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Effective implementation of the Accelerate Pheno™ system for positive blood cultures

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Using conventional methods, organism identification (ID) and antibiotic susceptibility testing (AST) results are available ∼1.5–3 days after positive blood culture. New technologies can reduce this time to 8–12 h, allowing therapy to be optimized substantially sooner. To make full use of fast ID and AST results requires overcoming various hurdles to effective implementation, including restructuring laboratory workflows to optimize timeliness of results and modifying clinical pathways to respond more quickly when results are available. Efficient laboratory procedures and clinical interventions coupled with fast and accurate identification and AST results have the potential to substantially reduce overall costs and provide more-sophisticated and effective patient management.

Timely administration of appropriate antibiotics has been well documented as a strong predictor of sepsis survival.[1–3] However, empirical therapy decisions based on patient risk factors, infection source and local epidemiology are estimated to result in 12%–25% of patients being started on inappropriate empirical therapy. Furthermore, growing concern over antibiotic resistance, in particular among Gram-negative bacteria, has led many to resort to very broad-spectrum empirical coverage, consisting of vancomycin and a carbapenem, or double Gram-negative coverage.[4,5] Conventional practice is to optimize therapy once the organism identification (ID) and antibiotic susceptibility testing (AST) results are known. Today, this information is available 35.1–72.3 h after blood culture collection.[6–11]

Newer techniques, including the Accelerate PhenoTest™ BC kit used with the Accelerate Pheno™ system, significantly reduce the time to results (i.e. AST results are available 24.4–64.3 h sooner than with traditional methods), providing an opportunity for therapy optimization within hours of presentation, as opposed to days. The analytical accuracy and time savings of the Accelerate Pheno™ system are now well documented, in this Supplement and elsewhere.[6–14] However, despite the seemingly obvious benefit of providing more rapid ID and AST results for patients with bacteraemia, several hurdles exist to the effective implementation of the Accelerate Pheno™ system, and other rapid diagnostic technologies, in the real world. These challenges include restructuring laboratory workflows to optimize the timeliness of results, the willingness of clinicians to respond to microbiology data that are available much more quickly than was previously possible, and dealing with the uncertainty surrounding the long-term economic benefits associated with the use of rapid diagnostic tests for patients with sepsis.

Optimal use of rapid ID and AST technology requires testing of specimens as soon as they flag positive in blood culture instruments. However, many laboratories are not staffed 24/7, limiting the impact of rapid testing for blood cultures that turn positive after regular laboratory working hours. Several studies have demonstrated the value of responding to positive blood cultures around the clock, including simple steps such as performing and reporting Gram stain results.[15,16] In one study, addition of a night shift to respond to positive blood cultures resulted in earlier identification and appropriate therapy for the 27% of patients with blood cultures that flagged positive on the night shift who were inadequately covered by empirical regimens.[15] However, quantifying the financial benefit associated with performing this task, in order to justify the expense of expanding laboratory work hours, is challenging. Such expansion of work hours requires the laboratory to look outside its own doors, to the potential for cost avoidance for other departments, as described further below. Even without this expansion of laboratory work hours, benefits can theoretically be achieved through the use of the Accelerate Pheno™ system on samples that are batched in the morning after flagging positive overnight, as opposed to performing the traditional techniques of subculture and ID and AST the following day. Notably, the University Hospital La Princesa (Madrid, Spain), the first routine user of the Accelerate Pheno™ system in Europe, offers an interesting example of how it is possible to overcome the challenges posed by the laboratory workflow. Hospital microbiologists are on site from 08:00 to 15:00 h at this hospital, after which a resident is

on duty for emergencies. An automated, electronic reporting solution co-developed by Accelerate Diagnostics, Inc. and the hospital, enables an efficient communication flow from the Accelerate Pheno™ system to clinical departments around the clock. Studies demonstrating the benefit of this reporting structure are currently under way at this institution.

