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Syndromic Multiplex Polymerase Chain Reaction (mPCR) Testing and Antimicrobial Stewardship: Current Practice and Future Directions

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Abstract

Purpose of Review Syndromic multiplex polymerase chain reaction (mPCR) panels offer the antimicrobial steward a rapid tool for optimizing and de-escalating antimicrobials. In this review, we analyze the role of syndromic mPCR in respiratory, gastrointestinal, and central nervous system infections within the context of antimicrobial stewardship efforts.

Recent Findings For all mPCR syndromic panels, multiple studies analyzed the pre-and-post implementation impact of mPCR on antimicrobial utilization. Prospective studies and trials of respiratory mPCR stewardship interventions, including diagnostic algorithms, educational efforts, co-testing with procalcitonin, and targeted provider feedback currently exist. For gastrointestinal and cerebrospinal fluid mPCR, fewer peer-reviewed reports exist for the use of mPCR in antimicrobial stewardship. These studies demonstrated an inconsistent trend towards decreasing antibiotic use with mPCR. This is further limited by a lack of statistical significance, the absence of controlled, prospective trials, and issues with data generalizability.

Summary Antibiotic overuse may improve when mPCR is coupled with electronic medical record algorithm-based approaches and direct provider feedback by an antimicrobial stewardship professional. mPCR may prove a useful tool for antimicrobial stewardship but future studies are needed to define the best practice for its utilization.

Keywords Multiplex PCR · Syndromic panel · Antimicrobial stewardship · Molecular diagnostics

Introduction

Since the approval by the FDA of the first multiplex Polymerase Chain Reaction (mPCR) panel for the detection of respiratory pathogens, the BioFire Respiratory Pathogen Panel, the landscape of syndromic multiplex PCR panel testing continues to evolve [1, 2]. These tests, which subsequently expanded to include gastrointestinal (GI), bloodstream, and central nervous system (CNS) syndromic panels in addition to the respiratory panel, promise rapid turnaround times with high sensitivity and specificity when compared to more traditional methods such as culture [3]. Clinicians can gain rapid information regarding the nature of a patient's illness to guide clinical care, such as the timely initiation of targeted antimicrobials. Challenges remain in defining the best utilization of these syndromic panels in clinical care, and while many practice guidelines contain statements advising consideration of PCR-based diagnosis as part of the diagnostic workup, there are no recommendations provided on the best utilization of these panels [4, 5].

Additionally, global concern about the rise of antimicrobial resistance driven by antibiotic overprescribing continues to increase. Syndromic mPCR panels offer rapid information useful to target or remove antimicrobials in the clinical context

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of a patient. The Society for Healthcare Epidemiology of America (SHEA) recently released a white paper outlining research needs for antimicrobial stewardship. Among the many suggested high-value targets for stewardship, mPCR has obvious benefits to drive practice changes in the prescription of antibiotics via diagnostic stewardship. This review provides an overview of the antimicrobial stewardship intervention landscape for respiratory, GI, and CNS panels. It will examine the types of studies conducted, the methods taken for stewardship, and the results of those efforts in improving the appropriate use of antibiotics.

