**CURRENT PRACTICE AND MEDICAL VALUE OF MOLECULAR ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST) IN SEPSIS CURRENT SETTING.**

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Abstract

Sepsis is a serious and life-threatening condition that arises when the body's response to infection leads to organ dysfunction. Despite recent advances in medical treatment, sepsis continues to be a major cause of morbidity and mortality worldwide. Early and accurate diagnosis of sepsis is critical for effective management and improved outcomes. In recent years, molecular microbiology has emerged as a valuable tool for the rapid detection and identification of pathogens in sepsis. This approach involves the use of nucleic acid-based techniques such as polymerase chain reaction (PCR) and next-generation sequencing (NGS) to detect the presence of pathogen DNA or RNA in patient samples.

In addition to molecular microbiology, antimicrobial susceptibility testing (AST) plays a crucial role in the management of sepsis. AST helps clinicians choose the most appropriate antimicrobial agents for treatment based on the susceptibility profile of the pathogen. This approach can help to prevent the emergence of antimicrobial resistance and improve patient outcomes.

In this review, we discuss that despite these advances, sepsis remains a major challenge for healthcare systems worldwide. Mortality rates associated with sepsis remain high, particularly in resource-limited settings. Efforts to improve the diagnosis and management of sepsis continue, with a focus on developing new diagnostic tools, improving antimicrobial stewardship, and implementing evidence-based interventions to reduce the incidence and severity of sepsis. With continued research and innovation, it is hoped that these efforts will lead to improved outcomes for patients with sepsis.

INTRODUCTION

Sepsis is a major concern worldwide due to its high morbidity, mortality, and financial cost to health systems. Globally, sepsis carries a significantly high burden (49 million incident cases) and accounted for 19% of all deaths worldwide in 2017 1, of which several could be prevented. Sepsis causes one death every 3–4 seconds. Recent large-scale epidemiological studies showed that the mortality rate of sepsis has decreased, but its incidence continues to increase.2 However, the true incidence of sepsis is likely to be underestimated, especially in low-income countries. The lack of public awareness of sepsis and the serious consequences of delays in recognition and treatment are major contributors to the alarming annual increase of 8–13% in sepsis cases over the last decade. Sepsis is heterogeneous, with varying aetiologies, pathogeneses, and clinical manifestations, making fundamental research, clinical translation, and precision medicine in sepsis challenging.

There are many definitions used for sepsis, but it is usually defined as an infection associated with organ failure3, 4. Sepsis is frequently caused by Blood Stream Infections (BSI). BSI are a serious condition that can lead to sepsis, organ failure, and death if not treated promptly and effectively. Rapid detection and identification of the infecting pathogen are crucial for appropriate antimicrobial therapy and improving patient outcomes. Current clinical practice for detecting BSI involves collecting blood cultures (BC), which can take several days to yield both the identification of the pathogen and the associated antimicrobial susceptibilities. This delay can be problematic, as patients may continue to receive inappropriate or inadequate treatment until these are known. Different studies enlighten the importance of positive BC: a positive BC was found in 17% of US septic patients5; positive BC were responsible for as high as 66% of all pediatric admissions for sepsis in Switzerland6.

*RAPID DIAGNOSTIC TESTS FOR SEPSIS MANAGEMENT*

One potential solution to this unmet need is the development and implementation of rapid diagnostic tests for BSI. These tests should detect specific pathogens or markers of infection in blood samples within hours, allowing for faster diagnosis and targeted antimicrobial therapy. Several rapid diagnostic tests are currently available, including polymerase chain reaction (PCR) assays, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, and flow cytometry-based assays. Not all of these tests are yet CE-marked or FDA approved, and more importantly, few can be deployed directly on the blood sample, but rather, need to be performed on the isolate grown from a positive culture. Accordingly, the delay to identification (ID) and antimicrobial susceptibility testing (AST) of the organism in a positive blood culture is not decreased at all. Clinicians can only act to rationalize antimicrobial prescriptions once an accurate ID and AST have been obtained, which remains highly dependent on the time to positive blood culture. Nevertheless, these tests have shown promising results in clinical studies, with improved time to microbiological diagnosis compared to traditional BC methods7.

