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Narrative review

Bloodstream infections – Standard and progress in pathogen diagnostics

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ABSTRACT

Background: Bloodstream infection (BSI) is a major public health burden worldwide, with high mortality. Patient outcome is critically influenced by delayed therapy, and fast and accurate pathogen diagnostics decisively improves the care of patients. During the past two decades major improvements have been made in the diagnostic performance of blood culture diagnostics through actions on pre-analysis and time to result.

Aims: To review and discuss the literature for standard procedures and the progress in BSI pathogen diagnostics, and to propose a new mindset to reach an improved diagnostic workflow.

Sources: Scientific articles and reviews available through NCBI/Pubmed.

Content: Blood culture performance relies largely on the quality of its pre-analytical phase that is improved with educational actions monitored by using key performance indicators, and external quality assessment. Advanced blood culture systems now provide tools for an automated estimation of bottle filling. These proved efficient to facilitate effective training for improving blood collection. On analytic aspects, rapid methods for pathogen identification, among which matrix-assisted laser desorption/ionization time of flight mass spectrometry dominates, and rapid antimicrobial susceptibility testing are reviewed. These technical developments call for improvements in all other steps, especially in pre- and post-analytic logistics to give the full reciprocation of these techniques on patient management. This aspect is summarized by the term 'microbiologistics', which covers all possible improvements in the logistic chain from sampling to report.

Implications: Progress in BSI pathogen diagnostics is based on a bundle approach that includes optimization of the pre-analytical parameters, rapid start of incubation, the use of rapid methods, reorganization (e.g. 24/7, transportation service) and a close involvement of antimicrobial stewardship teams. These developments lead to define a new standard for bloodstream infection diagnostics.

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Introduction

With an estimated burden of 1 200 000 episodes of bloodstream infection (BSI) each year in Europe and long-term sequelae, BSI represents an increasing public health concern [1]. Delayed effective therapy is associated with worse outcome [2,3]. Fast and accurate diagnosis of the causing microorganism and a correct susceptibility testing improves the care of patients with BSI/sepsis

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and leads to a more precise therapy which grows in importance with antimicrobial resistance increase [4–7]. The detection of the causing pathogen with molecular techniques has, so far, been proven suboptimal [7] and blood culture (BC) remains the reference standard and first line tool in the pathogen diagnostics of BSIs and sepsis [7].

The introduction of continuous monitoring blood culture systems (CMBCs) in the 1990s led to an improved standardization of BC diagnostics with easier ordering and optimized culture media yield [8]. However, this development was not followed by other improvements in the area for the next decades while CMBCSs partly obscured the fact that pre-analytics are critical to detect BSI pathogen. During the last decade, however, a dramatic progress in the development of rapid diagnostic tests relying on innovative technologies has occurred [9]. Also, the importance of the logistics and the improvement of quality management of BC diagnostics are increasingly recognized [10]. This resulted in a multifaceted range of actions to improve the microbiological diagnosis of BSI (Fig. 1), and many of them are complementary. Here, we review the standards of BSI pathogen diagnostics, the progress in this area, in terms of reduced time to result (TTR) and quality of results and propose new timelines to aim for in modern BC diagnostics.

Standards in BSI pathogen diagnostics

The performance of BSI diagnostics is to a large extent determined by the pre-analytical process including the skin preparation, the amount of blood per bottle, the number of bottles collected per episode and the time to bottle incubation [11,12] (Table 1). It is however striking how far real-life conditions in many cases are from recommendations [11,13–15].

The classical analytical process of microbiological BSI diagnostics that prevailed until end of 2000s is shown in Fig. 2. However, the introduction of new methods in clinical microbiology deeply rushed practices during the latest decade and outdates the classical process. The high variability in utility, dissemination and cost of the new techniques (such as matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS)) makes it challenging to define the current standard of BSI pathogen diagnostics [13]. In the absence of dedicated guidelines the novel methods have been adopted very differently [13]. Before the introduction of MALDI-TOF MS, the typical TTR was 2–4 days for a positive BC, which is too slow for affecting acute patient management. However, in European microbiology laboratories, MALDI-TOF MS systems have now almost completely replaced time-consuming biochemical identification [13]. The full process of BC diagnostics is thus able to move towards the lowest possible TTR and at the very latest a final species identification and an antimicrobial susceptibility testing (AST) report should be available within 24 hr following bottle positive signal (Table 1). To reach this target and also increase the sensitivity and specificity of the BC process, several steps need to be addressed.

