The Impact of Clinical Pathways on Antibiotic Prescribing for Acute Otitis Media and Pharyngitis in the Emergency Department

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Background: Although Italian pediatric antimicrobial prescription rates are among the highest in Europe, little action has been taken to improve the appropriateness of antimicrobial prescriptions. The primary aim of this study was to assess changes in antibiotic prescription before and after acute otitis media (AOM) and group A streptococcus (GAS) pharyngitis Clinical Pathway (CP) implementation; secondary aims were to compare treatment failures and to assess change in the total antibiotics costs before and after CP implementation.

Methods: Pre-post quasi-experimental study comparing the 6-month period before CP implementation (baseline period: October 15, 2014, through April 15, 2015) to the 6 months after intervention (postintervention: October 15, 2015, through April 15, 2016).

Results: Two hundred ninety-five pre- and 278 postintervention emergency department visits were associated with AOM. After CP implementation, there was an increase in "wait and see" approach and a decrease in overall prescription of broad-spectrum antibiotics from 53.2% to 32.4% ($P < 0.001$). One hundred fifty-one pre- and 166 postimplementation clinic visits were associated with GAS pharyngitis, with a decrease in broad-spectrum prescription after CP implementation (46.4% vs. 6.6%; $P < 0.001$). For both conditions, no difference was found in treatment failure, and total antibiotics cost was significantly reduced after CP implementation, with a decrease especially in broad-spectrum antibiotics costs.

Conclusions: A reduction in broad-spectrum antibiotic prescriptions and a reduction in the total cost of antibiotics for AOM and GAS pharyngitis along with an increase in "wait and see" prescribing for AOM indicate effectiveness of CP for antimicrobial stewardship in this setting.

Key Words: acute otitis media, group A streptococcus pharyngitis, clinical pathways, pediatric emergency department, antimicrobial stewardship program

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Antibiotics represent the most widely prescribed therapeutic agents in children worldwide, both in hospital and community settings, especially in preschool age.[1,2] Although antibiotics are prescribed more frequently in Italy than in other European countries, with an overuse of third-generation cephalosporins and penicillin plus beta-lactamase inhibitors,[3] to our knowledge, this is the first study to assess implementation of Antimicrobial Stewardship Program (ASP) measures in an Italian pediatric emergency department (PED).

In the United States, ASPs have been shown to reduce inappropriate antimicrobial use and resistance, enhance patient safety and lower drug costs.[4,5] A well-established ASP typically includes proactive interventions like prospective audits and feedback to prescribers and formulary restriction with prior antimicrobial authorization. Each of these interventions has shown to decrease unnecessary antimicrobial exposure, reduce costs and improve patient outcomes. In limited resource settings where a robust antimicrobial stewardship team may be difficult to establish, clinical pathways (CPs) represent the most reasonable and feasible first step for implementation.[6]

A CP is a task-oriented plan that details essential steps in the care of patients with a specific clinical problem and describes the patient's expected clinical course. Evidence indicates that CPs are an effective means to change antibiotic prescribing behavior in primary care and inpatient settings[6–10] and to standardize care without adversely affecting patient safety or outcomes.[9]

Because CPs have proven a promising tool to reduce antibiotic prescriptions in primary care and in-hospital settings, we hypothesized that their implementation in the PED would decrease overall prescription and cost of antibiotics, especially broad-spectrum, for common childhood infections acute otitis media (AOM) and group A streptococcus (GAS) pharyngitis.

Because PEDs are uniquely positioned at the interface of inpatient and outpatient settings, PED physicians could influence prescribing trends in both locations. Challenges in antibiotic prescribing in the PED setting include high turnover rates for both patients and practitioners and rapid decision-making, making application of some ASP interventions like prospective audits and feedback or formulary restriction quite difficult.[11]

The primary aim of this study was to assess changes in antibiotic prescription, especially broad-spectrum, before and after CP implementation for AOM and pharyngitis in a large Italian PED. Secondary aims were to compare treatment failures and to assess the change in the total antibiotics costs before and after CP implementation.

MATERIALS AND METHODS

Study Design

CPs were implemented from October 1, 2015, through October 15, 2015. We conducted a prepost quasi-experimental study to assess changes in antibiotic prescribing during the 6-month period before CP implementation (preintervention: October 15, 2014, through April 15, 2015) and during the 6 months after intervention (postintervention: October 15, 2015, through April 15, 2016). The same months have been analyzed in each period to control for effects

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of seasonality. The study was conducted at the PED of the Department for Woman and Child Health at Padua University Hospital.

