Point-of-Care Testing in Children With Respiratory Tract Infections and Its Impact on Management and Patient Flow

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Infectious diseases are the most frequent cause for medical consultations in children, contributing to morbidity and mortality worldwide. However, securing an accurate infectious disease diagnosis is a major challenge with immediate impact on the quality of patient care. This is particularly the case for respiratory tract infections, which can be of viral and/or bacterial origin, often clinically indistinguishable from each other. Clinicians tend to over-diagnose bacterial infections, resulting in unnecessary “just-in-case” prescriptions of antibiotics,1 which is not only an established driver of antimicrobial resistance, but can also have negative effects on an individual level as well. Furthermore, a diagnosis solely on clinical grounds is often hampered by the nonspecificity of clinical symptoms, highlighting the need for accurate, objective diagnostic tools. Since the majority of children are seen in ambulatory care, point-of-care testing (POCT), that is, tests with an actionable turn-around time that can be run within an emergency department (ED) or a pediatrician’s office without the need for a laboratory or dedicated staff, is of particular importance.

In general, there are 2 different angles on infectious diseases diagnostics. While measuring host-response biomarkers can give a first impression on whether an infection is present and if it is more likely to be of bacterial or of viral etiology, microbiological testing enables the identification of a defined pathogen. However, both have their pertinent limitations. Many host-response biomarkers can be induced by noninfectious states, for example, trauma, tumors, autoimmune diseases, or surgery, hence, reducing specificity. Pathogen testing, in turn, suffers from other constraints, such as long turn-around times (laboratory-based tests), low sensitivity (antigen-based POCT), or the inaccessibility of the infected site, for example, in lower respiratory tract infection. In addition, not every detected microorganism is necessarily a causative pathogen, since some bacteria can be part of the “normal” microbiome and viral shedding can occur as a result of past infection (eg, adenovirus).

In the following, we discuss existing and novel tools for POCT with the potential to accelerate patient flow, facilitate appropriate management, and ultimately improve patient outcomes.

PATHOGEN DETECTION: HOW MANY BIRDS WITH HOW MANY STONES?

Here, we focus on pathogen-specific POCTs detecting influenza virus, respiratory syncytial virus, severe acute respiratory syndrome coronavirus 2, and Group A streptococci (GAS).

Rapid Antigen Detection Tests (RADTs), which are mostly lateral flow assays, are frequently used in ED settings to quickly identify single pathogens. Their power lies in simple handling, little material being required, and short turn-around times. However, performance characteristics vary greatly between different target pathogens and test manufacturers. A large systematic review yielded an impact of influenza POCT on increased antiviral prescribing and a reduction in subsequent blood test and chest radiographies. However, no effect could be demonstrated on hospital admission, antibiotic prescribing, or time spent in the ED.2

Nevertheless, a positive rapid test result for influenza or respiratory syncytial virus was associated with reduced antibiotic prescriptions in a different study regarding...
febrile children with respiratory symptoms (adjusted odds ratio, 0.6; 95% confidence interval [CI], 0.5–0.8).4

Data on severe acute respiratory syndrome coronavirus 2 POCT in children are mainly limited to diagnostic accuracy. A recent systematic review reported a sensitivity of 64.2% (95% CI, 57.4%–70.5%) and a high specificity of 99.1% (95% CI, 98.2%–99.5%), despite large inter-study and inter-test variability.4 Of note, sensitivity was higher in symptomatic compared with asymptomatic children (71.8% vs. 56.2%).

An alternative way to detect pathogens at the point of care are nucleic acid amplification tests (NAATs) (also called molecular POCT) that can be operated in a similarly rapid way. Dubois et al5 systematically reviewed NAATs for GAS, showing that overall, they provide higher sensitivities compared with RADTs (96.8% vs. 82.3%). Of note, most of the included studies reported to conduct NAATs in laboratory settings, thereby not meeting the criteria for POCT. Furthermore, the higher costs of NAATs make them less suitable for resource-limited settings. Rao et al6 reported in a single-center study that NAAT led to a higher rate of appropriate antibiotic use (97.1% vs. 87.5%) than RADT in children with GAS.

In the past years, several companies have developed and introduced multiplex polymerase chain reaction (PCR) assays into the market. These are designed to detect around 20 different pathogens, mostly viruses, and to a lesser extent, bacteria and fungi.7 With a turn-around time of under an hour, the assays are more appealing than conventional laboratory-based methods.

Compared with standard of care, their use was associated with a shorter duration of intravenous antibiotic treatment in a single-center study performed in children with signs of a respiratory tract infection.8 A subgroup analysis of children with comorbidities that were tested with a multiplex PCR assay showed a reduction in antibiotic treatment duration and hospitalization costs.9 Limitations of this technology are its higher costs, varying sensitivity for particular target pathogens (eg, herpes simplex virus), the sometimes difficult-to-interpret result constellations with co-detections, and the difficulties of switching to a different manufacturer once one specific platform has been implemented. Table 1 provides an overview on study results regarding the impact of different POCTs on clinical outcomes.

