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ORIGINAL



# Performance and economic evaluation of the molecular detection of pathogens for patients with severe infections: the EVAMICA open-label, cluster-randomised, interventional crossover trial

Emmanuelle Cambau<sup>1,2\*</sup> , Isabelle Durand-Zaleski<sup>3,4</sup>, Stéphane Bretagne<sup>5,6,7,8</sup>, Christian Brun-Buisson<sup>9</sup>, Catherine Cordonnier<sup>10</sup>, Xavier Duval<sup>11</sup>, Stéphanie Herwegh<sup>12</sup>, Julien Pottecher<sup>13</sup>, René Courcol<sup>12</sup>, Sylvie Bastuji-Garin<sup>14,15,16</sup> and The EVAMICA study team

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## Abstract

**Purpose:** Microbiological diagnosis (MD) of infections remains insufficient. The resulting empirical antimicrobial therapy leads to multidrug resistance and inappropriate treatments. We therefore evaluated the cost-effectiveness of direct molecular detection of pathogens in blood for patients with severe sepsis (SES), febrile neutropenia (FN) and suspected infective endocarditis (SIE).

**Methods:** Patients were enrolled in a multicentre, open-label, cluster-randomised crossover trial conducted during two consecutive periods, randomly assigned as control period (CP; standard diagnostic workup) or intervention period (IP; additional testing with LightCycler<sup>®</sup>SeptiFast). Multilevel models used to account for clustering were stratified by clinical setting (SES, FN, SIE).

**Results:** A total of 1416 patients (907 SES, 440 FN, 69 SIE) were evaluated for the primary endpoint (rate of blood MD). For SES patients, the MD rate was higher during IP than during CP [42.6% (198/465) vs. 28.1% (125/442), odds ratio (OR) 1.89, 95% confidence interval (CI) 1.43–2.50;  $P < 0.001$ ], with an absolute increase of 14.5% (95% CI 8.4–20.7). A trend towards an association was observed for SIE [35.4% (17/48) vs. 9.5% (2/21); OR 6.22 (0.98–39.6)], but not for FN [32.1% (70/218) vs. 30.2% (67/222),  $P = 0.66$ ]. Overall, turn-around time was shorter during IP than during CP (22.9 vs. 49.5 h,  $P < 0.001$ ) and hospital costs were similar (median, mean  $\pm$  SD: IP €14,826, €18,118  $\pm$  17,775; CP €17,828, €18,653  $\pm$  15,966). Bootstrap analysis of the incremental cost-effectiveness ratio showed weak dominance of intervention in SES patients.

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**Take-home message:** Direct detection by PCR of bacterial and fungal DNA increases the number of patients with confirmed microbial aetiology of severe sepsis, and appropriate antimicrobial therapy can be given more rapidly. Molecular detection of pathogens was shown to be cost-effective when performed in addition to blood cultures in patients with severe sepsis.

**Conclusion:** Addition of molecular detection to standard care improves MD and thus efficiency of healthcare resource usage in patients with SES.

*ClinicalTrials.gov* registration number: NCT00709358.

**Keywords:** Sepsis, Bacteremia, PCR, Aetiological source

## Introduction

The incidence of sepsis is rising and the severe forms [severe sepsis (SES) including septic shock] are still a major cause of death [1, 2]. Patients requiring immunosuppressive therapy are more prevalent with febrile neutropenia (FN) being a frequent life-threatening complication [3]. Infective endocarditis is also increasing in incidence, with high mortality and morbidity [4, 5]. Early initiation of appropriate antimicrobial therapy reduces the morbidity and mortality of these severe infections, prompting the prescription of broad-spectrum antimicrobial agents before the results of microbiological diagnosis (MD) are known [6–8]. This empirical first-line therapy is one of the factors explaining the increase in antimicrobial-resistance prevalence [9]. Moreover, antimicrobial therapy usually remains empirical, since microbial documentation in the blood is usually obtained for a maximum of 30% of cases for FN, and 35–50% for SES [10–13].

Blood cultures (BC) are still the main biological tools for identifying the microbial pathogen(s) associated with severe infections [14]. Their results are critical for the choice of an appropriate antimicrobial treatment, especially in cases of resistant bacteria [2, 15, 16]. However, their low positivity rates (10–20% overall) and delayed results (median 2–3 days) make them useful mostly for escalation or de-escalation in the days following the onset of sepsis [17, 18]. Molecular detection has been developed to provide a shorter time to results and to detect microbial nucleic acids in patients with receipt of antibiotic therapy [12]. Meta-analyses for testing molecular detection of pathogen in the blood have reported these tests as less sensitive and less specific than BCs, taken as the gold standard, and consequently these tests are rarely used in the diagnostic standard workup [19, 20]. It should be noted that in the previous studies, many cases were shown with positive molecular tests and BC-negative with clinical status showing signs of bloodstream infections [21, 22]. The cost-effectiveness of molecular direct testing in blood remains unknown [23].

We conducted a multicentre open-label cluster-randomised crossover clinical trial to assess the clinical and economic impact of molecular detection of pathogens in blood for patients with severe infections, such as SES, FN, and suspicion of infective endocarditis (SIE) [24]. Our hypothesis was that molecular direct testing,

in addition to a conventional workup, would provide relevant and timely information for the adjustment of antimicrobial therapy and that the additional cost would be offset by successful infection management.

## Methods

### Study procedures and participants

The study was conducted in 55 clinical wards of 18 university hospitals (each hospital being a cluster) during two consecutive 6-month periods, randomly assigned as intervention (IP) or control (CP) (standard care) periods. Details of the protocol are provided in the supplementary text and at the clinical trials website (<https://clinicaltrials.gov> NCT00709358). Patients aged  $\geq 18$  years were consecutively enrolled when meeting the diagnosis of (1) SES (including septic shock) [1, 10] (2) a first episode of FN [3, 13] or (3) suspicion of infective endocarditis, as defined below.