Progress in sampling procedures, blood volumes and quality management

An increasing awareness of the importance of pre-analytics in BSI diagnostic quality is seen through a number of initiatives for improvement, the recognition of the low achievement of the recommended targets for contamination and blood volume, and not least the recognition of the need for extra tools to visualize and promote improvements [10,16].

Several approaches are available to address the quality challenges in BSI pathogen diagnostics. First, continuous quality improvements have grown in importance [10]. They include, in addition to quality management systems, implementation of relevant key performance indicators (KPIs) to monitor critical points in the BC process that mostly focus on critical pre-analytical criteria

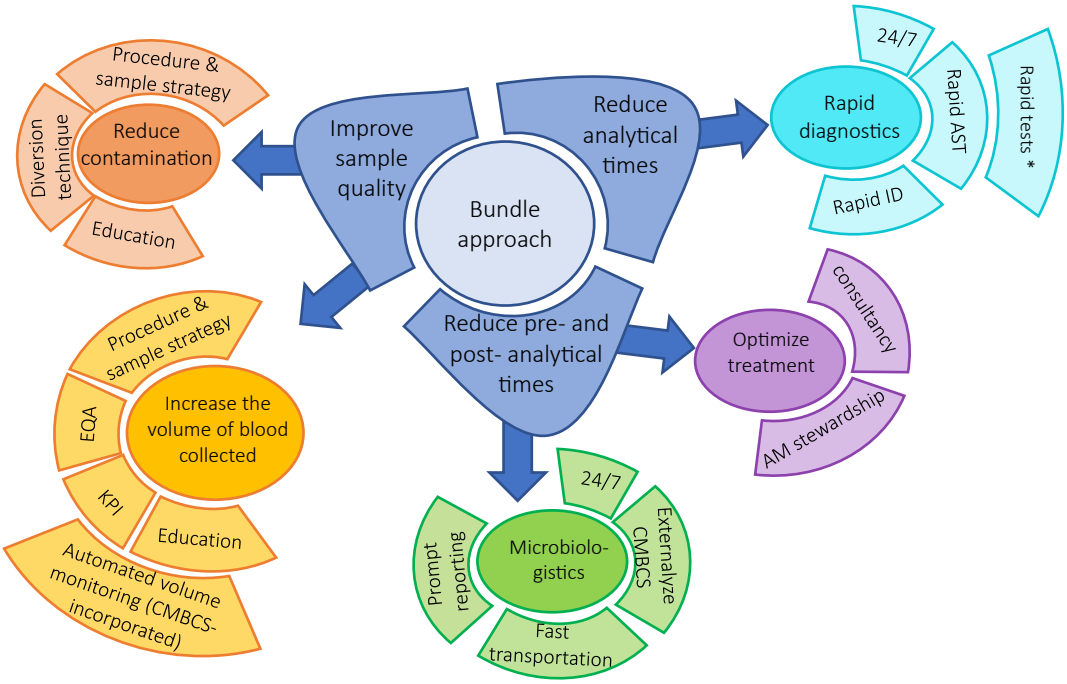

Fig. 1. Summary of all the actions to improve the bloodstream infection pathogen diagnostics. Types of actions belong to three complementary axes and actions aim to manage sample quality, times before and after analysis and analytical times. Each action per se is associated with a limited improvement but combination of several actions significantly improves diagnosis. Improvement is maximum when programme include actions on sampling quality, rapid diagnostics and logistics. KPI, key performance indicator; EQA, external quality assessment; CMBCS, continuous-monitoring blood culture system; AM stewardship, antimicrobial stewardship. *Rapid tests (e.g. *mecA* detection) may be needed in area of high level of resistance.

Table 1
State-of-the-art in microbiological diagnostics of bloodstream infections

