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Effectiveness of the BioFire FilmArray for the rapid detection of bloodstream infection in haematological patients with febrile neutropenia (the ONFIRE study): study protocol of a prospective, multicentre observational study at three reference university hospitals in Spain

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ABSTRACT

Introduction Bloodstream infection (BSI) due to multidrug-resistant Gram-negative bacilli is a serious global health problem that has a profound impact on severely immunosuppressed neutropenic haematological patients. Prompt institution of appropriate antimicrobial therapy is crucial for improving outcomes in these patients, and in an era of multidrug resistance, antimicrobial stewardship programmes are mandatory. Blood cultures, the current gold standard for the diagnosis of BSI, present two main drawbacks: the prolonged time to results and their low sensitivity, especially if the patient has received antimicrobial treatment before blood extraction. The aim of this study is to determine whether a molecular technique, the BioFire FilmArray Blood Culture Identification 2 (BCID2) panel, achieves higher sensitivity and specificity than conventional blood cultures for the microbiological diagnosis of BSI in haematological patients with febrile neutropenia.

Methods and analysis This multicentre, prospective, observational study will be conducted at three reference university hospitals in Spain. The population will comprise haematological patients scheduled to undergo diagnostic blood cultures as standard care for the microbiological diagnosis of the febrile neutropenia episode. The BioFire FilmArray panel will be performed in patients with positive blood cultures at the time of blood culture positivity and in patients with negative blood cultures at 48 hours of incubation. The primary endpoint will be the sensitivity and specificity of the BioFire FilmArray BCID2 panel compared with conventional blood cultures. The secondary endpoints will be this same comparison in the subgroup of patients with recent (<48 hour) or concomitant use of systemic antibiotics and comparison of BioFire FilmArray and conventional blood cultures in terms of identifying time to antibiotic resistance.

Ethics and dissemination The study protocol has been approved by the Clinical Research Ethics Committee at Bellvitge Hospital (reference number ICPS029/22) and the Institutional Review Boards at each participating site. All patients' personal data will be processed, disclosed and transferred in accordance with Organic Law 3/2018 of 5 December 2018 and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016. All data will be collected, stored and processed anonymously. Results will be reported at conferences and in peer-reviewed publications regardless of whether the hypothesis is demonstrated. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigators and will follow the recommendations of the International Committee of Medical Journal Editors.

Discussion The aim of this study is to assess the impact of the BCID2 panel on the diagnostic yield of BSI in

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multicentre design will allow recording of a large number of febrile neutropenia episodes.
⇒ The results obtained should be readily generalisable to other settings.
⇒ The prospective design of the study will optimise the quality of data collection.
⇒ The sample size has been calculated assuming that only 30% of haematological patients with febrile neutropenia develop documented bloodstream infection.

haematological patients with febrile neutropenia. Unlike previous studies, which focused on patients with documented BSI, our research will include all patients with febrile neutropenia.

Trials registration number NCT06787326.

INTRODUCTION

Bloodstream infection (BSI) due to multidrug-resistant Gram-negative bacilli is a serious global health problem which has a major impact on severely immunosuppressed neutropenic haematological patients.[1–3] In this patient population, BSI usually occurs in the setting of febrile neutropenia and is associated with significant mortality.[2] In this scenario, early appropriate empirical antimicrobial therapy is a crucial determinant of improved outcomes.[4] Furthermore, reducing unnecessary antimicrobial usage and avoiding the overuse of broad-spectrum antibiotics is important in the battle against antibiotic resistance and also with regard to containing healthcare costs.

