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TITOLO TESI

DEVELOPMENT AND IMPLEMENTATION OF PEDIATRIC IN-HOSPITAL

ANTIMICROBIAL STEWARDSHIP POLICY THROUGH PEDIATRIC CLINICAL PATHWAYS

Coordinatore: Ch.mo Prof. Carlo Giaquinto

Supervisore: Ch.mo Prof. Carlo Giaquinto

Dottorando : Daniele Dona'

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INTRODUCTION

The emergence of multi-drug resistant organisms and their rapid global spread has transformed resistance from a challenge of an effective prescription to an important global public health threat with a substantial impact on patient outcomes such as duration of hospitalization, mortality, as well as on healthcare costs.

The European Antimicrobial Resistance Surveillance Network (EARS-Net) system has reported a dangerous rise in both Gram-positive and Gram-negative multidrug resistance bacteria in the last years showing that some countries such as Italy and Greece are strongly contributing to this worrisome increase.

In the US, each year at least 2 million people become infected with multi-drug resistant bacteria and at least 12,000 die as a direct result of these infections. In the EU the infections result in an estimated 25,000 deaths in 29 countries (5.1 per 100 000 inhabitants). Nevertheless, adverse drug events and excessive costs of treatment are also reasons for concern.

Antimicrobials are the most common prescribed drugs in the community and in hospitals, especially in the pediatric age. Unfortunately at the current time antibiotics are often unnecessarily prescribed both in the community, where too many people and especially children are receiving broad-spectrum antibiotics for viral infections, and in the hospital, where unnecessary long courses of broad-spectrum antibiotics drive antimicrobial resistance.

Although prudent antibiotic prescribing has been a high priority in the EU, there has not been a true focus on prescription patterns in the pediatric population.

For these reasons, in order to maintain efficacy of currently available drugs, initiatives such as antimicrobial stewardship programs have become increasingly vital.

Antimicrobial stewardship encompasses a heterogeneous set of interventions. Antimicrobial stewardship practices frequently focus on antimicrobial agent selection, dose, frequency and route. Each antimicrobial stewardship programs utilizes any number of these interventions based on local practices, resistance trends, and available resources. Guidelines for stewardship identify several potential strategies including: disease-specific clinical pathways, audit with feedback and formulary restriction with preauthorization of select agents. Each intervention has demonstrated decreased unnecessary antimicrobial exposure, reduced costs, and improved patient outcomes

A recent evaluation of various interventions concluded that active clinician education targeting multiple conditions is most likely to impact community antibiotic use. Clinical pathways are an effective means to change antibiotic prescribing behavior. Their purpose is to standardize care without adversely affecting patient safety or outcomes.

According to the most recent evidences, I've developed and implemented pediatric in-hospital antimicrobial stewardship policy through pediatric clinical pathways with the aim of creating a feasible, efficient, sharable and sustainable tool that can effectively influence prescribing practices without compromising clinical outcomes.

My PhD research protocol was articulated to study antimicrobial use and the way to optimize it from different perspectives. The first part of my work focused on epidemiological studies to evaluate the antibiotic prescription pattern in different settings. The overall pattern of antimicrobial use in Italy was studied (1) and then more specially the management of community-acquired pneumonia (5).

I then focused more specifically on Antimicrobial Stewardship. A systematic review in all different settings (2) and in the Neonatal Intensive Care unit (3) provided the background to implement some specific strategies such as Clinical Pathways, in the Pediatric Emergency Department, which has been evaluated for acute otitis media, pharyngitis (4,7) and community-acquired pneumonia (6,7), and in the Surgical Pediatric Department for the perioperative antibiotic prophylaxis (8).

Publications:

1) De Luca M#, Donà D#, Montagnani C, Lo Vecchio A, Romanengo M, Tagliabue C, Centenari C, D'Argenio P, Lundin R, Giaquinto C, Galli L, Guarino A, Esposito S, Sharland M, Versporten A, Goossens H, Nicolini G. Antibiotic Prescriptions and Prophylaxis in Italian Children. Is It Time to Change? Data from the ARPEC Project. PLoS One. 2016 May 16;11(5):e0154662. doi: 10.1371/journal.pone.0154662.eCollection 2016. PubMed PMID: 27182926;

2) Donà D, Mozzo E, Mardegan V, Trafojer U, Lago P, Salvadori S, Baraldi E, Giaquinto C. Antibiotics Prescriptions in the Neonatal Intensive Care Unit: How to Overcome Everyday Challenges. Am J Perinatol. 2017 Oct;34(12):1169-1177. doi: 10.1055/s-0037-1602426. Epub 2017 Apr 10. PubMed PMID: 28395369.

Donà D, Baraldi M, Brigado G, Lundin R, Perilongo G, Hamdy R, Zaoutis T, Da Dalt L, Giaquinto C. The impact of Clinical Pathways on antibiotic prescribing for acute otitis media and pharyngitis in the Emergency Department. Pediatr Infect Dis J, accepted on September 2017. In pres Donà D, Luise D, Da Dalt L, Giaquinto C.

5) Treatment of Community-Acquired Pneumonia: Are All Countries Treating Children in the Same Way? A Literature Review. International Journal of Pediatrics. Volume 2017 (2017), Article ID 4239268, 13 pages, https://doi.org/10.1155/2017/4239268s

6) Donà D, Zingarella S, Gastaldi A, Lundin R, Perilongo G, Frigo AC, Hamdy R, Zaoutis T, Da Dalt L, Giaquinto C. Effects of a clinical pathway on antibiotic prescriptions for pediatric community-acquired pneumonia. Accepted by PLoS One, October 2017

CHAPTER I

Antibiotic Prescriptions and Prophylaxis in Italian Children. Is It Time to Change? Data from the ARPEC Project

De Luca M#, **Donà D#**, Montagnani C, Lo Vecchio A, Romanengo M, Tagliabue C, Centenari C, D'Argenio P, Lundin R, Giaquinto C, Galli L, Guarino A, Esposito S, Sharland M, Versporten A, Goossens H, Nicolini G. Antibiotic **Prescriptions and Prophylaxis in Italian Children. Is It Time to Change? Data from the ARPEC Project**. **PLoS One**. 2016 May 16;11(5):e0154662.
doi: 10.1371/journal.pone.0154662.eCollection 2016. PubMed PMID: 27182926; PubMed Central PMCID: PMC4868290.
#Contributed equally

Abstract

Background

Antimicrobials are the most commonly prescribed drugs. Many studies have evaluated antibiotic prescriptions in the paediatric outpatient but few studies describing the real antibiotic consumption in Italian children's hospitals have been published. Point-prevalence survey (PPS) has been shown to be a simple, feasible and reliable standardized method for antimicrobials surveillance in children and neonates admitted to the hospital. In this paper, we presented data from a PPS on antimicrobial prescriptions carried out in 7 large Italian paediatric institutions.

Methods

A 1-day PPS on antibiotic use in hospitalized neonates and children was performed in Italy between October and December 2012 as part of the Antibiotic Resistance and Prescribing in European Children project (ARPEC). Seven institutions in seven Italian cities were involved. The survey included all admitted patients less than 18 years of age present in the ward at 8:00 am on the day of the survey, who had at least one on-going antibiotic prescription. For all patients data about age, weight, underlying disease, antimicrobial agent, dose and indication for treatment were collected.

Results

The PPS was performed in 61 wards within 7 Italian institutions. A total of 899 patients were eligible and 349 (38.9%) had an on-going prescription for one or more antibiotics, with variable rates among the hospitals (25.7% - 53.8%). We describe antibiotic prescriptions separately in neonates (<30 days old) and children (> = 30 days to <18 years old). In the neonatal cohort, 62.8% received antibiotics for prophylaxis and only 37.2% on those on antibiotics were treated for infection. Penicillins and aminoglycosides were the most prescribed antibiotic classes. In the paediatric cohort, 64.4% of patients were receiving antibiotics for treatment of infections and 35.5% for prophylaxis. Third generation cephalosporins and penicillin plus inhibitors were the top two antibiotic classes. The main reason for prescribing antibiotic therapy in children was lower respiratory tract infections (LRTI), followed by febrile neutropenia/fever in oncologic patients, while, in neonates, sepsis was the most common indication for treatment. Focusing on prescriptions for LRTI, 43.3% of patients were treated with 3rd generation cephalosporins, followed by macrolides (26.9%),

quinolones (16.4%) and carbapenems (14.9%) and 50.1% of LRTI cases were receiving more than one antibiotic. For neutropenic fever/fever in oncologic patients, the preferred antibiotics were penicillins with inhibitors (47.8%), followed by carbapenems (34.8%), aminoglycosides (26.1%) and glycopeptides (26.1%). Overall, the 60.9% of patients were treated with a combination therapy.

Conclusions

Our study provides insight on the Italian situation in terms of antibiotic prescriptions in hospitalized neonates and children. An over-use of third generation cephalosporins both for prophylaxis and treatment was the most worrisome finding. A misuse and abuse of carbapenems and quinolones was also noted. Antibiotic stewardship programs should immediately identify feasible targets to monitor and modify the prescription patterns in children's hospital, also considering the continuous and alarming emergence of MDR bacteria.

Background

Antimicrobials are the most commonly prescribed drugs in the community and hospital setting, especially among paediatric patients [1]. However, antibiotics are often unnecessarily used both in the community, where too many children receive broad-spectrum antibiotics for viral infections, and in the hospital, where long courses of broad-spectrum antibiotics are frequently prescribed [2]. Recent studies have found that up to 50% of antimicrobial prescriptions are inappropriate [3,4].

The emergence of multi-drug resistant (MDR) pathogens and their rapid global spread, strictly associated with an inappropriate use of antimicrobials, are important global public health threats with a substantial impact on patient outcomes such as hospital length of stay and mortality, as well as on healthcare costs [5–8]. The European Antimicrobial Resistance Surveillance Network (EARS-Net) system has reported a dangerous rise in MDR bacteria in the last years showing that some countries such as Italy are strongly contributing to this worrying increase [9].