Diagnostic procedure	State-of-the-art[a]	Comment	Reference
Blood sampling			
Skin preparation	The contamination rate is <3%, optimally <1%	Contamination is defined as a microorganism recovered from BC bottle that is indeed absent in the patient blood. Most often, contaminations are bacteria from the skin microbiota (e.g. coagulase negative staphylococci, coryneforms) Contamination rate is defined as the number of contaminated samples (whatever the number of positive bottles) per 100 samples (whatever the number of bottles collected). Contamination rate is reduced by compliance with skin preparation best practice, diversion technique, single sampling strategy and prior careful disinfection of bottle's septum	[12]
Bottle-filling (adult patient)	The volume of blood per bottle is 8–10 mL	These two parameters result in a total volume of blood cultured of at least 40 mL to ensure optimal BC sensitivity	[10,11,16,78]
Number of bottles collected per episode (adult patient)	4–6 bottles are collected (4 acceptable only if all bottles properly filled) Rate of solitary BC (2 bottles) below 10%	For children, refer to article in the current theme review [77]	
Specimen transport	<4 hr for the majority of BC	With decentralized BC cabinets 2 hr should be aimed for	
Species identification	The result of species identification is available on the same day of BC positivity	Achievable with MALDI-TOF MS performed directly from positive blood cultures or from short sub-cultures on solid medium. Also achievable with genotypic rapid methods for the most frequent pathogens	[9,61]
AST	The preliminary or final AST report is available on the same or at latest next day of BC positivity	Achievable by AST initiation on the same day from positive BCs (inoculation of short sub-cultures on solid medium, of microbial pellet, or directly of positive BC broth) instead of application of overnight colonies	[36]
Reporting of positive results	100% of new positive episodes, both identification and AST, are promptly reported to clinicians	By an active and prompt communication of the index information (e.g. positive flagged BC, Gram stain result or result of the direct identification) through a phone call or an electronic alert. Subsequent information (obtained on Day 1) can be reported using electronic report, except when new information is identified as being critical to patient care (e.g. AST result that shows prompt treatment change is required due to ineffective antibiotic regimen) Index information should preferably be also communicated to an Antibiotic Stewardship Team or an Infectious Diseases department	[10]

AST, antimicrobial susceptibility testing; BC, blood culture; MALDI-TOF MS, matrix-assisted laser desorption/ionization time of flight mass spectrometry.
[a] State-of-the-art statements represent authors' opinion on what is currently feasible and what should be implemented as requirement for timely and qualitative diagnostics of bloodstream infections.

[10] (Table 2). Such monitoring easily highlights what pre-analytical factor needs to be improved, and training (e.g. of nurse or phlebotomists) has thus become pivotal to improve, for example, bottle filling and the quality of skin preparation [14,15]. However, adequate filling may be moderate also in post-intervention assessments [15] and training effects may also fade with time, which calls for new strategies to reach effective training. Second, manufacturers have implemented technical features for automated estimation of the bottle filling in CMBCSs either with a direct or an indirect estimation of the amount of blood cultured (Table 2) [17,18]. Data are easily acquired and can be used as an educational tool for quality improvement on the departmental level as summarized in Table 2 [14,15]. Third, initiatives to promote external quality assessment (EQA) of the BC pre-analytical quality in European hospitals have been instituted (www.ctcb.com). The current level of quality at a population level (laboratories) is measured, and the EQA helps monitoring the efficiency and actions of improvement at a hospital/community level [19,20]. Although none of these approaches directly improves the pre-analytical quality *per se*, the specific steps in the process are better visualized and targets can be set to improve the BC quality.

Promising strategies to prevent contamination include, as recently reviewed [12], the single puncture sampling [11] and the diversion technique as presented in Table 2. The latter consists in diverting the first millilitre of blood either in an additional sample tube or using a dedicated device, which reduces contamination to a varying extent in clinical studies [21,22].

Rapid identification from positive BC

As MALDI-TOF MS is used in most laboratories across Europe for the species identification from cultured isolates [13], it is reasonable to use this technology for further applications, notably for shortening time to BSI pathogen diagnostics. Two major MALDI-TOF MS-based approaches are available to reach rapid identification from positive BC: direct identification and identification using short sub-culture on solid medium (Fig. 3).

The microorganisms in BC broth are not readily available for identification, and separation of microorganisms is therefore required. In the direct identification, the BC suspension is usually treated with detersive agent followed by a centrifugation procedure and in some protocols protein extraction with ethanol and formic acid [23,24]. Finally a MALDI-TOF MS measurement is performed [23–25]. This method enables very rapid identification (20–40 min processing time), a report at the same time as the report of the Gram stain and an impact on patients' management [9,26,27]. However, the method has some limitations where suboptimal integration into the workflow might lead to batch processing [25,27] with reduced effects on patient management. The identification rates with this method can reach 80% except for yeasts [23–25,28]. The problems with logistic changes in the laboratory seem to be less pronounced with the identification from positive BC using short sub-culture on solid medium, which is currently the most commonly used approach [13]. The method allows reliable identification by MALDI-TOF MS after a short incubation step (only a few hours) without any additional processing [23,29]. Mixed cultures cannot be reliably recognized by any of the two methods, thus still warranting Gram stain directly from the BC and incubation of agar plates overnight for control. However, this does not constitute a significant drawback as only a minority of positive BCs include more than one species [23,29].