Blood cultures are the gold standard for the diagnosis of BSI, but their usefulness is limited by their prolonged time to results and sensitivities ranging from 10% or less to around 50%.[5] Recent advances in automated platforms have markedly reduced the time needed for identifying pathogens in blood cultures to approximately 10–24 hours. In this regard, the BioFire FilmArray Blood Culture Identification 2 (BCID2) panel is an automated nested multiplex PCR system that allows the simultaneous detection of 43 different targets (15 Gram-negative bacteria, 11 Gram-positive bacteria, 7 fungal pathogens and 10 antimicrobial resistance genes) from positively flagged blood cultures within 1 hour.[6 7] Several studies have examined the detection rate and accuracy of the FilmArray system in the general population and have reported success rates of >95% in identifying common pathogens, a figure comparable to those recorded with the matrix assisted laser desorption ionization-time of flight-mass spectrometry (MALDI-TOF MS) system.[8–10] Furthermore, other reports have shown that the BioFire FilmArray system identifies organisms and resistance genes faster than culture-based methods.[11–13] Early identification of pathogens and antibiotic resistance is crucial for improving adequate antibiotic use, for lowering antimicrobial consumption and for reducing the use of broad-spectrum antimicrobials.[2] In this regard, the FilmArray assay has been shown to be a useful tool for optimising antimicrobial prescription.[12–14]

Neutropenic cancer patients are a unique population, with frequent episodes of chemotherapy-induced febrile neutropenia. However, only 40% of these patients develop a clinically or microbiologically documented infection, and only 30% develop BSI.[15] Neutropenic patients with infection and particularly BSI are nonetheless a very high-risk population with potentially fatal outcomes. Therefore, the implementation of recent molecular microbiological techniques that favour rapid, accurate diagnosis of the aetiology of BSI, as well as the possible resistant pathogens, may be very useful in order to optimise antibiotic treatment in these high-risk patients. Their application may also help to optimise the use of antimicrobial agents, reduce the use of broad-spectrum antibiotics (thus leading to rapid de-escalation) and avoid the treatment of contaminants.

At present, data regarding the usefulness of different molecular techniques in neutropenic cancer patients are limited.[16–20] Only two of the studies performed use the BCID panel[21 22]; they were both designed to assess the impact of this molecular technique on clinical outcomes such as time to adequate antibiotic therapy and other antimicrobial stewardship strategies, as well as mortality and length of hospital stay in patients with documented BSI. As a result, the usefulness of the BCID2 panel for assessing diagnostic yield of BSI in patients with febrile neutropenia is yet to be established.

This study aims to assess whether the BioFire FilmArray BCID2 panel improves the diagnostic yield of BSI in high-risk haematological patients with febrile neutropenia in comparison with conventional blood cultures.

Objectives of the study

The aim of the study is to assess the effectiveness of the BioFire FilmArray BCID2 panel for the rapid identification of the causative agents of BSIs in high-risk haematological neutropenic patients with febrile neutropenia.

Primary objective

To assess whether the molecular technique BioFire FilmArray BCID2 panel obtains higher sensitivity and specificity than conventional blood cultures for the microbiological diagnosis of BSI in haematological patients with febrile neutropenia.

Secondary objective

To assess whether the increase in diagnostic performance of the BioFire FilmArray BCID2 panel is more significant in the subgroup of patients with recent (<48 hour) or concomitant use of systemic antibiotics than in those undergoing conventional blood cultures.

METHODS AND ANALYSIS

Study design

A multicentre, prospective, observational study will be conducted at three Spanish university hospitals: Vall Hebron University Hospital, Gregorio Marañón General University Hospital (GMGUH) and Bellvitge University Hospital/Institut Català d'Oncologia-Hospitalet (BUH/ICO). The study will be conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (See Research Checklist).[23]

Study population

This study will include adult patients (age ≥18 years) hospitalised for the treatment of leukaemia, lymphoproliferative syndrome, myelodysplastic syndrome, multiple myeloma, medullary aplasia or patients undergoing an autologous or allogeneic haematopoietic stem cell

transplant (HSCT) or receiving CAR-T cell therapy, who develop febrile neutropenia (defined as axillary temperature ≥38.0°C and <500 neutrophils/mm^3 or <1000 with an expected rapid fall in 24–48 hours) and who are scheduled to undergo diagnostic blood cultures as standard care for the microbiological diagnosis of the febrile neutropenia episode. Both patients receiving and not receiving antibiotic treatment will be included, and each patient may be included more than once for different episodes of febrile neutropenia if there is at least a 4-week interval between the episodes (and from the index blood cultures). The following patients will be excluded: those with axillary temperature <37.5°C, those with a high clinical suspicion of a non-infectious cause of fever at the moment when blood cultures are drawn (eg, high suspicion of drug-related fever, infusion reaction), previously enrolled patients in whom the time between inclusion and the current episode is less than 4 weeks and patients with febrile neutropenia in whom no blood cultures are drawn.

