

## Clinical impact of rapid susceptibility testing on MHR-SIR directly from blood cultures

Benoît Pilmis<sup>1</sup>, Michael Thy<sup>1</sup>, Julien Diep<sup>1</sup>, Sophie Krob<sup>1</sup>, Claire Périllaud<sup>2</sup>, Carine Couzigou<sup>1,3</sup>, Barbara Vidal<sup>1,3</sup>, Assaf Mizrahi<sup>2</sup>, Julie Lourtet-Hascoët<sup>1</sup>, Alban Le Monnier<sup>2</sup> and Jean-Claude Nguyen Van<sup>2\*</sup>

<sup>1</sup>Equipe mobile de microbiologie clinique, Groupe Hospitalier Paris Saint-Joseph, 75014 Paris, France; <sup>2</sup>Service de microbiologie clinique et dosage des anti-infectieux, Groupe Hospitalier Paris Saint-Joseph, 75014 Paris, France; <sup>3</sup>Equipe opérationnelle d'hygiène, Groupe Hospitalier Paris Saint-Joseph, 75014 Paris, France

\*Corresponding author. Tel: +33144127835; E-mail: jcnguyen@hpsj.fr

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**Background:** In a previous study, we demonstrated that rapid antibiotic susceptibility tests (ASTs) can be performed directly on blood culture samples tested on Mueller–Hinton Rapid agar (MHR-SIR) with a time delay of 6–8 h.

**Objectives:** Using this rapid disc diffusion method, we analysed the clinical impact associated with rapid reporting of results in our hospital setting.

**Methods:** All patients with bloodstream infections (BSIs) related to Enterobacteriaceae or *Staphylococcus aureus* were prospectively included in the study. The rapid ASTs were performed by incubation of positive blood cultures on MHR-SIR for 6–8 h by direct inoculation according to BSAC recommendations.

**Results:** One hundred and sixty-seven patients with BSIs were included as MHR-guided adaptation therapy cases. Eighty percent had Enterobacteriaceae-related BSIs, of which 12 (9%) were ESBL producers and 20% were *S. aureus*-related BSIs. A urinary or intra-abdominal infection was observed in 44.3% and 19.8%, respectively, of Enterobacteriaceae-related infections. The most frequent sources of infections for *S. aureus* BSIs were cutaneous and endovascular, in 43% and 23% of cases, respectively. Forty-four percent of the patients benefited from therapeutic modification according to the results of the MHR-SIR AST. Thus, empirical antibiotic therapy was modified by using antibiotic therapy that had too wide a spectrum or was unsuitable in 26% and 18% of cases, respectively. Compared with the 24 h required for the reference method, the median length of time to provision of susceptibility test results by MHR-SIR was 7 h.

**Conclusions:** This study showed a significant time saving (17 h) on the appropriateness of antibiotic prescription and demonstrated a significant impact regarding the choice and reduction of the spectrum of antibiotic therapy.

## Introduction

Bloodstream infections are serious infections and can lead to a state of septic shock where delay in adequate antibiotic therapy increases the risk of morbidity and mortality.<sup>1–3</sup> In cases of septic shock, current guidelines recommend empirical administration of broad-spectrum intravenous antibiotic therapy as soon as possible after recognition and within 1 h for both sepsis and septic shock. After identification of the causative bacteria and with the results of the antimicrobial susceptibility tests (ASTs), the spectrum of antibiotic therapy should be narrowed.<sup>4</sup> The use of rapid ASTs has been shown to reduce mortality, length of stay in hospital, time until alteration of antimicrobial therapy and the cost of hospitalization.<sup>5</sup> Although Gram staining and bacterial identification by MALDI-TOF MS directly on positive blood cultures<sup>6</sup> can help

physicians to focus empirical antibiotic therapy, ASTs are crucial for the management of bloodstream infections. The rate of initial inappropriate antibiotic prescriptions in bloodstream infections is sometimes reported as being surprisingly high (59%).<sup>7</sup> Clinicians should be aware of the commonly ignored drug-resistant pathogens, and efforts should be made to avoid delaying the administration of appropriate antibiotic therapy. Thus, the global increase in antimicrobial resistance warrants renewed interest in rapid ASTs.<sup>8</sup>