AOM and pharyngitis CPs were developed by the Division of Pediatric Infectious Diseases and PED of Padua in collaboration with the Division of Pediatric Infectious Diseases of the Children's Hospital of Philadelphia (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/D36 and Supplemental Digital Content 2, http://links.lww.com/INF/D37). CPs were delivered as laminated pocket cards, and 3 educational lectures were presented to physicians and residents on how to implement these tools in practice. This study was approved by the Institutional Review Board of Department for Woman and Child Health at the University of Padua. An informed consent form was sent to the families, and follow-up data were included only when authorized.

Study Population

All patients 2 months to 15 years of age with an *International Classification of Diseases, 9th Revision, Clinical Modification* code or descriptive diagnosis of AOM or pharyngitis at the PED in Padua during the pre and postintervention periods were included in the study.

AOM exclusion criteria were immunodeficiency or immunosuppressive therapy, tympanostomy tubes at the time of diagnosis, craniofacial abnormalities, cystic fibrosis, concomitant bacterial infections involving other sites or systemic bacterial infection, diabetes, chronic otitis media, AOM complicated by mastoiditis and AOM with an ongoing antibiotic therapy at admission.

Pharyngitis exclusion criteria were immunodeficiency or immunosuppressive therapy, concomitant bacterial infections involving other sites or systemic bacterial infection, previous tonsillectomy, chronic diseases, admission to the Pediatric Department or to Short-Stay Emergency Department Observation Unit for feeding difficulties and pharyngitis with an ongoing antibiotic therapy at the time of admission.

Using data from the Padua PED from November 2014 to April 2015 for both AOM and pharyngitis, we anticipated a population of 300 eligible patients in both pre- and postimplementation periods for both conditions. Power was calculated using the sampsi command in STATA 12 (College Station, TX), assuming a potential 25% change in the primary outcome of proportion of broad-spectrum antibiotic prescriptions. The anticipated change in prescription of broad-spectrum antibiotics is based on changes in primary outcomes from pre- to postimplementation periods in a retrospective assessment of the impact of an inpatient CP for cellulitis and cutaneous abscess ranging from 15% to 35%.[7] Given these parameters, power for AOM was estimated to be 98%, while for pharyngitis it was estimated at 85%.

Data Source

Antimicrobial use and clinical and demographic data for all patients were extracted manually from electronic medical records using REDCap® data collection forms designed for the 2 conditions.

Broad-spectrum antimicrobials were defined as: β-lactam and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, fluoroquinolones and macrolides.

A study survey number was assigned to each patient to ensure data privacy. No personally identifying data were collected.

PED visits occurring for the same patient greater than 30 days apart were analyzed as separate events.

Two different authors independently collect the data (M.B., G.B.). Disagreements were resolved by consensus.

To evaluate the safety of the intervention, we collected data on treatment failure within 30 days after discharge through a standardized telephone survey to the family.

To assess treatment costs, generic drug price for each antibiotic prescribed was based on official market prices per unit in Italy.[12]

Outcomes

Primary Outcomes

The following aspects of antibiotic prescriptions for AOM and pharyngitis were assessed: (1) proportion of "wait and see" approach (AOM only); (2) proportion of antimicrobial prescriptions by specific disease and active agent; (3) dosage of the most prescribed antibiotics, expressed in mg/kg/day and (4) duration of therapy, expressed in days of therapy (DOTs).

Secondary Outcome

Any of the following at 30 days follow-up were considered treatment failure: (1) change in antibiotic prescription for persistence or worsening of symptoms; (2) treatment change for antibiotic side effects; (3) new antibiotic prescription within 30 days from discharge for relapse of symptoms and (4) in case of AOM, new antibiotic prescription after "wait and see" approach.

The economic impact of CPs was investigated using total cost of overall antibiotic therapy and each class of antibiotic per 1000 patient day (PD) in both periods. For oral antibiotics, 2 formulations were considered: oral suspension and tablets. Oral suspension was used for children less than 40 kg and tablets for those 40 kg or more. Starting from total mg/patient/episode, the number of packages needed for completing the treatment course was computed. This was possible because in Italy antibiotics are sold prepackaged in specific quantities.

Data Analysis

Data were analyzed using STATA®13 and QIMacros p-chart software.

Results were summarized as frequencies and percentages for categorical variables and as median, minimum and maximum for continuous variables. Comparison of categorical variables in the pre- vs. postintervention period was conducted with χ^2 or Fisher exact test. Continuous variables were compared with Wilcoxon rank sum test. In this analysis, the dependent outcome variables were summarized for each month in the time series.

RESULTS

Primary Aim

AOM Prescriptions

Over the 6-month preintervention period, 13,262 children were seen in the PED, in comparison with 12,335 children during the 6-month postintervention period.

