Infectious diseases

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20.1 Introduction

The measurement and monitoring of biochemical parameters such as blood glucose, blood gases, electrolytes and cardiac markers have particularly benefited from recent advances in POCT. More and more, this form of analysis is now positively impacting the field of infectious diseases as well. This trend has been driven, on the one hand, by methodical improvements that make it possible to miniaturize and simplify test systems (▶ Chapter 9, 10) and by the constant demand from many physicians for immediate test results, on the other. Meanwhile, the range of microbiological parameters available at the POC has been extended considerably (◘ Table 20.1). A POCT result, however, should always be regarded and interpreted in the context of the clinical symptoms and the current epidemiological situation. Proper handling of POCT systems and strict consideration of pre-analytical limitations are decisive in obtaining reliable test results.

Many microbiological POCT systems tend to be designed as rapid tests. In general, such tests can be carried out in a few simple steps by medical assistants or physicians without laboratory equipment or laboratory experience. An evaluable test result is delivered at the patient's bedside within not more than one hour. Under certain circumstances, patients can even carry out the test themselves, for example, as with some rapid HIV or malaria tests. Rapid microbiological tests usually verify microbial antigens. Less often, diagnostics is based on the detection of antibodies, e.g. in the rapid HIV test or rapid detection of heterophilic antibodies for diagnosing infectious mononucleosis (◘ Table 20.1).

Respiratory tract secretions are often used to detect microbial antigens in patients with respiratory tract infections (influenza virus, respiratory syncytial virus, Streptococcus pyogenes). Similarly, stool specimens of patients with gastrointestinal tract infections (Helicobacter pylori, Shiga toxin-producing E. coli, adenovirus, rotavirus) are examined. However, the corresponding urine tests are also available to detect antigens in legionella and pneumococcal infections [14, 19, 27, 40]. Blood samples

◘ **Table 20.1** Rapid microbiological-virological tests in POCT format (as per 2016)

Type of infection	Virology	Microbiology
Sexually transmitted infections	HBV, HCV, HIV, HPV	GBS [21], CT [29, 35, 37, 49, 50], NG, MG, TV
Respiratory infections	Influenza A/B [7, 23, 31, 39], RSV	GAS [36], Legionella [14], Pneumococci [19, 27, 40], MTB/RIF
Gastrointestinal infections	Norovirus, Rotavirus [6, 8, 30, 48], Enterovirus	CDI [33, 45, 46], EHEC [25, 28, 44]
Nosocomial infections	Norovirus, Rotavirus [6, 8, 30, 48]	CDI [33, 45, 46], MRSA, VRE, CARBA-R
Tropical medicine and veterinary virology	Dengue Virus [2], avian Influenza [4], Yellow Fever Virus [12], MERS Corona Virus [3], Foot-and-Mouth Virus [1], Ebola Virus [16]	Malaria [11, 18, 22, 34, 38]
Antibody detection	HIV [9], EBV [10, 15, 20, 42]	

CARBA-R carbapenem-resistant Enterobacteriaceae; *CDI* Clostridium difficile; *CT* Chlamydia trachomatis; *EBV* Epstein-Barr Virus; *EHEC* enterohemorrhagic E. coli; *GAS* group A Streptococci; *GBS* group B Streptococci; *MRSA* methicillin-resistant Staphylococcus aureus; *MG* Mycoplasma genitalium; *MTB/RIF* Mycobacterium tuberculosis/rifampicin-resistance; *NG* Neisseria gonorrhoeae; *RSV* Respiratory Syncytial Virus; *TV* Trichomonas vaginalis

are usually used to detect antibodies (HIV, infectious mononucleosis), in particular cases, saliva samples are also used, as with some rapid HIV self-tests [9, 10, 15, 20, 42].

20.2 POCT-guided therapy

From the perspective of an infectious disease specialist, POC testing is always indicated in the case of life-threatening infections that require immediate and targeted treatment.

This is where the time advantage associated with POCT over conventional diagnostics truly comes to bear: The total analysis time needed for rapid tests is usually only 15–30 minutes. Even under optimal conditions, analysis in a central laboratory cannot compete with this. Unless tests are carried out directly in the hospital's own lab, it often takes at least 1–2 hours to transport the specimens to the laboratory. Then, further time is needed for the actual analysis, including the necessary preparation (pipetting, incubation etc.), in addition to the time taken to report the results back to the requesting physician. Therefore, even for urgent requests, the total analysis time can be 1–2 days.