Several commercial systems based on multiplexed PCR or microarray have been marketed during the last years to allow the identification of bacterial and fungal pathogens from positive BC

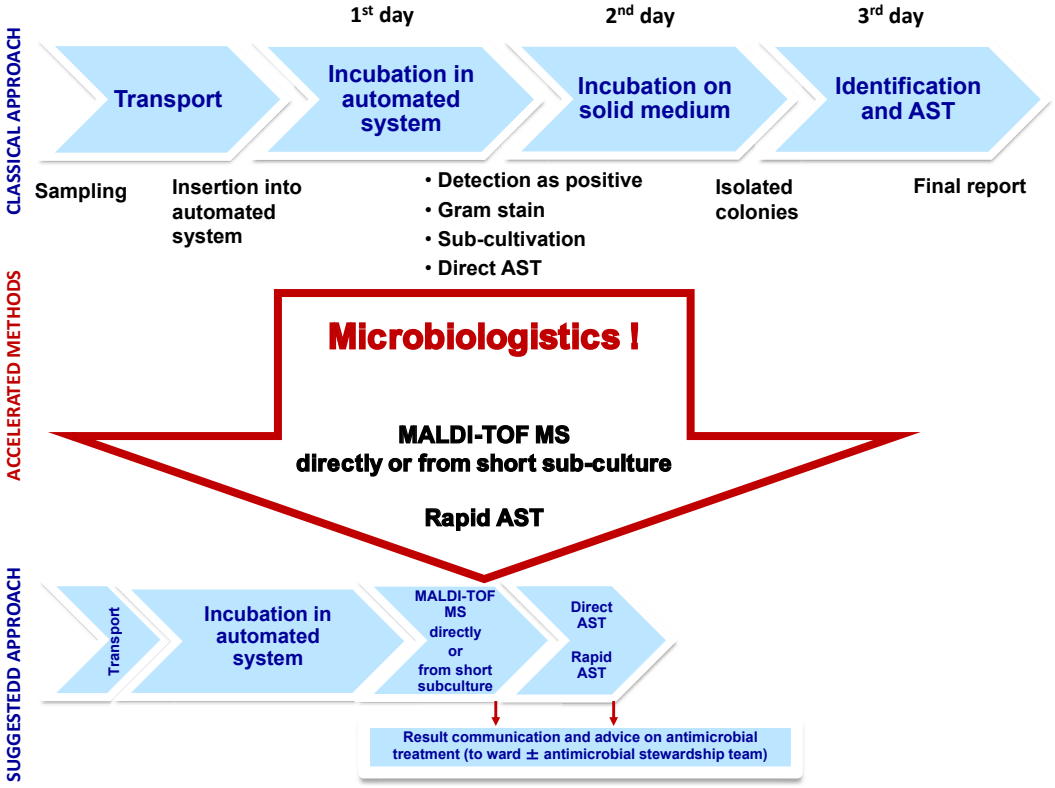

Fig. 2. Classical approach for the diagnostics of bloodstream infections and current possibilities of process acceleration. In the classical approach, blood culture (BC) bottles are inserted into the continuously monitoring automated BC incubators. In case of growth detection, Gram stain is prepared from the positive BC broth and the result of microscopy is immediately communicated to a clinician. At the same time, positive BC broth is sub-cultivated onto agar plates followed by overnight incubation to grow microbial colonies which are used for identification and antimicrobial susceptibility testing (AST). The novel approaches enable to drastically reduce time to result by reducing transportation time using microbiologistics (inside/outside the laboratory), by using rapid identification and rapid AST methods either from positive broth or after a short subculture. MALDI-TOF, matrix-assisted laser desorption/ionization time of flight.

within 1–4 hr [30–32]. Although giving a reliable result for the included pathogens, they all share the common drawbacks of being expensive, only process a few samples simultaneously and have limited panels of pathogens [30–32]. As the MALDI-TOF MS-based methods provide identification from positive BC in similar time for a larger range of microorganisms, with much lower cost for laboratories and can be very well combined with rapid AST [33–35], the advantages of the molecular systems for rapid species identification are not clearly recognizable.