During the preintervention period, 334 patients were evaluated for AOM, accounting for 2.5% (334/13,262) of total PED visits. The same proportion was observed in the postintervention period (332/12,335 [2.7%]; $P = 0.4$). The study population pre- and postintervention is shown in Figure, Supplemental Digital Content 3, http://links.lww.com/INF/D38.

The 2 populations were similar with respect to sex and age, with an overall male predominance and an increased incidence of AOM in children younger than 5 years (Table, Supplemental Digital Content 4, http://links.lww.com/INF/D39).

Antimicrobial Prescription Rate for AOM

For AOM, there was an increase of proportion of "wait and see" approach in the post-CP period as compared with the pre-CP period (21.7% [64/295] vs. 33.1% [92/278]; $P < 0.01$) and, when antibiotics were prescribed, an increase of amoxicillin prescriptions (32.0% [74/231] vs. 51.6% [96/186], $P < 0.001$) with a concomitant decrease in broad-spectrum antibiotics prescription (68.0%

[157/231] vs. 48.4% [90/186], $P < 0.001$). This included a statistically significant reduction in cephalosporin prescriptions (20.3% [47/231] vs. 8.6% [16/186]; $P < 0.001$; Table 1).

A significant and stable difference in antibiotic prescribing for AOM between pre- and postintervention groups was reported (Fig. 1A), especially for uncomplicated AOM (AOM without otorrhea; Fig. 1B).

Antibiotics Dosage for AOM

Dosage comparison was conducted for amoxicillin and amoxicillin–clavulanate as these were the most commonly prescribed antibiotics. Wilcoxon rank sum test comparing overall pre- and postintervention median dose found a significant increase in dose for both drugs ($P < 0.001$), and the trend analysis showed that the optimal dosage recommended by the CP was reached by both antibiotics within 1 month post-CP implementation and remained stable during the 6-month postintervention period (Fig., Supplemental Digital Content 5, http://links.lww.com/INF/D40).

Treatment Duration for AOM

In line with the AOM CP, analysis was stratified by age (< 2 years old, ≥ 2 years old) and disease severity (complicated vs. uncomplicated AOM), independently from the prescribed oral agent.

TABLE 1. Treatment Option of AOM and GAS Pharyngitis

	AOM					GAS Pharyngitis				
	Preintervention Period		Postintervention Period			Preintervention Period		Postintervention Period		
	295		278			298		366		
Treatment Option for Included Patients	n	%	n	%	*P* Value	n	%	n	%	*P* Value
Treatment										
"Wait and see" for AOM or no antibiotic treatment for GAS pharyngitis	64	21.7	92	33.1	< 0.01	147	49.3	200	54.6	0.17
Antibiotic therapy	231	78.3	186	66.9	< 0.01	151	50.7	166	45.4	0.17
Type of antibiotics										
Amoxicillin	74	32.0	96	51.6	< 0.001	81	53.6	155	93.4	< 0.001
Broad spectrum (amoxi-clavulanate + cephalosporins + macrolides)	157	68.0	90	48.4	< 0.001	70	46.4	11	6.6	< 0.001
Amoxicillin-clavulanate	106	45.9	70	37.6	0.09	60	39.7	5	3.0	< 0.001
Cephalosporins	47	20.3	16	8.6	< 0.001	10	6.6	6	3.6	0.28
Macrolides	4	1.7	4	2.2	0.76	—	—	—	—	—

n Indicates the number of patient for each category.