Many studies have evaluated antibiotic prescriptions in the paediatric outpatient population highlighting the problem that Italian prescribing habits that differ from those of other European countries. An Italian child is more likely to be exposed to antibiotics than children are in North Europe [10] and, in particular, the prevalence of antibiotic prescriptions in childhood have been reported to be 4 times higher than in the UK and 6 times higher than in the Netherlands [11,12]. Moreover, Italy reported the highest prescription rate (1.3 per infants per year) in a study comparing antibiotic use in the first year of life in five European countries [13]. In fact, data from the Gagliotti et al study in 2006 show that the 55% of Italian infants in the community have already received at least one course of antibiotics at 1 year of age and 84% at 2 years of age [14].

Although a positive correlation between outpatient and inpatient antibiotic use has been noted [15], few studies describing the real antibiotic consumption in Italian children's hospitals have been published. A single centre study was carried out in Rome in 2008 [16] confirming the abuse of antibiotics observed in the outpatient population. A more recent paper evaluating the trend of antibiotic use in all the paediatric wards of Emilia-Romagna Region over an 8-year-period [17] indicated a slight increase of antibiotic consumption over

time, an inadequate tendency to prefer penicillin plus inhibitors to plain penicillins, an over-use of third generation cephalosporins and a worrisome increase in linezolid prescriptions.

In this paper, we present the results of a point-prevalence survey (PPS) on antibiotic prescriptions carried out in seven large Italian paediatric institutions in 2012. The aims of our study were: i) to describe prevalence rates of antibiotic prescriptions for prophylaxis and treatment of infections for neonatal (<30 days) and paediatric (age ≥30 days) patients in seven Italian centres; ii) to evaluate antibiotic prescriptions, indications, number and type of antibiotic agents and administration route in the same age sub-groups both for prophylaxis and treatment of infections; iii) to describe over-all consumption and off-label use of particular classes of antibiotics, such as carbapenems and quinolones, in our cohort; and iiii) to identify targets for improving the quality of antimicrobial prescribing in these centres.

Methods

This research has been conducted according to the principles expressed in the Declaration of Helsinki. Ethical approval has been obtained for the coordinating centre. No consent was given, because data were collected by reviewing medical charts and were analyzed anonymously. Every patient record was given a unique non-identifiable survey number, which was automatically generated by a computer program specifically designed for anonymous data entry.

A 1-day PPS on antibiotic use in hospitalized children was performed in Italy between October and December 2012 as part of the Antibiotic Resistance and Prescribing in European Children project (ARPEC). Seven paediatric or mixed adult-paediatric hospitals in seven Italian cities were involved (Genoa, Milan, Padua, Florence, Viareggio, Rome and Naples). The survey included all admitted patients less than 18 years of age present in the ward at 8:00 am on the day of the survey who had at least one on-going antibiotic prescription. The wards of admission were: medical (general neonatal and maternal wards, and general paediatric wards), special medical (cardiology, nephrology, onco-hematology, neuromuscolary, neurology, bronchopneumology, infectious diseases unit), neonatal and paediatric intensive care (NICUs and PICUs), surgical (neonatal surgery, paediatric surgery, orthopedics, neurosurgery). For feasibility reasons, one hospital provided data from randomly selected wards, maintaining the patient distribution among medical, special medical, surgical and intensive care units, in agreement with the coordinating centre. Full details of the ARPEC methodology are described elsewhere [18].

Results

The PPS was performed in 61 wards within seven Italian institutions. Characteristics of the centres involved are shown in **Table 1**. A total of 899 patients was present in the hospitals at 8:00 am on the day of the survey and 349 (38.9%) of these had an on-going prescription for one or more antibiotics. However, this rate was variable among the hospitals ranging from 25.7% to 53.8% (**Table 1**). Combination therapies were variably used among the institutions (21.7–60.3%) with a ratio between number of prescribed antibiotics and treated patients ranging from 1.25 to 1.76 (**Table 1**).

City	Hospital Characteristics	Treated patients	Total patients	Rates of treatment	Beds	Bed occupancy	N° of prescribed antibiotics	N° of prescribed antibiotics/ treated patients	Combination therapies	Combination therapies/ treated patients
Rome	Teaching hospital, tertiary hospital	63	117	53.8%	136	86.0%	111	1.76	38	60.3%
Padua	Teaching hospital, tertiary hospital	70	185	37.8%	213	86.9%	124	1.77	36	51.4%
Florence	Teaching hospital, tertiary hospital	59	144	41.0%	169	85.2%	98	1.66	26	44.1%
Milan	Teaching hospital, specialized hospital	38	100	38.0%	128	78.1%	55	1.45	14	36.8%
Genoa	Teaching hospital, tertiary hospital	83	217	38.2%	314	69.1%	104	1.25	18	21.7%
Naples	Teaching hospital, specialized hospital	28	109	25.7%	122	89.3%	42	1.50	11	39.3%
Viareggio	Secondary hospital	8	27	29.6%	45	60.0%	9	1.13	1	12.5%
TOT	-	349	899	38.8%	1127	79.8%	543	1.56	144	41.3%

Table 1. Characteristics of the 7 Italian institutions involved in the ARPEC project.

A wide variability also existed in the proportions of patients treated with at least one antibiotic stratified by ward type. In particular, special medical wards and intensive care units accounted for higher proportions of patients receiving antibiotics compared to surgical and medical wards (**Fig. 1**).
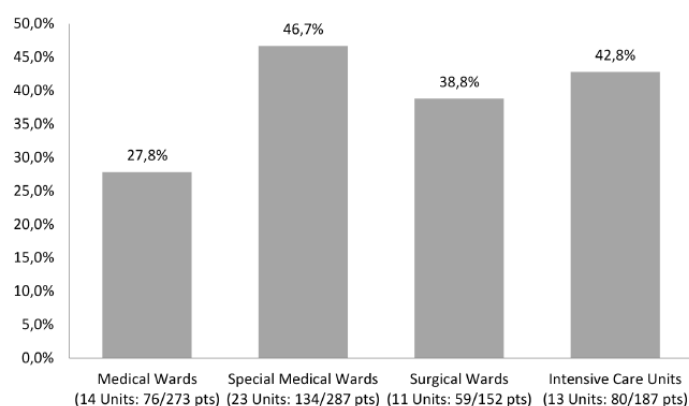
Figure 1. Proportion of paediatric patients treated with at least one antibiotic by ward type.

Characteristics of all patients enrolled are summarized in **Table 2**. Median patient age was 24 months and 12.3% were less than 30 days old. Overall, 24.6% of patients were affected by a medical/surgical underlying condition and the most frequent was an oncologic/hematologic disease. Noteworthy is that the rate of oncologic/hematologic patients admitted to the hospital at the time of the survey was 5% (45/899), but this rate increased to 22.3% (78/349) looking at the group of patients receiving antibiotics. These data reflect the fact that oncologic and hematologic patients were responsible for a large proportion of antibiotic consumption in our survey.

Median age	2 years (IQR 0.5–9)
Neonates	12.3% (n = 43/349)
Children	87.7% (n = 306/349)
Male/Female	201/148
Underlying conditions:	86/349
• Oncologic/hematologic disease	22.3%
• Surgical problem	20.8%
• Chronic lung disease	7.6%
• Respiratory distress syndrome	7.6%
• Chronic neurological condition	7%
• Congenital heart disease	6.7%
• Genetic and metabolic disease	6.4%
• Chronic renal disease	5.2%
• Prematurity and IUGR	4.9%
• Gastrointestinal disease	4.3%
• Other/unknown	4%
• Congenital immunodeficiency	2.4%
• Rheumatological disease	0.6%

Abbreviations: IQR= interquartile range

Table 2. Characteristics of the 349 Italian patients enrolled in the 24-hour ARPEC PPS.

We analyzed antibiotic prescriptions separately in neonates and children (**Table 3**).

	NEONATES		CHILDREN	
Department of admission:				
	NICU	36 (83.7%)	Special medical ward	131 (42.8%)
	General neonatal and paediatric department	4 (9.3%)	General paediatric ward	72 (23.5%)
	Special medical wards	3 (7%)	Surgery	59 (19.3%)
			PICU	26 (8.5%)
			NICU	18 (5.9%)
Indications to antibiotic therapy:				
	Prophylaxis for medical problems	24 (55.8%)	LRTI	68 (22.1%)
	Sepsis	13 (30.2%)	Prophylaxis for surgical disease	57 (18.6%)
	Prophylaxis for surgical problems	3 (7%)	Prophylaxis for medical problem	52 (16.9%)
	Skin and soft tissue infections	1 (2.3%)	Febrile neutropenia/fever in oncologic patient	23 (7.5%)
	Pyrexia of unknown origin	1 (2.3%)	Treatment for surgical disease	16 (5.2%)
	LRTI	1 (2.3%)	Other/unknown	15 (4.9%)
			Sepsis	13 (4.2%)
			UTI (upper and lower)	12 (3.9%)
			Upper respiratory tract infection	8 (2.6%)
			Catheter related bloodstream infection	8 (2.6%)
			Skin and soft tissue infection	7 (2.3%)
			Gastrointestinal tract infection	7 (2.3%)
			Pyrexia of unknown origin	6 (1.9%)
			CNS infection	6 (1.9%)
			Joint/bone infection	4 (1.3%)
			Tubercolosis	2 (1%)
			Lymphadenitis	1 (0.3%)
			Acute osteomyelitis	1 (0.3%)
Associations with antifungal agents	8 (18.6%)		48 (15.6%)	
Associations with antiviral agents	0		21 (6.8%)	

Table 3. Demographic characteristics and antibiotic prescription patterns of the neonates and children enrolled in the study.