Modification of clinical pathways to respond to the rapid ID and AST results is a further challenge.[17] While the majority of physicians covering the night shift will escalate therapy if it is found that a patient is being inadequately treated, many are reluctant to de-escalate therapy without consultation with the primary team. This is because these individuals may not be aware of all the complexities associated with the patient's case. Furthermore, the perception of patient harm is considerably less when the causative pathogen is covered by the empirical regimen, as management of the acute infection is the most immediate concern, overriding drug toxicities or risk of *Clostridioides* (*Clostridium*) *difficile* infection. However, drug toxicities exist, even for antimicrobials generally regarded as 'safe'.[18] Indeed, studies have demonstrated that even during working hours the primary team may be reluctant to de-escalate therapy for patients based on the results of rapid testing without the support and encouragement of an antibiotic stewardship team or infectious diseases service.[19] In these situations, the primary team may only be willing to de-escalate therapy for patients that are already clinically improving.[20] Traditional management of patients involves evaluation of laboratory data once a day, during morning rounds, for opportunities to de-escalate therapy. This model is well suited to a system where microbiology laboratory data are provided only in daily increments. Availability of new data for patients on an hourly basis requires clinicians to anticipate these earlier results and to be prepared to respond to them.[21,22] Furthermore, physicians often misinterpret multiplex PCR results, without clear interpretation of what the presence (or absence) of resistance determinants indicates with regard to therapy. Essential to this process is clear education at the time of the Accelerate Pheno™ system launch, to ensure providers are aware of the change in laboratory practices. An example of an efficient clinical response driven by Accelerate Pheno™ system results is provided once again by La Princesa University Hospital, where the Accelerate Pheno™ system combined with automated electronic reporting is being incorporated into 'Codigo Sepsis' ('Sepsis Code'), a protocol designed to identify and manage patients with sepsis inside the hospital. The implementation of this joint solution allows physicians to act upon faster MIC results 24/7, and fully benefit from the clinical value of the Accelerate technology as described in a recent publication.[23] In that study, antimicrobial treatment was modified upon receiving Accelerate Pheno™ system results in 48% of sepsis cases. Examples of clinical interventions included both escalation and de-escalation. In a retrospective study, the availability of Accelerate Pheno™ system results, coupled with stewardship personnel, would have allowed modification of treatment in >50% of patients.[7] Schneider and co-authors report in this Supplement that 25% of patients would have been put on active therapy sooner if Accelerate Pheno™ system results had been available.[24] Additionally, Henig and co-authors report in this Supplement that 37.2% of patients would have received definitive therapy more rapidly if Accelerate Pheno™ system results had been available, and de-escalation was the treatment modification for 90.9% of these patients.[25]

The benefits of antibiotic de-escalation in the ICU are well documented.[26–29] For example, a study that evaluated in-hospital and 90 day mortality of antibiotic de-escalation informed by traditional microbiology testing for patients admitted to the ICU with severe sepsis or septic shock demonstrated that de-escalation was protective against these endpoints, including among patients who were already on effective empirical coverage, in an analysis controlling for patient disease severity.[20] However, these studies have assessed de-escalation in the timeframe of traditional diagnostic testing, and the incremental value of a more rapid antibiotic de-escalation for critically ill patients has not been documented. Theoretical benefits are similar to those of de-escalation in general, including less impact on the patient's microbiome as well as reduced risk of *C. difficile* infection, antibiotic-associated toxicities and subsequent MDR infections. Studies evaluating antibiotic duration reveal that patients with longer courses of antibiotics have an increased likelihood of secondary infections and more-resistant pathogens in recurrent infections.[30,31] Several studies have also indicated that $\geq$2 days of piperacillin/tazobactam plus vancomycin therapy is associated with increased risk of acute kidney injury.[32,33] Such data demonstrate the negative impact of even short-course empirical therapy, and an opportunity to impact therapy with more rapid de-escalation, which is possible with the Accelerate Pheno™ system. Moreover, while not well described to date, data presented in the review by Bhalodi *et al.*[34] (this Supplement) demonstrate the significant impact of antibiotic exposure on the patient's microbiome. Antimicrobials have been shown to alter a patient's microbiome very early in the course of therapy, creating an environment for pathogens such as *C. difficile* and enterococci to proliferate, which results in subsequent harm. Although the effects of antimicrobials on the microbiota are still being uncovered, research efforts continue to better understand the relationship between the intestinal microbiota and organ dysfunction. Similarly, the risks associated with rapid de-escalation of therapy have also not been documented. Bundling the Accelerate Pheno™ system with tests for biomarkers (such as procalcitonin) that indicate patient response to therapy may provide further support for rapid de-escalation. Additionally, novel patient stratification models that predict the likelihood of early response to therapy, such as those that have been developed to predict sepsis risk,[35] together with Accelerate Pheno™ system results, may allow physicians to target patients for rapid de-escalation.