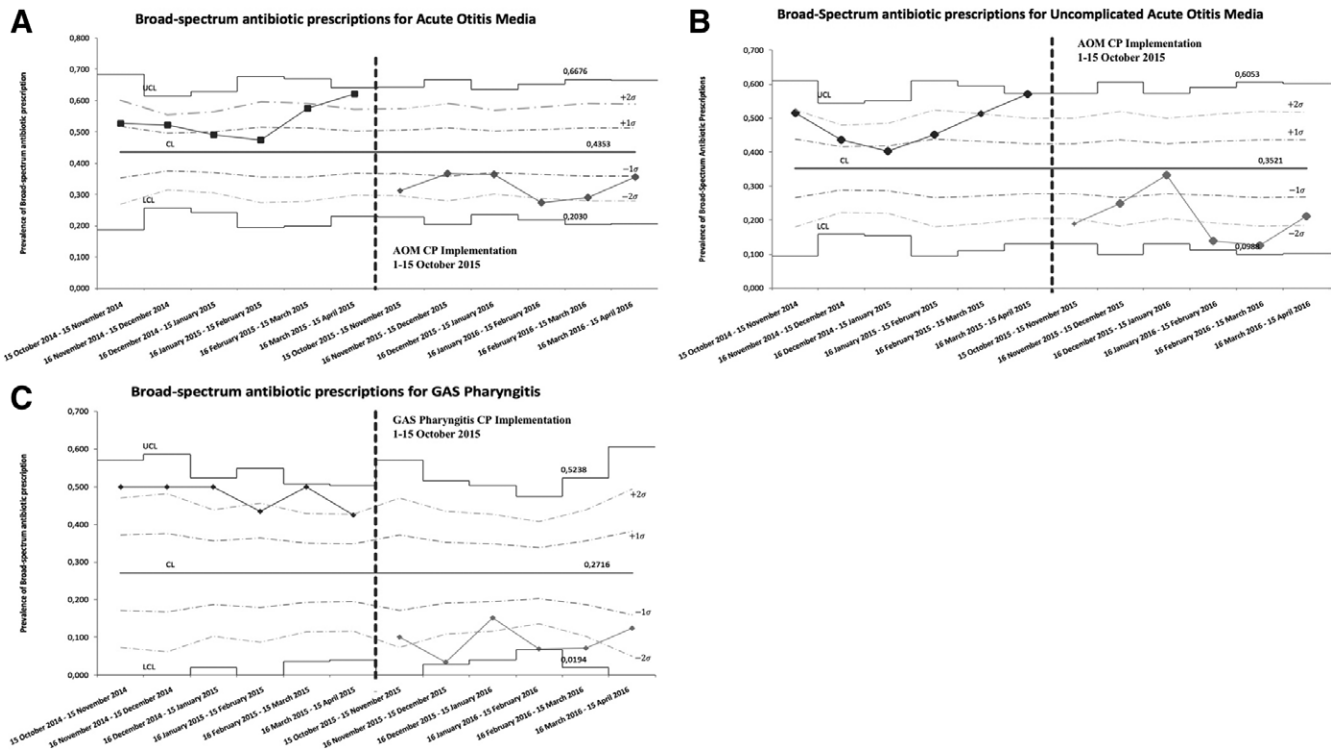

FIGURE 1. p control chart describing the variation of broad-spectrum antibiotics prescription for acute otitis media (A); uncomplicated acute otitis media (B); GAS Pharyngitis (C). The line represents the broad-spectrum antibiotic prescriptions. UCL indicates Upper Control Limit; CL, Control Limit; LCL, Low Control Limit; σ the standard deviation of the sample data; AOM, Acute Otitis Media; CP, Clinical Pathway; GAS Pharyngitis, Group A Streptococcus Pharyngitis.