There are many well-documented cases in infectious disease medicine, and particularly in critical care medicine, where such time savings can confer a very beneficial effect on therapeutic outcomes. Kumar et al. [26] have shown that the survival rate of sepsis patients in intensive care correlated directly to early, clinically effective initial antibiotic treatment. A treatment delay of more than 2 hours can lower the survival rate to as much as <60 %.

Not only decisions about the treatment of life-threatening or highly acute infections such as sepsis, but also general decisions that need to be made within a short time frame are considerably facilitated by POCT. The immediate availability of rapid HIV test results, for example, is helpful for decision-making about prophylactic antiretroviral treatment during childbirth or for people with occupational exposure to HIV. Intrapartum detection of group B streptococci in women in labor or the detection of plasmodia spp., including self-testing by patients with suspected malaria infection, are similar situations where POCT proves its merits. Here, too, the presence of a pathogen can be detected immediately using an antigen test whereupon early, targeted antimicrobial therapy can lessen or even prevent infection. POCT is also useful for guiding treatment of viral infections. The effectiveness of zanamivir or oseltamivir in influenza treatment depends on them being given no later than 36–48 hours after the first symptoms develop [32]. This approach is similar with the respiratory syncytial virus (RSV). Studies have shown that treatment with ribavirin in RSV bronchopneumonia is only successful if initiated early enough [5].

20.3 Transmission prophylaxis through POCT

Besides playing a role as a decision-making aid for individual patients, POCT is also designed to prevent the spread of infection (transmission prophylaxis). Such targeted situations not only arise in hospitals where there is the risk of an undetected pathogen spreading from patient to patient. There are also constellations when a transmission risk is associated with outpatients. For example, it is well known that a high percentage of patients coming to an HIV or sexual health clinic will skip their follow-up appointment because they fear an unfavorable diagnosis [43]. Although this avoidance behavior is understandable, it is a problem insofar as test results usually confirm infection (HIV, gonorrhea or chlamydia infection). As such, this has far-reaching consequences for the patients themselves as well as for their sexual partner(s). Data from the USA spotlight the extent of this problem. In one study of an HIV clinic, more than a quarter of the 68,000 people seeking advice and undergoing a conventional HIV test did not attend their scheduled 2-week follow-up appointment to pick up the test result. This was different when the rapid HIV test was

performed. Only 2.3 % of the 33,000 people that had the rapid test left the clinic before receiving their test result [47].

20.4 Pre-analytical confounders and influencing factors

Generally, rapid microbiological tests – like all testing methods – are subject to a variety of pre-analytical (and analytical) confounders and influencing factors that can negatively impact the diagnostic conclusiveness of the findings. This problem can be clearly illustrated using a rapid influenza diagnostic test as an example [39]. The following have a significant impact:

- Choice of specimen and where taken (nasal wash is better than throat swab)
- Specimen-taking instruments (swabs with gel are generally less useful than those without)
- The patient's activities immediately before the test. For example, the amount of detectable virus is reduced if the patient has eaten, drunk or gargled.

Other influencing factors include the time of sample collection – preferably the first 2–3 days after disease onset as virus shedding then declines rapidly – and the age of the person – children shed influenza viruses at a higher rate than adults. Other rapid tests are also affected by similar confounders and influencing factors.

20.5 POC test handling

The fact that many rapid microbiological tests are supplied in apparently easy-to-use formats, e.g. in the form of strips, cassettes or cartridges with pre-packaged diagnostic reagents for single-use on disposable devices, should not deceive. The handling of such tests is not trivial at all. Rather, it can be problematical, especially when it comes to sample collection. Indeed, evaluation studies on rapid detection tests for streptococci have clearly shown that the quality and reliability of test results is essentially dependent on the training and experience of the person taking the throat swab or performing the rapid test. Moreover, some rapid streptococcal tests have relatively subjective reading endpoints, often making interpretation prone to errors [36].