Data collection

Data will be collected prospectively. The following information will be recorded for all cases: patient's age and sex (according to the official documentation of each participant), underlying disease and immunosuppressive therapies, clinical presentation, vital signs (including axillary temperature), duration of neutropenia, collection date of the initial blood culture (day 0), cultures from other sites of infection collected within a time window of 10 days, blood count and chemistry (including inflammatory biomarkers) and antimicrobial prescription (previous, current and posterior to the onset of febrile neutropenia during study observation and 30 days before). Data regarding the microbiological results of the samples collected for each episode of febrile neutropenia will be recorded. Dates and times of the febrile neutropenia episode, drawing of blood cultures and of their reception at Microbiology Laboratory will be registered. For both strategies (BioFire FilmArray and companion blood cultures), time to microorganism and species identification and resistance mechanisms and time to their detection will be registered, and also whether the microorganisms will be isolated in the aerobic or anaerobic blood culture set.

Intervention

Patients admitted to the haematology wards of the participating centres and receiving chemotherapy, CAR-T or HSCT will be followed up daily by the attending physicians in order to identify those eligible for the study. The researchers will explain the nature of the study to the patients who meet the inclusion criteria and will ask them to provide signed informed consent. For the overall cohort, day 0 will correspond to the day of febrile neutropenia onset, and blood samples will be drawn for microbiological studies and for determinations of biochemistry and blood count. Multiple sets of blood cultures will be taken from several venopunctures following hospital policy. Only the first two sets of blood cultures obtained at day 0 will be processed using the BioFire FilmArray BCID2 panel. For the subgroup of patients receiving systemic antibiotics, day 0 will be assigned based on the suspicion of BSI according to the criteria of the treating physician. Consecutive blood cultures and cultures from other sites will be performed at the request of the physician and will be processed in the microbiology laboratory. Patients will be assessed daily during their hospitalisation by the study investigators and followed until day 30, discharge or death, whichever comes first. Episodes of febrile neutropenia will be classified as 'clinically documented infection' (when there is a clinically evident focus of infection, eg, pneumonia, neutropenic enterocolitis, perianal infection) or 'fever of unknown origin'.

Patient and public involvement

Patients and the public were not involved in the design or development of the study, as this possibility was not contemplated in the initial project design in 2021.

Definitions

For the purpose of the analysis, companion blood cultures will be considered positive if an organism is recovered from at least one of the two bottles in one set. In the case of common skin-colonising microorganisms such as coagulase-negative staphylococci, two positive sets of blood cultures will be necessary to make the diagnosis of catheter-related BSI.

The BioFire FilmArray BCID2 panel result will be considered positive if one or more micro-organisms is detected, and negative if none is detected. 'Proven positive result' will be defined as positive concordant results obtained in both the BioFire FilmArray BCID2 Panel and the companion blood cultures. 'Probable positive result' will be defined in the case of a negative blood culture but a positive BioFire FilmArray result, if the detected organism is isolated within 14 days from a clinical blood culture specimen collected at a different time or from another site (such as the abdomen, urine, catheter or lungs), indicating a plausible cause of infection. 'Possible positive result' will be defined in the case of a negative blood culture but a positive BioFire FilmArray result in the absence of supporting culture data if the detected organism was a plausible cause of disease (eg, *Escherichia coli* in a patient with neutropenic enterocolitis). Patients will be considered to be receiving an active antibiotic at the time of testing if they have received at least one antibiotic dose in the 2 days before sample collection. For each FilmArray positive result episode, the group classification will be discussed and adjudicated by a committee comprising investigators from the Infectious Diseases and Microbiology Departments (AB, CG, JLA, ESE, ABT, GLdE, AAP, BV, MM, AEP). Controversial results from the blood cultures and the BioFire FilmArray panel (such as positive results with coagulase-negative staphylococci and other skin contaminants) will be particularly discussed.

