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Review

Total Laboratory Automation in Clinical Microbiology: A Note on Needs, Challenges, and Applications in a Pandemic Scenario

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Abstract: Recently, an increasing number of publications on automation in diagnostic laboratories, especially in microbiology, has illustrated its potential impact on modern medicine by enhancing the overall quality of culture-based microbiology testing. In the context of clinical microbiology, total laboratory automation (TLA) is now defined as automating the testing workflow, which comprises all phases from sample inoculation to outcome analysis. Hence, there is a need to design or implement proper laboratory automation management processes to enhance workflow, reduce analysis time, and deliver high-quality results without delay in treatment initiation. This review-cum-perspective article highlights the need and current advancements in diagnostic microbiology automation that could revolutionize laboratory operations in healthcare settings. Automation of the workflow is a crucial advancement in the recent history of laboratory diagnostics that unites many diagnostic specializations into a single track to increase the effectiveness, administration, standardization, reliability, and safety of lab tests. While clinical chemistry laboratories adopted and deployed laboratory automation decades earlier, the process of implementing them into routine clinical microbiological practices has several bottlenecks and is still a lengthy process and fraught with technical and regulatory challenges. Moreover, due to outbreaks including the COVID-19 pandemic of recent times, testing volumes are increasing, and automation could probably be a great solution for small and mid-sized laboratories. This article lists the TLA remedies and the specimen-processing tools that are presently available. The need and challenges to implementing automation in microbiological laboratories are discussed with a note on applications in pandemic scenarios.

***Keywords*:** automation, laboratory automation, TLA, microbiology, diagnostic, pandemic, COVID-19

1. Introduction

In laboratory medicine operations, a transition from physical work to machines could be called laboratory automation [1]. In reality, all devices in the laboratory, with the simple example of centrifuges, are a kind of automation [2]. Historically, manual techniques have been used for culture-based microbiological laboratory testing [3]. Clinical samples must first go through a series of meticulous, repetitive steps that can be automated [4]. High-throughput automated solutions could make it easier to process samples, save money, and provide more testing versatility [5]. Therefore, clinical microbiology automation has a huge potential to transform laboratory practices in hospitals and clinical reference laboratories [6-7].

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Even though clinical microbiology labs began using automation in the 1960s, with limited success, the usage of machines became an integral part of diagnostic laboratories in the early 90s for microbial detection in blood cultures, screening urine samples for infections, antibiotic susceptibility testing, and quantifying antimicrobial agents in body fluids [8]. Thereby, automation facilitated a more rapid diagnosis and eliminated many manual tests. Moreover, automated tests were more sensitive and specific than conventional manual techniques [3, 8]. However, while automation has steadily spread through many diagnostic disciplines recently, clinical laboratories have mostly resisted this shift [9]. To enhance the clinical relevance of microbiological findings, it is now essential to develop an appropriate workflow management process to speed up analysis and deliver superior results without delaying treatment [10]. Implementing automation, computerization, and personnel reorganization could improve response time and the effectiveness of diagnostic techniques.

The first clinical bacteriology laboratory automation system was introduced in 2006. It quickly showed its value by boosting productivity, enabling an ongoing increase in sample numbers despite tight finances and a lack of staff [7]. Since then, automated microbial identification, continuous monitoring of blood culture systems, and antimicrobial susceptibility testing methods have become popular [9]. However many labs have little to no automation in their microbiology sample processing and culture workup sections, which continue depending on subjective interpretations [9].

In clinical microbiology laboratories, the term “automation” is now most frequently used to describe tools for processing microbiology specimens and microbiology total laboratory automation (TLA) systems [1, 9]. Except for some labs in Western Europe, Australia, and Middle Eastern countries, very few labs have effectuated TLA; those that adopted automation have observed an increase in testing accuracy, lowering of turnaround times, enhancement in laboratory efficiency, and higher flexibility in the level of skill needed to perform work in the laboratory [11-15].

The COVID-19 pandemic situation has brought attention to the demand for medium- and small-sized laboratories to serve communities that do not have simple or quick access to large laboratories. Both clinicians and researchers are faced with the daunting task of scaling up the testing by high sample throughput methods to detect nucleic acid or antibodies in people exposed to the virus. In such instances, laboratory automation offers an advantage over conventional testing platforms.

The major goal of this review is to draw attention to the technological advancement in clinical diagnostic microbiology driving toward TLA. The TLA solutions and the currently accessible specimen-processing equipment are listed.

Additionally, the necessity of additional research to adequately evaluate the advantages of automation in microbiological laboratories is emphasized. The operational and staffing difficulties that clinical microbiology laboratories and TLA applications would face in a pandemic scenario are also discussed in this paper.