In particular, an increased infection risk for the examiner is one of the disadvantages specifically afflicting infectious disease medicine. This is not completely avoidable as, during testing, the examiner is exposed to the patient's specimen (respiratory secretion, stool, urine, blood), which potentially contain pathogens.

20.6 Performance capability of POCT diagnostics

POCT methods have been continuously developed and improved over the past 10–15 years. The majority of tests nowadays use immunochromatography (▶ Chapter 9) with moderate to high sensitivity (70–90 %) and relatively high specificity (>95 %). In exceptional cases, like with rapid HIV tests, today's POCT methods can achieve results that are indeed as reliable as those of conventional diagnostics. Some POCT systems with potentially limited sensitivity to a suspected pathogen (e.g. influenza viruses, RSV, rotaviruses, noroviruses or adenoviruses) may be compromised by patterns of seasonal variations in the prevalence of that organism. This has a considerable impact on the clinical reliability of the test, as exemplified by the immunochromatographic rapid influenza diagnostic test (◘ Fig. 20.1). A low prevalence (2.5 % in the example given) is expected at the start of a seasonal flu outbreak. Despite high sensitivity (80 % in this example) and very high specificity (95 %), the negative predictive value (99 %) of the test is expected to be significantly higher than the positive predictive value (29 %). This is because the rapid test shows false-positive (49-fold) more often than true-positive (20-fold) results under these circumstances. Not until the prevalence rises to 10 %, which can certainly happen during a severe flu outbreak, does the positive predictive value increase

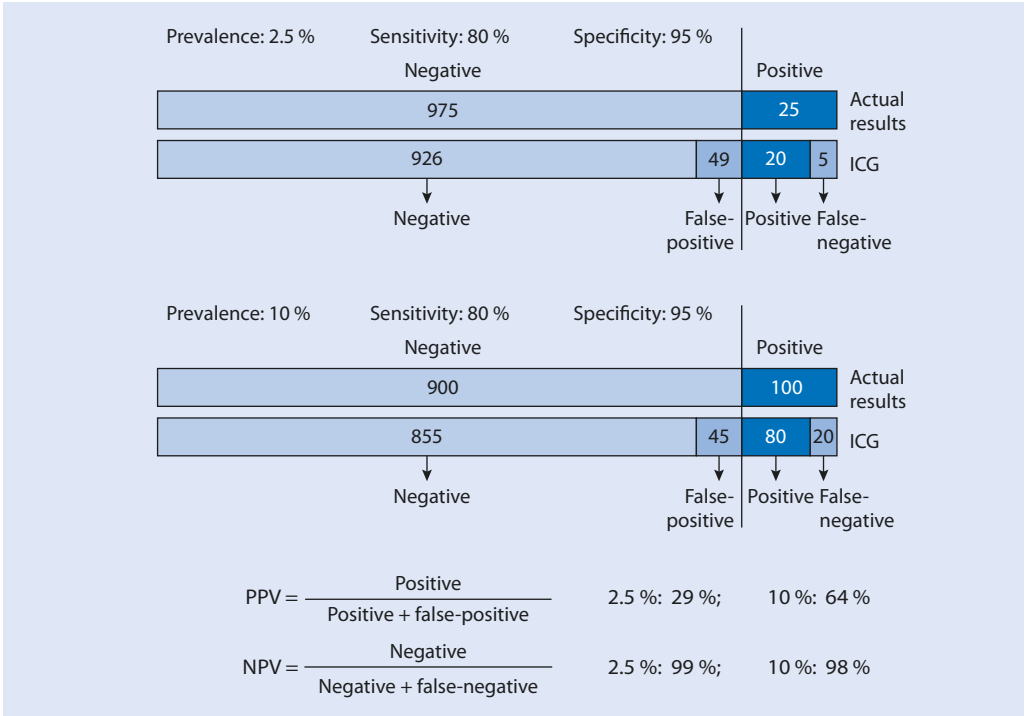

Fig. 20.1 Correlation between prevalence (2.5 % vs. 10 %), test sensitivity and specificity, negative predictive value (NPV) and positive predictive value (PPV) in a simulated rapid influenza diagnostic test based on immunochromatography (ICG)

(64 %). Of course, the biostatistical relationships shown here hold true for other infectious diseases that follow a seasonal pattern as well. In other words, the use of tests with limited sensitivity can yield more false results at the start of an outbreak when prevalence is still low. This, in turn, could certainly lead to an underappreciation of the extent of a disease [17] and must be taken into account when using POCT.