Neonates

At the time of the survey, 248 neonates were admitted in participating hospitals and 43 were receiving antibiotics (17.3%). As shown in **Table 3**, neonates treated with antibiotics were mostly admitted in the NICUs (83.7%, 36/43). Moreover, 62.8% (27/43) of newborns were receiving antibiotics for prophylaxis and only 37.2% (16/43) were being treated for infection. The top two active antibiotic prescriptions were penicillins (69.8%, 30/43) and aminoglycosides (58.1%, 25/43). Details about indications to receive antibiotics are summarized in **Table 3**. All antibiotic classes prescribed are listed in **Fig 2**.
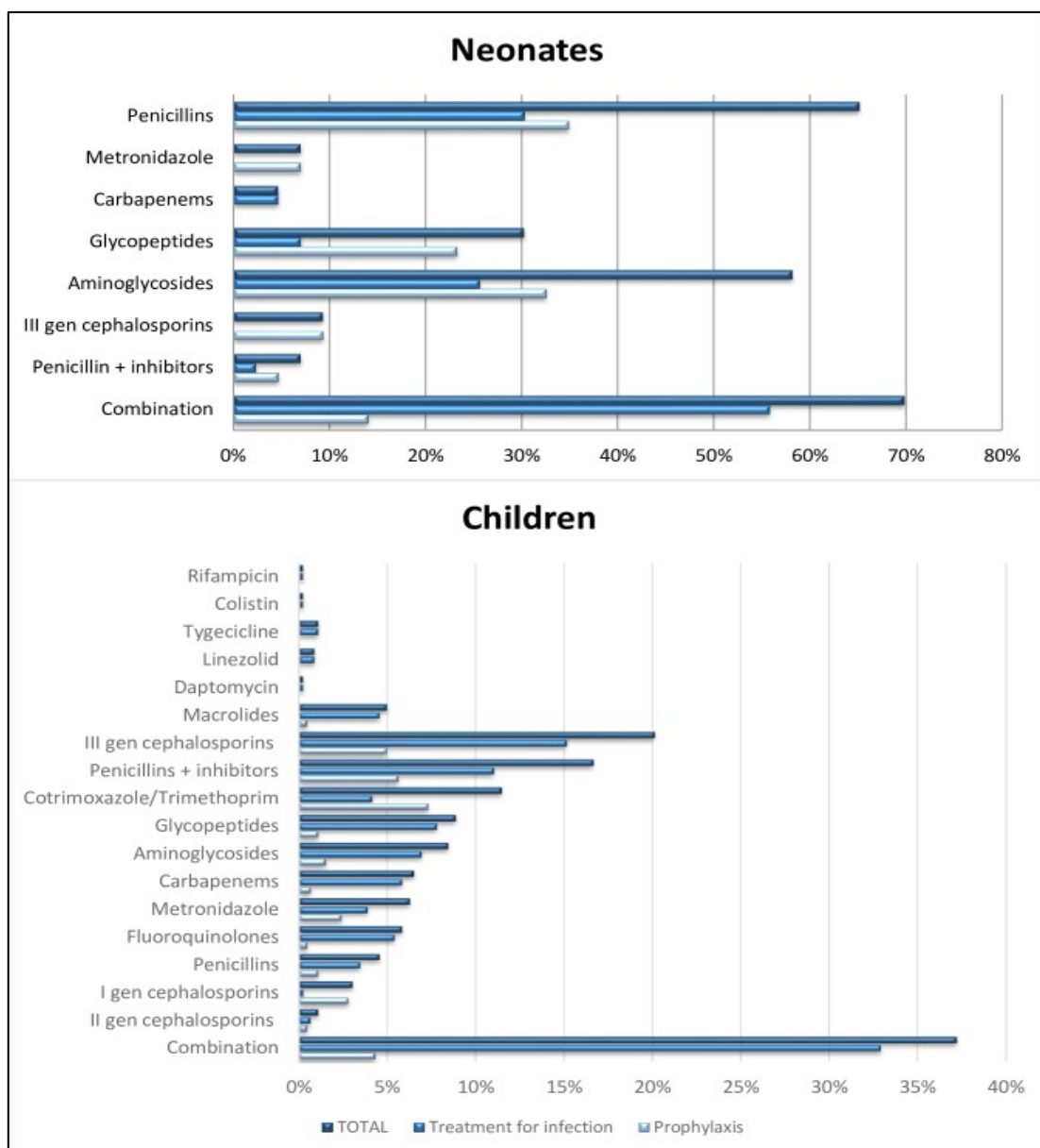

Figure 2. Antibiotic prescriptions among the neonates and children.

Antibiotic prophylaxis in neonates

The main indication to prescribe antibiotic prophylaxis was medical risk factors (e.g. prematurity, maternal fever during labor, prolonged rupture of the membranes), accounting for 55.8% of all indications for antibiotic therapy in the neonatal subset. The other neonatal patients were receiving prophylaxis for surgical reasons. Monotherapy was prescribed in 10 of the 27 patients on prophylaxis (37%), and penicillin was the most prescribed antibiotic (7/10). Combination therapies in the other 17/27 patients (63%) were variable: penicillins were combined with aminoglycosides in 7/17 cases, while glycopeptides were used with third generation cephalosporins in 3 cases and with aminoglycosides in 3 cases. The last 4 patients received 3 drug combination therapy, including glycopeptides plus aminoglycosides combined with metronidazole (2/4) or penicillin (2/4).

Antibiotic treatment in neonates

Among all the indications for antibiotic treatment of infection in neonates, the most common was sepsis (30.2%, 13/43). Monotherapy was used just in two cases (one case treated with ampicillin and the other treated with meropenem). Penicillins plus aminoglycosides was by far the preferred combination therapy (8/11), while in the other patients (3/11) glycopeptides were used widely in combination with other classes of antibiotics.

Children

The paediatric group was composed of 651 patients, 47% (306/651) of whom had an active antibiotic prescription at the time of the PPS. In the group of patients with active antibiotic prescriptions, 64.4% (197/306) were being treated for infections and 35.5% (109/306) for prophylaxis (**Table 3**). Third generation cephalosporins and penicillin plus enzyme inhibitors were the most commonly used antibiotic classes. More details about indications to therapy are reported in **Table 3**. All antibiotic classes prescribed are listed in "**Fig 2**".

Antibiotic prophylaxis in children

Approximately half of the children on antibiotics for prophylaxis received antibiotics for surgical reasons (52.3%, 57/109), the others for medical problems (47.7%, 52/109). The most prescribed antibiotics were third generation cephalosporins for surgery (35.9%, 20/57), used as monotherapy in 14/20 cases and combined most often with metronidazole in the other cases (3/20). Cotrimoxazole was the most commonly prescribed agent for the medical problems (67.3%, 35/52), mainly used as monotherapy (30/35).

Antibiotic treatment in children

The main reason for prescribing antibiotics for infection among children was lower respiratory tract infections (LRTI) (34%, 67/197), followed by febrile neutropenia/fever in oncologic patients (11.7%, 23/197). Focusing on prescriptions for LRTI, 43.3% (29/67) of patients were treated with third generation cephalosporins, followed by macrolides (26.9%, 18/67), quinolones (16.4%, 11/67) and carbapenems (14.9%, 10/67). Cephalosporins were used as monotherapy in 13/29 cases and combined in the other 16 cases, mostly with macrolides (6/16). For 73.1% (49/67) of children with LRTI, the route of antibiotic administration was parenteral.

For oncology patients affected by neutropenic fever/fever, the preferred antibiotics were penicillins with enzyme inhibitors (47.8%, 11/23), followed by carbapenems (34.8%, 8/23), aminoglycosides (26.1%, 6/23) and glycopeptides (26.1%, 6/23). Penicillins with enzyme inhibitors were used in monotherapy in 5/11 cases and combined mostly with aminoglycosides in the other 6 cases. Carbapenem monotherapy was prescribed in 4/8 cases, while combination therapy with anti-Gram positive agents (glycopeptides or oxazolidinones) was preferred in the other cases. The route of antibiotic administration was parenteral in the 95.7% of cases (22/23).

Use of Carbapenems

Among the 899 patients admitted to the hospital at the time of the survey, 32 (3.6%) were being treated with carbapenems. Focusing on the group of 349 patients with active antibiotic prescriptions at the time of the PPS, 8.9% (32/349) were receiving carbapenems (in particular 4.6% [2/43] in the neonatal group and 9.8% [30/306] in the paediatric group). Considering the overall rates of therapy by department, those with the highest rates of carbapenem prescription were the special medical wards (14.2%, 19/134) and the intensive care units (11.2%, 9/80), compared to 2.6% (2/76) in medical wards and 1.7% (1/59) in surgical wards. Indications for prescription of carbapenems were community-acquired infections in 53.1% of cases, hospital-acquired infections in 37.5% and prophylaxis in 9.3%. Febrile neutropenia was the most common reason for carbapenem prescription (34.8%, 8/23). Therapy was empirically prescribed in 62.5% (20/32) of patients. Carbapenems were mostly prescribed in combination with one or more other antibiotics (65.6%, 21/32), most commonly with glycopeptides (10/21), followed by quinolones (4/21), cotrimoxazole (4/21) and aminoglycosides (3/21). Meropenem was the most prescribed carbapenem, with great heterogeneity in doses and number of administrations recorded. Daily doses of meropenem ranged from 19 mg/kg/day to 129 mg/kg/day, while the mean dose was 70 mg/kg/day. Off-label

prescription of carbapenems (i.e. below 3 months of age) was recorded in 18.7% (6/32) of patients and the indications were LRTI, sepsis and surgical prophylaxis.

Use of Quinolones

In the entire cohort of patients admitted to the hospital, 3% (27/899) were prescribed quinolones. Among the patients with active antibiotic prescriptions, this rate was 7.7% (27/349). None of them were neonates, but 37% (10/27) were below 2 years of age. Considering the overall rates of prescriptions into the departments, the special medical wards (10.4%, 14/134) and intensive care units (7.5%, 6/80) reported the highest rates of quinolone prescription, compared to 6.6% (5/76) in medical wards and 3.4% (2/59) in surgical wards. Indications for prescription of quinolones were community-acquired infections in 44.4% of cases, hospital-acquired infections in 40.7%and prophylaxis in 14.8%. Considering the rates of antibiotic prescription by indication, the most common indication was LRTI (17.6%, 12/67). Among the group affected by LRTI, 41.6% (5/12) had an underlying chronic lung disease including cystic fibrosis and 25% (3/12) congenital immunodeficiency. In general, quinolone therapy was empirically prescribed in 63% of patients. Quinolones were prescribed as monotherapy just in 29.6% (8/27) of patients. In the other cases, they were widely combined with other antibiotics (70.4%, 19/27), especially with third generation cephalosporins (5/19). The mostly prescribed quinolone was ciprofloxacin. Focusing on ciprofloxacin, the prescribed daily dose ranged from 6 mg/kg/day to 30 mg/kg/day, while the mean dose was 18 mg/kg/day.