During the two periods, at least two BC sets were collected within 24 h after inclusion [14]. During IP, direct molecular testing was additionally performed on blood using the CE-IVD LightCycler® SeptiFast test (LSF; Roche Diagnostics, Meylan, France) (see supplemental methods for details on testing). During the two periods, additional BCs and other specimens were submitted for microbiological examination at the discretion of the physician and processed following general guidelines [14]. The results of microbiological tests, including LSF tests during IP, were transmitted to clinical wards in a timeline for physicians to initiate or modify antimicrobial therapy following general recommendations [3, 7, 25].

### Endpoints

The primary endpoint was MD, i.e. detection of pathogens in the blood samples using results of BCs during CP and of both BCs and molecular tests during IP.

Secondary endpoints included the pathogens identified, the turn-around time (TAT) (i.e., time interval from taking blood samples to transmission of results), and the number of patients receiving an appropriate treatment. Appropriateness was evaluated by comparing the pathogen detected and the list of antimicrobial agents prescribed within the 7 days after inclusion [3, 7, 25]. The complications were observed until the end of the study (EOS) (discharge, death, 30 days for SES and FN, 45 days for SIE). Costs were measured at the EOS.

### Statistical analysis

The study was designed as a superiority trial. With the hypothesis of an effect modification by type of infection, the study was powered on the primary endpoint in subgroups of SES and FN. Assuming a documentation prevalence of 35–50% in SES [10] and 30% in FN, [11, 13], at least 480 and 440 patients in the SES and FN groups, respectively, were needed to show a 15% absolute difference, considering a two-sided type I error of 0.05, a type II error of 0.10, an intracluster correlation coefficient of 0.01, and an 18-hospital number of clusters. Sample size was not estimated for SIE, since the overall number of cases was supposed to be lower than 150 [5].

Prevalence of the primary endpoint was compared between the two groups with the  $\chi^2$  test, and the absolute risk reduction (ARR) was calculated with their 95% confidence interval (CI). To account for clustering (confounding and effect modification by centre), a random-centre effect logistic regression (multilevel model with patients at level 1 and hospital at level 2) was analysed. To estimate the intervention effect, we computed the odds ratios (ORs) and their 95% CIs in a multilevel model, taking into account the order of intervention to control for a potential carryover effect.

### Cost-effectiveness evaluation

The prospective economic evaluation was concurrent with the randomized trial, in accordance with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement [26]. We estimated the incremental cost-effectiveness of using LSF in addition to a standard workup from the perspective of the hospital with a 30-day time horizon [27, 28]. Effectiveness was defined as the primary endpoint. Hospital resources were valued by adjusting the 2013 average national cost of each patient's diagnosis related group (DRG) with their actual length of stay and resources used during their hospitalisation. Types of resources and unit costs are described in Supplementary Table 2. A cost-effectiveness analysis was conducted to estimate incremental costs (difference in per-patient costs between groups) per incremental microbial documentation. The uncertainty of the results was analysed by the non-parametric bootstrap method to make multiple estimates of the ICER by randomly re-sampling the patient population to create sub-samples. Using this bootstrap analysis, the scatter plot of 1,000 ICERs is presented on the cost-effectiveness plane [29, 30]. Data reporting was performed according to CONSORT (Consolidated Standards of Reporting Trials) guidelines [31].

## Results

### Patients and primary outcome

Of 1459 eligible patients, 1416 were included as 731 during IP and 685 during CP (Fig. 1), and as 907 (64%) with

SES, 440 (31.1%) with FN, and 69 (4.9%) with SIE. Patient characteristics, depicted in Table 1, were not different between the two periods.

During IP, MD was positive for 285/731 (39.0%) patients compared with 193/685 (28.2%) during CP ( $P < 0.001$ ) (Table 2). A higher MD rate was also significantly observed when excluding 41 cases with putative contaminants (e.g. one test positive with coagulase-negative staphylococci) observed at a rate of 2.7 and 3%, in CP and IP, respectively. Using multilevel modelling, neither centre-effect ( $P = 0.65$ ) nor effect-modification by centre ( $P = 0.85$ ) were observed, but a significant effect with regard to the subgroup of infection ( $P = 0.03$ ). Kappa's agreement between the results of molecular tests and those of BCs was poor ( $0.2693 \pm 0.0366$  SD) with only 83 patients with both positive molecular test and BCs in the IP.

Among patients suffering from SES, 198/464 (42.6%) patients had MD during IP, compared with 124/442 (28.1%) during CP (OR 1.89, 95% CI 1.43–2.50,  $P < 0.001$ ). The intervention resulted in an absolute increase in the MD rate by 14.5% (95% CI 8.4–20.7). MD was significantly associated with the primary site of infection being other than pulmonary, with community-acquired infection and with severity criteria (Table 3). Multivariate analysis adjusted for these variables did not change the association between the IP and the MD rate (OR 1.89; 95% CI 1.36–2.63,  $P = 0.001$ ).

The MD rate was similar for patients with FN, and only a trend for an association was observed among patients with SIE (Table 2).