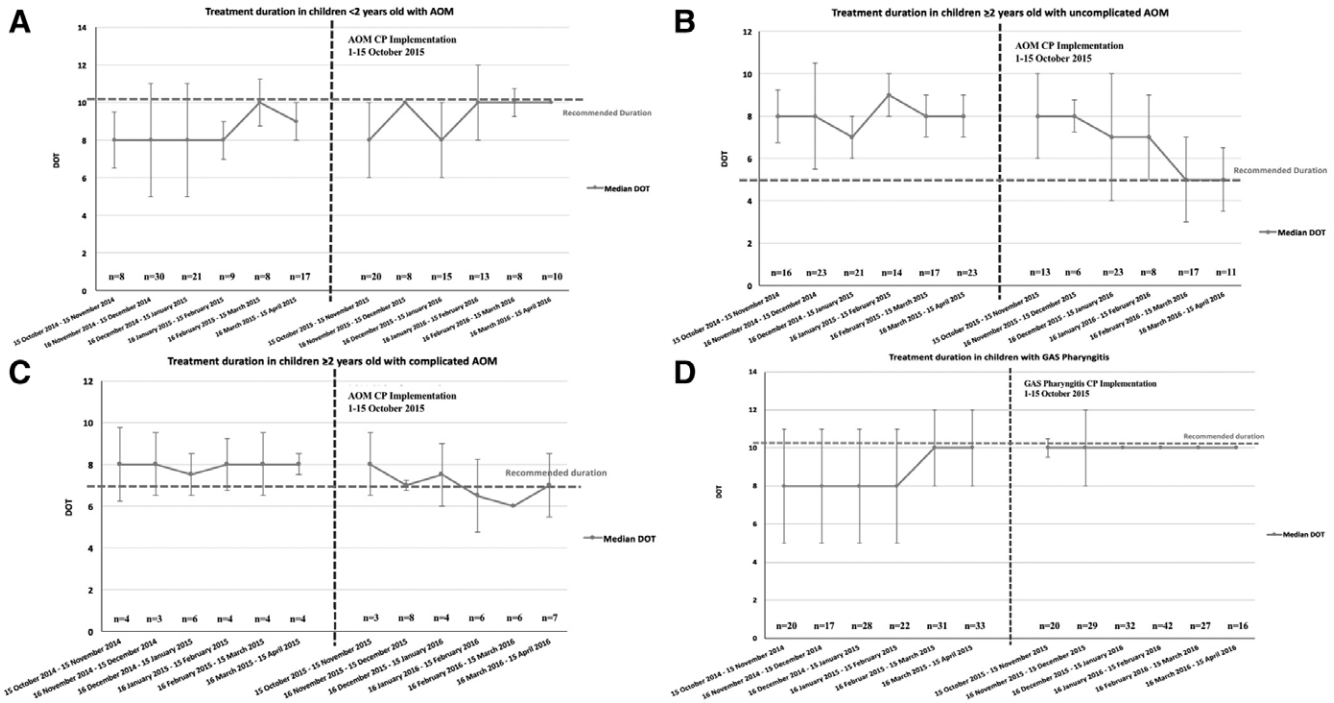

FIGURE 2. Duration of therapy in median DOT and interquartile range each month in pre- and post-intervention period: for children <2 years with acute otitis media (A); for children ≥2 years with uncomplicated AOM (B); for children ≥2 years with complicated AOM (C); for children with GAS Pharyngitis (D). CP indicates Clinical Pathways; DOT, Days of Therapy; AOM, Acute Otitis Media; GAS Pharyngitis Group A Streptococcus Pharyngitis; n the sample size.

In children < 2 years old, median DOT fluctuated between 8 and 10 for the first 3 months after CP implementation and then met the recommended duration of 10 days in the last 3 months both for uncomplicated and complicated AOM. Wilcoxon rank sum test comparing pre- and postintervention median DOTs found a significant increase ($P < 0.001$) in the postintervention group (Fig. 2A).

In children ≥ 2 years old with uncomplicated AOM, median DOT decreased after CP implementation and met the recommended duration of 5 days only in the last 2 months of the postimplementation period. The difference between median DOT in the 2 periods was statistically significant ($P < 0.001$; Fig. 2B).

For children ≥ 2 years old with complicated AOM, median DOT was in line with recommended treatment duration in both pre- and postintervention periods, with no significant difference over time (Fig. 2C).

Pharyngitis Prescriptions

During the preintervention period, 388 patients were evaluated for pharyngitis, accounting for 2.9% (388/13,262) of total PED visits, while in the postintervention period, patients were 448/12,335 (3.6%), $P < 0.002$ (Fig., Supplemental Digital Content 6, http://links.lww.com/INF/D41).

The groups included in each study period were similar with respect to sex, with a slight male predominance and with a higher incidence among older children (Table, Supplemental Digital Content 7, http://links.lww.com/INF/D42).

Antimicrobial Prescription Rate for Pharyngitis

CP implementation was associated with an increase in proportion of amoxicillin prescriptions (53.6% [81/151] vs. 93.4% [155/166]; $P < 0.001$) with a concomitant decrease in broad-spectrum antibiotic prescription (46.4% [70/151] vs. 6.6% [11/166]; $P < 0.001$). This included a statistically significant reduction in amoxicillin–clavulanate prescriptions (39.7% [60/151] vs. 3.0% [5/166]; $P < 0.001$; Table 1).

Analyzing pharyngitis prescriptions by month, a remarkable and stable reduction in broad-spectrum antibiotic prescriptions was reported in the postintervention period (Fig. 1C).

Antibiotic Dosage for GAS Pharyngitis

Amoxicillin dose was in line with 50 mg/kg/day guidelines in both pre- and postintervention periods, with no significant change between the 2.

Treatment Duration for GAS Pharyngitis

Median DOT for GAS pharyngitis met the recommended 10 days in the last 2 months of the preimplementation period and remained stable in the postimplementation period (Fig. 2D). Wilcoxon rank sum test comparing overall pre- and postintervention median DOT found a significant increase in postintervention ($P < 0.001$).

Secondary Aim

AOM Treatment Failure

AOM follow-up for treatment failure evaluation was available for 214/295 (72.5%) and 206/278 (74.1%) children in pre- and postintervention periods, respectively. The subgroups available for follow-up were similar to the starting populations in terms of demographic data and treatment choices.

The difference between overall treatment failure rates in pre- and postintervention groups was not statistically significant (12.1% [26/214] vs. 11.2% [23/206]; $P = 0.75$), both in the group treated with antibiotics ($P = 0.10$) and in the "wait and see" group ($P = 0.14$; Table 2).