Discussion

The 1-day ARPEC PPS provided very useful data on hospital antibiotic prescriptions for paediatric and neonatal patients in Italy. According to data collected in seven large Italian institutions, 38.9% of inpatients received at least one antibiotic prescription during hospitalization. This rate is similar to the mean rate reported from the worldwide ARPEC PPS (36.7%) [18].

To better analyze antibiotic prescription patterns and their appropriateness, we assessed antibiotic prescriptions for prophylaxis and treatment of infection separately.

Our results show that overall 39% of patients were prescribed antibiotics for prophylaxis with the highest rate observed in the neonatal population (63% of neonatal prescriptions were for this indication). The main indication for neonatal prophylaxis was the presence of perinatal conditions (e.g. prematurity, maternal fever during labor, prolonged rupture of the membranes). Prophylactic monotherapy was prescribed just in 37% of neonates and penicillin was the preferred agent, while combination prophylactic therapies including penicillin plus aminoglycosides or glycopeptides plus cephalosporins/aminoglycosides were widely used in neonatal patients. This approach is not in-line with the international literature. Although neonates represent a high risk population due to their immature immune system and the invasive procedure they are likely to undergo in NICU (e.g. indwelling catheters, invasive mechanical ventilation), recent reviews reject the routine use of antibiotic prophylaxis due to lack of efficacy in many conditions [19–22]. Moreover, in 2010 the Center for Disease Control and Prevention revised their guidelines regarding the prevention of perinatal Group B streptococcal disease in healthy neonates, restricting the need for prophylaxis only to well-defined subgroups of patients [23]. Prolonged courses of antibiotics have also been associated with increased risk of necrotizing enterocolitis or death in low birth weight infants [24].

In the paediatric group, the rate of antibiotic prescriptions for prophylaxis was 35.5% of all the prescriptions. Approximately, half of these patients were receiving antibiotics for surgical prophylaxis in accordance with previous European reports in which the proportion of children receiving surgical prophylaxis ranged from 13 to 42% [25, 26]. Third generation cephalosporins ranked first in prescription frequency in this scenario, used often in monotherapy but combined with metronidazole in some cases, confirming their alarming overuse for this indication. This problem in fact was already raised by Ciofi et al in 2008 [16], but a recent paper published by Buccellato et al in 2015 shows that a limitation on the prescriptions of these drugs has not yet been reached [17]. However, it is worth noting that this finding was very variable among the seven centers, since some hospitals preferred the first generation cephalosporins for surgical prophylaxis, as suggested by international guidelines [27].

Cotrimoxazole was the most prescribed antibiotic for medical prophylaxis, used alone in most cases. As explanation, most of the treated children were affected by onco-hematological diseases and cotrimoxazole is the best treatment to prevent *Pneumocystis jirovecii* pneumonia in immunocompromised patients [28].

Regarding the prescription patterns for treatment of infection, the 37.2% of our neonatal cohort was prescribed at least one antibiotic for treating an infection, the main reason was sepsis and the most common antibiotic class was penicillins, combined with aminoglycosides in a large number of patients, in line with international literature [29, 30]. It is hard to compare prescription habits in our centres with other NICUs because of a wide variability of the rate of neonates prescribed antibiotics across hospitals, as shown by a recent multicenter study involving 127 NICUs in the US [31]. The 40-fold variations in prescription frequencies noted in this study did not appear to be related to higher infection burden, necrotizing enterocolitis incidence, surgical volume or mortality rate [31]. They have instead been attributed to frequent inappropriate courses of antibiotics in inpatient neonates, more commonly owing to an unnecessary antibiotic continuation than starting of a non-required therapy [32].

Focusing instead on the paediatric group, we noticed an excessive use of third generation cephalosporins for treatment of infection similar to that seen for surgical prophylactic use, as underlined before. In children with LRTIs, ceftriaxone was the most prescribed antibiotic, used as monotherapy or often combined with macrolides, with a wide total daily dose variability ranging from 12.1 mg/kg/day to 153.8 mg/kg/day. The frequent choice of ceftriaxone as first line therapy for treatment of uncomplicated LRTIs and, in some cases, the high dosage prescribed, are reasons of concern because they are not supported by current guidelines [33]. In fact, other European countries, as the UK and France, seem to have different prescribing patterns for LRTI, preferring amoxicillin/clavulanic acid as first line therapy [34].

An abuse of parenteral cephalosporins in Italian hospitalized children was already denounced in a study conducted by Esposito in 2001 [35] and is a well-known problem also in the adult population [36].

Noteworthy was also the widespread use of carbapenems and quinolones. Indeed, in our study population, among the 349 patients receiving antibiotics, 8.9% were being treated with carbapenems, whereas proportion of carbapenems for therapeutic use reported in the literature in European paediatric units is 4,2% [37]. Though carbapenems were prescribed in most cases for fever in cancer patients, which often requires aggressive antibiotic treatment considering the patients' immunological status and predisposition to severe infections, we are concerned about the increasingly popular usage of these agents for community acquired-infections, empiric treatment

and combination therapy. This is a very alarming finding, considering the doubling of carbapenem resistance rates in invasive isolates of *Klebsiella pneumoniae* reported by the European Antimicrobial Resistance Surveillance Network (EARS-Net)'s report from 2010 to 2013 [9] for Italy. We also found 18.7% off-label use in patients below 3 months of life, but this could be explained by the involvement of many of our centers in the European NEOMERO study, which aimed to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal sepsis and meningitis [38].

Similar problems were noticed also for quinolone prescription. Quinolones were widely used in our cohort, even if the license for the use of this antibiotic class below 18 years of age is restricted to few rare indications such as cystic fibrosis with pulmonary exacerbations, complicated urinary tract infections, post exposure prophylaxis against inhalational anthrax and severe infections with allergies to other antibiotics [39,40]. Among our patients, the main indication for treatment with quinolones was LRTI. In this group of patients, quinolones were often prescribed empirically and combined with other drugs, though current guidelines do not suggest quinolones as a first-line treatment considering that infections caused by pneumococci or atypical bacteria can still be successfully treated with high doses of β-lactams [41]. Furthermore, the Scottish Antimicrobial Prescribing Group (SAGP) in 2008 and the National Institute for Health and Care Excellence (NICE) in 2015 [42] recommended to avoid the use of quinolones as first line agents for empirical treatment of most commonly infections in primary care, because the overuse of these broad-spectrum antibiotics is associated with a significantly increased risk of *Clostridium difficile* infection [43,44]. The wide use of quinolones in our cohort could be explained by the finding that most of our patients receiving this treatment had underlying chronic pulmonary diseases, such as cystic fibrosis or secondary to immunodeficiencies, but the lack of data about their microbiological status did not allow us to evaluate the appropriateness of these prescriptions.

Our study highlights many feasible targets that need a prompt intervention with appropriate antimicrobial stewardship programs. International guidelines for stewardship identify a wide set of interventions including: disease-specific clinical pathways, audit with feedback and formulary restriction with preauthorization of select agents. The best type of interventions must be tailored according to local practices, resistance trends, and available resources [4]. While the most effective antimicrobial stewardship programs are built on proactive interventions, in settings where a robust antimicrobial stewardship team is hard to establish, clinical pathways tool represent a reasonable and feasible first step for implementation standardizing care without adversely affecting patient safety or outcomes [45, 46]. Moreover, annual PPS could be a useful tool to measure the impact of these interventions on antibiotic prescribing practices [18]. Thus, implementation of clinical

pathways in Italian paediatric hospitals associated with annual PPSs could be a good start to reduce the abuse and misuse of antibiotics.

Our study has some limitations. First, data about microbiological isolates and antibiotic susceptibility tests, length of therapies and prophylaxis and previous antibiotic courses could have been useful to better define the appropriateness of antimicrobial prescriptions. Moreover, the characteristics of involved institutions may have affected at least in part the reliability of some results. Most institutions are in fact tertiary care hospitals that usually manage more complicated and severe cases, which might significantly impact antibiotic prescriptions. In addition, the heterogeneity among institutions, in terms of presence/absence of onco-hematology departments or intensive care units, may strongly affect antimicrobial prescription patterns. Finally, the survey was conducted in 2012 and since then a greater awareness of antibiotic stewardship programs has spread among Italian hospitals [47–49].

Conclusions

Our study took a picture of the Italian situation in terms of antibiotic prescriptions in hospitalized neonates and children and identified many feasible targets that require a prompt intervention to reduce the abuse and misuse of antibiotics. Antibiotic stewardship programs should immediately introduce measures to control prescription patterns in particular for prophylaxis, both in neonatal and paediatric populations, and to limit the over-use of third generation cephalosporins, that seems to persist over-time. Surveillance and educational programs are also needed to restrict the use of carbapenems to more severe conditions. The implementation of disease-specific clinical pathways associated with annual PPSs could be a good way to monitor and ameliorate antibiotic prescription patterns in neonatal and paediatric inpatients over time, in order to reduce as much as possible the worrisome emergence of MDR bacteria in this vulnerable population.

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CHAPTER II

Antimicrobial stewardship programs in pediatric care: a systematic review

Abstract

Background

Antibiotics are the most common prescribed drugs among children in hospitals and communities. It has been demonstrated that a great number of these prescriptions are inappropriate or unnecessary. Antibiotic abuse and misuse increases the risk for serious side effects, raises costs, and heavily contributes to the antimicrobial resistance emergency. Therefore, the implementation of strategies to improve the appropriateness of antibiotic prescription has become an urgent public health priority. Antimicrobial stewardship programs (ASPs) are key instruments to tackle this emergency. The primary aim of this systematic review is to summarize the current state of evidence of the effects of ASPs in pediatrics worldwide; our secondary aim is to compare ASPs practice and implementation between US and Europe.

Methods

PubMed and Cochrane Library were systematically searched to identify studies reporting on ASP in children aged 18 years conducted in outpatients or in-hospital settings. Two investigators independently reviewed identified articles for inclusion and extracted relevant data.

Results

Of the 6435 studies screened, 82 were eligible for inclusion in this study. Most of the studies originated from the US (63%), while a minority from Europe (13%). Forty-nine (60%) studies used a before-and after design and only ten (12%) were randomized trials. The vast majority (85%) described an in-hospital ASP, half of the interventions involved mixed pediatric wards, and 6 (7%) studies were performed in Emergency Department. Only 10 (12%) studies were focused on the costs of an ASP.