Microbiology studies

For each patient, two sets (three sets at GMGUH) of aerobic and anaerobic blood cultures (referred to as 'companion blood cultures') will be performed in accordance with hospital practices and the manufacturer's recommendations (see online supplemental additional file 2 for details of the techniques applied at each hospital). Blood cultures will be collected from different sites (peripheral veins and/or catheters, in patients carrying central venous catheters). The volume of whole blood should be 8–10 mL per bottle.

Blood culture bottles will be incubated at 35°C until they yield a positive signal or for up to 5 days in an automated system (see online supplemental additional file 2 for details of the techniques applied in each hospital). Positive blood culture bottles will be processed for identification and antimicrobial susceptibility testing by conventional and direct methods, which are detailed below. Time to positivity of each positive flagged blood culture will be registered.

Conventional microbiological methods

Positive blood culture bottles will be directly subjected to Gram staining and will be subcultured on different agar solid media. At the same time, an aliquot of the sample will be taken for direct identification and antimicrobial susceptibility testing using mass spectrometry (see online supplemental additional file 2 for details of the techniques used at each hospital). At BUH/ICO: direct identification by mass spectrometry will be performed following the protocol based on two-step centrifugation. Results will be interpreted according to manufacturer's instructions. Antimicrobial susceptibility testing by microdilution assay (see online supplemental additional file 2 for details of the techniques used at each hospital) will be carried out from isolated colonies on solid media after 18–24 hours of incubation. Results will be interpreted according to the European Committee on Antimicrobial Susceptibility Testing 2024 guidelines (www.eucast.org). In the same way, mass spectrometry will be repeated from the growth colony when direct identification has been unsuccessful.

Mechanisms of antimicrobial resistance

The mechanism of antimicrobial resistance in bacteria isolated from positive blood cultures will be studied by the most frequently used phenotypic and genotypic microbiological methods. Double disk synergy will be used to detect extended spectrum β-lactamases and immunochromatography or PCR to detect carbapenemases.

BioFire FilmArray BCID2 Panel

The BioFire FilmArray BCID2 panels (BioFire Diagnostics, a BioMérieux Company, Salt Lake City, Utah, USA) will be processed following the manufacturer's instructions (https://www.biomerieux.com/us/en/our-offer/clinical-products/biofire-blood-culture-identification-2-panel.html). BioFire FilmArray will be performed in patients with positive blood cultures at the time of blood culture positivity and in patients with negative blood cultures at 48 hours of incubation. For negative blood cultures, 200 µL of the aerobic bottle and 200 µL of the anaerobic bottle will be mixed, centrifuged and resuspended in 200 µL of double distilled water. For positive blood cultures, 200 µL of the sample from the positive bottle will be collected. Both types of sample will be diluted in Sample Buffer (1 mL) and carefully mixed. The BioFire FilmArray BCID2 panel will first be rehydrated using rehydration solution (1.5 mL), followed by inoculation with a diluted blood sample. The BioFire FilmArray BCID2 panel will be loaded onto the FilmArray instrument for nucleic acid extraction, amplification and analysis. The targets included in this panel are provided in the online supplemental additional file 1.

For both strategies (companion blood cultures and BioFire FilmArray), the time to species identification and the time to resistance mechanism detection will be recorded.

The usefulness of the two techniques will also be assessed in the subgroup of patients with recent (<48 hour) or concomitant use of systemic antibiotics, and in those presenting with hypotension, in whom a microbiological diagnosis of the febrile neutropenia episode is more likely.

Care teams will be permitted to order additional blood cultures and other types of cultures at their discretion or at any time, without input from the research team. These assays will be referred to as 'clinical cultures' so as to distinguish them from the companion blood cultures collected concurrently with the BioFire FilmArray samples.

Other measurements

- Determinations of biochemistry and blood count: blood samples will be collected at day 0 and day 2±24 hours and, afterwards, according to clinical criteria.
- Determinations of the inflammatory biomarkers will be performed at day 0 and day 2±24 hours and afterwards according to clinical criteria, using the following technique: C reactive protein: immunoturbidimetric assay in a Cobas c702 analyser (Roche Diagnostics), with a detection limit of 1 mg/L.

Study outcomes

Primary endpoint

The sensitivity and specificity of the BioFire FilmArray BCID2 panel compared with conventional blood cultures.