TABLE 2. Treatment and Treatment Failure During Follow-up of Patients With AOM and GAS Pharyngitis

	AOM					GAS Pharyngitis				
	Preintervention Period		Postintervention Period			Preintervention Period		Postintervention Period		
	214 (72.5% of Total AOM)		206 (74.1% of Total AOM)			98 (64.9% of GAS Pharyngitis)		118 (71.1% of GAS Pharyngitis)		
Patients Available for Follow-up	n	%	n	%	*P* Value	n	%	n	%	*P* Value
Treatment										
Wait and see	48	22.4	66	32.0	< 0.05					
Antibiotic therapy	166	77.6	140	68.0	< 0.05					
Type of antibiotics										
Amoxicillin	55	25.7	73	35.4	< 0.05	52	53.1	109	92.4	< 0.001
Broad spectrum (amoxi-clavulanate + cephalosporins + macrolides)	111	51.9	67	32.5	< 0.001	46	46.9	9	7.6	< 0.001
Amoxicillin + clavulanate	78	36.5	50	24.3	< 0.01	40	40.8	3	2.5	< 0.001
Cephalosporins	30	14.0	14	6.8	< 0.05	6	6.1	6	5.1	0.97
Macrolides	3	1.4	3	1.5	0.96	—	—	—	—	—
Treatment failures	**26**	**12.1**	**23**	**11.2**	**0.75**	**6**	**6.1**	**8**	**6.8**	**0.93**
Changed antibiotic for persistence or worsening of symptoms	12	5.6	5	2.4	0.10	2	2.0	3	2.5	0.83
Changed antibiotic for side effects	3	1.4	4	1.9	0.96	2	2.0	2	1.7	0.75
Antibiotic prescriptions for another AOM episode within 30 days after discharge	4	1.9	1	0.5	0.39	2	2.0	3	2.5	0.83
Antibiotic prescription after "wait and see"	7	3.3	13	6.3	0.14					

n Indicates the number of patient for each category.

Pharyngitis Treatment Failure

For pharyngitis treated with antibiotics, treatment failure follow-up was available for 98/151 (64.9%) and 118/166 (71.1%) children in pre- and postintervention periods, respectively.

Also for GAS pharyngitis, subgroups available for follow-up were similar to the starting populations in terms of demographic data and treatment choices.

The difference between overall treatment failure rates in pre- and postintervention groups was not statistically significant (6.1% [6/98] vs. 6.8% [8/118]; $P = 0.93$; Table 2).

Total Cost for AOM

In the period before CP implementation, AOM antibiotics cost per 1000 PD was €8033.08, with €7014.20 (87.3% of total antibiotics costs) for broad-spectrum. Following CP implementation, total cost per 1000 PD reduced to €5878.30, with €4382.67 for broad-spectrum antibiotics (Table 3).

The proportion of total antibiotics costs for cephalosporins, which represented an important part of broad-spectrum costs in the preintervention period, decreased dramatically in the postintervention (€2921.05 [36.4%] vs. €794.51 [13.5%]; $P < 0.001$), with a concurrent increase in the proportion of antibiotics costs for amoxicillin–clavulanate (€3965.36 [49.4%] vs. €3441.81 [58.6%]; $P < 0.001$).

Trend analysis confirmed a stable reduction after CP implementation, especially for the proportion of antibiotics costs for broad-spectrum antibiotics (Fig., Supplemental Digital Content 8, http://links.lww.com/INF/D43).

Total Cost for Pharyngitis

Before CP implementation, antibiotics for pharyngitis cost per 1000 PD amounted to €9337.68, with €6738.61 (72.2%) for broad-spectrum antibiotics. During the postimplementation period, the total cost decreased to €6247.23, with a dramatic reduction in the proportion of antibiotics costs from broad-spectrum antibiotics (€1060.78; Table 3).

By drug, the proportion of antibiotics costs from amoxicillin–clavulanate reduced dramatically (€5752.58 [61.1%] vs. €531.45 [8.5%]; $P < 0.001$). Also proportion of antibiotics costs from cephalosporins significantly reduced (€986.03 [10.6%] vs. €529.34 [8.5%]; $P < 0.001$).

Trend analysis over time demonstrates an immediate decrease in overall and the proportion of broad-spectrum antibiotics costs after CP implementation (Fig., Supplemental Digital Content 9, http://links.lww.com/INF/D44).