Conclusions

ASPs pediatric has significant impact on reducing targeted- and nontargeted-antimicrobial use, costs, and resistances both in inpatient and outpatients settings. Despite these results, pediatric ASPs are spreading rapidly in the US, while their implementation in Europe is still challenging. Further efforts in developing more ASPs are needed.

Background

Antimicrobials are the most common prescribed drugs, especially in paediatrics [1-3].

It has been estimated that 37-61% of hospitalized infants and children receive antibiotics [4-8]. Moreover, it has been demonstrated that from 20 to 50% of prescriptions are unnecessary or inappropriate [9-13]. Too many children still receive broad-spectrum antibiotics for viral infections or antibiotic courses significantly longer than needed [14-18].

This unnecessary exposure increases the risk for serious side effects, raises costs, and heavily contributes to the antimicrobial resistance emergency [7, 19]. Although antimicrobial resistance occurs naturally or can be acquired through gene transfer, antimicrobial misuse promotes the selection of resistant organisms [20, 21]. The emergence of resistant pathogens and their rapid global spread has rapidly become an important global public health threat with a substantial burden for patients, prolonging hospital stays, increasing incidence of *Clostridium difficile* infection and mortality as well as increasing healthcare costs [22-27]. Indeed, if antibiotic prescribing in adults and children could be reduced, selection and transmission of resistant strains would decrease. This is particularly important since there has been a steady decline in the number of new antibacterial drugs approved over the last few decades on both sides of the Atlantic [28, 29].

The World Health Organization and the United Nations at the General Assembly of 2016 identified the development of country-level and institutional antimicrobial stewardship programs (ASPs) key instruments to tackle this emergency [30, 31].

From 2007, the Infectious Disease Society of America (IDSA) formally introduced the concept of ASP as a set of coordinated interventions designed for improving antimicrobial use (appropriate agent, dose, route of administration and therapy duration) without compromising patient outcome [32]. The Pediatric Infectious Diseases Committee on Antimicrobial Stewardship has defined the development of ASPs in three different settings—inpatients, special populations (e.g. oncology) and outpatients. Indeed, ASPs characteristics may vary to best fit the needs of different setting [33]. The primary aim of this systematic review is to summarize the current state of evidence of the effects of ASPs in paediatrics worldwide; our secondary aim is to compare ASPs practice and implementation between US and Europe.

Materials and methods

Study design and Search strategy

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34]. In conjunction with a medical librarian, we conducted a systematic search of Pubmed and Cochrane Library databases including citations from January 1, 2007 to October 23, 2017 with a strategy combining Medical Subject Heading (MeSH) and free-text terms for 'children' AND 'antimicrobial' AND 'stewardship'. The full strategy is provided in the **Supporting information**.

Inclusion criteria

Studies were eligible for full-text review if they included all of the following: patients younger than 18 years and conducted in outpatients or in-hospital settings. Randomized controlled trials, controlled and non-controlled pre- and post- studies, controlled and non-controlled interrupted time series and cohort studies were included.

Exclusion criteria

Review articles, case series, letters, notes, conference abstracts and opinion articles were excluded. Papers on both adults and children where extraction of paediatric data was not possible were also excluded. We excluded studies published in non-English language and before 2007 because AS concept was formally introduced in 2007.

Study selection

Title and abstract as well as full-text assessment was conducted independently by two investigators (DD and MD); any differences in opinion regarding study selection and study details were resolved by a consensus. Three rounds of article assessment were conducted before selecting the final list for data abstraction. The selection process is summarized in **Figure 1**.

Data collection

Data were extracted using a standardized data collection form, which summarized information about: authors, year of publication, study design, country, study period, setting, multicentric involvement, type of intervention and main results.

Figure 1. Flow-chart of the study selection process

Results

Of 6435 title and abstracts, 82 were eligible for inclusion in this study.

Most of the studies originate from the US (52/82, 63.4%) while other AS experiences are sparse.

Only 11/82 (13.4%) papers describe an implementation of ASP in Europe while seven originate from low-income countries.

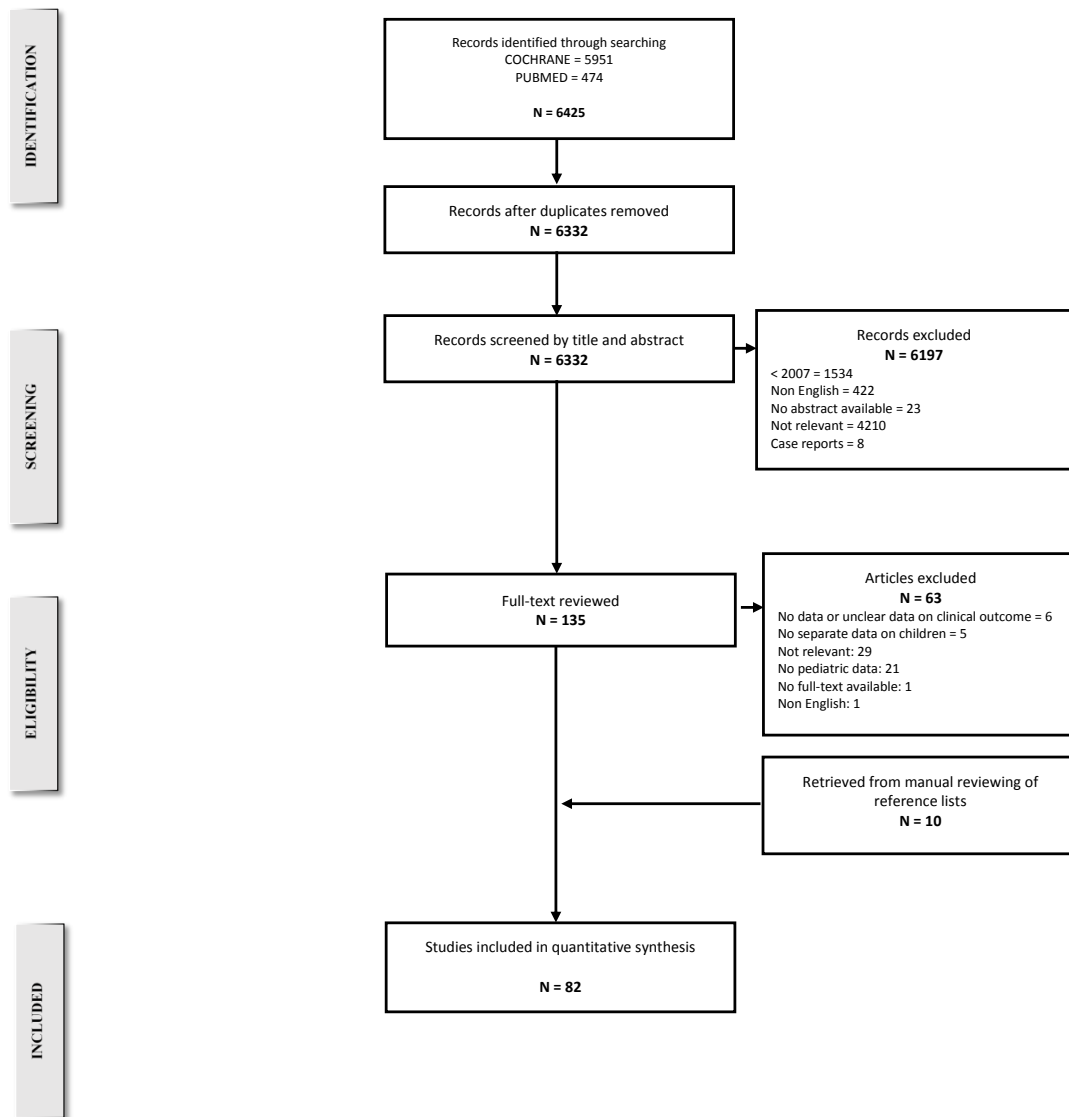Authors, year of publication, study design, country, study period, setting, multicentric involvement, type of intervention and main results are summarized in **table 1**.

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Agwu et al, 2008[116]	Before and after	US	Jul 2004 - Jun 2005; Jul 2005 - Jun 2006	Hospital (all wards)	Yes	Pre-authorization	A $370,069 reduction in projected annual cost associated with restricted antimicrobial use and an 11.6% reduction in the number of dispensed doses
Ajayi et al, 2008[60]	Before and after	Southwest Nigeria	Mar 2002 - Oct 2004	Outpatient	No	Education involving parents	Increase in the correct use of chloroquine from 2.6% to 52.3%
Akter et al, 2009[77]	Before and after	Bangladesh	1998 - 2000	Hospital (all wards)	Yes	Education	Appropriate antimicrobial therapy for pneumonia and diarrhea increased by 16.4% and 56.8% respectively
Al-Tawfiq et al, 2017[61]	Observational	Saudi Arabia	Dec 2012 - Dec 2013	Outpatient	No	Audit and feedback + Education	The monthly rate of prescription of inappropriate antibiotics significantly decreased from 12.3% to 3.8%
Ambroggio et al, 2013[78]	Before and after	US	May 2011 - July 2012	ED and pediatric ward	No	CP	Appropriate first-line antibiotic prescriptions for CAP increased from of 0% to 100% at the ED and on the hospital medicine resident teams from 30% to 100%
Aronson et al, 2015[79]	Retrospective	US	2014	ED	Yes	Guidelines	Ceftriaxone use at ED discharge varied significantly based on CPG recommendations
Baer et al, 2013[46]	Randomized trial	Switzerland	Jan 2009 - Feb 2010	ED	Yes	Laboratory (PCT)	Mean duration of antibiotic exposure was reduced from 6.3 to 4.5 days under PCT guidance for all LRTI and from 9.1 to 5.7 days for pneumonia
Berild et al, 2008[7]	Before and after	Russia	Oct - Dec 2002; Oct - Dec 2003; Oct - Dec 2004	Two Pediatric wards	No	Guidelines	The percentage of patients with GII who received antibiotics decreased from 94% in 2002 to 41% in 2003, but increased to 73% in 2004. In RTI patients these percentages were 90% in 2002, 53% in 2003 and 83% in 2004
Bourgeois et al, 2010[62]	Randomized trial	US	Oct 2006 - Apr 2007	Outpatient	Yes	Computerized decision support	Prescriptions for ARI significantly reduced (31.7% vs 39.9%; P = .02) as the use of macrolides (6.2% vs 9.5%; P = .02)
Cantey et al, 2016[59]	Observational	US	Oct 2011 - Nov 2012); Oct 2013 - Jun 2014	NICU	No	A 48h electronic "hard stop"	Antibiotic use declined from 343·2 days of therapy per 1000 patient-days to 252·2 days of therapy per 1000 patient-days

