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The Impact of Point-of-Care Polymerase Chain Reaction Testing on Prescribing Practices in Primary Care for Management of Strep A: A Retrospective Before–After Study

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Background. Rapid antigen detection tests (RADTs) are the standard of care (SOC) for testing in patients with suspected group A β-hemolytic *Streptococcus* (Strep A) infection. Due to lower sensitivity, guidelines recommend confirmatory microbiological culture following negative RADT results. This process is time-consuming, and adherence is often poor, resulting in high rates of inappropriate antibiotic prescribing. We sought to evaluate the impact of switching from RADTs to point-of-care (POC) polymerase chain reaction (PCR) testing on use of antibiotics in primary care, when used as part of an antibiotic stewardship initiative.

Methods. In this retrospective before–after study, electronic medical records of any patients presenting with suspected acute pharyngitis (June 2018–May 2019) across 15 outpatient primary care clinics were evaluated. Strep A was detected using the cobas Strep A assay (cobas Liat system).

Results. Analysis of 10 081 eligible patient records showed that POC PCR testing resulted in a 44.1% reduction in antibiotic prescribing for patients with a negative POC PCR test result (10.1% PCR vs 18.0% RADT; *P* < .0001). Rates of antibiotic prescription varied across clinical sites, ranging between 10.7% and 33.8% and 12.4% and 34.4% during the use of PCR tests and RADTs, respectively. POC PCR had no impact on prescription rates in patients with positive POC test results compared to RADTs (76.2% vs 76.5%, respectively). More than 99% of antibiotics were prescribed during the initial primary care encounter.

Conclusions. As part of a broader antibiotic stewardship initiative, implementation of POC PCR as SOC in outpatients with acute pharyngitis symptoms reduced the volume of inappropriate antibiotic prescriptions.

Keywords. antibiotic stewardship; nucleic acid amplification test; point-of-care testing; rapid antigen detection test; *Streptococcus pyogenes*.

In 2018, in the United States (US) alone, >11 million people visited their physician complaining of throat symptoms [1]. Most pharyngitis episodes are of viral etiology, although a proportion (estimated 15%–37% in children [2, 3] and 5%–24% in adults [4, 5]) are caused by group A β-hemolytic *Streptococcus pyogenes* (hereafter referred to as Strep A), the most common bacterial cause of acute pharyngitis [2]. The Infectious Diseases Society of America published guidelines in 2012 that recommended rapid antigen diagnostic tests (RADTs) as the standard of care (SOC) for diagnosing Strep A, with the option for bacterial culture to confirm negative results in some patient populations [5]. The major benefits of RADTs are the speed of diagnosis and ease of use [6, 7], which provide results during a primary care visit to inform care [8]. The trade-off is that the majority of RADTs for Strep A have limited diagnostic sensitivity compared to culture (70%–90%) [7], resulting in an unacceptably high rate of false-negative results. For some patients, this necessitates laboratory-based culture to confirm negatives [5], incurring delays of up to 48 hours [9].

Despite the recommendations for the diagnosis of Strep A pharyngitis, testing is not always deployed as intended, with many clinicians either not testing patients at all or only relying on RADTs [8]. This results in higher rates of antibiotic prescribing than necessary [8], with at least 30% of antibiotics being inappropriately prescribed [10]. In the US, antibiotics are prescribed for between 47% and 73% of adults with pharyngitis [11–13]. These numbers are of concern since the vast majority of pharyngitis cases are caused by viral infection [3–5].

Inappropriate antibiotic prescribing in the outpatient setting contributes to the acceleration of antimicrobial resistance [14]. To address this problem, the Centers for Disease Control and Prevention has released guidance for healthcare professionals regarding outpatient antibiotic stewardship to encourage commitment to optimizing antibiotic prescription, regular tracking and reporting of prescribing practices, and the provision of education and expertise in antibiotic stewardship for both clinicians and patients [15]. Similarly, engaging in all-antibiotic stewardship, patient stewardship, and visit stewardship has been posited to improve outpatient antibiotic stewardship [16]. Since prescription of antibiotics for presumed viral infection contributes to inappropriate antibiotic prescribing, improved diagnostic testing could help tackle this issue.