DISCUSSION

Our study showed sustained changes in physician prescribing behaviors for AOM after implementation of a CP. Prescribing changes included an immediate increase in "wait and see" approach and amoxicillin prescriptions with a concomitant decrease in broad-spectrum antibiotic prescriptions. This difference was more pronounced among uncomplicated AOM cases than all cases, indicating that AOM CP implementation was associated with a lower reduction in prescription of broad-spectrum antibiotics for AOM with otorrhea (complicated AOM). Further analysis of broad-spectrum antibiotic prescriptions showed a statistically significant reduction in cephalosporin prescription after intervention, as expected. While amoxicillin–clavulanate is the recommended first-line antibiotic for complicated AOM, oral second- and third-generation cephalosporins are considered an option only in the case of non-IgE–mediated penicillin allergy.[13] Indeed, according to a meta-analysis by Pichichero,[14] cross reaction between penicillins and second- or third-generation cephalosporins is a rare event (incidence of less than 2%). It is important to note that these alternative antibiotics vary in their efficacy against AOM pathogens. The only cephalosporin that has been demonstrated superior to penicillin in *S. pneumoniae* eradication, even if resistant, is ceftriaxone. For this reason, it is suggested

TABLE 3. Antibiotic Prescription Indication, Type and Expenditure per 1000 PD for AOM and GAS Pharyngitis

	AOM									GAS Pharyngitis							
	Preintervention Period				Postintervention Period					Preintervention Period				Postintervention Period			
	295				278					151				166			
	Prescription		Expenditure/ 1000PD		Prescription		Expenditure/ 1000 PD			Prescription		Expenditure/ 1000 PD		Prescription		Expenditure/ 1000 PD		
Total Patient	n	%	€	%	n	%	€	%	*P* Value	n	%	€	%	n	%	€	%	*P* Value
Treatment																		
"Wait and see"	64	21.7			92	33.1												
Antibiotic therapy	231	78.3	8,033.08		186	66.9	5,878.30			151		9,337.68		166		6,247.23		
Type of antibiotics																		
Amoxicillin	74	32.0	1,018.88	12.7	96	51.6	1,495.63	25.4	< 0.001	81	53.6	2,599.07	27.8	155	93.4	5,186.45	83.0	< 0.001
Broad spectrum (amoxicillin-clavulanate+cephalosporins + macrolides)	157	68.0	7,014.20	87.3	90	48.4	4,382.67	74.6	< 0.001	70	46.4	6,738.61	72.2	11	6.6	1,060.78	17.0	< 0.001
Amoxicillin-clavulanate	106	45.9	3,965.36	49.4	70	37.6	3,441.81	58.6	< 0.001	60	39.7	5,752.58	61.6	5	3.0	531.45	8.5	< 0.001
Cephalosporins	47	20.3	2,921.05	36.4	16	8.6	794.51	13.5	< 0.001	10	6.6	986.03	10.6	6	3.6	529.34	8.5	< 0.001
Macrolides	4	1.7	128.80	1.6	4	2.2	146.35	2.5	0.002									

n Indicates the number of patient for each category.

as last line therapy after amoxicillin–clavulanate treatment failure. Macrolides are indicated only in the case of IgE-mediated penicillin allergy. Due to high prevalence of resistant *S. pneumoniae* (around 50%),[15] this drug could be ineffective. No international and national guidelines recommend the use of macrolides as first-line therapy.[13,16]

Regarding antibiotic dosage for AOM, our CP recommends an amoxicillin dose of 75 mg/kg/day administered every 8 hours. No clear consensus has been expressed on dosage and administration intervals in the literature. The recommendation for 75 mg/kg/day was made based upon local *S. pneumoniae* resistance patterns and previous pharmacokinetic and pharmacodynamic studies that have shown maximum eradication rate only at high doses of amoxicillin administered in 3 divided doses.[16] Dosage recommendations for the amoxicillin component of amoxicillin–clavulanate were 75 mg/kg in our AOM CP. In Italy, the only available formulation is 7:1, which means that an excessive increase in the amoxicillin component could be accompanied by clavulanate-related gastrointestinal side effects. However, despite the increase in dosage postimplementation, no difference in terms of side effects was observed between pre- and postintervention groups.

In contrast with rapid adoption of the recommended therapy duration of 10 days for children < 2 years old in the postimplementation period, recommended treatment duration for children > 2 years old with uncomplicated AOM of 5 days was adhered to more slowly after CP implementation, with higher adherence rates observed only after 3–4 months. Although we do not have data on prescriber's motivations, we speculate that this could reflect pediatricians' initial discomfort with AOM short-course treatment.