Rapid AST from positive BC

Timely AST report is essential for the definitive choice of targeted antimicrobial treatment. The current possibilities for AST acceleration have recently been reviewed [36]. Practical, affordable and automated systems that would allow 'laboratory-friendly' high-throughput rapid testing from blood or from positive BCs are currently not available for routine diagnostics. Owing to the long testing times, AST is usually not finished in the same working shift [37,38]. Taking into account limited working hours of microbiology laboratories [13], the AST report will only be available on the next day in most settings [37]. Nevertheless, it is possible, and should be advocated, to start AST on the same day instead of application of overnight colonies. By doing so, result is usually available one day earlier. The same-day inoculation can be performed from positive BC by using a microbial pellet after centrifugation [28,34,35,39], by inoculation of sub-cultures from positive BCs shortly (a few hours) incubated on agar plates [40] or directly from positive BC [41,42]. With direct inoculation of bacterial pellets, accurate results were achieved for Gram-negative rods [34,35], but poorer accuracy was reported for Gram-positive cocci [35,39] and yeasts [28]. Inoculation of short sub-cultures from solid medium results in more accurate AST results [40,43,44], probably due to a better inoculum standardization [40], and can be combined with MALDI-TOF MS identification from the same short cultures in a practical process [33]. A procedure for direct application of positive BC broth onto agar plates [41] and the breakpoints for early result reading of this method [42] have recently been issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) after testing the concept in clinical laboratories across Europe [45,46]. The method seems promising but further evaluation is needed to assess workflow integration, including the visual reading of inhibition zones and the potential need for multiple plate examinations. MALDI-TOF MS-based universal phenotypic AST is one of the promising technologies in the development as it can efficiently be combined with MALDI-TOF MS identification [34]. Polymicrobial blood samples and species with slow growth represent a limitation for direct AST whatever method is used [36,47,48].

Some molecular systems for microbial identification from positive BCs and from whole blood have included selected resistance gene markers in their multiplex panels [30–32]. This information has been shown beneficial in case of *mecA* detection [49], but is in many areas of limited practical value. Importantly, for many resistance mechanisms negative result does not exclude phenotypic resistance due to other resistance mechanisms than those included in the test [33,36,50]. Thus, physicians often do not change antibiotic regimen in the light of only molecular results, with a loss of interest for such rapid diagnostics [51].

Table 2
Tools and strategies to control the quality of the pre-analytical phase of blood culture

Type of progress	Characteristics	Comments	References
1. Use KPIs to monitor and manage the preanalytical process	KPI defined by a threshold[a] to monitor and define continuous quality improvement initiatives. Pre-analytical KPI include: • Rate of bottles not reaching the recommended volume of blood (target). This KPI should be linked to items 2, 3, 4, 6 (see below) to reach optimal values and to be optimally monitored • Rate of solitary BC per 24 hr. This KPI can be improved with items 3 and 6 (see below) • Rate of BC with long time to bottle load • Rate of contamination. This KPI is to be linked to items 3, 5 and 6 (see below) to obtain optimal values	Should be regularly monitored Unsatisfactory results (i.e. not reaching minimal acceptable threshold) should trigger actions of improvement (e.g. training, reorganization, etc.) according to, e.g. Deming p-d-c-a cycle (plan, do, check, act) Participating to EQA programmes (item 4, see below) contributes to promote actions of improvements	[10,14–16]
2. CMBCS-incorporated automated systems to monitor the volume of blood	The Bactec FX system (BD, USA) estimates by measuring the CO_2 produced by red blood cells from at least 25 bottles (batch, ward level)	Mean error of 0.2–0.3 mL Device accuracy affected by low haematocrit (higher error margin, i.e. 1 mL) Volume monitoring limited to batch (no report possible on the reporting of result)	[14,15,17,79]
	The BC system Virtuo (bioMerieux) estimates using a photometric detection of liquid level for each bottle	Median error (range) of 1.40 (0.82–1.88) and 0.21 (−0.46–0.88) mL compared to the median weight-based volume in aerobic and anaerobic bottles, respectively	[18]
3. Education	To improve order quality (prescribers)	Order improved when written procedure describing how many BC sets to order is available Regular feedback to wards that poorly comply order procedure Communicate on the consequence of not complying the number of bottles to culture (default of sensitivity)	
	To improve sample quality (samplers)	Training proved efficient to improve the rate of bottle filled with >5 mL of blood Improvements may be only moderate despite intervention and time-consuming when performed alone but good improvements when combined with regular feedbacks that are facilitated by CMBCS-incorporated automated systems Needs to improve performance in training methods	[14,15,80]
4. EQA programme in Europe	Joint initiatives from CTCB and ESGBIES concerning EQA to assess the volume of blood cultured (rate of bottles not reaching minimum volume of blood KPI and rate of solitary BC per 24 hr), in progress[b]	Assesses the current level of quality at a population level (laboratories) Estimates gap to the targeted values according to state-of-art methods Helps promoting actions of improvement as it shows when a lab performance requires improvement (low rank and far from target) Helps monitoring actions of improvement	[81]
5. Diversion technique	Diversion tube or device diverts the initial first millilitre of blood to remove any potentially contaminated skin plug	Unambiguously reduces contamination rates Range of rate reduction varies between studies (contamination from 1.5- to 8-fold less)	[21,22,82]
6. Single sampling strategy	Alternative sample strategy	Reduces the rate of solitary BC, thus improves the total volume of blood cultured and sensitivity Reduce the contamination rate	[11,83,84]