In clinical microbiology laboratories, the disc diffusion method described by Bauer *et al.*<sup>9</sup> in 1966 is still one of the most frequently used AST methods. Faster AST systems are increasingly being developed and utilized in microbiology laboratories, especially

automated systems for broth microdilution. Automated microdilution AST systems [VITEK® 2 (bioMérieux), Phoenix™ (Becton Dickinson Diagnostic Systems), Microscan WalkAway® (Siemens Medical Solutions Diagnostics) and Sensititre ARIS 2X (Trek Diagnostic Systems)] provide results within 6–12 h but have a number of disadvantages, including fixed drug panels, a reduced range of concentrations tested, being uninterpretable in the case of polymicrobial infections, and poor detection of synergism/antagonism phenomena.<sup>10</sup>

New rapid and direct methods are also being developed using MALDI-TOF technologies,<sup>11</sup> microcalorimetry,<sup>12</sup> microfluidic platforms,<sup>13</sup> rapid colorimetric tests,<sup>14</sup> DNA amplification,<sup>15</sup> microarrays<sup>16</sup> and multiplex PCR systems<sup>17,18</sup> to detect resistances in bacteria.<sup>19</sup> Although these techniques are rapid and efficient, some remain expensive and require special equipment. Moreover, they have certain limitations; for example, PCR-based techniques identify resistance genes but the presence of these resistance markers may not always correlate with phenotypic resistance.

Disc diffusion is an economical, robust, accurate, reliable and highly standardized AST testing method. The advantages include flexible drug testing, low consumable costs and recognition of phenomena such as synergism for the detection of ESBLs and/or antagonism for the detection of AmpCs or macrolide-inducible clindamycin resistance.<sup>10,20</sup>

A pertinent strategy would combine the robustness of classic disc diffusion methods with the use of Mueller–Hinton Rapid agar (MHR-SIR), in order to obtain the complete susceptibility profile of the bacteria within 6–8 h directly from blood samples. Our previous study demonstrated an excellent categorical agreement (97.7% for Enterobacteriaceae; 97.8% for *S. aureus*) and correlation between inhibition zone diameters for MHR-SIR and standard Mueller–Hinton (MH) methods.<sup>21</sup> In case of discrepancies [major error (resistant to susceptible) and very major error (susceptible to resistant)] between results of inhibition zone diameters with MH and MHR-SIR methods, MICs were verified by a reference technique (broth microdilution method, Sensititre, Thermo Fisher Scientific). Despite some discrepancies, there are several benefits using the MHR-SIR method. AST by MHR-SIR is a rapid and reliable method for Enterobacteriaceae and *S. aureus* performed directly from positive blood cultures.

The aim of this study was to measure the clinical impact associated with rapid reporting of AST MHR-SIR results directly from blood cultures after 6–8 h of incubation on the same day that the bacteraemia was detected.

## Methods

### Hospital setting

This case-control study was conducted between June 2015 and June 2018 at the Hospital Paris Saint-Joseph, a 670 bed tertiary care hospital.

In our hospital, each day the antimicrobial stewardship team composed of three infectious disease specialists received in real time the information from the microbiology laboratory concerning positive blood cultures, including Gram stain and antibiotic susceptibility test results. The first results of Gram staining and rapid microbial identification by MALDI-TOF MS were transmitted in real time to the antimicrobial stewardship team, and if necessary the antimicrobial stewardship team modified the therapeutic decision depending on species identification.

### Case-control selection

Eligibility criteria were the presence of an active infection defined as a positive blood culture and clinical definition of sepsis caused by at least Enterobacteriaceae or *Staphylococcus aureus* and requirement for an empirical antibiotic therapy. All patients were screened daily for eligibility.

Exclusion criteria were (i) infections related to bacteria other than Enterobacteriaceae or *S. aureus* and (ii) a moribund patient or a patient in palliative care, for whom the clinician decided not to introduce antibiotic therapy.

The study included two periods. Period 1 was from June 2015 to December 2016. A conventional strategy was followed using the standard method of disc diffusion with 16–24 h of incubation according to the recommendations of EUCAST. Patients treated according to the routine method formed the control group.