Conventional rapid tests are unable to detect any prevailing antibiotic resistances. Therefore, important information about therapeutic options may be lacking. Not only this, but epidemiological patterns regarding the development of resistant bacterial strains are no longer detected or else do not become apparent until later.

20.7 Molecular biological (PCR) tests

Immunological testing has certain limitations. Detection is difficult owing to the limited amount of microbial antigens released with particular regard to colonization of mucous membranes associated with low pathogen counts (e.g. group B streptococcus in the vagina) or intracellular pathogens (e.g. chlamydia in cervical smears). New testing concepts had to be developed in order to detect these pathogens. Given the degree of analytical sensitivity required, PCR methods and other nucleic acid amplification techniques (NAT) with greater sensitivity have been added to the diagnostic arsenal and further developed for faster and easier use.

The most important innovation in this context was the development of fully automated

PCR kits and ready-to-use, reagent-coated single-use cartridges where all PCR steps (sample exposure, amplification and detection) run in sequence without any further manual input. The market leader is the GeneXpert system, supplied by Cepheid (▶ Chapter 10). This fully automated PCR device is so easy to use that it is possible for trained staff to carry out the test near the patient, outside a laboratory setting. The American Food and Drug Administration (FDA) approved the GeneXpert as a rapid test according to CLIA criteria. At present, the technique is listed in the "moderate complex" category, reserved for accredited laboratories. The "CLIA-waived" classification, meaning without being subject to laboratory use, is still pending.

In addition to its primary function of pathogen detection, PCR can also be used for simultaneous analysis of resistance determinants or virulence factors. Linked assays incorporating multiplex technology allow more complex questions to be processed within one PCR run (e.g. detection of the following: S. aureus plus detection of methicillin resistance (mecA); two determinants (vanA and vanB) of vancomycin resistance in enterococci; clostridium difficile toxin B, also encompassing binary toxins and the tcdC deletion to detect highly virulent variants; mycobacterium tuberculosis also encompassing the rifampicin resistance (rpo) for detecting multi-drug resistant tuberculosis strains; simultaneous detection of influenza A, A/H1N1 and influenza B). The recently available i-system by Alere, which relies on isothermal amplification to detect the influenza A/B viruses and group A streptococci, (▶ Chapter 10) can boast significantly better sensitivity and specificity compared to the antigen detection method with the correspondingly more reliable results [7, 23, 31]. Besides its i-system, Alere also offers the q-Analyzer as a fully automated NAT platform.

Rapid molecular biological test methods on an **isothermal basis** are increasingly used for the diagnostics of tropical viral infections as well as in veterinary virology. Supplied in a portable case lab, they provide an advantage in areas with little infrastructure and can deliver reliable results [1, 2, 3, 4, 12, 13, 16]. An overview of the available assays for near-patient molecular biological test systems is shown in ◘ Tab. 20.2.

Progress in PCR and other NAT technologies has made near-patient testing accessible for a series of other pathogens and infectious diseases. Currently, the existing lack of clarity as to what molecular biological tests are medically and economically feasible for which patients is in need of further scientific evaluation.

20.8 Cost effectiveness and medical benefit

The disadvantage cited and the constant criticism raised in regards to most POCT methods pertain to the extra costs incurred by new systems [24]. Even assuming that near-patient diagnostics saves on laboratory tests and associated costs, POCT processes in general, and molecular assays in particular, are significantly more expensive than conventional (laboratory) tests. Moreover, POCT can create extra work for staff that were not previously involved in diagnostic tasks and possibly needs to be considered in job planning [24]. The question inevitably arises, as to how far near-patient microbiological analysis actually adds value to justify the added financial expenditure. Comprehensive reviews of this topic are rare and, if available, do not give the full picture either. The main difficulty is that the issues relating to the weighing of cost-effectiveness against the medical benefit of near-patient testing are multifactorial and complex, with all aspects above and beyond this being closely interlinked. It is therefore not possible to find a global solution. In fact, a well-justified estimation depends much more on the circumstances of the individual case. In addition, international study data cannot simply be applied to the situation in Germany because hospitals charge health insurance companies, using the German (diagnosis-related group) DRG system.