Respiratory Multiplex Pathogen Panels and Antimicrobial Stewardship

The introduction of the BioFire FilmArray Respiratory Pathogen panel in 2011 marked a new era of rapid diagnostic testing for respiratory viral and bacterial pathogens. Since then, several other panels have been approved, including the Verigene, Luminex x-TAG series, eSensor Respiratory Virus Panel (RVP), and ePlex systems. This review is not meant to be a comprehensive review of the technical details of respiratory mPCR panels, and more comprehensive technical reviews are available elsewhere [1, 6]. In general, the sensitivities and specificities of the panels vary by which test is used and what virus is tested. The BioFire Respiratory Pathogen panel has nearly 99–100% specificity for the viruses included, but the sensitivity for certain viruses ranges from 57-100% depending on the study examined and the virus in question. In one example, Popwich et al. found that the FilmArray Respiratory Pathogen panel was 57% sensitive for adenovirus, whereas Rand et al. found sensitivity of 90% [7, 8]. For the eSensor RVP, the reported sensitivities range from 92 to 100% with specificity of 100% [1, 7]. For the x-TAG series, sensitivity and specificity are reported by panel types x-TAG RVP, x-TAG RVP Fast, and Nx-TAG. Nx-TAG is the current version of rapid syndromic mPCR available from Luminex, and reported sensitivity is 93–100% for most viruses with the exception of coronavirus HKU1 and OC43, with reported sensitivities of 67% each. Additionally calculated specificity is >97% for all included viral pathogens in this study [9]. Examining the underlying data, low sample numbers may limit interpretation of these results for the Nx-TAG, with only 3 positives in the sample set for coronavirus HKU1 and OC43. Generally, mPCR for respiratory pathogens should be considered sensitive and specific for identifying respiratory pathogens.

One advantage syndromic mPCR panels offer over more traditional methods is in the turnaround time of the panel. Depending on the collection method and timing for sample processing, the turnaround time can be as low as 1.5 h, but can be longer if samples are run in a batched fashion [10–17]. This faster turnaround time translates into better antibiotic prescribing in some cases; in one example, a multiplex influenza/RSV assay changed the antimicrobials prescribed in 58% of patients in an emergency room setting, decreasing inappropriate antibiotic and antiviral prescriptions by 24.5% and 9%, respectively [12]. In the context of identifying influenza infections, multiple studies showed influenza virus-positive patients receive fewer antibiotics than influenza-negative patients [11–13]. More of these patients also receive oseltamivir or other antiviral medications, and mPCR reduces the time to delivery of antiviral medications [17]. The absence of influenza or the positive presence of another pathogen did not significantly change the rate of antibiotics prescribed, and there was no difference in the rates of antibiotics, 48.6% vs 49.3% in one study. Of the patients with a positive viral panel for influenza or other non-influenza viruses, 32% still received antibiotics [17]. In the ResPOC trial, one of the few randomized controlled trials pertaining to stewardship and mPCR panels, patients were randomized over two respiratory virus seasons to utilize the BioFire Respiratory Panel or an in-house PCR to determine the effect on antibiotic utilization. No significant differences were found in the number of patients who received antibiotics or the mean duration of antibiotics. Importantly, significantly fewer patients in the mPCR group than the control group received more than one dose of antibiotics [18]. Implementation of an mPCR respiratory panel alone appears not to have a replicable significant impact on antibiotic use or duration of antibiotics.

Adding an educational intervention to the stewardship process may reduce antimicrobial use. In a retrospective study by Keske et al., an educational intervention conducted during the implementation of a respiratory mPCR panel significantly increased the rate of discontinued antibiotics and overall decreased total antibiotic prescriptions [19]. In a randomized controlled trial by Branche et al., investigators educated providers on how to utilize an mPCR panel and procalcitonin (PCT) level algorithm for antibiotic de-escalation prior to the implementation of the study and were sent reminders of the algorithm on patient enrollment. While no difference was found in the duration of antibiotics overall, subsequent analysis found that algorithm adherent patients received significantly fewer days of antibiotics and fewer algorithm patients received antibiotics at discharge. The authors note that providers prescribed antibiotics for patients with high procalcitonin values more often than they withheld antibiotics for patients with low procalcitonin values [20]. In subsequent analysis, an admitting diagnosis of pneumonia was associated with overruling the algorithm in patients, with 7% of patients in the algorithm-adherent category carrying this diagnosis vs. 26% of patients in the non-adherent group [21]. Viewing these results, there may be ways to educate and promote adherence to directed therapy, such as encouraging more direct algorithm adherence, or providing education on viral pneumonias.