A multifaceted approach to antimicrobial stewardship is required. Since July 2015, the University of California (UC) Davis health system has supported and promoted antibiotic stewardship to reduce inappropriate antibiotic prescribing outside the traditional hospital setting, including for Strep A. The program was first initiated in the emergency department and subsequently expanded to the outpatient setting in July 2017 [17].

Healthcare system-wide, we integrate both evidence-based and new experimental interventions into the existing outpatient stewardship program [17]. A strong commitment from leadership, furthering clinician and patient education, implementing locally adapted guidelines for antibiotic prescription, using an app designed to provide clinicians with easy-to-access up-to-date respiratory tract infection guidelines, clinical performance comparison, and reassessing diagnostic processes all contribute to achieving our antimicrobial stewardship goals.

In recent years, point-of-care (POC) nucleic acid amplification tests have become available for various infective agents including Strep A. These tests can be deployed at the POC to provide results in 15–24 minutes [18] to rapidly inform patient care and offer improved sensitivity compared to RADTs [9, 18–22]. This eliminates the previous trade-off between time and performance.

In this retrospective study, we assessed the impact of implementing the cobas Strep A assay for use on the cobas Liat system (Liat Strep A test), a POC polymerase chain reaction (PCR) assay, in the primary care outpatient setting for use in patients presenting with pharyngitis symptoms as part of an outpatient antimicrobial stewardship program. We evaluated the impact on antibiotic prescription rates across 15 primary care sites in the UC Davis health system, compared with SOC RADTs.

METHODS

Study Design
This multicenter study took place as part of an outpatient antibiotic stewardship program conducted by an antimicrobial stewardship champion site that has been targeting unnecessary prescribing practices for presumed viral infections since December 2017. Using a retrospective, before–after design, electronic medical records and laboratory information system data were collected to evaluate the impact of changing from an RADT plus optional culture approach to the use of the POC Liat Strep A test in terms of changes in clinical management and antibiotic prescribing patterns.

The control period was between June 2017 and May 2018, defined as the last complete season utilizing the previous SOC RADT (Quidel QuickVue+ Strep A test) [23]. The intervention period was between June 2018 and May 2019, defined as the first complete season using the Liat Strep A POC PCR testing strategy. Beginning September 2018 through May 2019, education on diagnostic testing for *Streptococcus*-related pharyngitis included guidance to no longer collect a follow-up culture sample after a negative POC PCR test. In addition, an algorithm directing appropriate management of suspected Strep A was distributed to providers and feedback (at least bimonthly) on Strep A POC PCR diagnostic test ordering and antibiotic selection was provided. This was a Strep A–focused intervention that was in the context of a broader antibiotic stewardship initiative with the goal of reducing inappropriate antibiotic prescriptions for upper respiratory infections as described by Morgan et al [24]. As part of the Strep A clinical algorithm provided to outpatient clinicians, penicillin V, amoxicillin, or benzathine penicillin G were recommended treatments if patients had no history of penicillin allergy. In cases of no type 1 hypersensitivity to penicillin, clinicians were advised to prescribe cephalexin or cefadroxil. In cases of type 1 hypersensitivity to penicillin, clinicians were advised to prescribe clindamycin, azithromycin, or clarithromycin.

Patient Consent Statement
This study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice Guidelines, applicable US Food and Drug Administration regulations, and the Helsinki Declaration. The protocol (protocol number LIA-INST-488) and patient de-identification procedure were approved by the UC Davis Institutional Review Board Administration (Institutional Review Board ID number 1480421-2) prior to the start of the study, with a waiver of informed consent for retrospective records review.

Patients
De-identified patient medical records and laboratory data were collected from 15 outpatient primary care clinics in the integrated UC Davis health system in the urban/rural Sacramento area of northern California, during the control period (use of RADT plus optional culture) and intervention period (use of POC PCR testing) for this study. Eligible patients were all those presenting to primary care clinics with suspected acute pharyngitis, regardless of age. Patients were identified using

International Classification of Diseases, Tenth Revision diagnostic codes for any of the following: streptococcal sore throat (J02.0), acute pharyngitis (J02.8, J02.9, J03.00, J03.01, J02.80, J03.81, J03.91), or acute tonsillitis (J03.90).