Period 2 was from January 2017 to June 2018, when MHR-guided adaptation therapy was used, as reported in our published study.<sup>21</sup>

### Microbiological procedures

Blood cultures were collected in BacT/ALERT bottles and incubated in Virtuo (bioMérieux, La Balme-les-Grottes, France). Once the blood culture was flagged as positive, Gram staining was performed, followed by identification with MALDI-TOF MS Andromas® (Beckman Coulter, Villepinte, France) directly on blood culture pellets using the AMUST® kit, as recommended in the manufacturer's instructions.<sup>22</sup>

AST was performed on positive blood samples by direct inoculation as recommended by BSAC<sup>23</sup> on MHR-SIR (i2a, Montpellier, France) and incubated for 6–8 h. As reported by Wootton,<sup>23</sup> the direct method depended on the Gram reaction of the infecting organism. For Gram-negative bacilli, one drop of the blood culture was placed in 5 mL of sterile water, then a sterile cotton-wool swab was dipped in the suspension and excess was removed by turning the swab against the inside of the container. The swab was used to spread the inoculum evenly over the surface of the susceptibility agar plate. For staphylococci, three drops of the blood culture were placed in 5 mL of sterile water, then we proceeded in the same way.

A panel of 32 antibiotic discs was tested for Enterobacteriaceae and 16 antibiotic discs were tested for *S. aureus*.<sup>21</sup> Inhibition zones were read from digital images with the SIRscan® 2000 Automatic system (i2a, France) and were interpreted according to the EUCAST recommendations.<sup>24</sup> The AST results were communicated via telephone to the antimicrobial stewardship team with a recommendation for adjustment of antibiotic therapy. Clinical and biological data including patient outcome were collected prospectively. Patients who had been discharged with empirical antibiotic therapy were contacted by the physician in charge so that treatment could be adapted if needed. We hypothesized that early identification and antimicrobial susceptibility testing of the bacteria would facilitate discharge planning for patients near the time of hospital discharge.<sup>25</sup>

### Antimicrobial adaptation strategies

In the conventional adaptation group (i.e. the controls), the  $\beta$ -lactam could be adapted according to the results of microbiological sample culturing (notably Enterobacteriaceae identification), and then definitively adapted according to AST results. In the MHR-guided adaptation group (i.e. the cases), the defined  $\beta$ -lactam was adapted according to the MHR results.

For other families of antibiotics, there is no consensus for definition of de-escalation.

### Definitions and endpoints

Appropriate antimicrobial therapy, defined as the gold standard, was the use of  $\beta$ -lactams active against the identified Enterobacteriaceae or *S. aureus* as determined by the antimicrobial stewardship team.

**Table 1.** Baseline characteristics of patients

|                           | All patients (n=330) | Conventional strategy (n=163) | MHR-guided adaptation therapy (n=167) | P     |
|---------------------------|----------------------|-------------------------------|---------------------------------------|-------|
| Demographic data          |                      |                               |                                       |       |
| male/female, n/n          | 179/151              | 88/75                         | 91/76                                 | >0.99 |
| age (years), median (IQR) | 72.6 (60.1–81.2)     | 72.5 (59.8–83.2)              | 72.7 (60.5–82)                        | >0.99 |
| Admission ward, n (%)     |                      |                               |                                       |       |
| medical                   | 270 (81.8)           | 133 (81.6)                    | 137 (82)                              | >0.99 |
| surgical                  | 34 (10.3)            | 15 (9.2)                      | 19 (11.4)                             | 0.58  |
| ICU                       | 26 (7.9)             | 15 (9.2)                      | 11 (6.6)                              | 0.41  |
| Immunodeficiencies, n (%) | 27 (8.2)             | 12 (7.4)                      | 15 (8.9)                              | >0.99 |

**Table 2.** Characteristics of infections at inclusion

|                                     | All patients (n=330) | Conventional strategy (n=163) | MHR-guided adaptation therapy (n=167) | P     |
|-------------------------------------|----------------------|-------------------------------|---------------------------------------|-------|
| Source of infection, n (%)          |                      |                               |                                       |       |
| urinary tract                       | 129 (39)             | 55 (33.7)                     | 74 (44.3)                             | 0.055 |
| intra-abdominal                     | 68 (20.6)            | 35 (21.5)                     | 33 (19.8)                             | 0.78  |
| catheter-related                    | 38 (11.5)            | 22 (13.5)                     | 15 (9)                                | 0.22  |
| skin and soft tissue                | 21 (6.4)             | 11 (6.7)                      | 10 (6)                                | 0.82  |
| respiratory tract                   | 15 (4.5)             | 6 (3.7)                       | 9 (5.4)                               | 0.59  |
| bone and joint                      | 24 (7.3)             | 13 (8)                        | 11 (6.6)                              | 0.39  |
| infective endocarditis <sup>a</sup> | 21 (6.4)             | 13 (8)                        | 8 (4.8)                               | 0.26  |
| primary bacteraemia <sup>a</sup>    | 15 (4.5)             | 8 (4.9)                       | 7 (4.2)                               | 0.77  |
| Isolated bacteria, n (%)            |                      |                               |                                       |       |
| Enterobacteriaceae                  | 251 (76)             | 118 (72.4)                    | 133 (79.6)                            | 0.15  |
| <i>S. aureus</i>                    | 79 (24)              | 45 (27.6)                     | 34 (20.4)                             | 0.1   |

<sup>a</sup>One patient had two infections: catheter-related infection complicated by *S. aureus* infectious endocarditis.