2. Need for automation, especially in a pandemic scenario

According to estimates, lab results may be the basis for as many as 70% of all medical decisions [16]. The clinical microbiology laboratory’s main job is to help with infectious illness diagnosis, which is essential for patient care and infection control [14]. The importance of the clinical microbiology laboratory cannot be understated, given the emergence and re-emergence of infectious diseases and the increased reporting of antibiotic resistance. The clinical microbiology laboratories are the sentinel labs acting as the first line of defense to correctly detect the existence of an impending threat if a bioterrorism incident were to occur [16]. Laboratory testing is anticipated to rise further due to universal healthcare and an aging baby boomer population.

During the recent COVID-19 pandemic, there has been a surge in demand for molecular diagnostic testing and serological testing due to the dissemination of infections and increased vaccination. Nevertheless, testing for no infection status also became mandatory for international travel. Hence, the need for automation has been deeply realized during this challenging time by small to mid-sized laboratories, which were accustomed to processing minimal samples routinely. With testing volumes rising exponentially in severely affected areas, automation has become the need of the hour since it would assist labs of all sizes in meeting the needs associated with ongoing COVID-19 testing. The continuing viral pandemic has put tremendous pressure on clinical diagnostic laboratories not only due to an increase in testing volumes but also other factors including biosafety, workforce management, and social distancing within the

laboratory [17-19]. Automation is a desirable alternative because medium- and small-sized laboratories will continue to experience an increase in test volumes with little to no increase in resources [18].

Automation helps manage any personnel shortages (if any) in the clinical microbiology laboratory while increasing productivity and preserving quality [20]. Since automation eliminates the inherent variability in a workflow that partially or fully relies on manual specimen handling, it is obvious that these solutions allow laboratories to establish sustainable processes for managing specimens. Choosing an automation system can also help deliver broad, multi-layered sustainability gains and provide a significant advantage to any laboratory [21].

There are several bottlenecks in deploying TLA in clinical microbiology laboratories, unlike clinical chemistry labs that have consistency in specimen types, volume, and containers and are automated making it easier to adopt TLA. The major bottlenecks in clinical microbiology laboratories are the diversity of sample types and variable collection media/containers for Microbiological cultures, subjective and manual interpretation of culture results, and increased cost for TLA due to lower sample volume (as compared to clinical chemistry test volumes). Some of these bottlenecks have been addressed with the advent of liquid-based swab transfer systems and the development of matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (MS) technology are two key technological advancements that have contributed to general improvements in the laboratory industry [9]. In traditional microbiology, swabs were transferred in a container made to retain a specimen connected to the swab while it was being transported; the swab was then used to inoculate the culture medium. The development of liquid-based swab transport devices, such as the ESwab (Copan, Murrieta, CA), allows for the automation of smear preparation through automated liquid-based specimen processors [9]. Also, MALDI-TOF MS helps in the rapid, accurate, and inexpensive identification of microorganisms isolated from clinical samples thereby reducing the subjective nature of culture identification; MALDI-TOF operations can be carried out with a little staff [9]. The adoption of liquid microbiology specimen transfer techniques and the standardized use of MALDI-TOF for identification would make collection and identification systems simpler and result in an automated workflow.

Detailed data on bacterial growth, morphology, and the kinetic effects of substances are also helpful in the development of new technology to measure bacterial phenotypes; however, gathering this information manually takes time, so systems are required that help automate the analysis of microfluidic devices to increase sample throughput [5].

3. Total laboratory automation-specimen processors and TLA solutions

Currently, the TLA refers to the automation of the diagnostic workflow, which includes all steps from inoculation to the outcome [2]. It was previously mentioned that a variety of technologies, including pre-analytical specimen processors to TLA with digital imaging that enables remote work-up of specimens, and diagnostic telemedicine, will undoubtedly have an impact on patient care [16]. Therefore, TLA must process various specimen containers, including agar plates, broths, and slides; bacterial culture specimens must be inoculated and incubated; and finally, the outcomes must be assessed and recorded.

There is a revolutionary change in automation in microbiology laboratories, as predicted sometime in the past [21]. Now there are automation solutions: including systems that provide microbiology TLA solutions and instruments that serve primarily as specimen processors. Different functions are carried out by processing equipment, including inoculating tubes and plated media, a broth culture subculture, plate streaking, plate labeling, and barcoding for specimen tracking and slide preparation. Total microbiology laboratory solutions include the functions of sample processors by adding modules to achieve varying levels of complete microbiology automation [9].