Adding a directed intervention by an external reviewer can improve antimicrobial stewardship using mPCR. In a prospective study by Lowe et al., an antimicrobial stewardship program (ASP) provider reviewed the patient's chart and the results of an mPCR panel to determine if a patient would benefit from an ASP consult to provide recommendations in an audit-and-feedback model. They achieved successful reduction of 1.3 days of antibiotics in the prospective ASP audit cohort, and if their recommendations were accepted, 3.6 fewer days of antibiotics [22]. Similarly, Abbas et al. at Virginia Commonwealth University Health System reported success with an ASP provider intensive measure. An ASP member contacted inpatient provider teams about patients with positive results from a respiratory mPCR panel and made recommendations to de-escalate, change, or discontinue antibiotics. The primary teams followed the recommendations of the ASP provider 66% of the time overall; however, when the recommendation was discontinuation or de-escalation, providers accepted 19% of the time [23]. More recently, the Cleveland Clinic Foundation Health system undertook a large, multisite trial of an ASP provider recommendation for patients with a positive mPCR panel. Of their interventions, primary teams followed only 47% (n=26) of the 55 recommendations. This did not translate into a significantly reduced duration of antibiotic therapy, and intervention of an ASP provider did not influence the de-escalation of any one antibiotic [24••]. These provider intensive interventions require the time of a trained professional to review charts and make recommendations to the primary medicine team, but a large percentage of recommendations are not accepted, which may be a limitation of this method and may not represent an appropriate utilization of stewardship resources.

In a possible demonstration of a rationale to overcome a stewardship provider intensive method, Moradi et al. combined several methods to reduce antibiotic use without the intervention of a trained provider. Patients in a pre-post quasi-experimental study with a PCT ≤0.25 ng/ml, a mPCR panel positive for 1 virus, and at least 1 systemic antibiotic automatically triggered an alert in the Electronic Medical Record (EMR) to display when any provider opened the chart. This "Best Practices Alert" (BPA) displayed for the provider the PCT value, mPCR results, and the active antibiotics. The provider was given options to suppress the alert temporarily or permanently, and the interactions by providers with this alert were tracked. Patients in the intervention group who triggered the alert had their average days of antibiotics reduced significantly by 2.2 days (5.8 vs 8.0). In the intervention group, more antibiotics were discontinued within 24 h of initiation, there were fewer days of antibiotic therapy, and fewer antibiotic prescriptions on discharge [25••]. Within the different strategies to improve antibiotic discontinuation, it appears that utilization of an EMR base practice alert, possibly in conjunction with procalcitonin, can improve the use of respiratory mPCR panels for stewardship.

Gastrointestinal Multiplex Pathogen Panels and Antimicrobial Stewardship

When compared to respiratory pathogen mPCR, fewer gastrointestinal (GI) mPCR stewardship investigations exist. Available panels include the BioFire FilmArray Gastrointestinal Panel, Luminex xTAG Gastrointestinal Pathogen Panel, and Verigene enteric pathogens panel. Like other mPCR panels, GI mPCR provides a faster turnaround time when compared to traditional methods such as stool culture and examination for ova and parasites [26, 27•, 28]. mPCR panels detect pathogens 10–36% more often than traditional methods depending on the panel used. Sensitivity for the BioFire FilmArray GI mPCR ranged from 94.5% for 7 of the 22 pathogens in the panel to 100% for 10 of 22 pathogens in one study. Specificity ranged from 93.4–100% depending on the target organism in the same study [29]. In the only direct comparison of the three enteric pathogen mPCR panels, the Verigene enteric pathogen mPCR panel reported sensitivity and specificity for Campylobacter of 83.3% and 99.3%, Salmonella 83.3% and 100%, Shigella 95.4% and 99.1%, Shiga-Toxin producing *Escherichia coli* 91.7% and 100%, norovirus 89.0% and 100%, and rotavirus of 71.4% and 100%. The Luminex panel analyzed in this study reported sensitivities of 91.7% for Campylobacter, 79.2% for Salmonella, 100% for Shigella, 91.7% for Shiga-Toxin producing *Escherichia coli*, 89.5% for norovirus, and 100% for rotavirus, with 100% specificity for all targets. The BioFire FilmArray mPCR was 94.7–100% sensitive for these targets, and 98.6–100% specific [30].