Another approach to addressing this unmet need is to implement protocols for rapid initiation of empiric antimicrobial therapy in patients at high risk for BSI. This could involve using clinical decision rules, such as the qSOFA score, to identify patients at high risk for sepsis and immediately initiating broad-spectrum antibiotics while awaiting culture results8. While this approach is not as specific as rapid diagnostic tests, it can still improve patient outcomes by ensuring that appropriate treatment is initiated as soon as possible.

Mortality linked to BSI ranges between 12-32% in North America and Europe, worsened by increasing rates of antimicrobial-resistant pathogens9, which are often not covered by initial empiric antimicrobial therapy. Conversely, overtreatment with unnecessarily broad-spectrum antimicrobials aggravates adverse drug events10 and favors the development and spread of antimicrobial resistance. Addressing the unmet need for a fast time to a positive result in patients at risk of sepsis requires a multifaceted approach that includes both rapid diagnostic tests and protocols for rapid initiation of empiric therapy. These strategies can help reduce the morbidity and mortality associated with BSI, its under or overtreatment, and improve patient outcomes.

In addition to time to a positive result in BSI, there is another layer of complexity: AST profiles for infecting pathogens. AST is an important tool in the management of infectious diseases, as it helps to guide the selection of appropriate antimicrobial therapy. The value of timely results is well recognized by healthcare practitioners. Traditional AST methods, such as disk diffusion and broth microdilution, can take up to 48 hours or longer to yield results, which can delay the initiation of targeted therapy and contribute to the development of antimicrobial resistance. Molecular testing methods for AST have been developed to address these limitations, and several are currently available in the market. Overall, molecular AST offers several advantages over traditional methods, including faster turnaround times, higher sensitivity and specificity, and the ability to detect specific resistance mechanisms11. These tests can help guide appropriate antimicrobial therapy, reduce the development of antimicrobial resistance, and improve patient outcomes. However, molecular tests only detect the presence of genes that have been included in the testing panel and do not assess the expression variability of the genes. Although molecular resistance tests works well for the management of gram positive infection (due to the high NPV of MRSA and Vancomycin resistance), the proper management of gram negative infection still relies on phenotypic AST given the complexity of resistance mechanisms. In addition, bacterial resistance to antimicrobials often results from the coexistence of several mechanisms (e.g. production of an enzyme that degrades the antibiotic in combination with a permeability defect of the membrane or efflux) that cannot be tested simultaneously in the same molecular panel.

*TECHNOLOGIES AVAILABLE FOR RAPID AST TESTING*

There are many molecular AST platforms currently in the market including different technologies such as those that evaluate morphological and/or physiological responses, PCR-based, small molecule biosensors with volatile detection, MALDI-TOF mass spectrometry, and whole-genome sequencing (WGS). MALDI-TOF has been used to identify bacterial species and detect specific resistance mechanisms, such as the presence of certain enzymes or mutations12. WGS can provide a comprehensive analysis of bacterial genomes, including the identification of specific resistance genes and mutations, and can be used for outbreak investigations and surveillance13.

The use of molecular testing with tests that can include AST results is expected to guide better treatment decisions and translate into improved patient outcomes. However, we foresee that the implementation of such an innovative diagnostic solution in the hospital will impact many elements from a laboratory and clinical standpoint. Therefore, we set up two Advisory Board sessions, one for Northern European countries and another for Southern Europe and the Middle East, to obtain feedback from a panel of microbiology, infectious disease, and critical care experts. In both sessions, we discussed the perceived value brought by fast AST systems in the management of BSI, helping to outline the target priority populations which could benefit most from fast AST solutions. We also explored the limitations linked to the current version of the system, and the challenges its routine implementation might present to the hospital. These discussions helped to pinpoint the knowledge gaps, and priorities for medical education, as well as the evidence generation streams needed for the demonstration and use of such fast AST solutions to their utmost value.

*VALUE OF FAST AST SYSTEMS*

The analytical validity of fast AST solutions was considered a very strong one by most of the panel members, although further improvements could be done, namely regarding pathogen/drug combinations and their scientific validity.

The pathogen/drug combinations tested in AST may vary depending on the clinical setting and the suspected infection. The scientific validity of pathogen/drug combinations in traditional AST is supported by extensive research, clinical validation and guidance from international ‘breakpoint setting’ committees. The accuracy and reliability of AST depend on several factors, including the testing method, the quality of the culture and inoculum, and the interpretation of the results14. Different testing methods may have different levels of accuracy and reliability, and the quality of the culture and inoculum can affect the results of the test. The interpretation of the results also requires expertise and knowledge of the pathogen and the drug being tested.