3.1 *Currently available specimen processors*

The first fully automated plating system for liquid specimens was introduced to the market in 2002 with the introduction of InocuLAB (Dynacon, Now BD). Currently, several other specimen processing instruments are now available, which include the WASP (Copan), Previ-Isola (BioMerieux), Innova (Becton-Dickinson), and Inoqula (KIESTRA) systems. The WASP (walk-away specimen processor) uses a conveyor system for "specimen load and unload" that uses different-sized pallets for tubes of various diameters. Its performance characteristics have been evaluated by Bourbeau and Swartz [22], which revealed no-contamination when urine transport tubes and E-swabs were

plated [23].

These new tools make it possible to inoculate samples accurately and efficiently. There are four main steps involved: (1) choosing the right petri dish, (2) inoculating the sample, (3) spreading the inoculum on agar plates, (4) obtaining isolated bacterial colonies after incubation, and (5) accurately labeling and sorting each inoculated media. Finding the ideal automated laboratory system is a challenge for medical bacteriologists. Indeed, depending on the quantity, diversity, and sorts of samples that will be processed by the automated system, several solutions will be recommended. Due to the difficulty of the computer connections between the laboratory information system and the instrument, the final choice is problematic because audits suggested by industries run the risk of being biased in favour of the solution provided by their company. Additionally, these automated systems may also be difficult to test on-site before the final decision. Significant additional benefits have been added by adding TLA to automated specimen processing for microbiology laboratories.

3.2 *Currently available TLA solutions*

Currently, three microbiology TLA systems for culture-based microbiology testing are in use: (1) Becton Dickinson's Kiestra TLA (BD Kiestra B.V., Drachten, Netherlands), (2) Copan's WASPLab and Copan Colibrí™ System (Copan Diagnostics, Murrieta, CA), and (3) Full microbiology laboratory automation (FMLA; bioMérieux, Inc., La Balme, France) [3]. All of these have plate conveyor systems, automated incubators with digital stations, and operational control software. To automate specimen processing and workup, all of these systems incorporate robotic plate management. The automation platform incorporates plate labeling and delivery, inoculation, spreading, incubation, and digital image analysis; its clinical performance is also validated [24-25].

The quality of culture reviews may be improved, and the training of new technicians could be enhanced with the use of an automated workflow management system. In contrast to conventional microbiology labs, plate reading can be done when incubation is sufficient on a plate and many stacks of plates can be effectively retrieved; plate image records could be retained, which facilitates a review of growth over time; microbiologists would get an opportunity to examine a patient's culture history. The Copan Colibrí™ System is the first instrument in its class that is FDA-cleared for the simultaneous preparation of MALDI-TOF slides for culture identification and McFarland suspension preparation for antimicrobial susceptibility testing (AST) on standard platforms like bioMérieux VITEK®2 and Beckman Coulter MicroScan as shown in a recent multicenter evaluation study [26].

The Copan PhenoMATRIX® artificial intelligence (AI) software suite offers WASPLab® users automatic reading, interpretation, and sorting of bacterial cultures, transforming how microbiologists interact with their work. PhenoMATRIX AI suite helps decrease hands-on time spent by technologists on negative and insignificant cultures which can be as high as 95% of culture plates (5% MRSA positivity rate) as shown in a recent study [27].

3.3 *Open-source 3D printer architecture for laboratory robotics*

Laboratory robotics involves using robots to automate repetitive tasks in labs, enhancing precision, efficiency, and productivity. A group of researchers from the United Kingdom has described low-cost, open-source, completely customizable high-throughput imaging systems for analytical microbiology applications. This system constitutes a Raspberry Pi camera module attached to an aluminum extrusion frame with 3D-printed joints that are controlled by an Arduino microcontroller running open-source Repetier Host Firmware [5]. The camera position is managed by straightforward G-code scripts, enabling specialized time-lapse photography of microdevices over a sizable imaging region. Remote access is controlled by open-source OctoPrint software. With the use of this highly efficient design, high-throughput microbiology analysis may be carried out in many formats (for bacterial mobility, colony growth, microtiter plates, and microfluidic devices) to observe how different culture media components and drugs affect bacterial growth. The size of the imaging area can be adjusted in the open-source robot design to make it appropriate for more sensitive growth detection utilizing fluorescent dyes.

4. Challenges in laboratory automation

The diagnostics industry faces numerous challenges, particularly concerning microbiology testing. In general, testing volumes are rising annually, primarily as a result of the aging population, diagnostics innovations, infection prevention requirements, and the increasing difficulties brought on by the detection and characterization of multidrug-resistant pathogens [9].