In a large retrospective analysis, patients whose diagnostic workup included mPCR received fewer antibiotics (36.2% vs 40.9%). Patients with PCR testing were also less likely to undergo additional endoscopy or imaging. There were important differences between the two groups in this study. The mPCR group was larger, older and more likely to be inpatient, limiting the interpretation of the true effect size of the mPCR intervention [31].

Similar to respiratory mPCR panels, using a stewardship intervention to educate clinicians on mPCR and appropriate antibiotic use appears to change prescribing habits. This approach helped Keske et al. reduce the inappropriate use of antibiotics from 42.9% to 25.8% in the post intervention period. This effect was maintained with a larger sample size in the post-intervention group while still allowing unrestricted access to the testing [32]. In the only prospective trial of GI mPCR, parallel cultures conducted in conjunction with the BioFire GI panel compared antimicrobial use in new inpatient and outpatients, both adults and children, to a historical

control group. The mPCR panel replaced conventional culture as the orderable test immediately prior to the study period. As the turnaround time of test results decreased, there was a significant trend towards targeted antibiotics being prescribed, and proportionally fewer patients had initiation of antimicrobial therapy empirically. There also appeared to be an increasing use of the test results to target antimicrobial therapy to the organism detected, as over a period of months from the implementation of the test, the increasing utilization of narrowly directed therapy was apparent [27•].

These studies suggest a role in the use of mPCR GI panels for stewardship of antimicrobials and resources, although diagnostic test stewardship is an important consideration. In a retrospective cohort of patients in a single hospital system, patients with an initial negative GI mPCR result were retested within 4 weeks of the initial negative result, and the vast majority remained negative, with no significant rate of conversion to positives [33]. In a subsequent follow up study from the same group, only 3.9% of tests for patients admitted >72 h were positive, ignoring viral shedding and suspected false positives [34]. Taken together, these results suggest that it is reasonable to test patients suspected to have infectious diarrhea with mPCR at least once; however, patients hospitalized for >72 h likely do not benefit from testing, and that repeat testing for patients with continued symptoms is unlikely to yield a different result.

Central Nervous System Multiplex Panels

Currently, the BioFire FilmArray Meningitis/Encephalitis (ME) panel is the only mPCR test approved by the U.S. Food and Drug Administration for cerebrospinal fluid analysis. It evaluates for 14 bacterial, viral, and fungal pathogens and can provide results within 1 h (https://www.biofiredx.com/products/the-filmarray-panels/filmarrayme/), which has been born out in clinical scenarios with several studies reporting a turnaround time of less than 2 h [35–37]. This provides inherent advantages over cultures, which can take days to result and can be insensitive while specific [38]. In addition, a recent systematic review and meta-analysis determined the overall sensitivity and specificity to be 90% (95% CI 86–93%) and 97% (95% CI 94–99%) [39]. Advantages in sensitivity, specificity, and turnaround time should allow for quick de-escalation of antimicrobials if results of the PCR are negative, something not noted in several retrospective pre-and-post implementation studies.

Dack et al. and Chang et al. both conducted retrospective observational studies of the effect of implementation of the BioFire Meningitis-Encephalitis Panel on antimicrobial usage. Both found negative mPCR panel patients had a median duration of 3 and 4 days of antimicrobial therapy, respectively, but did not prove a statistically significant decrease in antimicrobial use [36, 40]. The reasons given for possible continuation of antimicrobials include clinicians' concerns with mortality, or unfamiliarity with new technologies. In another pre-and-post implementation observational study, Radmard and colleagues learned that despite a rapid turn-around time of 1.5 h, the median time to narrowing or discontinuation of antimicrobial therapy was 26.5 h, with 25% of patients remaining on empiric therapy 24–48 h after negative panel results. Radmard et al. did not compare these results to the pre-mPCR time period and noted that because of the many factors associated with antimicrobial usage, they could not evaluate the mPCR ME panel for antimicrobial stewardship [37]. Mina et al. did find a significant difference in the duration antimicrobial usage, 9.5 ± 3.7 days in the mPCR group and 15.2 ± 5 days in the control group ($p = 0.007$). It is important to note the authors only conducted significance assessment on the presence of bacterial meningitis on the mPCR panel versus a control group that could have had non-bacterial meningitis, but did not have a mPCR panel collected [41].