*SHIFT TURNAROUND TIME*

From a laboratory standpoint, a fast AST turnaround time identifies the most effective antimicrobial agent(s) to treat a patient's infection, which can improve patient outcomes and reduce the spread of antibiotic resistance. There are several strategies that laboratories can use to achieve fast AST turnaround time. One approach is to use automated systems that can rapidly process large numbers of samples and provide results in a matter of hours. Another strategy is to use rapid diagnostic tests that quickly identify the pathogen causing infection and determine its susceptibility to various antibiotics. In addition, some laboratories may use data analytics and machine learning algorithms to analyze large amounts of AST data and identify patterns that can help predict which antimicrobial agents are most likely to be effective against certain pathogens15. The impact from a laboratory standpoint was well perceived by experts, as fast AST systems would allow same-shift results due to its short turnaround time, decreased hands-on time by the laboratory staff, and essentially, significantly decreased time-to-results compared with traditional methods due to the solution’s place in the diagnostic workup. Indeed, the system bypasses the need for sub-culturing before AST, as is currently required with conventional testing.

However, fast AST solutions would likely be perceived by the laboratory as an add-on to the current workflow to bring extra value, rather than a distinct replacement of current diagnostic methods in place. Therefore, the panel agreed that fast AST systems are not expected to lower the lab resources required, at least not in the first few years of utilization. Nevertheless, this assumption may still be debatable, as one expert indicated that a well performing, fast AST solution associated with a clear benefit for patients may constitute a trigger for hospitals to move towards a more efficient 24/7 lab re-organization set-up. This could benefit information flow with improved communication between shifts and amongst staff.

*CLINICIAN VALUE OF AST METHODS*. *TIME-TO-OPTIMAL ANTIBACTERIAL TREATMENT*

From a clinician's viewpoint, obtaining microbiological ID with AST results earlier would allow them to eliminate the guesswork associated with empirical treatment decisions, and provide actionable information they can trust and act upon to tailor patient management earlier. Fast AST solutions result in a shorter time-to-appropriate therapy. This is key for patients with sepsis, as this is a medical emergency in which each hour of delay to appropriate antibiotics increases the mortality rate16. Early escalation to the appropriate antimicrobial regimen is therefore crucial. Furthermore, this element is essential for patients with BSI, including those not so severe, but who are at increased risk of developing sepsis. Indeed, 10-25% of such patients are not covered by the appropriate empirical antimicrobial therapy initially and are likely to develop sepsis if the therapy is not escalated quickly. Moreover, it is also important to detect patients receiving antimicrobial therapy that is unnecessarily broad-spectrum. In these patients, de-escalation is key17, 18, even in sepsis patients, since overtreatment with broad-spectrum antibiotics could be linked to an almost 30% increased risk of *Clostridioides difficile* infection, along with an observed trend toward acute kidney injury, disruption of the gut microbiome, and a 7.8% difference in unadjusted inpatient mortality. It is worth noting that the increased mortality was seen only in patients who did not experience septic shock19.

Patients being treated sooner with the optimal regimen would lead to improved clinical outcomes, the most powerful of which would be a decrease in mortality. In addition to this, shorter time-to-appropriate antimicrobial treatment would have multiple positive impacts which can be summarized in the following streams:

From a patient standpoint, it leads to an overall shorter duration of antimicrobial therapy, which is associated with a decreased risk of antimicrobial driven adverse events (e.g. *C. difficile* infections, acute kidney injury, …). Also beneficial to the hospital, an earlier optimal therapy would lead to a decreased length of stay in the intensive care unit (ICU) and hospital (although, the experts from the Southern group cautioned about this indicator, considering a positive impact on mortality may also increase the length of stay, by avoiding rapid deaths in patients presenting in a critically ill condition). Nevertheless, a possible reduced time from IV to oral treatment could occur, allowing a quicker release from the hospital. There are also several indirect impacts foreseen, such as renal replacement-free days, mechanical ventilation-free days (if the BSI primary source of infection is pulmonary infection), and reduced readmissions to the hospital for infectious causes. Subsequently, these elements would lead to an overall decrease in healthcare resource utilization, and thus a reduction of the overall costs of Gram-negative BSI (GN-BSI) management.