RADT (Quidel QuickVue+ Strep A Test) Intended Use

During the control period, the RADT Quidel QuickVue+ Strep A test was used for Strep A diagnosis. This qualitative lateral-flow immunoassay directly detects the group A streptococcal antigen from throat swab specimens. This test provides results with 95% sensitivity and 98% specificity within 5–10 minutes [23].

Liat Strep A Test Intended Use

The Liat Strep A test is an in vitro qualitative assay designed to detect Strep A in throat swab specimens. The assay utilizes nucleic acid purification and PCR technology to detect *Streptococcus pyogenes* and is intended for use on the cobas Liat system. This test provides highly sensitive (98.3%) and highly specific (94.2%) results within 15 minutes [25]. Like RADTs utilized for Strep A diagnosis, the Liat Strep A test is Clinical Laboratory Improvement Amendment–waived for use in the outpatient clinical setting [25].

Data Collection

Medical records and laboratory information were collected from patients during the control period and intervention study periods for Strep A. Data collected included demographic information (age, gender, ethnicity, insurance type, clinic location) and clinical information (type of POC test, type of laboratory test, prescription, any allergy events).

Statistical Analysis

No formal sample size calculations were performed. All data analysis was performed using SAS/STAT software [26]. Comparison of demographics of patients included in this study was summarized using descriptive statistics between the control period and the intervention period. Summaries of clinical outcomes for antibiotic and antiviral use were reported overall and separately by clinic or by POC and/or culture results between the control period and the intervention period. The study was not designed to specifically investigate the impact of POC PCR testing on overall antibiotic use.

The continuity-adjusted χ^2 test of independence was used to evaluate the association between the control and intervention arms in terms of antibiotic use for the POC test–positive, POC test–negative, and no POC test groups using a .05 significance level.

RESULTS

Patients and Providers

A total of 5307 and 4774 eligible patient medical records were evaluated for the control period and intervention period, respectively, across 15 outpatient primary care clinics (Supplementary Table 1). Demographics were similar for both the intervention and control cohorts (Table 1). In the intervention and control periods, most patients were aged ≥18 years (64.1% vs 63.2%, respectively) and most were female (61.4% vs 62.3%, respectively). Healthcare providers were primarily physicians, with only 1 nurse practitioner shared across 2 of the primary care clinics.

Ordered Culture Assays

Overall, of patients who were tested at POC, there was a higher proportion of positive Strep A POC results during the intervention period compared with the control period (25.0% [604/2412] vs 19.2% [646/3368], respectively). The total number of laboratory cultures ordered during the intervention period, regardless of POC test result, was reduced compared with the control period (10.4% [495/4774] vs 32.1% [1701/5307] of patients, respectively) for all patients (Table 2). The proportion of both culture plus POC tests ordered dropped significantly ($P < .0001$) from 27.4% (1453/5307) in the control period to 3.3% (159/4774) in the intervention period. Furthermore, for patients who received a POC test during the intervention and control periods, there was a larger discrepancy of 6.6% (159/2412) vs 43.1% (1453/3368), respectively, between the number of laboratory cultures subsequently ordered. With the exception of 1 clinic, the number of cultures ordered decreased across all clinics in the intervention period, with the greater reductions seen in the clinics with the highest number of cultures ordered in the control period (Supplementary Table 2).

During the intervention period, healthcare providers were advised against additional microbiological culture in the event of a negative POC PCR result; in some cases, culture was still requested. Reasons for culture request were not collected. As a result of the guidelines, only 7.1% (125/1757) of POC PCR-negative tests had a culture order vs 52.4% (1423/2714) of RADT-negative tests.

Antibiotic Prescription

The rates of antibiotic prescription within 14 days of the initial clinic visit, including patients who were prescribed both antibiotics and antivirals during the initial clinic visit (within 0 days), were similar during both the intervention and control periods (25.1% [1200/4774] vs 26.2% [1390/5307], respectively; $P = .24$) (Table 3).