BC, blood culture; CMBCS, continuous monitoring blood culture system; CTCB, Centre Toulousain pour le Contrôle en Biologie; ESGBIES, ESCMID Study group for bloodstream infection, endocarditis and sepsis; EQA, external quality assessment; KPI, key performance indicator.

[a] Strengthened benchmarks are currently under development. Laboratories can use a reasonable optimal benchmark defined with (for instance) 80% of series or bottles complying with the targets presented in Table 1 (e.g. 80% of bottles filled with 8–10 mL).

[b] An EQA focusing on the actual total volume of blood cultured per episode, compliance with bottle filling and compliance with number of bottles ordered, implemented through an ESGBIES/CTCB collaboration and opened to any laboratory, is at the probationary step at time of article revision (first evaluation performed in 2019, second planned in 2020).

DNA-based identification from whole blood

As cultural diagnostics inevitably requires time for incubation of blood specimens, molecular systems have been suggested for direct detection and identification of pathogens from whole blood [52,53]. A number of studies have evaluated these systems regarding diagnostic accuracy [54], and some studies have investigated their clinical utility in retrospective [55,56] or prospective but not randomized [57,58] designs. Two randomized controlled trials [59,60] showed a more rapid communication of species identification to the clinicians [60] and earlier targeted antimicrobial therapy [59] when multiplex PCR was used. There was no significant effect on mortality [59,60]. In general, molecular diagnostics currently cannot replace BC [9,11,61] (Fig. 3). Furthermore, the clinical utility of direct PCR from whole blood can only be fully exploited if specimen is processed directly after sampling. As with all rapid methods, the molecular approaches need a 24/7 laboratory with skilled staff to maximize the positive effects [62], something which is not established in most of European microbiology laboratories [13] but has been implemented in more laboratories in the USA.

Microbiologistics: simple ways of speeding up BC processing

The implementation of MALDI-TOF MS and molecular approaches for species identification and rapid AST can lead to substantial decrease in the TTR. However, it is important that the introduction of these novel rapid methods also are accompanied by effective logistics in the pre- and post-analytic steps so that the total time from the patient with suspicion of BSI enters the hospital