*ANTIMICROBIAL STEWARDSHIP AND AST*

Magiorakos et al published a consensus definition of resistant pathogens20. Multidrug resistant (MDR) pathogens are bacteria that have developed resistance to two or more classes of antibiotics, while extensive drug resistant (XDR) pathogens are resistant to even more classes, including some of the broadest spectrum antibiotics available, often referred to as ‘last resort’ agents, such as colistin and carbapenems. Infections caused by MDR or XDR pathogens can be difficult to treat and may require prolonged hospitalization, more aggressive treatments, including combination therapy, and higher healthcare costs21. Preventing the spread of these pathogens is critical, and strategies such as infection control measures, antibiotic stewardship programs, and the development of new antibiotics are key to managing and controlling these infections22. Not all infections caused by MDR or XDR pathogens are untreatable, and treatment options may still be available. However, it is important to use antibiotics appropriately and to follow recommended infection control measures to help prevent the spread of these pathogens and to preserve the effectiveness of available antibiotics.

Antimicrobial stewardship (AMS) refers to a coordinated effort to promote the appropriate use of antimicrobial agents, including antibiotics, to reduce the emergence of antibiotic resistance and improve patient outcomes23. The goal of antimicrobial stewardship is to ensure that antibiotics are used only when necessary and that they are prescribed in the most effective way possible. AST is an important component of antimicrobial stewardship, allowing selection of effective antibiotics, avoiding unnecessary use of broad-spectrum antibiotics, and helping to prevent antimicrobial resistance24. AMS programs can help healthcare facilities implement best practices for AST and other aspects of antimicrobial use. These programs typically include guidelines for antibiotic use, education for healthcare providers, monitoring and feedback on antibiotic prescribing, and interventions to improve prescribing practices25. They are critical to improving overall quality of care when using molecular diagnostic techniques26.

The value of fast AST solutions would be further increased by the presence of an AMS program, to highlight and support the translation of fast ID and AST results into actionable patient management decisions. Such a multi-disciplinary team would also help to develop a protocol for patients selected for testing with the system, and associated prescription/ treatment modification guidance upon communication of results. AMS is critical for addressing the growing problem of antimicrobial resistance, which is a major public health concern worldwide. By promoting the appropriate use of antibiotics, antimicrobial stewardship can help preserve the effectiveness of these drugs for future generations. AST also has implications for Infection Prevention and Control: quicker identification of MDR and XDR pathogens means the ability to take timely and appropriate measures to slow down their spread by strict hand washing and isolation policies, which are essential, particularly in low-income settings. This could lead to shortening time-to-isolation, and conversely, decreasing the time of unnecessary isolation. There are other additional elements such as the value of obtaining antibiotic minimum inhibitory concentration (MIC) information, important for real-time optimization of antimicrobial dosage (guided by therapeutic drug monitoring [TDM]). This can help to avoid underdosing or overdosing, which can lead to treatment failure or toxicity. There are several benefits of TDM in sepsis, including the ability to individualize dosing to the patient's specific needs, optimize treatment efficacy, and minimize the risk of adverse events27. However, TDM requires careful interpretation of drug concentration data, and it should be used in conjunction with clinical evaluation and monitoring of other laboratory parameters.

*TARGET PATIENT POPULATIONS*

There would be dual value in the utilization of fast AST. First, rapid antimicrobial therapy escalation, when necessary, to avoid further clinical deterioration; and second, in facilitating de-escalation of unnecessarily broad-spectrum antimicrobials, to limit overtreatment and antimicrobial resistance. Several types of patients are likely to benefit, as displayed in Table 1.