Secondary endpoints

The sensitivity and specificity of the BioFire FilmArray BCID2 panel compared with conventional blood cultures in the subgroup of patients under antibiotic treatment or who received antibiotic 48 hours before the onset of the febrile neutropenia.

To assess whether the BioFire FilmArray BCID2 attains a shorter time to identification of antibiotic resistance

than conventional microbiology techniques (ie, phenotypic and genotypic methods, double disk synergy for extended spectrum β-lactamase detection and immunochromatography or PCR for carbapenemase detection).

Outcome assessment

For the primary endpoint

- The sensitivity (proportion of positive results) of the BioFire FilmArray BCID2 panel will be compared with that of the companion blood cultures. The results of the BioFire FilmArray samples that meet the definitions of 'proven positive result', 'probable positive result' and 'possible positive result' will be considered as positive. The results will be assessed at day 14 from the sample collection. The positive predictive value of the FilmArray panel will be calculated. The positive and negative percentage agreement of the two methods will be reported, with special attention to discordant results.
- The specificity (proportion of negative results) of the FilmArray BCID2 panel will be compared with that of the companion blood cultures. The results will be assessed at day 14 from the sample collection. The negative predictive value of the FilmArray panel will be calculated.

For the secondary endpoints

- The sensitivity of the Biofire FilmArray BCID2 panel will be compared with that of the companion blood cultures in the subgroup of patients with recent (<48 hour) or concomitant use of systemic antibiotics. The results of the Biofire FilmArray samples that meet the definitions of 'proven positive result', 'probable positive result' and 'possible positive result' will be considered as positive. The results will be assessed at day 14 from the collection of the blood sample. The positive predictive value of the FilmArray panel will be calculated.
- The specificity of the Biofire FilmArray BCID2 panel will be compared with that of the companion blood cultures in the subgroup of patients with recent (<48 hour) or concomitant use of systemic antibiotics. The results will be assessed at day 14 from the collection of the sample. The negative predictive value of the FilmArray panel will be calculated.
- The time to identification of antibiotic resistance will be measured by the hours from the arrival of the sample in the microbiology laboratory to the description of the susceptibility profile of the microorganism isolated.

Sample size

This study is designed to compare the sensitivity of the Biofire FilmArray BCID2 panel with that of conventional blood cultures for the identification of the microbiological aetiology of episodes of febrile neutropenia in haematological patients. The aim is to achieve an 8% increase in the number of microorganisms identified. Prior data indicate that the incidence of positive blood cultures in haematological patients with febrile neutropenia is approximately 30%. The expected incidence of positive results with the Biofire FilmArray BCID2 panel is 38%. We will need to study 228 episodes of febrile neutropenia in order to be able to reject the null hypothesis of equality with a power of 80%. A significance level of α=0.05 will be used. A loss to follow-up of 5% of the total sample will be assumed. McNemar's Z-test will be used to evaluate this null hypothesis.

Statistical analysis

Patients' demographic and clinical characteristics will be described at baseline as means and SD for continuous variables and as numbers and percentages for categorical variables. The percentages of positive results for the identification of micro-organisms in the bloodstream by the two microbiological techniques will be compared using McNemar's Z-test. Sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values will be calculated by using the blood cultures as the gold standard. The diagnostic accuracy of the BioFire FilmArray BCID2 panel will be calculated based on the identification of micro-organisms in the bloodstream. The overall accuracy of the two techniques will be evaluated by receiver operating characteristic curve (ROC) curves, and a 95% CI will be used. All analyses will be performed with statistical software R V.4.0 or superior. The time to species identification and time to antibiotic resistance identification of the two techniques will be described as medians and IQRs and will be compared using a Log Rank test.

ETHICS, DISSEMINATION AND PUBLICATION PLAN

Ethics

The study protocol has been approved by the Clinical Research Ethics Committee at Bellvitge Hospital (reference number ICPS029/22) and by the Institutional Review Boards at each participating site. The study will be conducted in accordance with the protocol and with the principles established in the latest version of the Declaration of Helsinki, with the standards of Good Clinical Practices as described in CPMP/ICH/135/95. In addition, all patients' personal data will be processed, disclosed and transferred in accordance with Organic Law 3/2018 of 5 December 2018 and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016.

