Introduction

Inappropriate antimicrobial prescribing is a major and modifiable contributor to the spread of antimicrobial resistance. In the United Kingdom (UK), 79% of antibiotics are prescribed by general practitioners (GPs) [1], most commonly for the diagnosis of acute respiratory tract infection [2], including tonsillitis.

Antibiotic treatment is indicated only for bacterial tonsillitis, the most common bacterial aetiology being group A *Streptococcus* (GAS). Current UK National Institute for Health and Care Excellence (NICE) guidance recommends considering an antibiotic prescription in children and adults with three or more Centor (tonsillar exudates, swollen tender anterior cervical nodes, fever, lack of cough, [4]) or four or more FeverPAIN ((Fever, Pus, rapid Attendance [illness ≤3 days], severe Inflammation, No cough or coryza [5]) criteria [3]. It is unclear whether this guidance is followed, as up to 83% patients with sore throat are prescribed antibiotics in some primary care practices [2], and many GPs do not use Centor or FeverPAIN criteria.

In December 2015 and for the first time in the UK, St. George's Hospital Pediatric Emergency Department (PED) implemented a nucleic acid amplification-based point-of-care test (POCT) for GAS, which has 98% sensitivity and specificity [6]. The aim of our study was to describe the pragmatic implementation of testing for GAS in pediatric tonsillitis and the association between test results and antibiotic prescribing at our center.

Methods

The Child Admission Bundle for Infection (CABIN) team, with support from PED leadership, disseminated an algorithm describing criteria for testing and proposed treatment of suspected GAS tonsillitis based on NICE guidance. It was emailed to all doctors working in PED, posted on PED teaching boards, and presented at PED teaching conferences, with in-person and email reminders throughout the data collection phase. The Alere™ i Strep A (Waltham, Massachusetts, USA) instrument was made available to PED clinicians. This molecular-based

test provides results in 8 minutes or less on an easy-to-use, small desktop platform. Staff were instructed to test throat swabs obtained from patients 16 years of age and younger who presented to St. George's Hospital PED between December 2015 and January 2017 with suspected tonsillitis if enough Centor or FeverPAIN criteria were met. As part of the CABIN 2 study [7], clinical information, including presence of Centor and FeverPAIN criteria, POCT results and outpatient antibiotic prescriptions, was collected on all patients in whom a rapid test was performed.

Centor criteria were defined as: presence of tonsillar exudates, swollen tender anterior cervical nodes, temperature greater than 38.3°C, absence of cough. FeverPAIN criteria were defined as: fever reported by the carers or measured in PED, presence of pus on tonsils, fever duration ≤ 3 days (as proxy for illness duration ≤ 3 days), documentation of tonsil inflammation, no cough or coryza.

We performed a descriptive analysis, measured the association between GAS POCT result and outpatient antibiotic prescribing using an odds ratio calculation, and defined the areas under the receiver-operating characteristic (ROC) curves for Centor score and FeverPAIN score. All statistical tests were performed using the software package R (Vienna, Austria).

Results

A total of 339 children were tested with the Strep A POCT. Sore throat or difficulty swallowing was documented in 107 (32%) cases. The median age was 2.8 years. One hundred and thirty-eight patients (45%) were female. Two hundred and eighty nine (85%) children had fever, 186 (55%) absence of cough, 144 (42%) tonsillar exudates and 101 (30%) had cervical lymphadenopathy.

Only 114 of 339 children (34%) fulfilled ≥ 3 Centor criteria, warranting POCT testing or empiric

treatment. The remaining 225 children (66%) had less than three criteria present: 8 (2%) fulfilled no criterion, 86 (25%) one and 133 (39%) two criteria.

With regards to the FeverPAIN criteria, tonsil inflammation was documented in 256 children (76%), absence of cough or coryza in 253 (75%), fever duration ≤ 3 days in 204 (60%), and purulent tonsils in 144 (42%). Only 168 (49%) of tested patients had 4 or more criteria, warranting testing or empiric treatment. Three cases (1%) fulfilled no criterion, 20 (6%) one, 58 (17%) two, and 90 (27%) three criteria.

Of 282 children with ≥ 3 Centor or ≥ 4 FeverPAIN criteria, 101 (36%) had both ≥ 3 Centor and ≥ 4 FeverPAIN criteria.

The most commonly listed diagnoses among children who received the POCT were as follows: tonsillitis (43%), viral illness, not otherwise specified (14%), upper respiratory tract infection (13%), Influenza or Influenza-like illness (3%), and Scarlet fever (2%). The diagnosis was missing in 2% of cases.