Table 1 Target population groups

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| --- |
| * *Elderly people: Older and/or frail adults are more susceptible to infections due to weakened immune systems and other age-related factors. They are also more likely to have chronic health conditions and be colonized or infected with resistant pathogens.* |
| * *Newborns and infants: Infants and newborns are at a higher risk of developing sepsis due to vulnerable host defences including their immature immune systems.* |
| * *People with weakened immune systems: People with weakened immune systems, such as those undergoing chemotherapy, on immunomodulatory therapy or with HIV/AIDS.* |
| * *Individuals with chronic medical conditions: People with chronic medical conditions, such as diabetes, lung disease, heart disease, kidney disease, or haematological conditions may be immunocompromised as a direct result of their underlying condition or as a result of medical treatment used to manage the underlying condition.* |
| * *Patients in intensive care units (ICUs): Patients in ICUs are at a higher risk of developing sepsis due to their weakened immune systems and the increased likelihood of developing infections from medical procedures or devices.* |
| * *Patients with wounds or burns: These patients are likely to have altered skin barrier function, which plays a critical role in protecting from infection.* |
| * *People who misuse drugs: Intravenous drug use or other forms of drug misuse can increase the risk of developing infections that can lead to sepsis.* |
| * *Patients with a history of frequent hospitalizations: People who have been frequently hospitalized or have had recent surgeries are more likely to develop infections that can lead to sepsis.* |

However, it is important to highlight a notable difference between experts: in those from Southern European and Middle Eastern countries, there was 100% agreement in prioritizing the use of such fast AST solutions in the sepsis priority sub-groups defined above whereas, in experts from Northern European countries, less value was perceived in the use of fast AST in sepsis and septic shock patients. Indeed, the experts stated that empiric broad spectrum antimicrobial therapy would already be given in these patients from the start and that clinicians would not be as likely to de-escalate for such severe cases. The Surviving Sepsis Campaign stated that the use of broad-spectrum antibiotics is recommended in the early management of sepsis to ensure prompt initiation of appropriate therapy. One of the recommendations of the campaign is the early use of broad-spectrum antibiotics for patients with sepsis28. Some reasons why broad-spectrum antibiotics are recommended in the management of sepsis are displayed in Figure 1.

*LOCAL EPIDEMIOLOGY AND REGIONAL RESISTANCE PATTERNS*

Hospitals and healthcare facilities are particularly vulnerable to the emergence and spread of antibiotic-resistant bacteria due to factors such as frequent use of antibiotics, high patient density, existing co-morbidities, indwelling devices, and compromised immune systems of patients. The local epidemiology of antibiotic resistance can vary depending on factors such as geographic location, patient demographics, and hospital practices.

To effectively manage antibiotic resistance, healthcare facilities should regularly monitor local resistance patterns and adjust their treatment protocols accordingly. This may involve implementing targeted infection control measures, using antibiotics more judiciously, and collaborating with local public health authorities to track and respond to outbreaks of resistant infections.

Overall, a comprehensive approach to antimicrobial stewardship that considers the local epidemiology of resistance is essential for mitigating the spread of resistant bacteria and ensuring effective treatment of infectious diseases29. We postulate that the divergence in North vs. South Europe opinions comes from two interlinked factors: the local level of resistance and clinician behaviors. Indeed, in settings with lower multidrug resistance such as Northern Europe, it is likely that the empiric antimicrobial treatment initially administered by clinicians would cover most cases of infection, since pathogens will frequently be susceptible to the chosen regimen. On the contrary, in higher antimicrobial resistance settings, such as Southern Europe and Middle Eastern countries, the initial empiric antimicrobial therapy may often fail to cover some resistant pathogens. This may shape perceptions and attitudes regarding the need for testing in different healthcare environments. Cultural differences in attitudes regarding the perception of risk and the approach to handling it may also be relevant. For instance, the statement that some experts would avoid de-escalating therapy in septic shock patients, despite an AST result nudging them to, highlights an underlying fear of error in clinical decisions, especially when it could have dramatic consequences for the patient under their responsibility.

*LIMITATIONS & FUTURE DEVELOPMENTS*

The need for accurate pathogen ID in addition to AST was highlighted. The experts from Southern Europe and Middle Eastern countries discussed which existing ID methodology was best suited to rapid solutions for complete ID and AST results. They recognised the epidemiological context regarding resistance levels, as well as lab organization/workflow (i.e. opening hours, staff resources, 24/7-office hours, BC processing), would play a role here. In areas with lower antimicrobial resistance, a MALDI-TOF system would be suitable, whereas in areas with higher resistance levels, multiplex PCR-based identification could play a critical role, due to the added-value brought by the detection of resistance markers.

The need to validate some additional Gram-negative pathogens was also brought up by the Southern European and Middle Eastern expert group, including some which are important for critically ill and immunocompromised patients: *S. maltophilia*, *M. morganii*, *S. marcescens*, and the *B. cepacia* complex. For many of these pathogens, fast AST could complement some limitations of mPCR panels such as BCID2 (relatively narrow repertoire of detectable resistance mechanisms; risk of overcalling resistance due to the presence of, but not expressed, resistance genes; inability to differentiate among different types of KPC)30.