However, it is to be expected that POCT systems will soon play an increasing role in gen-

Tab. 20.2 Analytical spectrum of molecular biological near-patient diagnostics (as per 2016)

System	Multiplexity	Virology	Microbiology	Human genetics/ oncology
Alere i-System	Single test	FLU A/B	GAS	
bioMérieux FilmArray	Multiplex assay	Gastrointestinal panel: 22 commonly occurring gastrointestinal pathogens (viruses, bacteria, protozoans) Respiratory panel: 20 respiratory viruses and bacteria		
Roche Cobas LIAT	Single test	FLU A/B	GAS	
	Multiplex assay	FLU A/B + RSV		
Atlas io	Single test	NORO	CT, NG, TV, MG, CDI, MRSA	
	Multiplex assay		CT + NG + TV + MG	
Spartan RX	Microarray			CYP 2C20
Cepheid GeneXpert	Single test	HIV [a], HBV, HCV, HPV, FLU A/B, EBO, EV, NORO	GBS, CT, NG, TV, MTB/RIF, CDI, MRSA, VRE, CARBA-R	BCR-ABL
	Multiplex assay	FLU A/B + RSV		Factor II + V mutation

BCR-ABL transcription product BCR-ABL; *CARBA-R* carbapenem-resistant Enterobacteriaceae; *CDI* Clostridium difficile; *CT* Chlamydia trachomatis; *FLU A/B* Influenza A/B; *EBO* Ebola Virus; *EV* Enterovirus; GAS group A Streptococci; *GBS* group B Streptococci; *MRSA* methicillin-resistant Staphylococcus aureus; *MG* Mycoplasma genitalium; *MTB/RIF* Mycobacterium tuberculosis/ rifampicin resistance; *NG* Neisseria gonorrhoeae; *NORO* Norovirus; *RSV* Respiratory Syncytial Virus; *TV* Trichomonas vaginalis
[a] also quantitative, as viral load test.

eral medical care in the future as the density of physician coverage is projected to decrease. This will lead to a significant deterioration in patient care, particularly in the lowlands and rural areas if not counteracted. New ways must be found to maintain high quality care in non-metropolitan areas. POCT-based laboratory diagnostics will then gain in relevance.

20.9 Molecular MRSA screening

A closer look at molecular MRSA screening illustrates the conflict between cost-effectiveness on the one hand and medical benefits on the other [41]. With modern PCR tests, nasal MRSA colonization can be detected faster and more reliably than with many routine culture methods. It is indisputable that the sooner appropriate hygienic measures are put in place after a positive MRSA status identification, the lower is the risk that the infection will spread to other patients [41].

In terms of the cost of an MRSA culture (approx. € 3–5; approx. € 10–15 for a positive result) versus PCR (single-test cartridge approx. € 30–40), PCR is at least 2–3 times more expensive than the culture method. However, this additional cost for PCR testing may be justified when considering that every MRSA transmission prevented by early detection can save a hospital several thousand euros in added costs. Therefore, the cost-benefit ratio shifts in favor of PCR. Even when each case is balanced against a successful coding in the DRG flat rate payment system, the added costs incurred by MRSA transmission are only partially compensated. Furthermore, every new, preventable

case of MRSA has the potential to impact negatively on public image and may result in lost revenue due to canceled admissions, which most hospitals should be eager to avoid [41].

Since the screening of all patients in a hospital is not financially viable, the cost-benefit consideration ultimately focuses on which patient group should be targeted using PCR analysis in order to establish the MRSA status more quickly and, then, which of them should be screened with a traditional culture method. A definitive answer (e.g. from larger meta-analyses) is not yet available. Nevertheless, the current data suggest that the benefit of molecular MRSA screening will only outweigh the costs for patients with a particularly high MRSA risk, e.g. in areas with a high MRSA prevalence [41]. At present, German hospitals remain hesitant. As long as there are no generally applicable recommendations issued (e.g. from the Robert-Koch-Institute, Berlin) on the use of molecular biological tests, the high costs and organizational constraints of MRSA-PCR – similar to a lack of effective hygiene management structures – will prevent screening from being carried out at all or, when, only to answer specific questions, mostly for quickly managing bed capacities.

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