Of patients who had a negative POC test, there was a statistically significant, 44.1% reduction in the number of antibiotics prescribed within 0 days during the intervention period compared with the control period (10.1% vs 18.0%, respectively; $P < .0001$). Rates of antibiotic prescription were comparable between the initial visits of the intervention and control periods in patients with a positive POC test result (76.2% vs 76.5%, respectively; $P = .95$). Of eligible patients, 36.5% and 49.5% had

Table 1. Patient Demographics and Characteristics

Characteristic	Control Period (POC RADT)	Intervention Period (POC PCR)
Total, No.	5307	4774
Age, y, No. (%)		
<6	329 (6.2)	361 (7.6)
6–17	1624 (30.6)	1354 (28.4)
≥18	3354 (63.2)	3059 (64.1)
Gender, No. (%)		
Female	3304 (62.3)	2931 (61.40)
Male	2003 (37.7)	1842 (38.6)
Nonbinary	0 (0.0)	1 (<0.1)
Ethnicity, No. (%)		
American Indian/Alaskan Native	52 (1.0)	36 (0.8)
Asian	449 (8.5)	414 (8.7)
Black/African-American	239 (4.5)	230 (4.8)
Native Hawaiian/Pacific Islander	52 (1.0)	42 (0.9)
White	3498 (65.9)	3116 (65.3)
Multiple/other	743 (14.0)	699 (14.6)
Not reported	274 (5.2)	237 (5.0)
Insurance type, No. (%)		
Medicare	455 (8.6)	500 (10.5)
Medicaid	75 (1.4)	125 (2.6)
Private	4645 (87.5)	4025 (84.3)
Military	124 (2.3)	115 (2.4)
None	8 (0.2)	9 (0.2)
Clinic location, No. (%)		
Non-hospital-based clinic (total)	4671 (88.0)	4191 (87.8)
Hospital-based clinic	636 (12.0)	583 (12.2)

Abbreviations: PCR, polymerase chain reaction; POC, point-of-care; RADT, rapid antigen detection test.

no POC tests performed in the control or intervention periods, respectively. Antibiotic prescription rates during the initial clinic visit were comparable between the intervention and control periods in those with no POC test results (23.4% vs 20.9%, respectively; *P* = .06) (Table 3).

The rates of antibiotic prescription varied considerably across the primary care clinics included in this study. The 25th, 50th, and 75th percentiles for antibiotic prescription were 20.6%, 25.1%, and 27.9%, respectively, for the control period and 23.2%, 24.5%, and 28.1%, respectively, for the intervention period. The impact of POC PCR testing on antibiotic prescription during the intervention period also varied by individual clinics, from 61.4% reduction in prescribing at Clinic 10 to a 30.3% increase at Clinic 2 (Supplementary Table 3).

During both the intervention and control periods of this study, >99% of all antibiotics were prescribed during the initial visit (Table 3). During the control period, only 2 additional POC-negative, culture-positive patients were prescribed antibiotics subsequent to their initial clinic visit, whereas none were additionally prescribed during the intervention period (Supplementary Table 4).

Documented Allergy Events

Within 30 days of antibiotic prescription, 0.4% (5/1381) and 0.5% (6/1194) of patients from the control and intervention periods, respectively, experienced an allergic reaction. No allergy events were recorded in patients prescribed antivirals, or with a combination of antibiotics and antivirals.

DISCUSSION

During this study, we evaluated the impact of POC PCR on rates of antibiotic prescribing for pharyngitis in the outpatient setting, as part of a broader antibiotic stewardship initiative. While there was no overall impact on the rates of antibiotic prescriptions between the control and intervention periods, implementing POC PCR testing for Strep A resulted in a statistically significant 44.1% reduction in antibiotic prescriptions in patients who tested negative at POC compared with the use of SOC RADTs. We also found that fewer cultures were performed compared with negative RADTs during the control period, suggesting that in some cases, rather than reflex to culture, no culture sample was submitted by the primary care physician. Increasing diagnostic sensitivity may therefore improve patient management.