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Caruso et al, 2017[55]	Before and after	US	Jan 2012 – Dec 2013; Jan 2014 – Dec 2016; Jan 2016 – May 2016	Hospital (all wards)	No	Electronic medical record order set + utilization of pharmacists to prepare antibiotic. (perioperative prophylaxis)	The rate of compliance of administering cefazolin at 30 mg.kg-1 was significantly higher when given after an electronic order than when given verbally, 94% vs 76%
Chan et al, 2015[80]	Before and after	US	Apr 2001 – Mar 2004; Apr 2004 – Mar 2007	Hospital (all wards)	No	Audit and feedback	Vancomycin use declined from 378 doses administered/1000 patient-days to 208 doses administered/1000 patient- days (45%). Following the implementation of preauthorization, vancomycin use decreased by an additional 16%
Chiu et al, 2011[81]	Before and after	US	6 months 2005-2006; 6 months 2006-2007	NICU	Yes	Guidelines	Vancomycin start rates were reduced from 6.9 to 4.5 per 1000 patient-days (35% reduction; P <0.01) at Brigham and Women's Hospital, and from 17 to 6.4 per 1000 patient-days (62% reduction; P < 0.0001) at Massachusetts General Hospital. The number of infants exposed to vancomycin decreased from 5.2 to 3.1 per 1000 patient-days (40% reduction; P < 0.008) at Brigham and Women's Hospital, and 10.8 to 5.5 per 1000 patient-days (49% reduction; P < 0.009) at Massachusetts General Hospital. Causes of infection, duration of bacteremia, and incidence of complications or deaths attributable to late-onset infection did not change significantly at either institution
Dassner et al, 2017[82]	Before and after	US	Jul 2014 - Jun 2015	Hospital (all wards)	No	Pre-authorization	Appropriateness of second-sign restricted antibiotic use significantly increased (84.5% to 92.9%)

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Dimopoulou et al., 2016[54]	Before and after	Greece	Apr 2013 - Dec 2014	Hospital (all wards)	No	Guidelines (perioperative prophylaxis)	The percentage of patients receiving appropriate perioperative antimicrobial prophylaxis improved from 6.2% to 77.1%
Di Pentima et al, 2009[84]	Prospective	US	Apr 2004 - Mar 2005	Hospital (all wards)	No	Audit and feedback	Errors rate associated with these was 0.09/1000 doses administered and 5 errors/1000 patient days
Di Pentima et al, 2010[83]	Prospective	US	Apr 2004 - Mar 2007	Hospital (all wards)	No	Audit and feedback	Density of vancomycin use declined overtime from 378 doses administered/1000 patient-days to 255 doses administered/1000 patient-days. The rate of vancomycin prescription errors decreased
Di Pentima et al, 2011[117]	Before and after	US	Apr 2004 - Mar 2007	Hospital (all wards)	No	Audit and feedback	Total antimicrobial use decreased to 1904 doses administered per 1000 patient-days per year. Targeted- antimicrobial use declined from 1250 to 988 doses administered per 1000 patient-days per year. Nontargeted-antimicrobial use declined from 1839 to 916 doses administered per 1000 patient-days per year. Rates of antimicrobial resistance to broad-spectrum antimicrobials among the most common Gram-negative bacilli remained low and stable over time
Ding et al., 2008[118]	Before and after	China	Jan 2002 - Dec 2006	PICU	No	Guidelines + Education + control of antibiotic prescriptions with the use of a guideline	Reduction in the rate of antibiotic cost/patient/day (P<0.05); a decrease in the prescription rate of third-generation cephalosporins and macrolides (P<0.01); an increase in the prescription rate of b-lactam/b-lactamas inhibitors and second-generation cephalosporins (P<0.01); a reduction in the empiric treatment (P<0.01); and a significant reduction in the incidence rates of bacterial resistance for imipenem-, cefepime-, and ceftazidime-resistant Pseudomonas aeruginosa (P<0.05), and cefepime-resistant Escherichia coli and Klebsiella pneumoniae (P<0.01)

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Dommett et al, 2009[131]	Prospective	UK	Apr 2004 - Mar 2005	Oncology	Yes	Guidelines and checklist	Low hospital readmission rate (8/143 episodes; 5.6%), no intensive care admissions and no deaths in LR episodes
Doyon et al, 2009[85]	Before and after	Canada	Oct 2004 - Mar 2005; Oct 2005 - Jan 2006; Jan 2006 - Mar 2006	Hospital (all wards)	No	Guidelines	Guidelines compliance increased from 131/652 (20.1%) to 264/499 (52.9%). An inappropriate choice of antibiotic agent decreased from 347/521 (66.6%) to 99/235 (42.1)
Esposito et al., 2011[47]	Randomized trial	Italy	Oct 2008 - Sep 2010	Hospital (all wards)	No	Laboratory (PCT)	The PCT group received significantly fewer antibiotic prescriptions (85.8% vs 100%; $p < 0.05$), were exposed to antibiotics for a shorter time (5.37 vs 10.96 days; $p < 0.05$), and experienced fewer antibiotic-related adverse events (3.9% vs 25.2%; $p < 0.05$), regardless of CAP severity. There was no significant difference in recurrence of respiratory symptoms and new antibiotic prescription in the month following enrollment
Finkelstein et al., 2008[63]	Randomized trial	US	Sep 1998 - Mar 2004	Outpatient	Yes	Audit and feedback + Guideline + Education + Education involving parents	4.2 % decrease among children aged 24 to <48 months and 6.7% decrease among those aged 48 to <72 months
Forrest et al, 2013[64]	Randomized trial	US	Dec 2007 - Sep 2010	Outpatient	Yes	Computerized decision support	The increase from baseline to intervention periods in adherence to guidelines was larger for CDS compared with non-CDS visits

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Gerber et al, 2013[65]	Randomized trial	US	Oct 2008 - Jun 2011	Outpatient	Yes	Audit and feedback + Education	Broad-spectrum antibiotic prescribing decreased from 26.8% to 14.3% vs from 28.4% to 22.6% in controls. CAP off-guideline prescribing decreased from 15.7% to 4.2% among intervention practices compared with 17.1% to 16.3% in controls. Acute sinusitis off-guideline prescribing decreased from 38.9% to 18.8% in intervention practices and from 40.0% to 33.9% in controls. Off-guideline prescribing was uncommon at baseline and changed little for streptococcal pharyngitis and for viral infections
Geurts et al, 2013[119]	Before and after	The Netherlands	Jan 2008 - Jan 2009; Apr 2010 - Apr 2011	ED	No	Guidelines	Guidelines compliance increased (24.9 % pre vs 46.7 % post)
Gill et al, 2009[76]	Before and after	Philippines	May 2003 - Aug 2004	NICU	Yes	Guidelines (simplified package of infection control measures)	Staff hand hygiene compliance improved and overall mortality declined. Colonization with resistant pathogens and sepsis rates did not change significantly at either NICU
Gillon et al, 2017[86]	Before and after	US	2009 - 2014	Hospital (all wards)	No	Audit and feedback	Monthly vancomycin use decreased from 114 DoTs/1000 patient-days to 89 DoTs/1000 patient-days
Goldman et al, 2015[87]	Retrospective	US	Mar 2008 - Mar 2013	Hospital (all wards)	No	Audit and feedback	Third-generation cephalosporins, (0.20) were the antimicrobials with the highest predictive probability of an ASP recommendation whereas linezolid (0.05) had the lowest probability
Gong et al, 2016[88]	Before and after	China	Jan 2011 - Apr 2011; May 2011 - Sep 2011; Oct 2011 - Nov 2012	Hospital (all wards)	No	Pre-authorization + financially punished audit and feedback	The proportion of both antibiotic prescriptions and expenditure on antibiotics dropped immediately

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Hersh at al, 2015[89]	Retrospective	US	2007 - 2012	Hospital (all wards)	Yes		8 of 9 ASP+ hospitals revealed declines in antibiotic use, with an average monthly decline in days of therapy/1000 patient-days of 5.7%. For the select subset of antibiotics, the average monthly decline was 8.2%
Hersh et al, 2017[66]	Before and after	US	May 2013 - Apr 2014; May 2014 - May 2015	Outpatient	No	Audit and feedback	Introduction of the program was associated with a 24% reduction in OPAT use
Holzmann-Pazgal et al, 2015[90]	Before and after	US	Oct 2012 - Apr 2014	NICU	No	Audit and feedback + Education	Vancomycin utilization and administration duration >3 days significantly decreased but it was not affected by addition of audit and feedback
Horikoshi et al, 2016[91]	Retrospective	Japan	Mar 2010 - Mar 2015	Hospital (all wards)	No	Pre-authorization	Administration of carbapenems, piperacillin/tazobactam, and ceftazidime decreased significantly. Antibiotic costs were reduced by 26,000 USD annually. None of the antipseudomonal agents showed decreased sensitivity
Horikoshi et al, 2017[92]	Retrospective	Japan	Oct 2011 - Sep 2015	Hospital (all wards)	No	Pre-authorization + audit and feedback	DOTs of cefepime, piperacillin/tazobactam, meropenem, vancomycin, liposomal amphotericin B, and fosfluconazole decreased by 20%, 45%, 57%, 38%, 85% and 44%, respectively(p<0.05). The total cost of antibiotic and antifungal agents decreased by 27%, for a savings of $59,905 USD annually
Horikoshi et al, 2017[93]	Before and after	Japan	Apr 2010 - Sep 2011; Oct 2011 - Mar 2017	Hospital (all wards)	No	Pre-authorization + audit and feedback	A positive correlation was observed between the carbapenem resistance rate in Pseudomonas aeruginosa and DOT (0.76, p = 0.04). The carbapenem resistance rate in P. aeruginosa (p < 0.01) and DOT (p < 0.01) decreased significantly