All participants will be asked to sign the informed consent document. Before signing, all patients will be informed of the study objectives and procedures. They will also be informed that their data will be treated with strict confidentiality. On the consent form, participants will be asked if they agree to the collection of biological specimens by the research team: biological specimens will be blood samples for determining the clinical performance of a new microbiological technique, the BioFire FilmArray BCID2 panel, in comparison with standard

blood cultures, for the aetiological diagnosis of episodes of febrile neutropenia. In accordance with the Spanish legislation dating from 2007, the samples will be collected directly from the participants, and all biological specimens will be destroyed upon completion of the study. The study will be completed when the results have been published.

All data will be treated anonymously. Anonymisation will be carried out by each participating centre and will proceed by coding patient identifiers; this means that all patient identifiers will be replaced by an anonymous code, and that any information linking an anonymous code with a patient identifier will be kept secure by each participating centre. Thus, the privacy and confidentiality of all data will be protected.

Data availability

Individual data cannot be shared because of privacy restrictions. Raw anonymised data relating to primary and secondary outcomes and safety can be shared upon request with researchers who provide a methodologically reasonable proposal. Requests for data can be sent to the corresponding author (CG), at the earliest 18 months after publication of the main study results, so as to allow the authors to publish the substudies. Interested researchers must obtain the approval of the BUH Ethics Committee.

Dissemination and publication plan

Results will be reported at conferences and in peer-reviewed publications regardless of whether the hypothesis is demonstrated. The first publication will be based on data from the three participating centres and will be analysed as stipulated in the protocol with the statisticians' supervision. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigators and will follow the recommendations of the International Committee of Medical Journal Editors.

Planned study dates

Study start: July 2024.

Start of recruitment: January 2025.

End of recruitment: August 2026.

Publication of results: December 2026.

DISCUSSION

This study examines the effectiveness of the BCID2 panel for assessing the diagnostic yield of BSI in haematological patients with febrile neutropenia. Two previous studies have assessed the usefulness of the BCID2 panel in this patient population, but they only included patients with documented BSI and focused mainly on antimicrobial stewardship outcomes.[21 22] Conversely, our study will be the first to assess the effectiveness of this microbiological technique for the diagnosis of BSI in all patients with febrile neutropenia, not only in those with confirmed BSI.

Buss *et al* conducted a three-arm pre/post intervention quasiexperimental study to evaluate the impact of the BCID with and without an antimicrobial stewardship programme in neutropenic cancer patients with BSI. Although there were no significant differences in time to appropriate antimicrobial therapy, mortality or readmission between the groups, the BCID panel significantly shortened (>40 hours) the time to organism identification. This significant difference may be due to the fact that species identification using MALDI-TOF was not performed directly from the BACTEC bottle but from the colony grown on the agar plate. However, this benefit did not translate into significant differences in primary clinical outcomes.[21]

Similarly, Pérez-Lazo *et al* studied the impact of BCID2 implementation combined with antimicrobial stewardship in patients with BSI and found a significant reduction in time to appropriate antimicrobial therapy but no improvement in other clinical outcomes such as relapse, in-hospital mortality or 30-day readmission. In that study, the species identification was performed by conventional phenotypical methods and VITEK-2 systems and not by MALDI-TOF.[22]

The results of our study should provide useful information regarding the routine use of the Biofire FilmArray Panel for the rapid diagnosis of BSI in haematological patients with febrile neutropenia.

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Contributors All authors have been involved in the study concept. CG, AB, GLdE, CA, NL, PM, AAP, MM and JC have been involved in design of the study. AB, JLA, ESE, ABT, MM, AAP, CM, IC, APG, IRA, and IAG are responsible for the recruitment

and follow up of the patients, as well as for the data collection. GLdE, CA, DB, PG, BV, APE, NL and PM are the responsible of the microbiological analyses of the study. CG, AB and JC drafted and revised the manuscript. All authors reviewed and approved the final version of the manuscript. CG is the guarantor.

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Competing interests NL has participated in educational activities sponsored by bioMérieux and in clinical validation studies of in vitro diagnostic medical devices from bioMérieux. The remaining authors have no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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