Table 2. Point-of-Care and Culture Tests Ordered During the Control and Intervention Periods

	Tests Ordered, No. (%)	
Characteristic	Control Period (POC RADT)	Intervention Period (POC PCR)
Total patients, No.	5307	4774
Total POC Strep A tests, No.	3368	2412
Strep A positive[a]	646 (19.2)	604 (25.0)
Strep A negative[a]	2714 (80.6)	1757 (72.8)
Invalid/other[a]	8 (0.2)	51 (2.1)
Total cultures, No.	1701	495
Group A, positive[a]	115 (6.8)	58 (11.7)
Group C/G, positive[a]	1 (0.1)	2 (0.4)
Other bacteria, positive[a]	29 (1.7)	2 (0.4)
Negative[a]	1556 (91.5)	433 (87.5)
Culture + POC, No.	1453	159
Group A positive[a]	96 (6.6)	11 (6.9)
POC positive[b]	23 (24.0)	8 (72.7)
POC negative[b]	72 (75.0)	2 (18.2)
Invalid/other[b]	1 (1.0)	1 (9.1)
Group C/G positive[a]	1 (0.1)	2 (1.3)
POC positive[b]	0 (0.0)	0 (0.0)
POC negative[b]	1 (100.0)	2 (100.0)
Invalid/other[b]	0 (0.0)	0 (0.0)
Other bacteria positive[a]	26 (1.5)	1 (0.2)
POC positive[b]	1 (3.9)	0 (0.0)
POC negative[b]	25 (96.2)	1 (100.0)
Invalid/other[b]	0 (0.0)	0 (0.0)
Negative[a]	1330 (91.5)	145 (91.2)
POC positive[b]	3 (0.2)	3 (2.1)
POC negative[b]	1325 (99.6)	120 (82.8)
Invalid/other[b]	2 (0.2)	22 (15.2)
Culture + no POC, No.	248	336
Group A, positive[a]	19 (7.7)	47 (14.0)
Group C/G, positive[a]	0 (0.0)	0 (0.0)
Other bacteria, positive[a]	3 (1.2)	1 (0.3)
Negative[a]	226 (91.1)	288 (85.7)

Abbreviations: PCR, polymerase chain reaction; POC, point-of-care; RADT, rapid antigen detection test; Strep A, group A β-hemolytic *Streptococcus pyogenes*.

[a]Percentages calculated as no./No.

[b]Percentages calculated using the total of group positive (group A, C/G, other) or negative and the denominator.

The prescribing changes between the intervention and control periods demonstrate that the greater diagnostic accuracy of the POC PCR, compared with that of the RADT, allows clinicians to have greater certainty in the result [27] and reduces the likelihood of the clinician resorting to empiric antibiotic therapy [28]. The false-positive rate for POC PCR, calculated based on samples with both valid culture and POC test results, was 2.4%, which is to be expected based on the reported assay specificity [25]. Risk of false positives from contamination with previous positive samples is also higher for assays with high sensitivity [25]. The ability to reliably discriminate between a bacterial or viral infection and decide whether antibiotics are the best option will result in improved patient care, fewer antibiotic-related adverse events, and reduced rates of inappropriate antibiotic prescription [15, 29]. Furthermore, adherence to the algorithm directing appropriate management of suspected Strep A would discourage antibiotic prescribing in the case of a negative POC test result.

This study found that the antibiotic prescribing rate was 76% in those with either a positive RADT or POC PCR test result. In a previous pediatric primary care study, antibiotics were prescribed to 87% of patients following positive RADT test plus culture and to 95% of patients positive by POC PCR [21]. Thus, while it might be expected that prescribing rates would reach 100% in those with positive test results, it appears that other factors may contribute to prescribing decisions. We also found that >99% of all antibiotic prescriptions were written during the initial clinic visit. This reflects a lack of utility for laboratory culture regarding Strep A testing and highlights the importance of rapid and accurate diagnostic information in guiding clinician decision-making.