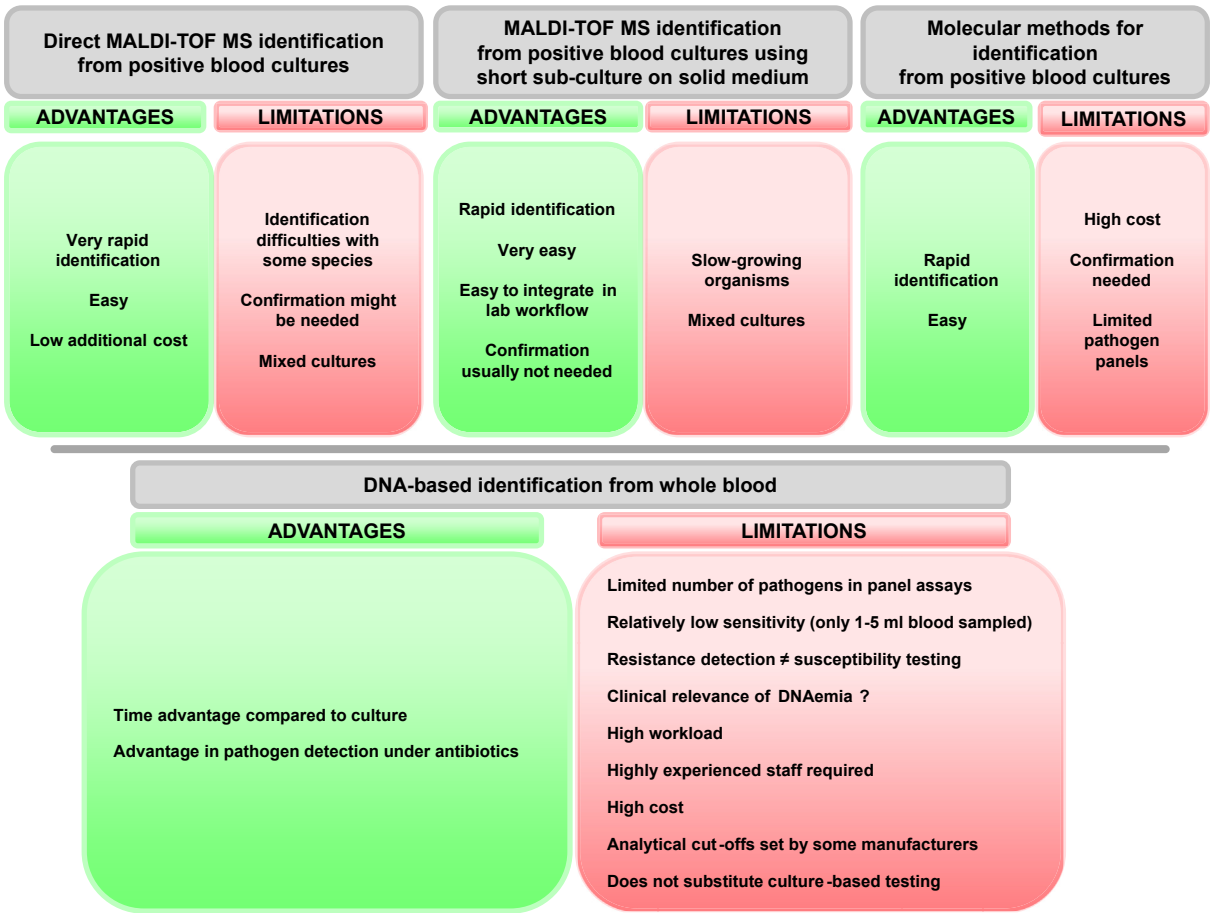

Fig. 3. Advantages and limitations of direct matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) identification from positive blood cultures, MALDI-TOF MS identification from positive blood cultures using short sub-culture on solid medium, and DNA-based identification from whole blood.

to a report is reduced (Fig. 2). For this process, we think that the term "microbiologistics" can be introduced as it in a witty manner includes all aspects of logistics in microbiology. The total time to report and the quality of BC can be improved by shortening the time to start the incubation of BC vials [63–65]. These include four main types of actions, all complementary. First, a microbiology laboratory open 24/7 will ideally lead to a reduced time to the introduction of BC vials, processing of positive samples and also a rapid report to the clinician [65]. The 24/7 approach also needs to be supplemented with optimal pre-analytic transport chains of the samples [65] as shown in Table 3. Second, a cost-effective step is the placement of the CMBCS outside the laboratory [63]. This step will in itself lead to more rapid Gram stain/species reports for most samples and will not lead to false negative results [63]. The efficiency of this approach depends on the transport time of the positively flagged bottles, and a timely transport to the microbiological laboratory to ensure the effectivity of this approach is paramount (Table 3). Optimal transport of bottles either before or after incubation is compelling and it relies on a continuous transport system. The use of automated system (e.g., pneumatic tubes) that is independent from rounds at set times is preferred. Finally, early introduction will lead to a more rapid process [66] and will lead to a higher recovery of pathogens [64,67].

After optimal transport and analysis it is important that the result is communicated rapidly [68]. The report should be electronic and contain a very clear guidance regarding the importance of the pathogen and AST result [69] or even better, additionally be communicated with an antibiotic stewardship team [31,70] to reach full clinical value of the BC result.