A recent prospective observational trial in France studied the effect of mPCR diagnosis of meningitis/encephalitis on the management of patients with suspected CNS infections. The use of an mPCR panel led to an earlier discontinuation of empiric antimicrobials in 32% of the cases. The authors additionally observed a reduction in the length of stay for 18% of patients. A significant limitation to this study is the absence of reporting tests of statistical significance [42•]. Overall, a lack of more generalizable data limits a more nuanced review of CNS mPCR use in antimicrobial stewardship.

Although there is limited evidence that the CNS mPCR panel reduces antimicrobial use, several groups reported potential cost savings that can be achieved by using mPCR in the diagnosis of CNS infections. DiDodato et al. estimated cost savings based on a standardized cost of stay in Canadian hospitals for CNS infections. Using observational data from pre-and-post introduction of the mPCR ME panel at a community-based university affiliated hospital, they estimated a cost savings per patient case of $2319 CDN ($1693 USD), calculated by determining the change in time to discharge. The cost savings in their model were driven by time to definitive microbiologic reporting, which happened earlier in the group utilizing mPCR. Costs of microbiologic diagnosis during the same period were stable and thought to be offset by changes in the standard of care when utilizing mPCR, so the cost of the mPCR panel was not included in the final analysis [43]. In a separate study from France, the reduction in hospital stay from using an mPCR ME panel resulted in estimated savings of 201 €/patient (~$245 USD). Soucek et al. identified cost savings of $38.73 USD in antimicrobials when using a CNS mPCR panel. When including the cost of diagnostic testing, that gap narrowed to <$1 USD ($P$=0.15) [44]. These studies are useful in justifying the cost of the mPCR panel, which can run >$100 USD.

Table 1 Multiplex PCR and antimicrobial and diagnostic stewardship: key findings

PCR panel pathogen type	Key references	Key findings and author comments
Respiratory mPCR panel	Branche et al. [20], Branche et al. [21], Keske et al. [19], Abbas et al. [23], Lowe et al. [26], Srinivas et al. [24••], Moradi et al. [25••]	• Respiratory mPCR increases more timely antiviral prescriptions for influenza • Combining a respiratory mPCR panel with a procalcitonin-based algorithm can improve stewardship, but algorithm adherence is critical • Educational interventions when implementing mPCR panels may be useful in improving stewardship • mPCR results are most useful when tied to direct antimicrobial atewardship activities • When algorithms incorporating mPCR results are utilized, assessing end-user guideline adherence is critical for optimizing and refining these protocols • Decision support within Electronic Medical Records that incorporates mPCR results can reduce antibiotic use
Gastrointestinal mPCR Panel	Keske et al. [32], Axeldrad et al. [31], Beal et al. [26], Cybulski et al. [27•]	• GI mPCR are associated with improved test turn-around time when compared with traditional methods • GI mPCR can decrease antimicrobial duration • Educational interventions can optimize the use of GI mPCR panels • Diagnostic stewardship is critical as positive results do not necessarily indicate active infection • The optimal role of Antimicrobial Stewardship Programs in PCR test review and intervention needs to be defined
Central nervous system mPCR panel	Dack et al. [40], Chang et al. [36], Radmard et al. [37], Mina et al. [41]	• One mPCR panel, the BioFire FilmArray meningitis-encephalitis panel, is U.S. FDA approved • CNS mPCR is associated with improved turnaround time (over traditional methods) • mPCR may have suboptimal sensitivity for Cryptococcus compared to traditional diagnostic testing; this has important implications for testing and clinical management • Positive test results for specific viruses have to be interpreted in context (as these may represent systemic reactivation and not active infection) • The optimal role of Antimicrobial Stewardship Programs in mPCR test review and intervention needs to be defined • CNS mPCR is promising but more research is needed