Table 3. Anti-infective Prescriptions for Strep A, Within 0 Days and 14 Days of Clinic Visit

Characteristic	Control Period (POC RADT)		Intervention Period (POC PCR)	
	Within 0 Days	Within 14 Days	Within 0 Days	Within 14 Days
Patients[a], No.	5307	5307	4774	4774
Anti-infective prescriptions[b]				
Antibiotics only	1381 (26.0)	1390 (26.2)	1194 (25.0)	1200 (25.1)
Antivirals only	40 (0.8)	41 (0.8)	25 (0.5)	25 (0.5)
Antivirals and antibiotics together	9 (0.2)	9 (0.2)	7 (0.2)	7 (0.2)
POC tests performed, No.[c]	3368	3368	2412	2412
POC test positive, No.	646	646	604	604
Antibiotic prescription	494 (76.5)	494 (76.5)	460 (76.2)	460 (76.2)
Antiviral prescription	0 (0.0)	0 (0.0)	6 (1.0)	6 (1.0)
POC test negative, No.	2714	2714	1757	1757
Antibiotic prescription	489 (18.0)	494 (18.2)	177 (10.1)	179 (10.2)
Antiviral prescription	33 (1.2)	34 (1.3)	18 (1.0)	18 (1.0)
No POC test, No.	1939	1939	2362	2362
Antibiotic prescription	406 (20.9)	410 (21.1)	552 (23.4)	556 (23.5)
Antiviral prescription	16 (0.8)	16 (0.8)	8 (0.3)	8 (0.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: PCR, polymerase chain reaction; POC, point-of-care; RADT, rapid antigen detection test.

[a]The total number of anti-infective prescriptions may not equal the number of POC tests performed, as invalid POC tests were excluded, but patients with an invalid test may still have received antibiotics.

[b]One patient may receive multiple anti-infective prescriptions.

[c]The total number of tests performed includes tests that yielded an invalid result (control period, n = 8; intervention period, n = 51).

An interesting finding of this study is the range in antibiotic prescription change between primary care clinics, despite the same diagnostic intervention being implemented in all. While most clinics recorded a reduction in antibiotic prescription of up to 61%, 5 of 15 sites (clinics 1, 2, 12, 14, and 15) saw an increase, in the range of 0.2%–30.2%. This variation is likely the result of different existing prescribing practices, clinician attitudes, and patient preferences [30–32], and again prompts the need for a multifaceted approach for effective antimicrobial stewardship. Also of interest is that, despite suspected Strep A diagnosis, quite a large proportion of patients had no POC tests performed in the control or intervention periods and, of these, 20.9%–23.5% were prescribed antibiotics. This finding suggests that more work is needed to improve antibiotic stewardship by reducing empiric antibiotic prescribing for pharyngitis.

Antibiotic stewardship practices are being increasingly implemented in healthcare systems across the globe with promising results [33], and the US system is no exception [17, 34–36]. Despite existing interventions, this study highlights the positive impact that improved diagnostic testing practices can have on antibiotic prescription rates. The use of the cobas Liat POC PCR assay in an existing antimicrobial stewardship champion site demonstrates that a comprehensive stewardship program should leverage diagnostic testing as well as technological and behavioral interventions. Future stewardship initiatives could also consider clinical outcomes and the treatment of bacterial colonization.

We did note several limitations to our project. First, our healthcare system has had a robust outpatient antimicrobial stewardship program with committed leadership support and resources since December 2017 [17]. Therefore, the results of implementation of POC PCR testing cannot be determined independently but rather should be considered in the light of other interventions that were ongoing during the intervention period. This study is also a single healthcare system study in California, which as a state has devoted increased attention to stewardship, including regulations in the hospital and long-term setting, and active targeting of primary care providers for education and behavior change. Finally, diagnostic coding practices may vary between clinics, and both chief complaints reported and those targeted for POC PCR testing may not have accurately captured all Strep A–positive patients.

In conclusion, our study finds that diagnostics have a significant role to play in reducing the volume of inappropriate antibiotic prescription but should be implemented with a full range of interventions to achieve comprehensive antimicrobial stewardship.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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