Antibiotic escalation and de-escalation were defined according to Weiss *et al.*; <sup>26</sup> 'optimal antimicrobial therapy' was defined as the use of amoxicillin, amoxicillin/clavulanate or cefotaxime for WT Enterobacteriaceae, cefepime for AmpC-overproducing Enterobacteriaceae and carbapenems for ESBL-producing Enterobacteriaceae.

### Statistical analysis

Categorical variables are presented as frequencies and percentages. Quantitative variables are presented as the mean (SD) or median (IQR). To identify differences between MHR and conventional methods we used parametric and non-parametric tests; the  $\chi^2$  test or Fisher's exact test was used to compare categorical variables and the Mann-Whitney test was used to compare quantitative variables. An unfavourable outcome was defined as in-hospital mortality. As a first step, variables showing associations at a significance level of  $\alpha=0.20$  in univariable analysis were selected for inclusion in the multivariable model.

We investigated the relationship between unfavourable outcome and potential predictors by performing a multivariable logistic analysis. Statistical analysis was performed using the R 2.11.1 statistical package (R Development Core Team; R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

### Ethics

This study was approved by the local clinical research ethics committee at Groupe Hospitalier Paris Saint-Joseph and registered under GERM-IRB registration number 0000347.

## Results

### Patient characteristics

From June 2015 to June 2018, 330 patients treated for bloodstream infections related to Enterobacteriaceae or *S. aureus* were prospectively included in the study; 167 of these patients were included as cases. Baseline characteristics of the patients included were similar in the two groups (Table 1).

### Infections

Characteristics of infections are presented in Table 2.

Enterobacteriaceae were isolated in 251 (76%) cases and *S. aureus* was isolated in 79 (24%) cases. The MHR-SIR disc diffusion method allowed early reading for the most important pathogens isolated from positive blood cultures, such as Enterobacteriaceae and *S. aureus*, which accounted for 50% of all blood culture isolates in our laboratory in the period 2015–17.

Distribution of Enterobacteriaceae was as follows: *Escherichia coli* (63%), *Klebsiella* sp. (15.3%), *Enterobacter* sp. (14.5%), *Citrobacter* sp. (2.4%), *Serratia* sp. (1.6%), *Salmonella* sp. (1.6%), *Proteus* sp. (1.8%) and *Yersinia* sp. (0.8%). There was no significant difference between the two groups before and after MHR-SIR in the distribution of Enterobacteriaceae.

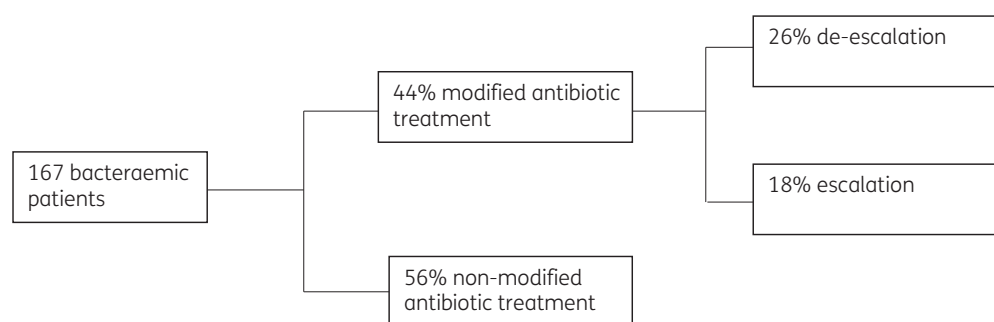


**Figure 1.** Scheme of modification of antibiotic therapy.

ESBL-producing Enterobacteriaceae were isolated in 6.8% of cases and the prevalence of MRSA bacteraemia was 8.9%.