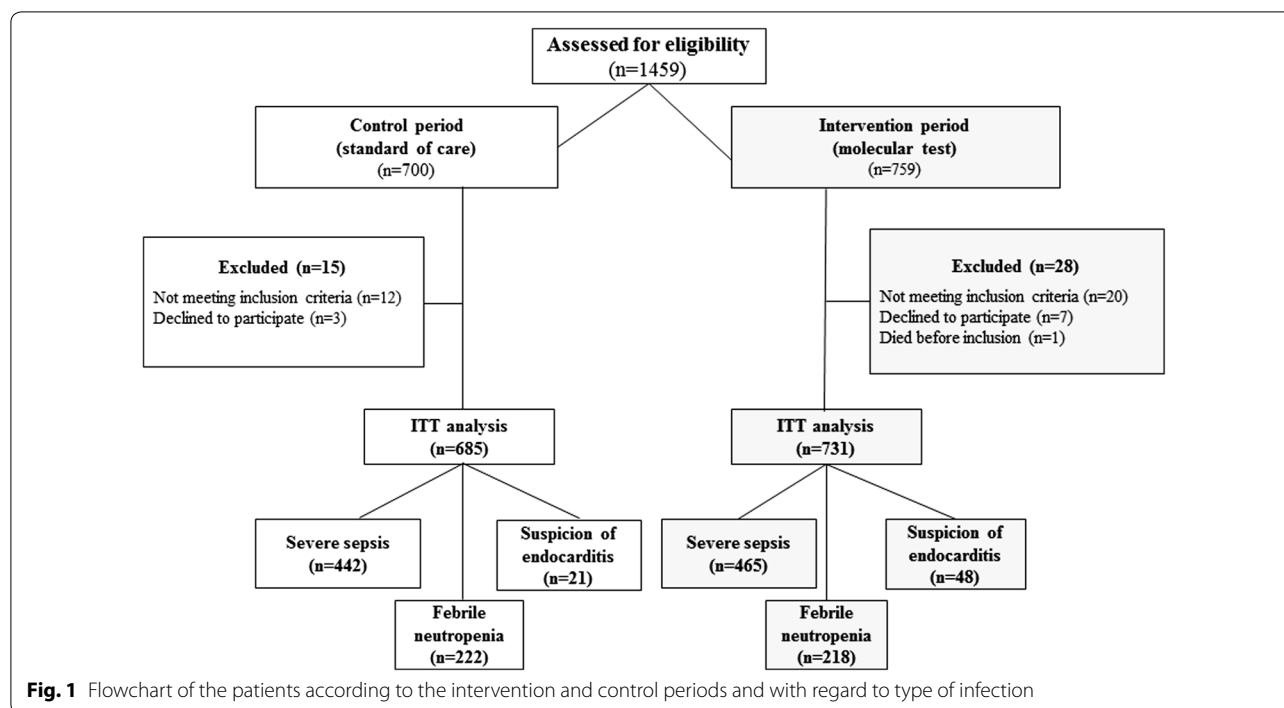
### Secondary outcomes

#### Pathogens identified

The use of the molecular test resulted in a significantly higher number of patients in whom Gram-negative bacilli (GNB), Gram-positive cocci (GPC), or fungi were detected in their blood (Table 2; Fig. 2). This was observed in the whole population, as well as in patients with SES [19.6 vs. 11.5% for GNB,  $P < 0.001$ ; 23.7 vs. 15.6% for GPC,  $P = 0.002$ ; and 2.8% (13 cases) vs. 0.7% (3 cases) for fungi,  $P = 0.02$ , for IP and CP, respectively]. The detection of bacterial species not included in LSF (e.g., strict anaerobes, *Salmonella* spp., *Bacillus* spp. and others) was similar in the two periods ( $P = 0.18$ ). Polymicrobial infections (concomitant detection of more than one pathogen in the blood) were more often detected during IP [160/731 (22%) vs. 75/685 (11%),  $P = 0.001$ ]. The pathogens detected during the two periods are detailed in Table 4.

#### Time interval from blood collection to results

Among the patients with positive MD, the median TAT from blood collection to technical validation on the one



hand and to transmission to the clinicians on the other hand, were significantly shorter during IP (Table 2). It has to be noted that, for patients with SES, the median TAT was below 24 h. Results were first transmitted by telephone (73.6%), computer interface (23.6%), Fax (14.5%), and mailing (10.9%). Interaction between laboratories and wards was as usual for discussion of the results.

#### Appropriate antimicrobial treatment

Considering the 1416 included patients, antimicrobial agents prescribed were beta-lactams (95.5%), aminoglycosides (43.2%), fluoroquinolones (26.5%), glycopeptides (21.1%), other antibiotics (31.7%), and antifungal agents (17.7%), with no difference between the two periods (Supplementary Table 3). In this whole population, a significantly higher number of patients received an appropriate therapy during IP (Table 2). However, when only the 478 patients with positive MD were considered, the rates of appropriate therapy were similar for the two periods (90.5 and 90.2%, respectively). An optimal treatment, i.e. more targeted towards the etiological microbes was observed in 263/395 (66.6%) patients with no difference between CP and IP (70.7 and 63.9%,  $P = 0.16$ ) (supplementary figure). During IP, when 285 cases were observed as MD-positive, clinicians attested they modified the antimicrobial treatment according to the LSF results in 29.4% (79/269 answers) out of which de-escalation was done for 49 cases (62%).

#### Complications and mortality

Complications were observed in 362 cases (31.7% of 1142 patients documented for complications) as an extension of the infection ( $n = 190$ , 16.6%) or a new infection episode ( $n = 172$ , 15.1%), with no difference between the two periods [32.1% (185/577) and 29.6% (167/565),  $P = 0.34$ ]. Among SES patients, the 7-day mortality rate was 17.3% (149/863) with no significant difference between the two periods (18.7 vs. 15.8% in IP and CP, respectively;  $P = 0.38$ ), even when analyses were adjusted for confounders (Supplementary Table 4). We checked that there were no relation between the positivity of the molecular test and mortality.

#### Economic evaluation

The cost-effectiveness analysis used information from all patients with complete primary outcome and cost data. Resource utilisation and costs are presented in Table 5. The costs associated with the molecular test were calculated at an average of €475.20 per test including technician time, with each patient having an average of 1.9 tests. There were no significant differences between the two periods even for investigations or number of days with antimicrobial treatment (13.1 days in both periods) (Table 5). Median total costs were €14,826 vs. €17,828, for IP and CP, respectively ( $P = 0.8$ ). Sub-group analyses by disease did not show a cost difference either.