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Hsu et al, 2016[67]	Prospective	US	Jul 2010 - Mar 2014	Outpatient	No	A comprehensive assessment tool for regimen simplification	Patients who had recommendations implemented within 6 months had a 7-fold higher probability of achieving a 0.7 log10 reduction in VL by 6 months, and this benefit remained significant after controlling for adherence [adjusted OR 6.8 (95% CI 1.03-44.9, p <0.05)]
Hum et al, 2014[120]	Prospective	US	Jul 2010 - May 2012	NICU	Yes	clinical decision support (CDS) tool	Most (63%) survey respondents were aware of the CDS tool, but fewer (37%) used it during their most recent NICU rotation
Hurlimann et al, 2015[68]	Randomized trial	Switzerland	Jan 2011 - 31 Dec 2012	Outpatient	Yes	Guidelines	The intervention was less effective in pediatric practices than in general or internal practices
Hurst et al, 2016[94]	Before and after	US	Oct 2010 - Sep 2014	Hospital (all wards)	No	Audit and feedback	Overall antimicrobial use decreased by 10.9% during the 4 years of the analysis. Vancomycin use decreased by 25.7%, meropenem by 22.2% without a compensatory increase of other antipseudomonal agents
Kreitmeyr et al, 2017[132]	Before and after	Germany	Sep 2014 - Dec 2014; Sep 2015 - Dec 2015	Hospital (all wards)	No	Audit and feedback	Overall days-of-therapy and length-of-therapy decreased by 10.5 and 7.7%, respectively. Use of cephalosporins and fluoroquinolones decreased by 35.5 and 59.9%, whereas the use of penicillins increased by 15.0%. An increase in dosage accuracy was noted (78.8 vs. 97.6%) and guideline adherence for CAP improved from 39.5 to 93.5%
Labenne et al, 2007[133]	Prospective	France	Feb 2002 - Jun 2003	NICU	Yes	Guidelines for EOS	The EONI cure rate was 96.8% without infectious relapse

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Lee et al, 2016[95]	Before and after	US	Sep 2010 - Aug 2011; Sep 2011 - Aug 2012; Sep 2012 - Aug 2013.	Hospital (all wards)	No	Guideline education	+ Hospital-wide targeted broad-spectrum antibiotic days of therapy/1,000 patient-days decreased from 33% to 70%. The overall antibiotic days of therapy decreased 41%, 21%, and 18%, and targeted broad-spectrum antibiotic days of therapy decreased by 99%, 75%, and 61% in the cardiac, pediatric, and neonatal ICUs, respectively. Yearly purchases of our most common broad-spectrum antibiotics decreased 62% from $230,059 to $86,887 after guideline implementation. Median monthly purchases of these drugs before implementation were $19,389 and $11,043 after implementation (p < 0.001)
Lee et al, 2007[96]	Before and after	South Korea	Jan 1999 - Dec 2005	Hospital (all wards)	No	Pre-authorization	Piperacillin/tazobactam use increased from 2.2 to 108.0 days on antibiotics/1000 patient admission days/year (AD) (P<0.001), whereas extended-spectrum cephalosporin use decreased from 175.0 to 96.9 AD (P<0.001). Among 252 strains of E. coli and K. pneumoniae, the overall prevalence of ESBL producers decreased from 39.8% (41/103) to 22.8% (18/79) (p< 0.018)
Liem et al, 2010[97]	Retrospective	The Netherlands	1990-2008	NICU	No	Audit and feedback	Total antimicrobial use, expressed as DOT decreased significantly, from 9.0 to 5.8
Lighter-Fisher et al, 2017[98]	Before and after	US	Jan 2010 - Dec 2011; Jan 2014 - Dec 2015	Hospital (all wards)	No	Audit and feedback	Total antimicrobial days of therapy and length of therapy decreased significantly. The susceptibility profiles of common bacterial pathogens to antibiotics remained stable
Mainous et al, 2013[69]	Before and after	US	Oct 2009 - Dec 2009; Jan 2010 - Mar 2011	Outpatient	Yes	Computerized decision support	Decline of 19.7% in broad-spectrum antibiotic prescriptions versus an increase of 0.9% in control practices

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Malcolmson et al, 2017[50]	Retrospective	US	Oct 2009 - Jul 2010; Oct 2013 - Jul 2014	Hospital (all wards)	No	Laboratory - MALDI-TOF technology and ASP	Time to optimal therapy reduced (77.0 to 54.2 h). In the subgroup analysis of Gram-negative bacteremia, time to effective and optimal therapy were significantly reduced (2.0 vs 0.7 h and 146.8 vs 48.0 h, respectively)
McCulloh et al, 2015[99]	Retrospective	US	Mar 2008 - Jun 2013	Hospital (all wards)	No	Audit and feedback	Ceftriaxone was the most common antibiotic associated with a recommendation (154/350, 44.0%); community-acquired pneumonia was the most common diagnosis (105/350, 30.0%). Disagreement with ASP recommendations was associated with a decreased length of stay of 15.4 (95% confidence interval −33.2 to 1.1) hours but not 30-day readmission prevalence
Messacar et al, 2017[51]	Before and after	US	Jan 2015 - Mar 2015	Hospital (all wards)	No	Laboratory - FilmArray blood culture identification panel	The median time to optimal therapy decreased from 60.2 hours to 26.7 hours. Among children with blood cultures that contained true pathogens, the time to effective antimicrobial therapy decreased from 6.9 to 3.4 hours. Unnecessary antibiotic initiation for children with a culture that contained organisms considered to be contaminants decreased from 76% to 26%
Messacar et al, 2017[121]	Before and after	US	Oct 2010 - Sep 2015	Hospital (all wards)	No	Audit and feedback	Mean monthly ID consultations per 1000 admissions increased from 31.0 to 42.0
Metjian et al, 2008[100]	Prospective	US	Apr 2005 - Jul 2005	Hospital(all wards)	No	Pre-authorization + audit and feedback	Forty-five percent of calls required an intervention by the ASP:1) Targeting the known or suspected pathogens (20%); 2) Consultation (43%); 3) Optimize antimicrobial treatment (33%); and 4) Stop antimicrobial treatment (4%)

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Miloslavsky et al, 2017[122]	Before and after	US	2010 - 2013; Jan 2015 - Feb 2016	Hospital (all wards)	No	Guidelines	The time to therapeutic trough decreased from 2.78 to 1.56 days. Vancomycin-related toxicity was unchanged by the intervention (6.1% versus 4.5%)
Money et al, 2017[101]	Retrospective	US	2009 - 2016	NICU	No	Protocol based on a neonatal early-onset sepsis (EOS) calculator	Antibiotic use decreased from 99% to 2.5%. Average length of therapy decreased from 2.08 to 0.05 days
Murki et al., 2010[102]	Before and after	India	Jan 2007 - Dec 2008	NICU	No	Cephalosporins restriction policy	Five-fold decrease in the use of cephalosporins and nearly two folds increase in the use of ampicillin and ciprofloxacin. The incidence of ESBL gram negatives decreased by 22% (47% to 25%). Cefotaxime and ciprofloxacin resistance decreased (cefotaxime 81% vs 51%; ciprofloxacin 56%% vs 29%)
Murni et al, 2015[103]	Before and after	Indonesia	Dec 2010 - Nov 2011; Dec 2011 - Feb 2012; Mar 2012 - Feb 2013	PICU and Pediatric wards	No	Guidelines + Infection control practices implementation	Major reduction in HAIs, from 22.6% to 8.6%. Inappropriate antibiotic use declined from 43% to 20.6%. Hand hygiene compliance increased from 18.9% to 62.9%. In-hospital mortality decreased from 10.4% to 8%
Newland et al, 2012[104]	Before and after	US	Mar 2008 - Dec 2010	Hospital (all wards)	No	Audit and feedback	Antibiotic use decreased from 883 DoT and 567 LoT per 1000 patient-days to 787 DoT and 523 LoT per 1000 patient days. Select antibiotics dropped from 353 DoT and 294 LoT per 1000 patient-days to 311 DoT and 256 LoT per 1000 patient days. Antibiotic monthly usage was 6% less for both DoT and LoT per 1000 patient-days
Newman et al, 2012[105]	Before and after	US	Jul 2007 - Jul 2009	Hospital (all wards)	No	Audit and feedback + Guidelines	34% increase in ampicillin use. Discharge antibiotics also changed, significant increase in amoxicillin and a significant decrease in cefdinir and amoxicillin/clavulanate

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Nguyen-Ha et al, 2016[106]	Before and after	US	first quarter 2008 - third quarter 2013	Hospital (all wards)	No	Audit and feedback + Guidelines	Blunting of a preexisting increasing trend for caspofungin drug starts and use and a significant downward trend for vancomycin drug starts (relative change −12%) and use (−25%). Although meropenem use was already low due to preexisting requirements for preauthorization, a decline in drug use (−31%, P = .021) and a nonsignificant decline in drug starts (−21%, P = .067) were noted
Noorani et al, 2011[123]	Observational	North Pakistan	Oct 2000 - Apr 2001	Hospital (all wards)	Yes	Guidelines	Health workers adherence improved from 14% to 29% after training and 65% with on the job support
Nzegwu et al, 2017[107]	Before and after (time-series study)	US	Jan 2011 - Jun 2016	NICU	No	Audit and feedback	Antibiotic use decreased by 14.7 DOT per 1,000 patient days. Ampicillin use, decreased significantly, declining by 22.5 DOT per 1,000 patient days. Late-onset sepsis per 100 NICU days of clinical service decreased significantly, with an average reduction of 2.65 evaluations per year per provider
Osterholt et al, 2009[70]	Before and after	Africa (Benin)	1999, 2001, 2002, 2004	Outpatient	Yes	Guideline+ supervision	Per-protocol analyses suggested that health workers with training plus study supports performed better than those with training plus usual supports (20.4 and 19.2 percentage-point improvements for recommended treatment [p = 0.08] and "recommended or adequate" treatment [p = 0.01], respectively).