Critical appraisal of progress

Despite many technical developments, BC is still the foundation in BSI pathogen diagnostics. We have here shown many possibilities to reduce the TTR and outlined the possible new standards to reach for BC diagnostics. Still, too many microbiologists claim that rapid diagnostic is not useful, because studies demonstrating impact of rapid methods on mortality are rare [71–74]. However, in the last years at least two meta-analyses have shown both cost-effectiveness and therapeutic improvements when rapid methods are in place [6,75]. The still disappointing impact on mortality is partly due to the fact that we are still too slow before/after producing results, as virtually all studies had been conducted without optimizing time to bottle load, and importantly mortality was reduced only when rapid methods were accompanied with antimicrobial stewardship [75]. Progress in BSI pathogens diagnostics should thus be based on a bundle approach that includes optimization of the pre-analytical parameters (skin preparation, volume of blood sampled), rapid start of incubation, rapid processing of positive flagged bottles the use of rapid methods, re-organization (e.g. 24/7, transportation service) and a close involvement of antimicrobial stewardship teams (Fig. 1). We are now facing organizational issues hindering the advantages of novel technologies by the current working patterns of most laboratories. Although the

Table 3
The impact of different aspects of 'microbiologistics' and the introduction of new techniques for rapid species identification and rapid AST on the time from sampling to first report

	Theoretical scenarios		Örebro county, Sweden 2018		
	Hospital 1	Hospital 2	University hospital emergency room	Regional hospital A	Regional hospital B
Introduction of BC vials	Daytime7 days per week	24/7	24/7	24/7	Sent to central lab 1–3 times per day
Processing of BC vials	Daytime7 days per week	24/7	Daytime7 days per week	Positive BCs are sent to central lab	Performed at central lab
Species identification	Overnight solid agar incubation	Direct MALDI	Direct MALDI	Performed at central lab	Performed at central lab
AST method	AST from subculture	Direct AST with early reading	Direct AST and early reading for Gram-negative bacteria daytime	Performed at central lab	Performed at central lab
Sampling to introduction (hr)	1–15	1–2	2 (1–3)	3 (2–4)	14 (12–14)
Sampling to positive BC[a] (hr)	13–27	13–15	na[b]		
Sampling to Gram stain report (hr)	14–28	14–17	na[b]		
Sampling to species identification (hr)	30–44	14–17	38 (29–44)	40 (35–50)	49 (36–63)
Sampling to first AST report (hr)	46–60	20–23	na[b]		

In the theoretical scenarios (left) Hospital 1 has not adopted any modern technology while Hospital 2 has adopted many steps to reach a much more rapid process. In the in practice part (right), monthly median values (in brackets the range of median values during one year) for the BC process in Örebro County, Sweden, has been calculated and illustrates that the impact of introduction 24/7 results in a 9–11 hr reduction for time to first results. At the University hospital BCs can be sent through pneumatic tube system to the laboratory for introduction 24/7. At regional hospital A, BCs are brought to the local laboratory and introduced 24/7. Positive cultures are sent to the clinical microbiology laboratory at the University Hospital (45 km) 1–3 times per day at fixed hours. In contrast, at regional hospital B, BCs are brought to the local laboratory and stored in room temperature before being sent to the clinical microbiology laboratory at the University Hospital (45 km) 1–3 times per day, at fixed hours, to start incubation. Importantly, the effect of introduction of BCs 24/7 at regional Hospital A will lead to a much faster median processing time compared to regional hospital B despite the transportation of positive BCs to a central lab. AST, antimicrobial susceptibility testing; BC, blood culture; MALDI, matrix-assisted laser desorption/ionization.

[a] The time to positivity was set to 12 hr in both examples.

[b] na, not analysed due to lack of confident data stored in the Laboratory Information System.

importance of logistics for the impact of CMBCSs was shown almost two decades ago [62,76] still only 42% of European laboratories insert BC bottles 24 h/day and only 13% start the processing of positive BC bottles around the clock, and less than 5% established 24-h service for validation and transmission of the identification and AST results for BC pathogens to clinicians [13].

Substantial improvements in diagnostics can be made without investment in sophisticated and expensive instruments through improving the 'microbiologistics'. Workflow modifications, namely externalizing the BC cabinets and/or by introducing BC diagnostics 24/7, will improve the TTR independent of techniques used in the laboratory [13,62]. It should finally be realized that clinical microbiologists are needed for the patient 24/7 and not only in the daytime from Monday to Friday.

Continuous improvement of the whole BSI diagnostic process, based on sampling quality and time to result, should be a priority to improve patient outcome and avoid unnecessary antibiotic treatment. This should be a pivotal guiding line of the European health policies.

Transparency declaration

B.L. reports grant from BD and non-financial support from Curetis. M.S. reports ongoing research collaborations with Q-linea and 1928D. E.A.I. is a co-inventor of patent applications in the field of diagnostic microbiology, owned by the University of Münster and licensed to Bruker Daltonik. E.A.I. received a speaker honorarium and reimbursement for congress travel cost from Bruker Daltonik. No external funding was received for this publication.

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