The rate of invalid results, a technical issue often related to incorrect handling of the Alere i Strep A, was 9% in our cohort. Figure 1 describes the flow of of participants according to group A *Streptococcus* POCT result and outpatient antibiotic prescription. Of 308 cases with a valid POCT result, 70 (23%) had a positive result and 107 (35%) resulted in an outpatient antibiotic prescription. Ninety-one percent of patients with a positive GAS POCT result were prescribed an antibiotic (n = 64), and 82% with a negative GAS POCT result did not receive a prescription (n = 195). There was no documented outpatient prescription in 6 cases with positive POCT result; these patients either received intravenous antibiotics or were admitted to the pediatric ward. Fourty-three children were prescribed an antibiotic, in most cases targeting GAS (penicillin), despite a negative GAS POCT result. Of 107 patients who received an antibiotic in this cohort, 43 (40%) had a negative GAS POCT result.

There was a strong and significant association between POCT result and antibiotic prescribing: 64 of 70 (91%) children with a positive result received a prescription, compared

with 43 of 238 (18%) children with a negative result (odds ratio [OR] 48, 95% confidence interval [CI] 20–119). In contrast, the association between clinical criteria and antibiotic prescribing was of a lesser magnitude. It was significant for the following factors: age ≥ 3 years (OR 3.11, CI 1.90-5.08), ≥ 3 Centor criteria (OR 2.30, CI 1.41-3.76) and ≥ 4 FeverPAIN criteria (OR 1.77, CI 1.10-2.85). Patient sex was not associated with outpatient antibiotic prescribing (OR 0.84, CI 0.52-1.34). Neither score, as used in this cohort, performed well in the prediction of a positive POCT result. The area under the ROC curve was 0.62 (CI 0.53-0.69) for the Centor score and 0.57 (CI 0.49-0.65) for the FeverPAIN score.

Discussion

In our cohort, GAS POCT results were highly associated with antibiotic prescribing. Moreover, only 35% of children with suspected tonsillitis in this cohort were prescribed antibiotics, compared to 60% during the 2014–2015 winter season (CABIN 2 unpublished data). While case-mix could not be adjusted for, this likely reflects improved antibiotic stewardship. These results highlight the potential role for a rapid POCT in improving antibiotic use in pediatric tonsillitis cases in the UK.

In contrast, the high proportion of cases that did not fulfil enough Centor or FeverPAIN criteria to justify testing or empiric antibiotic prescribing, 66% and 51% respectively, suggests these algorithms based on symptoms and signs were not consistently followed, and present an opportunity for improvement in diagnostic stewardship in this setting.

Our results are consistent with other reports of a GAS POCT used to support appropriate antibiotic prescribing [8]. This evaluation of the pragmatic implementation of a novel diagnostic was coupled with a qualitative analysis describing the knowledge, attitudes and practices of families and clinicians to the care provided in the emergency department. It included questionnaires about the acceptability of POCT in this setting [9].

A formal cost-effectiveness analysis was not undertaken as the POCT was immediately

deemed too expensive by clinicians to justify long-term adoption at this center.

A limitation of this study was the reliance on health records for documentation of Centor and FeverPAIN criteria. Data collection was therefore affected by the quality of clinical documentation, including missing data. For example, where tonsil inflammation was documented, it was assumed to be severe. This may have led to an overestimation of the true number of patients with enough criteria to warrant testing. Another example was the low documentation rate for sore throat, partially explained by the large proportion of young patients unable to verbalise symptoms and by poor documentation. Finally, POCT was performed in many cases despite the lack of sufficient Centor and FeverPAIN criteria, and the number of eligible patients who did not receive the POCT test is unknown; this raises the possibility of selection bias in the study. The performance of the two clinical scores in our cohort should be interpreted cautiously in view of these limitations.

It is important to note that the Centor criteria were not designed for use in persons younger than 16 years [4], and were not validated in some pediatric studies [10]; the FeverPAIN criteria have also not been assessed in children younger than 3 years [5]. Hence, there might be clinical justification for clinicians to test for GAS without relying on these clinical scores.

In the UK, the high performance of FeverPAIN criteria and cost of a POCT will pose a challenge to the widespread use of any test more expensive than a course of penicillin. In general practitioners' clinics, the total ten-minute consultation time and impact on workflow constitute additional challenges.

Conclusion

The use of a rapid, molecular-based GAS POCT may reduce unnecessary antibiotic prescriptions in UK PED settings. Nonetheless, opportunities to improve diagnostic and

antimicrobial stewardship were identified in this evaluation of the pragmatic implementation of a novel diagnostic into a clinical pathway. Other factors such as acceptability, cost and impact on workflow are important predictors of successful implementation and need to be further evaluated.

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