microbial identification procedures are cost-effective are necessary in order to justify their standardization (19).

The retrospective nature of our work might have led to decreased statistical power and otherwise avoidable information bias. A prospective design would be of interest, particularly if it involved the antibiotic stewardship team directly in terms of prescription advice. Indeed, Vardakas et al. showed that reduction in turnaround time thanks to rapid microbial identification only impacted mortality if associated with dedicated antibiotic stewardship (27). Huang et al. found in their pre-post study of 501 patients that a significant 28.1-hour reduction in turnaround time through direct Maldi-ToF MS on positive blood cultures, coupled with result communication ensured until midnight and custom recommendations by the stewardship team, improved time to effective antibiotic treatment by 9.7 hours ( $p=0.021$ ), which led to decreased mortality (14.5 vs 20.3%,  $p=0.021$ ) and shorter ICU stay ( $p=0.014$ )(9). However, such a study design implies a different interventional aspect, which was not our goal. The ecological benefit of earlier antibiotic modification could also be evaluated through a prospective interventional study, as the retrospective aspect did not allow for an unbiased evaluation of the appropriateness of antibiotic treatment, especially regarding possible streamlining or de-escalation.

## CONCLUSION

We found that a continuous workflow allowed for a significant reduction in turnaround times, which in turn led to a faster impact on antibiotic therapy and a reduction in the time to efficient treatment. A prospective study, coupled with hands-on antibiotic stewardship intervention, will hopefully confirm these results and yield an even greater clinical impact. Integrating a 24-hour processing of blood cultures appears to be effective and fruitful. Alongside innovative rapid identification and antibiotic susceptibility testing techniques, it should be the next step in the evolution of clinical microbiology laboratories.

### *Conflict of interest*

The authors have no conflict of interest to disclose regarding this study.

## REFERENCES

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;19:501-9.
2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:840-51.
3. Martiny D, Debaugnies F, Gateff D, Gérard M, Aoun M, Martin C, et al. Impact of rapid microbial identification directly from positive blood cultures using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on patient management. *Clin Microbiol Infect* 2013;19:568-81.
4. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589-96.
5. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010;54:4851-63.
6. Martiny D, Dediste A, Vandenberg O. Comparison of an in-house method and the commercial Sepsityper™ kit for bacterial identification directly from positive blood culture broths by matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry. *Eur J Clin Microbiol Infect Dis* 2012;31:2269-81.
7. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 2000;31:131-8.
8. Greutorex J, Ellington MJ, Koser CU, Rolfe KJ, Curran MD. New methods for identifying infectious diseases. *Br Med Bull* 2014;112:27-35.
9. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis* 2013;57:1237-45.
10. Stevenson LG, Drake SK, Murray PR. Rapid identification of bacteria in positive blood culture broths by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol* 2010;48:444-7.
11. Verroken A, Defourny L, le Polain de Waroux O, Belkhir L, Laterre P-F, Delmée M, et al. Clinical impact of MALDI-TOF MS identification and rapid susceptibility testing on adequate antimicrobial treatment in sepsis with positive blood cultures. *PLoS One* 2016;11:e0156299.
12. Maelegheer K, Nulens E. Same-day identification and antibiotic susceptibility testing on positive blood cultures: a simple and inexpensive procedure. *Eur J Clin Microbiol Infect Dis* 2017;36:681-7.
13. Randazzo A, Simon M, Goffinet P, Classen J-F, Hougardy N, Pierre P, et al. Optimal turnaround time for direct identification of microorganisms by mass spectrometry in blood culture. *J Microbiol Methods* 2016;130:1-5.

14. Vlek ALM, Bonten MJM, Boel CHE. Direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry improves appropriateness of antibiotic treatment of bacteremia. *PLoS One* 2012;7:e32589.
15. Clerc O, Prod'hom G, Vogne C, Bizzini A, Calandra T, Greub G. Impact of matrix-assisted laser desorption ionization time-of-flight mass spectrometry on the clinical management of patients with gram-negative bacteremia: a prospective observational study. *Clin Infect Dis* 2013;56:1101-7.
16. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant gram-negative bacteremia. *J Infect* 2014;69:216-25.
17. Schneiderhan W, Grundt A, Worner S, Findeisen P, Neumaier M. Work flow analysis of around-the-clock processing of blood culture samples and integrated MALDI-TOF mass spectrometry analysis for the diagnosis of bloodstream infections. *Clin Chem* 2013;59:1649-56.
18. Kerremans JJ, van der Bij AK, Goessens W, Verbrugh HA, Vos MC. Immediate incubation of blood cultures outside routine laboratory hours of operation accelerates antibiotic switching. *J Clin Microbiol* 2009;47:3520-3.
19. Dauwalder O, Vandenesch F. Clinical microbiology laboratory: from the Pasteur model to the 24/7 clinical chemistry concept. *Clin Microbiol Infect* 2014;20:593-4.
20. Barenfanger J, Drake C, Kacich G. Clinical and financial benefits of rapid bacterial identification and antimicrobial susceptibility testing. *J Clin Microbiol* 1999;37:1415-8.
21. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Land GA, et al. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. *Arch Pathol Lab Med* 2013;137:1247-54.
22. Eveillard M, Lemarié C, Cottin J, Hitoto H, Mahaza C, Kempf M, et al. Assessment of the usefulness of performing bacterial identification and antimicrobial susceptibility testing 24 h a day in a clinical microbiology laboratory. *Clin Microbiol Infect* 2010;16:1084-9.
23. Bruins M, Oord H, Bloembergen P, Wolfhagen M, Casparie A, Degener J, et al. Lack of effect of shorter turnaround time of microbiological procedures on clinical outcomes: a randomised controlled trial among hospitalised patients in the Netherlands. *Eur J Clin Microbiol Infect Dis* 2005;24:305-13.
24. Spivak ES, Cosgrove SE, Srinivasan A. Measuring appropriate antimicrobial use: attempts at opening the black box. *Clin Infect Dis* 2016;63:1639-44.
25. Munson EL, Diekema DJ, Beekmann SE, Chapin KC, Doern GV. Detection and treatment of bloodstream infection: laboratory reporting and antimicrobial management. *J Clin Microbiol* 2003;41:495-7.
26. Galar A, Leiva J, Espinosa M, Guillén-Grima F, Hernández S, Yuste JR. Clinical and economic evaluation of the impact of rapid microbiological diagnostic testing. *J Infect* 2012;65:302-9.
27. Vardakas KZ, Anifantaki FI, Trigkidis KK, Falagas ME. Rapid molecular diagnostic tests in patients with bacteremia: evaluation of their impact on decision making and clinical outcomes. *Eur J Clin Microbiol Infect Dis* 2015;34:2149-60.