Figure 3 shows the cost-effectiveness of the molecular test as a scatterplot of mean cost and effect

**Table 1 Demographic and baseline disease characteristics**

	Total population <i>n</i> = 1416	Control period <sup>a</sup> <i>n</i> = 685	Intervention period <sup>b</sup> <i>n</i> = 731
<b>Total population</b>			
Female gender (2/0)	500 (35.4)	247 (36.2)	253 (34.6)
Age, years	59 (48–70)	60 (48–71)	59 (48–70)
Medical admission	1236 (87.3)	591 (86.4)	645 (88.1)
Hospital-acquired infection	1024 (72.3)	490 (71.6)	534 (72.9)
<b>Type of severe infection</b>			
Sepsis	907 (64)	442 (64.6)	465 (63.5)
Febrile neutropenia	440 (31.1)	222 (32.5)	218 (29.8)
Suspicion of endocarditis	69 (4.9)	21 (3.1)	48 (6.6)
<b>Sepsis</b>			
	<i>n</i> = 907	<i>n</i> = 442	<i>n</i> = 465
Female gender (2/0)	297 (32.8)	146 (33.2)	151 (32.5)
Age, years	63 (51–73)	63 (51–73)	62 (51–73)
Medical admission	737 (81.3)	354 (81.0)	383 (82.4)
Hospital-acquired infection	582 (64.2)	279 (63.1)	303 (65.2)
Acquired in ICU	209 (23.0)	87 (19.7)	122 (26.2)
Respiratory as primary site of infection	490 (62.7)	251 (65.9)	239 (59.8)
SOFA score ( <i>n</i> = 1/5)	8 (5–11)	8 (5–11)	8 (5–11)
SAPS II (IQR)	46 (35–61)	44 (34–58)	47 (35–63)
<b>Febrile neutropenia</b>			
	<i>n</i> = 440	<i>n</i> = 222	<i>n</i> = 218
Female gender	179 (40.7)	93 (41.9)	86 (39.5)
Age, years	54 (41–62)	53 (41–62)	54 (42–61)
Hospital-acquired infection	390 (88.6)	197 (88.7)	193 (88.5)
<b>Haematologic disease (5/8)</b>			
Acute leukaemia	209 (49)	108 (49.8)	101 (48.1)
Lymphoproliferative disease	178 (41.7)	89 (41.0)	89 (42.4)
Other <sup>c</sup>	40 (9.4)	20 (9.2)	20 (9.5)
<b>Treatment phase (14/21)</b>			
First induction	110 (27.2)	63 (30.3)	47 (23.9)
Consolidation	118 (29.1)	74 (35.6)	44 (22.3)
Re-induction	177 (43.7)	71 (34.1)	106 (53.8)
<b>Endocarditis</b>			
	<i>n</i> = 69	<i>n</i> = 21	<i>n</i> = 48
Female gender	24 (34.8)	8 (40.0)	16 (32.7)
Age median (IQR) years old	63 (51–71)	62.5 (48–67.5)	63 (53–73)
Medical admission	62 (89.9)	18 (90.0)	44 (89.8)
Preexisting valvulopathy	42 (60.9)	12 (60.0)	30 (61.2)

Quantitative variables are expressed as median (interquartile range); qualitative variables are expressed as number (%)

ICU intensive care unit; SOFA Sepsis-related Organ Failure Assessment; SAPS Simplified Acute Physiology Score; (/) indicates the number of missing values in each group

<sup>a</sup> Control period was standard care

<sup>b</sup> Study period is the period when molecular detection was added to standard care

<sup>c</sup> Other: solid tumours (*n* = 20), acute transformation of myeloproliferative syndrome (*n* = 7), allogenic (*n* = 1) or autologous (*n* = 1) stem cell transplantation, aplastic anemia (*n* = 9), myelodysplastic syndrome (*n* = 2)

differences. The key uncertainty that drove the incremental cost-effectiveness ratio was the size of the effectiveness effect, represented on the horizontal axis. The difference in effectiveness was evenly distributed on each side of the vertical axis for patients with FN,

indicating no benefit during IP. The scatterplot for patients with SES indicated a weak dominance with a positive effectiveness effect and a reduced hospital cost as shown by the higher density below the horizontal axis.



**Table 2 Primary and secondary outcomes according to the study period in the intention-to-treat population**

	Total population n = 1416	Control period n = 685	Intervention period n = 731	P value <sup>a</sup>	OR (95% CI) <sup>b</sup>	ARR (95% CI) <sup>c</sup>
<i>Primary outcome</i>						
Microbiologically documented infection						
Total population (n = 1416, 685/731) <sup>d</sup>	478 (33.8)	193 (28.2)	285 (39.0)	<0.001	–	–
Severe sepsis (n = 907, 442/465)	322 (35.5)	124 (28.1)	198 (42.6)	<0.001	1.89 (1.43–2.50)	14.5 (8.4–20.7)
Febrile neutropenia (n = 440, 222/218)	137 (31.1)	67 (30.2)	70 (32.1)	0.66	1.08 (0.71–1.64)	–
Suspicion of endocarditis (n = 69, 21/48)	19 (27.5)	2 (9.5)	17 (35.4)	0.04	6.22 (0.98–39.6)	25.9 (7.4–44.4)
<i>Secondary outcomes</i>						
Pathogens identified <sup>e</sup> (n = 1416, 685/731)						
Gram-negative bacilli <sup>f</sup>	192 (13.6)	67 (9.8)	125 (17.1)	<0.001	1.88 (1.36–2.59)	7.32 (3.8–10.84)
Gram-positive cocci <sup>f</sup>	288 (20.3)	124 (18.1)	164 (22.4)	0.04	1.32 (1.01–1.72)	4.33 (0.16–8.51)
Fungi ( <i>Candida</i> or <i>Aspergillus</i> ) <sup>f</sup>	21 (1.5)	4 (0.6)	17 (2.3)	0.007	4.12 (1.38–12.36)	1.74 (0.51–2.97)
Not included in the molecular test (anaerobes or other bacteria) <sup>f</sup>	28 (2)	10 (1.5)	18 (2.5)	0.18	1.69 (0.77–3.70)	–
Time (h) to result validation						
Total population (n = 478, 193/285)	23.6 (14.9–32)	27.5 (20.8–50.9)	22.1 (10.8–27.3)	0.006		
Severe sepsis (n = 322, 124/198)	23.2 (14.2–29.3)	27.4 (19.2–57.0)	21.6 (10.3–26.3)	<0.001		
Febrile neutropenia (n = 137, 67/70)	28.5 (19.8–41.8)	31.5 (21–48.3)	26.8 (19.5–36.2)	0.97		
Time (h) to result transmission						
Total population (n = 478, 193/285)	27.5 (17.3–62)	48 (26.3–102)	23.1 (13.2–36.2)	<0.001		
Severe sepsis (n = 322, 124/198)	26 (16.9–59.4)	49.5 (23.6–116)	22.9 (12.5–32)	<0.001		
Febrile neutropenia (n = 137, 67/70)	38.2 (25.3–67.5)	54.8 (32.1–71.3)	30.8 (21–40.9)	0.15		
Appropriate antimicrobial treatment with regard to the bacteremia (n = 1375, 666/709)	395 (28.7)	157 (23.6)	238 (33.6)	<0.0001	1.63 (1.29–2.07)	