### TABLE 1. Summary of Studies Investigating the Clinical Impact of Point-of-Care Tests in Pediatric Cohorts

<table>
<thead>
<tr>
<th>Target</th>
<th>Test Type</th>
<th>Impact on Antibiotic Use</th>
<th>Impact on LOS</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAS</td>
<td>POC NAAT</td>
<td>+ Adequate prescription of antibiotics in 97.1% (vs. 87.5% RADT plus culture)6</td>
<td>–</td>
<td>No impact on follow-up visits6</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>POCT</td>
<td>+ More antivirals prescribed**</td>
<td>–</td>
<td>No impact on ED LOS**</td>
</tr>
<tr>
<td>RSV + influenza virus</td>
<td>POCT</td>
<td>+ Positive test result led to reduced antibiotic prescriptions (OR, 0.7; 95% CI, 0.6–0.9)</td>
<td>–</td>
<td>No impact on returning for further care**</td>
</tr>
<tr>
<td>Respiratory pathogens</td>
<td>Multiplex PCR panel</td>
<td>+ Higher rate of appropriate antibiotic therapy compared with antigen tests (83.6% vs. 87.9%)3</td>
<td>+</td>
<td>Positive test result associated with slightly shorter appointment duration (48.0 vs. 54.9 min)7</td>
</tr>
<tr>
<td>Host-response Biomarkers</td>
<td>CRP</td>
<td>+ Reduction of antibiotic treatment by 11.6% (631/1685 vs. 785/1599)**</td>
<td>+</td>
<td>Reduction of ED consultation time by an average of 120 min (60, IQR 33–125 vs. 180, IQR 158–208)9</td>
</tr>
<tr>
<td></td>
<td>PCT</td>
<td>– No reduction of antibiotic prescribing (risk difference, −3%; 95% CI, −14% to 8%)10</td>
<td>–</td>
<td>Increase in hospitalizations**</td>
</tr>
</tbody>
</table>

*Study population includes adults.

IQR indicates interquartile range; LOS, length of stay; OR, odds ratio; POC NAAT, point-of-care nucleic acid amplification test; RCTs, randomized controlled trials; RR, relative risk; RSV, respiratory syncytial virus.
in a high potential to cut down on antibiot-
ic overuse. A different test combines in a
semi-quantitative assay CRP and Myxovirus
resistance protein A, a virally-induced pro-
tein similar to TRAIL, in finger prick blood
samples, making it feasible especially in less
well-equipped settings.14

Transcriptomics have been another
exciting technology, which offers the oppor-
tunity to measure different gene transcripts at
once. Recent efforts demonstrated suitability
of this technology to be implemented into a
POCT platform. However, their utility and
cost-effectiveness on a larger scale still need
to be demonstrated.

COMBINED PATHOGEN AND
HOST TESTING: THE BEST OF
BOTH WORLDS

Although both approaches have been
investigated on their own, the combination
of both has been studied only rarely. A more
comprehensive approach to unbiased patho-
gen detection is metagenomic next genera-
tion sequencing. It enables a hypothesis-free
testing for nearly any organism’s DNA or
RNA and, depending on the technology used,
offers coverage of host genes as well.15 This
approach could also help to unravel cases in
which carriage microorganisms are found by
simultaneously probing the host response.
Nevertheless, applicability in the real-world
clinical setting has not been studied suf-
ficiently, and the question of causality of
detected sequences remains.

Fueled by the coronavirus disease
2019 pandemic, the market for POCT has
rapidly expanded during the last 2 years.
Other high-end technologies not described in
detail here can be expected to be more readily
available in the future for POCT, for example,
clustered regularly interspersed short palin-
dromic repeats-based diagnostics.

Notably, the implementation success
of a test or a test bundle is highly dependent
on simultaneous educational efforts address-
ing the practitioners who are expected to
order and ultimately interpret test results,
including, for example, the use of algorithms.
Other potential barriers may be inherent to
the very setting itself on both, micro and
macro levels, including technical feasibility
or reimbursement policies.

There are other factors that may influ-
ence how testing approaches may change
over time, such as seasonality and, related to
this, prevalence. In settings and times of
high prevalence of a given infectious disease,
RADTs may offer a very reasonable and cost-
effective approach to POCT. In contrast, mul-
tiple PCR arrays may be reserved for more
difficult-to-diagnose, hospitalized cases.
An ideal biomarker in turn should assist in
informing whether an antibiotic is necessary
in the first place, whereas using specific bio-
marker cutoffs to guide antibiotic treatment
duration is another potential use, albeit less
important for ED settings.

Ultimately, diagnostic equity should be
aimed for by stakeholders, since access to
modern diagnostics with real impact on
clinical outcomes is also a matter of justice
and should not be contingent on a patient’s or
their family’s income, or societal, religious,
ethnic, or geographic background.

In conclusion, POCT can be inte-
grated into routine diagnostics in pediatric
EDs, where rapid clinical decisions must be
undertaken. However, performing diagnostic
procedures that ultimately do not influence
clinical decision-making should be avoided.
Besides their impact in terms of diagnostic
accuracy, both pathogen tests and biomark-
ers have the potential to positively affect
outcomes such as length of stay or antibiotic
treatment, thereby contributing to antimi-
crobial stewardship efforts. There remains a
substantial need for further prospective, con-
trolled studies especially on host biomark-
ers and their impact on clinically relevant
outcomes in pediatric EDs in both high- and
low-resource settings.

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