The ability to use the technology on samples other than blood (i.e., other sterile fluids such as urine, CSF, and synovial fluid) was also identified as potentially valuable by the Northern expert group. The added value that would be brought by the validation of additional drugs to the system was agreed upon by both expert groups. More specifically, the Southern group mentioned the following, with the idea that such additions would benefit critically ill sepsis patients: imipenem/relebactam, cefiderocol, colistin, aztreonam/avibactam, and ampicillin/sulbactam.

The same group made suggestions about potential deletions as well, for antibiotics which they considered AST information brought little to no value: tobramycin (experts considered gentamicin and amikacin were sufficient), piperacillin (which, at least in Southern Europe and the Middle East, seems not to be used in clinical practice, especially not in the critically ill; its only benefit would be to have it as a marker of penicillinases, but it was not considered a priority), levofloxacin (ciprofloxacin being sufficient) and cefoxitin. Opinion was mixed on the benefit of including ceftazidime/clavulanate for obtaining Extended Spectrum Beta-Lactamase (ESBL) information in a short timeframe. MERINO trials, with their accepted limitations, suggest that knowing whether or not ESBL is present, is important, with mortality outcomes. Clinically, it also helps with de-escalation, choice of drug, and in low resistance settings - IPC interventions31.

The last suggestion related to the fast AST solutions was made by the Southern expert group regarding MIC range extensions. The most important one would concern meropenem and meropenem/vaborbactam in parallel, for which the range should be extended up to 128 μg/mL. Another one would be for ceftazidime/avibactam, which should be up to 16 μg/mL.

Clinician behaviors may be a barrier to the utilization of fast AST solutions to its utmost value, if clinicians do not act upon the available diagnostic test results, by risk-aversion and/or fear of changing long-engrained habits related to antimicrobial prescription. Moreover, the quick turnaround time of the system will likely require some crucial adaptations to fit the diagnostic result at the right place and time into the patient management information workflow. This will largely depend on the organization inside a given hospital. For example, in some settings with limited resources, only one experienced on-call physician may be available during night shifts, which may reduce the overall ability to act in an efficient and timely manner based on ID and AST results. Essentially, to avoid losing the value the system can bring, cross-functional collaboration is critical: between the microbiology laboratory and infectious disease physicians, the AMS teams, and the prescribing clinicians. In addition, workflow is key, such as having AMS teams with 24/7 availability, and systems to facilitate information flow and interpretation, such as a clinical decision support system (CDSS).

There might also be a cultural element linked to change management and communication influencing the implementation of such a new solution. What seemed to stand out, when comparing the opinions from regions, Northern countries were perhaps more compliant with clearly defined processes and roles. Such standardization, although generally enabling a high level of efficiency, might allow less room for shifts in perceptions and practices, which are necessary when implementing such a new tool. The Southern and Middle East countries, in comparison, seemed to describe more fluent communication flows between roles and departments, with less rigidity in their operational structures. Such flexibility seemed to make them more open to accommodating swiftly to changes required with an innovative fast AST system.

Furthermore, the ability of the system to provide MIC results will only translate into value for patients if the current knowledge gap around the use of such information in the management of severe infections is understood and addressed. The value of MIC will also rely on additional tools being available, such as TDM and the availability of appropriate expertise, to better monitor and adjust dosing appropriately to optimise the pharmacokinetic/pharmacodynamic indices of antibiotics in target population groups. In the Northern European countries’ session, only experts from Germany were regularly relying on TDM for antibiotics other than aminoglycosides and vancomycin. In France however (which was included in the Southern group for the present framework), several hospitals are using TDM for beta-lactams as well.

Finally, the element linked to higher cost is key: the acceptability of such a solution will indisputably rely on the demonstration of the overall value for money and improved clinical outcomes.