Additionally, several issues relating to the interpretation of CNS mPCR results have not been resolved. Several papers highlight concerns that the sensitivity of the BioFire CNS mPCR for Cryptococcus neoformans/gattii may be suboptimal when compared to traditional methods [37, 45–48]. However, a recent systematic review of cases reported in the literature found that most reported cryptococcus results lacked an appropriate comparator method or were compared to only a serum cryptococcal antigen, concluding that there was a higher negative predictive value to the mPCR panel than individual studies suggested, with an overall sensitivity and specificity of >90% [39]. Finally, positive Human Herpes Virus 6 (HHV-6), Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV) results must be interpreted in the appropriate context, as reactivation and active infection can both result as positive [39, 47]. At this time, mPCR CNS panels are promising for stewardship, but more study is needed to define best practices for their use.

Future Directions for Multiplex PCR Panels in Antimicrobial Stewardship

The use of mPCR panels to guide antimicrobial therapy and enhance antimicrobial stewardship shows promise, but more studies are needed to define their most optimal use. Table 1 summarizes the key findings from our review of stewardship literature related to respiratory, GI and CNS mPCR panels. If mPCR panels are adopted, incorporation of these technologies in local treatment guidelines is critical. Guidelines help frontline clinicians best utilize these tests and help reinforce best antimicrobial management practices. These algorithms may or may not include procalcitonin, as recently, the diagnostic sensitivity and specificity of elevated procalcitonin for distinguishing viral from bacterial pneumonia has been called into question [49].

Another way to optimize the use of mPCR is via EMR-based decision support. Moradi et al. did this via adding a Best

Practice Alert into their EMR [25••]. EMR tools can activate based on pre-set data criteria and can provide guidance directly to providers. Adding a EMR stewardship visualization tool worked for a Veterans Affairs Health System Hospital and could be combined with any one of the mPCR panels to improve utilization of antibiotics [50].

ASP personnel can actively review new mPCR results and provide best practice recommendations to providers directly. These efforts are most useful when ASP personnel are acting on these data in real-time [22, 23, 24••]. Compliance with ASP recommendations should be monitored and feedback to end users provided. When compliance is suboptimal, the reasons for this should be explored. ASP interventions utilizing real-time mPCR data are labor intensive and have significant implications for program staffing and resources.

In assessing the effectiveness of treatment guidelines incorporating mPCR panels, surveying providers about their rationale for following an algorithm (or not) may be useful to help optimize the use of these technologies. Importantly, providing feedback to providers about rates of antibiotic prescribing may improve subsequent antibiotic use [51].

For GI and CNS mPCR panels, there are no published, peer-reviewed studies available at the time of this publication that explore the use of EMR-based decision support in the context of antimicrobial stewardship. Extrapolating from respiratory mPCR studies, EMR-based decision support may optimize the use of these technologies. For both GI and respiratory mPCR panels, diagnostic test stewardship (via test restriction) appears critically important [34, 52, 53].

Conclusions

Respiratory, GI and CNS syndromic mPCR panels, as an isolated intervention, aid in the diagnosis of infectious pathogens yet do not consistently improve antimicrobial utilization. Wherever possible, these technologies should be incorporated into local treatment guidelines with active antimicrobial stewardship program oversight and support. The use of EMR-based decision support is also promising. Provider compliance with guidelines utilizing mPCR panels should be monitored and feedback should be provided. Additional research is needed to define best practices for the use of mPCR panels in both antimicrobial and diagnostic test stewardship.

Declarations

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of interest Theodore S. Rader, Michael P. Stevens, and Gonzalo Bearman declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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