Patients were empirically treated with third-generation cephalosporins (ceftriaxone, cefotaxime) (50%),  $\beta$ -lactam/ $\beta$ -lactamase inhibitor (24%) and carbapenems (2%), with no differences between groups for infections related to Gram-negative bacteria, and with first-generation cephalosporins (16%) or vancomycin (8%) for infections related to Gram-positive cocci. Twenty-one percent of patients received aminoglycosides as empirical dual antibiotic therapy. Eighty-four percent (140/167) of MHR-guided adaptation therapy and 74% (120/163) of controls received an appropriate empirical antibiotic therapy ( $P=0.21$ ).

### Clinical impact of rapid susceptibility testing on MHR-SIR

Forty-four percent of the patients benefited from therapeutic modification according to the results of the MHR-SIR AST (Figure 1). Once the results of the culture of the microbiological sample were available, escalation of the empirical antibiotic therapy was made in 18% (30/167) of cases and in 15% (24/163) of controls ( $P=0.45$ ). Furthermore, effective de-escalation was performed in 26% of cases (44/167) and 15% of controls (24/163) ( $P=0.046$ ). The mean time between positivity of blood culture and adaptation of the empirical antibiotic therapy was 18 h ( $\pm 3$  h and 40 min) in the control group and 7 h ( $\pm 2$  h and 30 min) in the case group ( $P<10^{-5}$ ).

Moreover, patient contact precautions were implemented according to MHR results in 9% of the cases because an ESBL had been identified. No significant difference in mortality between the two groups was observed in this study.

## Discussion

To the best of our knowledge, this is the first evaluation of the clinical impact of rapid susceptibility testing on MHR-SIR. It showed a demonstrable clinical impact; it was a faster method, leading to a median adaptation time of 7 h ( $\pm 2$  h and 30 min) compared with 24 h with the conventional method.

Some authors reported that inappropriate initial antimicrobial therapy for septic shock occurs in  $\sim 20\%$  of patients and is associated with a 5-fold reduction in survival.<sup>27</sup> Furthermore, several studies showed that reduced time for bacterial identification and antimicrobial susceptibility testing using rapid tests is correlated with improved mortality and reduced healthcare

costs.<sup>28,29</sup> The impact of this rapid AST on therapeutic decisions and adjustments in empirical antibiotic therapy is a major challenge. Thus, as reported by Blaschke et al.,<sup>30</sup> rapid availability of accurate results from AST is currently considered one of the most important unmet medical needs in the management of infectious diseases.

In our work, we have demonstrated that the rapid method by MHR-SIR directly from blood cultures allows significantly more effective de-escalation of treatment than the conventional technique thanks to the time saving. In this case, the benefit of an early result can be explained by the fact that antibiotic therapy is de-escalated in real time while the patient is still present in the hospital, whereas with the standard technique the patient would already be back home or transferred to another healthcare establishment. The advantage of MHR-SIR comes from the fact that in our hospital the information is 100% utilized by the mobile antimicrobial stewardship team, whereas with the conventional technique the information is transmitted to the new healthcare establishment, with the risk that it will not be used for one-third of patients.

In summary, the AST results were available 17 h sooner than those with the standard of care at low cost:  $<6$  US dollars for 16 antibiotics selected by the microbiologist. For our bacteraemic patients, nearly half of the antibiotic therapies have been modified and a quarter of the treatments have been de-escalated, while nearly a fifth have been escalated (Figure 1). According to cost-effectiveness studies, we believe that this is an important improvement in the management of bloodstream infections.<sup>31,32</sup>

### Limitations

The limits of our study are, first, that the clinical impact could depend on the working hours of the different laboratories. Second, the method was very efficient for Enterobacteriaceae and *S. aureus*, but not always possible in the delay of 8 h for other bacteria, such as *Pseudomonas aeruginosa*. Third, in this study period we did not have any carbapenemase-producing Enterobacteriaceae strains in blood culture. Thus, in our single study the low number of ESBL-producing strains and the absence of carbapenemase-producing strains may explain the lack of impact on mortality.

The impact of this rapid diagnostic test on therapeutic decisions and adjustments in empirical antibiotic therapy remains a major

challenge and larger prospective multicentre studies are needed to complete and confirm our results.

## Conclusions

This study based on rapid AST MHR-SIR showed a significant time saving (17 h) in assessing the appropriateness of antibiotic prescription and demonstrated a significant impact at very moderate cost on the choice and reduction of the spectrum of antibiotic therapy. It represents added value when combined with its ability to enable efficient action in real time by the antimicrobial stewardship team.

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## Transparency declarations

None to declare.

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