Control period is standard care and intervention period is the period when molecular detection was added to standard care. (I) indicates the number of patients in each group. Variables are expressed as number (%)

OR odds ratios; CI confidence interval; ARR absolute risk reduction

<sup>a</sup> P value of the  $\chi^2$  or the Fisher's exact test as appropriate, and of linear mixed-effects model for time to result validation and transmission, adjusted for order of intervention (study period first or second)

<sup>b</sup> ORs (95% CI) were estimated using a random-center effect logistic regression adjusted for order of intervention (study period first or second)

<sup>c</sup> Absolute risk reduction (ARR) was calculated from percentage values

<sup>d</sup> OR and ARR were not estimated among the total population because of significant effect modification by type of severe infection ( $P = 0.03$ )

<sup>e</sup> Number of patients with at least the detailed pathogen isolated from blood

<sup>f</sup> For details, see Table 4

## Discussion

In this multicentre cluster-randomised crossover trial including 1416 patients, we found that adding direct molecular detection of pathogens in the blood of patients hospitalised with severe sepsis resulted in an overall higher microbial diagnosis rate than with conventional diagnosis, which was made on the basis of blood cultures. Moreover, the time to results was shorter in the IP, leading to bacteremia and fungemia being diagnosed in less than 24 h in most cases, without an increase in hospital costs.

In patients with severe infections, since the pathogen is recovered at most in 50%, the others are treated by empirical antimicrobial regimens without consideration of appropriateness or de-escalation being possible [1, 32]. Direct detection of microbial pathogens in the blood was developed in the 2000s to circumvent culture limitations [33]. LSF was the first commercial kit to provide standardisation and enable comparisons between studies [12, 34]. Since its clinical performance was mostly compared with blood cultures [22], meta-analyses concluded that it had a lack of sensitivity (68%)

**Table 3** Factors affecting microbiological documentation in the blood among the 907 patients with severe sepsis, univariate and multivariate analyses

	Microbiological documentation		Univariate analysis <sup>a</sup>		Multivariate analysis <sup>a,b</sup>	
	No (n = 585)	Yes (n = 322)	OR (95% CI)	P value	OR (95% CI)	P value
Intervention period (yes/no)	267 (45.6)	198 (61.5)	1.93 (1.46–2.56)	<0.001	1.89 (1.36–2.63)	0.001
Age, years (3/1) <sup>c</sup>	63 (51–73)	62 (50–73)	1.08 (0.94–1.24)	0.29	–	–
Female gender (2/0)	184 (31.6)	113 (35.1)	1.16 (0.87–1.55)	0.32	–	–
Medical admission	476 (81.4)	261 (81.1)	1.01 (0.70–1.44)	0.98	–	–
Respiratory primary site of infection <sup>d</sup> (87/39)	359 (72.2)	131 (46.1)	0.33 (0.23–0.44)	<0.001	0.35 (0.25–0.47)	<0.001
Hospital acquired infection	399 (68.2)	183 (56.8)	0.61 (0.46–0.82)	<0.001	0.55 (0.40–0.76)	<0.001
<b>Severity of the sepsis at inclusion</b>						
SOFA score (n = 5/1) <sup>e</sup>	8 (5–11)	8 (5–12)	1.05 (1.01–1.08)	0.005	1.06 (1.02–1.10)	0.002
Glasgow score (n = 43/23) <sup>f</sup>	14 (7–15)	14 (7–15)	1.17 (0.88–1.56)	0.29	–	–
SAPS (n = 7/6) <sup>g</sup>	45 (34–58)	49 (36–65)	1.16 (1.00–1.34)	0.047	–	–
Septic shock	318 (54.4)	187 (58.1)	1.16 (0.88–1.53)	0.30	–	–