28. Riest G, Linde H-J, Shah PM. Comparison of BacT/Alert and BACTEC NR 860 blood culture systems in a laboratory not continuously staffed. *Clin Microbiol Infect* 1997;3:345-51.
29. Sautter RL, Bills AR, Lang DL, Ruschell G, Heiter BJ, Bourbeau PP. Effects of delayed-entry conditions on the recovery and detection of microorganisms from BacT/ALERT and BACTEC blood culture bottles. *J Clin Microbiol* 2006;44:1245-9.
30. French K, Evans J, Tanner H, Gossain S, Hussain A. The clinical impact of rapid, direct MALDI-ToF identification of bacteria from positive blood cultures. *PLoS One* 2016;11:e0169332.
31. Trenholme GM, Kaplan RL, Karakusis PH, Stine T, Fuhrer J, Landau W, et al. Clinical impact of rapid identification and susceptibility testing of bacterial blood culture isolates. *J Clin Microbiol* 1989;27:1342-5.
32. Berild D, Mohseni A, Diep LM, Jensenius M, Ringertz SH. Adjustment of antibiotic treatment according to the results of blood cultures leads to decreased antibiotic use and costs. *J Antimicrob Chemother* 2006;57:326-30.
33. Fitzpatrick F, Turley M, Humphreys H, Smyth E. An after-hours clinical liaison blood culture service—is it worth it? *Clin Microbiol Infect* 2004;10:917-21.
34. Doern GV, Vautour R, Gaudet M, Levy B. Clinical impact of rapid In vitro susceptibility testing and bacterial identification. *J Clin Microbiol* 1994;32:1757-62.

## SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

## RESUME

### Objectif - Introduction

La prise en charge des bactériémies nécessite la mise en place d'une antibiothérapie précoce et efficace, secondairement adaptée aux résultats microbiologiques disponibles. Notre étude visait à évaluer l'impact du traitement et du rendu ininterrompus H24 des hémocultures sur la prescription d'antibiotiques et l'évolution des patients.

### Matériels et méthodes

Nous avons rétrospectivement évalué des épisodes de bactériémie monomicrobienne cliniquement significatifs sur deux périodes de 4 mois, au sein du CHU de Nice, avant et après l'ouverture H24 du laboratoire (PRE24 et POST24). L'identification bactérienne par spectrométrie de masse et les antibiogrammes étaient réalisés directement à partir des flacons détectés positifs. Le critère de jugement principal était le délai entre le prélèvement de l'hémoculture et la première modification de l'antibiothérapie survenant après communication des résultats microbiologiques. Les critères de jugements secondaires étaient les délais entre le prélèvement et : (i) la mise en place d'un traitement antibiotique efficace (TAE), défini comme comprenant au moins une molécule active in vitro sur le pathogène responsable, (ii) la détection de positivité du flacon (TTP), (iii) l'identification d'espèce, (iv) le rendu d'antibiogramme. La mortalité intra-hospitalière à 30 jours et la durée de séjour étaient également évaluées.

### Résultats

Au total, 548 épisodes de bactériémie chez 515 patients ont été inclus : 277 dans le groupe PRE24 et 271 dans le groupe POST24. Le délai moyen jusqu'à la première modification de l'antibiothérapie était réduit de 10.4h dans le groupe POST24 ( $p < 0.001$ ). Le délai moyen jusqu'au TAE était réduit de 4.8h dans le groupe POST24 pour les patients ayant un traitement empirique inefficace ou inexistant ( $p < 0.001$ ). Le TTP était réduit de 3.4h dans le groupe POST24 ( $p < 0.001$ ), le délai d'identification d'espèce de 6.9h ( $p < 0.001$ ), et le délai de rendu d'antibiogramme de 5.1h ( $p = 0.006$ ). La mortalité à J30 était de 10.8 vs 8.5% ( $p = 0.5$ ). La durée de séjour n'était pas modifiée entre les deux populations.

### Conclusion

Le traitement H24 des hémocultures permet une adaptation plus rapide du traitement antibiotique grâce à un rendu en continu des résultats.