One advantage of the Accelerate Pheno™ system is the availability of MIC-level susceptibility data, which agree well with reference methods as shown in the studies in this Supplement. Special attention is paid to the dosing of antimicrobials in the ICU because fluctuations in fluid status, organ function and perfusion can affect antibiotic pharmacokinetics and efficacy at the site of infection. Knowledge of the pathogen's MIC, as opposed to a resistance mechanism or susceptible/intermediate/resistant information without an MIC value, allows a more sophisticated adjustment of antimicrobial dosing in these more complex patients. While routine therapeutic drug monitoring has not yet reached the mainstream for drugs other than aminoglycosides and vancomycin, several studies have demonstrated the value of patient-level antimicrobial dose adjustments based on the patient's drug levels and the pathogen's MIC.[36,37] Availability of these data early in the course of infection may allow individualized antimicrobial dosing, which has the potential to improve outcomes, although these

benefits remain to be robustly demonstrated. This potential is, however, not purely theoretical. Real-world examples of the clinical benefits of a rapid MIC generated by the Accelerate Pheno™ system have been presented by Kidd *et al.*,[38] who showed that interventions, including antimicrobial treatment optimization and intravenous-to-oral antibiotic switch, occurred an average of 38.5 h faster than by traditional methods.

Finally, despite the clinical benefits described above, significant scepticism exists regarding the economic efficiency of the use of novel technologies, such as the Accelerate Pheno™ system, in routine practice. Without a doubt, the consumable reagents used in these technologies cost more than those used by conventional methods. Justification of this increased expenditure in the laboratory's budget again requires evaluation of costs across the spectrum of patient care. One recent study utilized such an approach, evaluating the cost-effectiveness of rapid diagnostic tests (RDTs) for bloodstream infections, alone or in combination with an antibiotic stewardship programme, based on US healthcare economics.[39] These findings clearly demonstrated a significant cost mitigation associated with the use of RDTs combined with antibiotic stewardship, from $55 932 per case to $31 274 per case, driven primarily by the reduction in length of hospitalization. Similarly, the probability of patient survival was increased (0.89) with the use of RDTs, as compared with standard of care (0.85), with a predicted 1 death avoided per 25 bacteraemic patients. Importantly, while clinical endpoints were similar, the cost benefits were not observed in those studies that employed RDTs without stewardship support.

Without question, the Accelerate Pheno™ system provides a novel opportunity for a more finessed management of patients with bacteraemia. However, this technology, and others, require significant modification to both laboratory and clinical pathways. As with any major change to the practice of patient management, it is expected that it will take time for data that demonstrate the value of these changes to emerge. As indicated by others,[40] emphasis on outcome-level studies is needed to ensure novel technologies improve the management of patients with sepsis. Nonetheless, the evidence generated to date by hospitals that have adopted the Accelerate Pheno™ system into routine practice suggests rapid clinical interventions have the potential to deliver significant benefits to individual patients and healthcare organizations relating to patient safety, quality of care, antimicrobial stewardship and infection prevention measures.

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