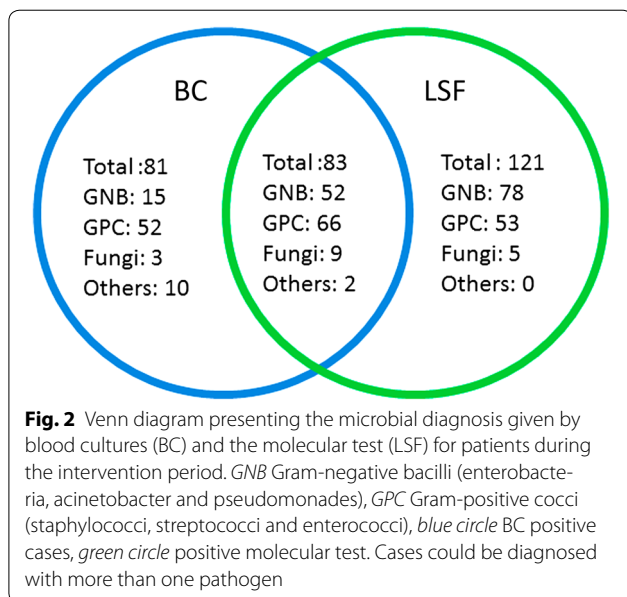
Quantitative variables are expressed as median (interquartile range), qualitative variables as numbers (%). (/) Indicates the number of missing values in each group OR odds ratio; CI confidence interval; ICU intensive care unit; SOFA Sepsis-related Organ Failure Assessment; SAPS Simplified Acute Physiology Score

<sup>a</sup> Univariate and multivariate analyses were performed using a random-center effect logistic regression adjusted for order of intervention (study period first or second)

<sup>b</sup> Multivariate analysis was also adjusted for the variables listed in the table

<sup>d</sup> Respiratory site of infection as compared to other sites (urinary tract, catheter-related, digestive tract, surgical site, ...)

OR and 95% CI are expressed per <sup>c</sup>1 SD increase; <sup>e</sup>per one point increase; <sup>f</sup>according to the median value (<14); and <sup>g</sup>per 1 SD increase in the log-transformed value



and specificity (86%) leading to abandoning the test [19, 20]. However, results which were seen as false-positives, i.e. low specificity, were also seen as true-positives when the clinical status was the gold standard (septic shock, for instance) or when the LSF results were compared with biomarkers of infection [12, 19, 35]. The presence of dormant or non-cultivable microbes in the blood can

also explain the discrepancy, as well as the fact that most patients have already received antimicrobial agents, leading to false-negative BCs [36]. This raised the question of whether blood cultures can still be considered the gold standard for documenting bloodstream infections. It is also known that, with regard to clinical status, BCs show a lack of specificity (one-third are falsely positive due to contaminants, leading to excess treatment) and sensitivity (at least half of them are falsely negative in patients with severe infections) [9–12, 37]. We therefore decided to investigate the relevance of the molecular detection of pathogens in an interventional study with the aetiological microbial diagnosis as the primary outcome, whatever the assay—blood culture or molecular test—providing the positive result. We hypothesised that adding molecular detection to conventional cultures would increase the number of cases with microbiological documentation.

The results we obtained in the CP for positive detection of pathogens in the blood were concordant with previous studies on large cohorts of severe sepsis, with similar severity scores and mortality rates, even with recent studies using the new definitions of sepsis [10, 38]. For FN, the positivity rate was also concordant with previous studies conducted on first episodes of FN, which is much higher than in secondary episodes [11, 13]. This high rate of positivity in the blood during IP is similar to that described in previous studies on direct molecular detection where infections were as severe as in our study [12].



**Table 4 List and number (%) of the microbial pathogens<sup>a</sup> per species that were detected in the blood<sup>b</sup> during the two periods**

Microbial pathogen group and species	Control period	Intervention period	Total
<b>Gram-negative bacilli (GNB)</b>			
Enterobacteria	66 (29.5)	116 (32.6)	182 (31.4)
<i>Citrobacter freundii</i>	1	0	1
<i>Citrobacter koseri</i>	1	0	1
<i>Enterobacter</i>	11	29	40
<i>Escherichia coli</i>	31	56	87
<i>Klebsiella</i>	18	28	46
<i>Proteus mirabilis</i>	1	1	2
<i>Providencia</i>	0	1	1
<i>Salmonella enterica</i>	2	0	2
<i>Serratia marcescens</i>	1	1	2
<i>Pseudomonas</i> and other strict aerobes bacteria	9 (4.0)	26 (7.3)	35 (6.0)
<i>Acinetobacter</i> sp.	1	1	2
<i>Pseudomonas aeruginosa</i>	8	21	29
<i>Pseudomonas putida</i>	0	1	1
<i>Stenotrophomonas maltophilia</i>	0	3	3
<b>Gram-positive cocci (GPC)</b>			
Staphylococci	78 (34.8)	104 (29.2)	182 (31.4)
<i>Staphylococcus aureus</i>	17	41	58
Coagulase negative staphylococci	61	63	124
Streptococci and enterococci	56 (25.0)	77 (21.6)	133 (22.9)
Nonhaemolytic streptococci	24	33	57
Haemolytic streptococci	2	1	3
Pneumococci	15	20	35
<i>Enterococcus faecalis</i>	7	15	22
<i>Enterococcus faecium</i>	5	8	13
Other enterococci	3	0	3
Strict anaerobic bacteria	5 (2.2)	8 (2.2)	13 (2.25)
<i>Bacteroides fragilis</i>	0	3	3
<i>Bacteroides merdae</i>	1	0	1
<i>Bacteroides</i> sp.	1	0	1
<i>Bacteroides thetaiotaomicron</i>	1	0	1
<i>Bacteroides vulgatus</i>	1	0	1
<i>Bilophila wadsworthia</i>	1	1	2
<i>Desulfovibrio</i> sp.	0	1	1
<i>Clostridium clostridioforme</i>	0	1	1
<i>Clostridium perfringens</i>	0	1	1
<i>Fusobacterium nucleatum</i>	0	2	2
Other bacteria	6 (2.7)	7 (2.0)	13 (2.25)
<i>Bacillus</i> sp.	2	0	2
<i>Corynebacterium</i> sp.	1	3	4
<i>Coxiella</i> sp.	1	0	1
<i>Haemophilus influenzae</i>	1	2	3
<i>Lactobacillus</i> sp.	1	1	2
<i>Neisseria</i> sp.	0	1	1
<b>Fungi</b>			
<i>Candida</i>	4 (1.8)	16 (4.5)	20 (3.5)
<i>Candida albicans</i>	2	8	10