According to pharyngitis CP, given the high susceptibility of GAS to penicillin and the unavailability of phenoxymethylpenicillin on the Italian market, amoxicillin was always the first antibiotic treatment choice suggested. 17-19 A dramatic increase in amoxicillin prescriptions was documented in the post-CP implementation period, with a concomitant decrease in broad-spectrum antibiotic use. This included a statistically significant reduction in amoxicillin–clavulanate prescriptions. No guideline considers amoxicillin–clavulanate suitable for acute GAS pharyngitis because *S. pyogenes* does not produce beta-lactamase and the use of clavulanate would only increase related side effects. Despite no medical indication in the preintervention period, 46% of patients received it.

As with patients diagnosed with AOM, despite a remarkable decrease in broad-spectrum antibiotic prescription, no significant difference in treatment failures was observed between pre- and postintervention periods.

Our results are in line with previous experience,[8,10] showing similar significant changes in antibiotic prescription after CP implementation for common illnesses. In contrast with what was reported by Samore et al,[8] where significant effects were achieved only during the second year of the intervention, in our study changes took place immediately after CP implementation.

Furthermore, for both diseases, despite less overall antibiotic exposure in the postintervention group, adverse events did not increase.

Regarding costs per 1000 PD, after AOM CP implementation, there was a significant reduction in total expense per 1000 PD, with a savings of more than €2000. In particular, there was a significant reduction of spending on broad-spectrum antibiotics, which decreased more than €2500, in agreement with several studies that reported an important decrease in the expense for broad-spectrum antibiotics after CP implementation.[20–22] For pharyngitis, the expense for generic antibiotics alone decreased more than €3000, with a reduction in broad-spectrum antibiotics of around €5500 and a 10-fold decrease seen in amoxicillin–clavulanate costs.

These data confirm that amoxicillin represents the most cost-effective first-line treatment choice for both diseases.

Furthermore, this was a low-cost intervention. CPs were delivered as laminated pocket cards (around €0.90 each), and 3 educational lectures were presented during weekly rounds with low impact on physicians' and residents' clinical activities. However, a periodical recall programs may substantially contribute to maintain results achieved, as reported by Potocki et al.[23]

This intervention could be repeatable and quickly diffusible to other Italian centers. It would also likely be useful in primary care settings because AOM and pharyngitis are almost always managed in primary care by family pediatricians in Italy, so the relevance of the cost reduction in this setting would be much higher with a much larger population of patients treated, as reported by Piovani et al.[24]

In summary, our data show that CPs for AOM and GAS pharyngitis are associated with reduced rates of antimicrobial prescription and antibiotics costs with no significant change in treatment failure rates.

This study has strengths and limitations. This is the first study that evaluates the effectiveness of antimicrobial stewardship through CPs in an Italian hospital. This intervention was designed to be feasible, generalizable and was developed by a multidisciplinary team to guarantee the best quality and a high level of coordination of interventions.

For a deeper comprehension of PED physician behavior, all patients with ongoing therapy were excluded, to minimize influences in treatment choices by other physicians.

This is the first study with a phone call follow-up to assess antimicrobial stewardship in the PED context. This allowed us to collect information about treatment failure directly speaking to the families, collecting granular details about treatment outcome, such as antibiotic change for persistence of symptoms or for side effects.

The primary limitation of our study is the retrospective nature of the analysis. Despite the fact that CPs included information on how to diagnose AOM and pharyngitis, identifying patients through *International Classification of Diseases, 9th Revision* or descriptive diagnosis, it is possible that we included misdiagnoses. Furthermore, this was a single-center study, so further validation of this tool should include other Italian PEDs. The quality of single antimicrobial prescriptions was not evaluated. Moreover, our analysis of treatment failure was underpowered due to the high number of children lost to follow-up for wrong or no available phone number. Lastly, the persistence of intervention impact at periods longer than 6 months postimplementation was not evaluated.

For cost analysis, we considered only the direct cost of antibiotics, without considering the indirect costs that could arise from side effects and treatment failure, which, anyway, were similar between the 2 groups. Moreover, only 2 types of oral formulation were considered. Furthermore, only the cost of the generic antibiotic was considered, at the expense of the national Health Care System, and we did not investigate whether the families had bought the generic form or not. Because Italian pharmacies sell only preestablished quantities of antibiotics, the costs of prescribed therapy were overestimated because not related to the exact amount of drugs mg but to the costs of antibiotics packages bought by each family.

CONCLUSIONS

CP represents a promising, resource-efficient antimicrobial stewardship tool, especially in a PED setting.

Evidence-based CP supported by adequate provider education can effectively influence prescribing practices, reducing overall and broad-spectrum antibiotic prescription, improving the efficiency of patient care and reducing total antibiotic expenditure without compromising clinical outcomes.

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