Although few automation-related advancements in clinical microbiology have been documented, their transition into normal use is still a difficult process with several technological and regulatory barriers [3, 28]. Even though automation of microbiological procedures may shorten the time it takes to process a sample, many investigations still use the same methodology. For example, the traditional agar plate approach, to cultivate bacteria and phenotypically analyse features like resistance to antibiotics [5]. The use of automation has been progressing slowly in clinical microbiology laboratories due to several variables [11]. The main reason is the complexity of automating microbiological testing; automation is too expensive, and no machine can replace a human in microbiology laboratories and small-sized laboratories [9]. The sample formats used in microbiological research are extremely diverse (e.g., soil samples, and medical samples like sputum and urine), and the techniques used for analyses range from microtiter plates and Petri dishes to microscope and bacterial identification strips like API strips [5]. Due to this reason, platforms for assessing microbiological investigations are typically extremely tailored for a particular experiment.

Some of the data-driven platforms where automation could be helpful are (1) visualizing microbiology data on dashboards [28-30], (2) microscopic image analysis [28, 31], (3) colonies on agar image analysis [28, 32-33], and (4) gene sequences and proteomic data comparison with pathogen phenotypes [28, 34-35].

Implementing TLA in clinical microbiology would probably place significant management and financial challenges. Before implementing a solution, the laboratory authorities should have a clear vision of their need and expectations of automation [21]. Further research is required to fully comprehend the financial and clinical effects of TLA on workflow management and patient outcomes as the price may vary on the extent of automation [16].

5. Discussion

By employing TLA, staff members may be able to complete more difficult jobs that will benefit from their expertise [6, 36-37]. Additionally, it might impact the demand for skilled technologists in laboratories. In a hypothetical clinical microbiology lab of the future, a patient's samples will be put on a belt conveyor and sent onto a mechanized line for inoculation and processing; technologists will only need to view the images of culture and submit them for identification by The Copan Colibrí™ System is the first instrument MALDI TOF; the system will then transfer the colony for susceptibility testing following identification [16].

This is a challenging time for clinical microbiology, as learnt during the COVID-19 crisis; different models have hypothesized varying outcomes of global lockdown and fatality rates [38-39]. For surveillance during infection outbreaks, appropriate infrastructure is required to analyze high-quality real-time data in formats that can be read by machines [28]. Automating manual processes would probably free up laboratory resources to do more testing in any outbreak scenario [40-41]. Workflow automation would solve staff shortages, as seen during the recent pandemic [42].

There is a need to continue studies to properly assess the measurable outcomes considering various scenarios [9]. A recent report has highlighted the determinants of limited studies documenting the benefits of TLA in clinical microbiology; those are (1) the effect of TLA on supply chain and labor for culture workup, (2) the time constraints in microorganism identification and antimicrobial sensitivity testing, (3) turnaround time to final reporting, (4) difficulty in an examination of plates early because of insufficient growth for identification and (or) antimicrobial susceptibility assays [43]. Also, additional studies are required to accurately estimate TLA's financial and operational impacts in diagnostic microbiology [9, 36, 44]. Besides that, it's critical to evaluate how TLA may affect clinical micro-organism identification, antimicrobial sensitivity screening, and its overall impact on patient care. Depending on the patient demographic, the clinical advantages might differ. Also, several factors, viz., accuracy, capacity, technical support, flexibility, capacity, flexibility, modularity, and costs (instrument, disposable supplies, and operational), should be considered while selecting a microbiology automation system [11]. Validation is also a crucial step in the regulatory

process that will determine the effectiveness of artificial intelligence and machine-learning-dependent algorithms in clinical microbiology for diagnostic monitoring [28].

Along with changing technologies in clinical microbiology laboratories, operational challenges have been growing with budget constraints, declining staff, and legally mandated testing. Additionally, laboratories must maintain quality to provide the best possible patient care. However, the role of clinical laboratories is evolving. To enhance diagnostics, it is now mandatory to use digitalization and machine learning potential [28, 45-46]. Applications for digitalization in patient care begin with standards for data and code management [47].

6. Conclusion

Automation in diagnostic laboratories, including microbiology, has played an increasingly important role in how modern medicine is practiced. Despite many challenges, TLA has excellent potential to enhance the overall quality of culture-based microbiology testing. There is a suggestion to incorporate more protein chemistry, wherever possible, in diagnosing infectious disease conditions which could be easier to automate compared to classic culture-based investigations. Considering the global threat of future pandemics, there is a growing demand to develop total automation in laboratory operation solutions which must be cost-effective yet efficient to be employed even in peripheral diagnostic centers. Though microbiological testing may change in the future, the microbiologist's expert interpretation of test results and the proposal of antimicrobial medications will remain valid.

Conflict of interest

The authors declare no competing financial interest.

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