**Table 4 continued**

Microbial pathogen group and species	Control period	Intervention period	Total
<i>Candida glabrata</i>	1	2	3
<i>Candida krusei</i>	0	1	1
<i>Candida parapsilosis</i>	0	1	1
<i>Candida</i> sp.	1	4	5
<i>Aspergillus fumigatus</i>	0	2 (0.6)	2 (0.3)
Total	224 (100)	356 (100)	580 (100)

<sup>a</sup> Multiple microbial pathogens could be isolated from one patient

<sup>b</sup> Pathogens were detected by blood cultures or by the molecular test

Because the aetiological microbes were more often documented in the IP, we looked at the consequences on the prescription of antimicrobial agents to treat the infection. We did not observe significant differences in prescription, either quantitatively (number of patients with treatment and cost per patient) or qualitatively (antimicrobial spectra), even for SES cases. This was probably because the treatment was not protocolled according to the pathogen identification, and the LSF test did not provide susceptibility results more than methicillin resistance of staphylococci [1, 3, 25]. It may also be due to the intervention itself, since polymicrobial infections and fungal infections were more often diagnosed, requiring broad-spectrum antibacterial agents and, in some cases, the addition of antifungal agents. Lastly, we did not detail the dosage of the agents, which was shown recently to be underestimated in most patients with severe infections [39]. Patients were managed under standard care conditions and, although the therapeutic approach may have varied between investigators, ward, and hospital centres, the results were mostly dependent upon the type of infection, and not the centre. The outcome was similar between the two periods, with a mortality rate concordant with the severity scores at inclusion [1, 10].

Because most molecular tests are more expensive than blood cultures, we investigated the cost of implementing systematic molecular detection in blood in addition to standard care. In a previous study, the cost was lower (€32,228 vs. €42,198) for 48 patients having LSF plus BC versus 54 patients having only BC [40]. In our study, the addition of LSF provided only a trend for lower hospital costs and higher effectiveness (i.e., microbiological diagnostic yield) for patients with SES. This was probably because the length of ICU stay was not affected by the earlier identification of micro-organisms, as also observed in other studies [8].

#### Limitations and strengths

There are two main limitations of our study. The first is that we present our results in 2016 when sepsis

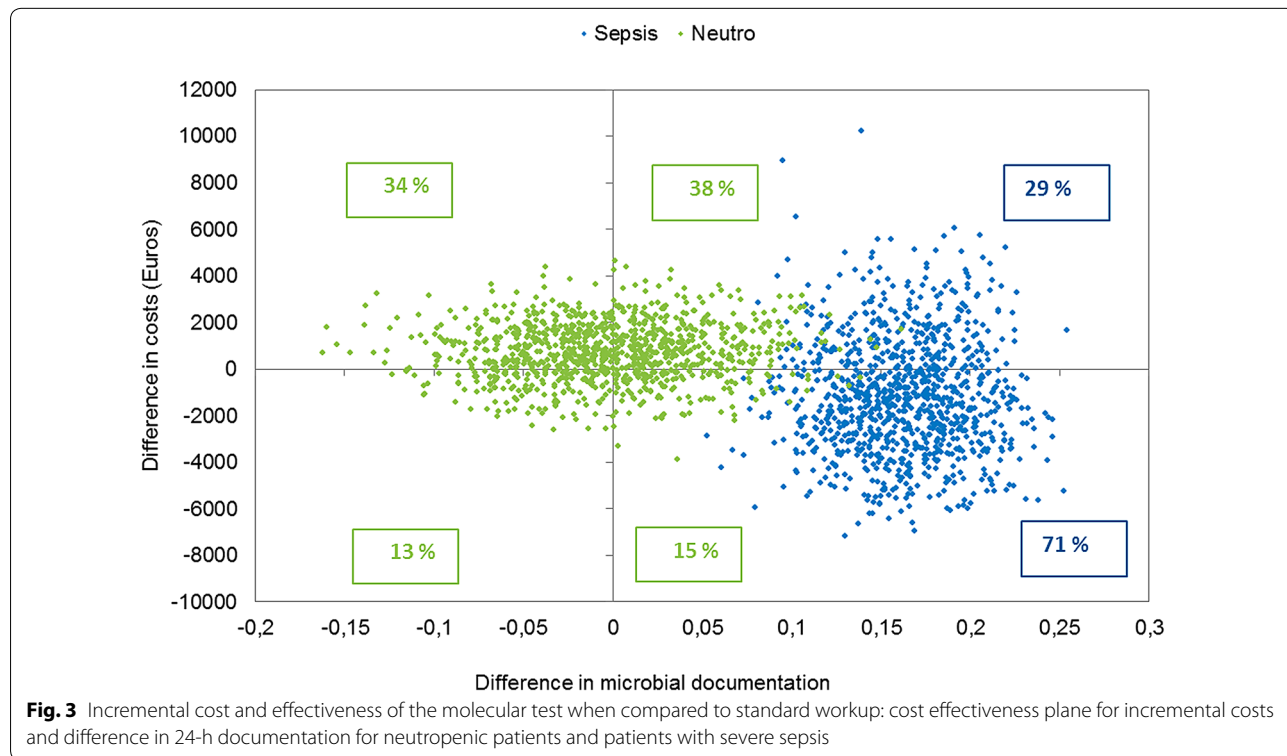
definitions have changed [41]. The strengths of our study remain since the patient characteristics were as severe as recent cohorts examined with the new sepsis criteria [8, 38]. The second limitation is the LSF test itself since it does not provide antimicrobial susceptibility testing results, as well as the most recent kits of this kind [42, 43]. Consequently, although MD was obtained for more patients and more rapidly during IP, we did not observe any difference in the antimicrobial treatment and outcomes. A recent controlled study showed that reducing TAT to pathogen identification in BCs, without specific AST as in our study, was able to decrease the prescription of broad-range antimicrobials and to increase de-escalation and appropriate escalation, at the condition that antibiotic stewardship is also provided [44], which was not done in our study. Minor weaknesses of the study concerns the suspicion of endocarditis, because the number of patients was too low to yield any conclusions since infective endocarditis infections are fairly rare (1/100,000 cases observed yearly) and their diagnosis, according to Duke and Li definitions, already includes microbiological results from BCs and from culture of removed valves [4]. Here, we aimed to include patients before diagnosis as we sought to include more documentation (i.e., we increased the number of cases with definite infective endocarditis). Although there was a trend in association, the numbers of patients with SIE were too small to show significant differences and a specific study for this indication is needed. Although we were disappointed by the results for patients with a first episode of FN, they confirmed the results of previous smaller studies [11, 34]. It was suggested that, in FN, the diagnostic yield of molecular detection could be higher in patients already receiving antimicrobial agents, i.e., at the second or later febrile episode, rather than in naïve patients. Regarding the lack of benefit for documenting FN, other assays should be explored and the infectious nature of the associated fever may need to be reconsidered.