*KNOWLEDGE GAPS / PRIORITIES FOR EDUCATION*

Knowledge gaps, which shape the priorities in terms of education, were identified as the following: (1)

the value of fast AST (and AMS, in settings where it is not yet fully recognized); (2) where needed, awareness around sepsis definition and management; (3) the importance of a multidisciplinary approach and how to improve workflow/process and teamwork to maximize the value of diagnostic information, e.g. integration with AMS teams who can support appropriate clinical decisions, which may be reassuring to clinicians knowing the responsibility is shared; (4) the utility of MIC: how phenotypic and genotypic information should be combined and interpreted, and which concrete actions it would triger. Regarding this last element, it is important to note a divergence of opinions between both Advisory Board groups: while in the South/ Middle East group, experts agreed it was key that training should be delivered to clinicians, the experts from the Northern group believed the understanding of MIC was rather the responsibility of microbiologists and infectious diseases physicians. Therefore, they did not perceive the necessity of clinician training, but rather, they viewed this distinction in responsibilities as an opportunity to foster a better relationship between clinicians and microbiologists, with the latter thus bringing added value to the discussion; (5) and local prescribing guidelines (important especially in settings where the AMS team is not available 24/7).

These knowledge gaps could be addressed by external medical education activities, e-learning modules with interactive case discussions, preceptorships, rotative trainee programs (e.g. ICU trainees rotating in microbiology labs for a few months), raising awareness, and creating advocates. To accelerate the impact of such educational actions, the importance of primarily addressing clinicians who manage the targeted population groups ‘on the shopfloor’, rather than Key Opinion Leaders (KOL) who, in the more traditional sense, tend to be more involved in research and may be slightly detached from daily clinical activity. Education and training would also be helpful, namely on the understanding of clinical behaviors, to best convey value messages and involvement of behavior change and implementation experts.

*EVIDENCE GENERATION NEEDS*

Interventional trials and RCTs are required to demonstrate the foreseen benefits. At a later stage, after routine adoption of the fast AST solutions, the generation of Real-World Evidence would be key. Priority focus should be given to demonstrating the overall value for money32. It is also of the utmost importance to document how the solution can be efficiently integrated with other components of the patient testing pathway, such as ID tools, host biomarker tests, as well as pre-analytical and post-analytical elements, linked to the workflow processes and team collaboration, e.g. the ability to collect samples and send them quickly to the laboratory; how the AST test results are then provided and used (i.e. laboratory information management systems and their integration with clinical records, IPC systems and AMS programs).

Given the global burden of antimicrobial resistance, interventions need to demonstrate positive impacts on clinically relevant patient outcomes, improvements in overall antibiotic susceptibility, as well as cost-effectiveness. Robust economic evaluations, which include considerations across the whole care pathway and multi-disciplinary team (including the laboratory staff) are needed to increase our understanding of the cost-effectiveness of these AST interventions in routine clinical practice and to inform policy decision makers.

The demonstration of the solution’s impact on mortality would likely be the most powerful demonstrator of value, but it may also be the most difficult to prove through a study. Indeed, it would require the integration of an exceptionally high number of patients and would rely on variable parameters like patient co-morbidities and the process of care. According to the Southern group, focusing on showing an impact on mortality in septic shock patients could be more feasible as a first step. As fast AST technologies become more widely used, a ‘big data’ approach to this challenge may be worth pursuing.

Conclusion

There was unanimous recognition, amongst experts attending the two Advisory Boards, of the strong value fast AST solutions can bring to improve the clinical outcomes of patients with BSI. However, heterogeneity between geographical settings with different hospital structures and local levels of resistance will likely require adaptation of the value messages, namely for the priority population targets. Moreover, the implementation of such a new diagnostic tool will have implications in terms of process/workflow changes inside the hospitals, and subsequently, a shift in mindsets will be required. The launch and sustainability of fast AST solutions in the market should therefore be accompanied by the right level of medical education and training for the hospital stakeholders likely to be impacted, as well as the generation of credible evidence to demonstrate the value such solutions can bring. Reducing the time-to-optimal therapy can help to avoid over-treatment by ensuring that patients receive appropriate treatment as soon as possible, thereby avoiding side effects or complications from unnecessary therapy. Additionally, by initiating the most effective treatment quickly, doctors are empowered to de-escalate if the patient's condition improves. From a society and public health viewpoint, a reduced time-to-optimal therapy reduces overtreatment by supporting quicker de-escalation, thus decreasing downstream selection pressure, which is weighted in favor of the development, and spread of resistant bacteria when de-escalation is delayed. This constitutes a key element in the fight against antimicrobial resistance.

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Figure 1. Interpretation of molecular testing in sepsis workflow.