The strengths of our study are the following. This is the first randomised interventional study on the use of

**Table 5 Cost (in euros) in total population for the control and intervention periods**

Measured parameters	Control period (n = 560)		Intervention period (n = 555)		P value <sup>a</sup>
	Mean cost ± SD (€)	Average number per patient ± SD	Mean cost ± SD (€)	Average number per patient ± SD	
<b>Total population</b>					
SeptiFast LightCycler test	8	0.02	892 ± 207	2 ± 0.4	NA
Blood cultures	125 ± 155	6 ± 7	109 ± 121	5 ± 6	0.25
Other diagnostic procedures	648 ± 481	17 ± 10	590 ± 454	15 ± 9	0.5
Anti-infective treatments	837 ± 2,304	4 ± 2	868 ± 2,250	4 ± 2	0.62
Length of hospital stay (days)		17 ± 11		17 ± 11	0.34
Total cost per patient	18,653 ± 15,966		18,118 ± 17,775		0.75
<b>Severe sepsis (n patients)</b>					
SeptiFast LightCycler test	3	0.01	904 ± 230	2 ± 0.5	NA
Blood cultures	110 ± 149	5 ± 7	100 ± 113	5 ± 5	0.32
Other diagnostic procedures	735 ± 538	19 ± 10	666 ± 473	17 ± 9	0.17
Anti-infective treatments	635 ± 1,884	4 ± 2	676 ± 2,175	4 ± 2	0.79
Length of hospital stay (days)		18 ± 12		16 ± 12	0.18
Total cost per patient	20,995 ± 17,593		19,329 ± 16,355		0.09
<b>Febrile neutropenia (n patients)</b>					
SeptiFast LightCycler test	22	0.12	882 ± 165	2 ± 0.4	NA
Blood cultures	160 ± 168	7 ± 8	132 ± 137	6 ± 6	0.08
Other diagnostic procedures	448 ± 283	19 ± 9	423 ± 325	13 ± 9	0.22
Anti-infective treatments	1,228 ± 2,997	4 ± 2	1,297 ± 2,444	4 ± 2	0.98
Length of hospital stay (days)		16 ± 9		16 ± 9	0.72
Total cost per patient	14,033 ± 10,844		16,230 ± 13,361		0.07

<sup>a</sup> P < 0.05 based on Student's t test for the mean



direct molecular detection of pathogens in the blood by a commercial test. The originality of this study is that we did not compare results of the molecular test to those of blood cultures taken as the gold standard, but instead evaluated what direct molecular testing brings in standard care with regard to clinical status assessing the primary outcome of microbial diagnosis. Strengths of the study also include its size and design. The study was planned as a cluster-randomised trial because of practical (cost of equipment and technical staff) and organisational (training of laboratory technicians on-site) constraints. This design allowed the optimisation of compliance with the assigned strategy. A common pitfall of cluster-randomised trials is an imbalance in patient characteristics and patient management. Therefore, we planned a crossover design to minimise imbalance between groups, and randomised the order of intervention. This crossover design was suitable because there was low risk of a carry-over effect. We obtained comparable baseline characteristics of severe sepsis groups during the two periods and adjustment for potential confounders did not change the results of the crude analysis. The strengths also include the molecular test itself since the main limiting factor of molecular tests in direct diagnosis is their analytical sensitivity, i.e. their ability to detect bacterial and fungal DNA without natural amplification by culture. LSF is one of the rare tests that can reproducibly detect 100 CFU/ml. The future test should be as sensitive as LSF but should detect resistance genes.

## Conclusions

Our study demonstrated, in a multicentre randomised controlled trial, that performing molecular detection of pathogens in addition to standard care of blood cultures, increases the number of septic patients with microbial diagnosis, and shortens the time to start a species-specific antimicrobial therapy. A step further is now necessary with molecular antimicrobial resistance testing combined with protocolled strategy with regard to epidemiological data of the centre or stewardship for antimicrobial agents. This can bring more impact, especially in cases of infection caused by multidrug-resistant pathogens [44].

## Electronic supplementary material

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#### Author contributions

EC, RC, CC, and SB conceived the idea for the study. SBJ and IDZ conceived the methodology for the clinical trial and the economic evaluation, including the statistics. RC, SH and EC conducted the technical microbiological work in the 18 different hospitals. CC assisted in the design of the protocol and interpretation of results for the febrile neutropenia; CBB and JP did the same for the sepsis indication; XD for the suspicion of infective endocarditis. All authors contributed to the analysis of the data. EC, SBJ, IDZ wrote the drafts. All authors contributed to the revision of the paper drafts.

#### Compliance with ethical standards

#### Conflicts of interest

The authors have no conflict of interest within the scope of this study.

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