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Parker et al, 2017[128]	Retrospective	US	Oct 2010 - Sep 2014	Hospital (all wards)	No	Audit and feedback	Pharmacy purchasing endorsed minimal financial benefit (decrease planning to post-ASP of $590 dollars per 1000 patient-days), EMR and PHIS data endorsed a decrease of $12 785 and $21 380 per 1000 patient-days, respectively, for a total yearly cost savings of $54 656 for pharmacy purchasing data, $1 184 336 for EMR data, and $2 117 522 for PHIS data
Powell et al, 2015[124]	Before and after	US	Jan 2009 - May 2012	ED	No	Guidelines + order template + individual chart audits	No statistical difference in utilization rates pre- and post-STGOT (4% vs 3%).
Putnam et al, 2015[56]	Before and after	US	2011-2014	Hospital (all wards)	No	Multiple interventions. 1. modification of preincisional checklist + creation of computerized physician order entry; 2.assignment to anesthetist of the role of antibiotic prophylaxis team leader + printing antibiotic guideline and attach to chart; 3.guidelines modification (perioperative prophylaxis)	Adherence to all guideline components remained unchanged (54vs55%, P = .38). Redosing significantly improved (7vs53%, P = .02), but correct type decreased (98vs70%, P <.01). The percentage of cases in which only one antibiotic guideline component was missed remained unchanged (35 34%, P =.46)

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Ross et al, 2016[134]	Before and after	US	Jan 2009 - Jan 2013	Hospital (all wards)	No	Pre-authorization	No change in level of mortality or trend in mortality (P =.37 and P= .57, respectively). no changes in either level of or trend in readmission (P =.88 and P= .28, respectively) or length of stay (P =.75 and P= .43, respectively)
Rutman et al, 2017[108]	Before and after	US	Aug 2011 - Aug 2013	ED and inpatients	No	CP	Increase in narrow-spectrum antibiotic (ampicillin) use from (8 to 54%)
Saha et al, 2017[109]	Before and after	US	Jul 2013 - Dec 2015	ED	Yes	Guidelines	The antibiotic discontinuation rate increased from a baseline mean of 4% to a mean of 84%
Seah et al, 2014[110]	Before and after	Singapore	Oct 2009 - Dec 2013	Hospital (all wards)	No	Audit and feedback	Significant decrease in daily defined dose per 100 patient-days by 55.6% from a baseline of 0.9 to 0.4 post-ASP and a reduction in DOTs per 100 patient days by 46.7% from a baseline of 1.5 to 0.8 post-ASP without significant changes in prescription rates. Cost increased from a pre-ASP mean of $175 per 100 patient-days to a peak of $238 and decreased significantly post-ASP to a mean of $149. The month-to-month change in cost decreased significantly post-ASP
Sick et al, 2013[129]	Retrospective	US	Jul 2005 - Jun 2011	Hospital (all wards), ED and PICU excluded	No	Pre-authorization	The average savings from the ASP was $103,787 (95% CI, $98,583–$109,172) per year, or $14,156 (95% CI, $13,446–$14,890) per 1,000 patient-days
Smith et al, 2012[111]	Before and after	US	Jan 2007 - Sep 2009	Hospital (all wards)	No	Guidelines	Ampicillin use increased from 2% at baseline to 6% after ASTF formation and 44% after guideline release. Ceftriaxone use increased slightly (from 56% to 59%) after ASTF formation but decreased to 28% after guideline release

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
So et al, 2015[53]	Before and after	Canada	Jul 2008; Sep 2011; Apr - May 2013	Hospital (all wards)	No	Guidelines + education + control (perioperative prophylaxis)	Significant improvements in appropriate antibiotic use (51.6%–67.0%), complete (26.2%–53.2%) and partial compliance (73.3%–88.7%), correct dosage (77.5%–90.7%), timing (83.3%–95.8%), redosing (62.5%–95.8%), and duration (47.1%–65.3%)
Stocker et al, 2010[48]	Randomized trial	Switzerland	Jun 2005 - Dec 2006	NICU and PICU	Yes	Laboratory (PCT)	PCT-guided decision-making resulted in a shortening of 22.4 h of antibiotic therapy
Stocker et al, 2017[49]	Randomized trial	Switzerland	May 2009 - Feb 2015	NICU and PICU	Yes	Laboratory (PCT)	For the procalcitonin group, the duration of antibiotic therapy was reduced (intention to treat: 55·1 vs 65·0 h; per protocol: 51·8 vs 64·0 h)
Torres et al, 2014[71]	Randomized trial	Argentina	Apr 2010 - Mar 2011	Outpatient	No	Prediction rule bacterial pneumonia score (BPS)	The use of antibiotics was significantly lower in the BPS group (46.6% vs. 86.6)
Turner et al, 2017[112]	Before and after	US	Apr 2012 - Mar 2013; Apr 2013 - Mar 2015	Hospital (all wards)	No	Audit and feedback	Antibiotic use decreased by 16.8% (95% confidence interval, 18.0% to −9.2%). Vancomycin use decreased by 38%, whereas antipseudomonal β-lactam use was unaltered. Drug-acquisition cost savings were estimated to be $67 000/year over the 2-year post-intervention period
Walker et al, 2017[135]	Before and after	US	Jan 2009 - Jun 2012; Jul 2012 - Mar 2016	OR	No	Guidelines (perioperative prophylaxis)	Surgical site infection rates were similar pre- and post-protocol, 14% and 9% respectively. The incidence of hospital-acquired infections (13.7% vs 8.7%) and multidrug-resistant organism (4.7% vs 1.6%) was similar between the 2 periods

Author	Study design	Country	Study period	Setting	Multicentric	Interventions	Main results
Wattier et al, 2017[113]	Before and after	US	Oct 2011 - Aug 2013; Sep 2013 - Jun 2015; Jul 2015 - Jun 2016	Oncology ward	No	Audit and feedback	Phase 1 had mixed effects–long-term reduction in tobramycin use (97% below projected at 18 months) but rebound with increasing slope in ciprofloxacin use (+18% per month). Following phase 2, tobramycin and ciprofloxacin use on the oncology service were both 99% below projected levels at 12 months. On the HSCT service, tobramycin use was 99% below the projected level and ciprofloxacin use was 96% below the projected level at 12 months
Webber et al, 2013[125]	Retrospective	US	60 days after the implementation period	Hospital (all wards)	Yes	Pre-authorization	437 incidents were documented, 1.1% of which were associated with ASP content or workflow
Weddle et al, 2013[114]	Before and after	US	3m and 1m before education and 3 post-intervention time points (1m, 3 m, and 9 m after education	ED	Yes	Education	The rate of inappropriate antibiotic use among all conditions was 10% before and 8% after the intervention. A decrease in inappropriate antibiotic prescribing was seen after the educational session
Willis et al, 2016[115]	Before and after	US	Jan 2009 - Jun 2014	Hospital (all wards)	Yes	Audit and feedback	Parenteral antimicrobial use was decreasing at our hospital by 3.7%/year, similar to the 3.4%/year found across children's hospitals. The rate of change after implementation of the ASP at our hospital was 11.1%/year, compared to 5.6%/year for other hospitals over the same period
Yu et al, 2016[52]	Before and after	US	Jul 2012 - Jun 2013	Hospital (all wards)	No	Laboratory - PBP2a antigen testing (A rapid test to detect methicillin resistance in Staphylococcus aureus)	Targeted antibiotic use for infections caused by methicillin-susceptible S. aureus improved (44%–80%), including when final culture results were not available

Table 1 Included studies of antibiotic stewardship programs.

Forty-eight (49/82, 59.8%) studies used before-and-after design, three (3/82, 3.7%) were observational studies, 12/82 (14.6%) were retrospective studies and seven (7/82, 8.5%) were prospective studies. Ten (10/82, 12.2%) were randomized trial.

Seventy studies (70/82, 85.4%) describe ASP implementation in a hospital setting. Most of them involve mixed wards in a Pediatric Hospital (44/82, 53.7%) while some of them are focused on specific settings: 11 on the NICU, six on the ED, four on the operating room, two on the oncology ward, two on both NICU and PICU, and one on the PICU. Twelve papers (12/82, 14.6%) describe ASP in an outpatient setting.

AS interventions stratified for different settings are summarized in **table 2**.

Sixty-seven (67/82, 81.7%) studies have as main outcome change in antimicrobial prescriptions. Other primary outcomes analyzed were: change in antimicrobial resistance (8/82, 9.8%), costs (10/82, 12.2%) and physicians' compliance (11/82, 13.4%)

Setting	Number of studies	Country	Study intervention
Mixed Wards	44	31 US 3 Japan 1 China 1 Canada 1 Indonesia 1 Bangladesh 1 Germany 1 Italy 1 Pakistan 1 Russia 1 Singapore 1 South Korea	16 Audit and feedback 7 Pre-authorization 5 Guidelines 4 Laboratory 4 Pre-authorization + Audit and Feedback 2 Audit and feedback + Guidelines 2 Guidelines + Education 2 Clinical Pathways 1 Education 1 Multiple interventions
Outpatients	12	7 US 1 Benin 1 Nigeria 1 Argentina 1 Saudi Arabia 1 Switzerland	4 Clinical Decision Support tool 3 Audit and Feedback + Education 2 Guidelines 1 Audit and Feedback 1 Prediction rule score 1 Education involving parents
NICU	10	6 US 1 France 1 Netherlands 1 India 1 Philippines	3 Guidelines 3 Audit and feedback 1 Pre-authorization 1 Restriction policy for cephalosporins 1 Clinical Decision Support tool 1 Package of infection control measures
Emergency Department	6	4 US 1 Switzerland 1 Netherlands	3 Guidelines 1 Guideline + Individual chart audits 1 Education sessions 1 Laboratory (use of PCT)
Perioperative prophylaxis	5	3 US 1 Canada 1 Greece	3 Multiple interventions (Guidelines, checklists, personal feedback, electronic medical record order set + utilization of pharmacists to prepare antibiotic) 2 Guidelines
NICU and PICU	2	2 Switzerland	2 Laboratory (use of PCT)
Oncology	2	1 US 1 UK	1 Audit and Feedback 1 Guidelines and Checklist
PICU	1	1 China	1 Education and guidelines

Abbreviations: *US=United States, PCT=Procalcitonin, NICU=Neonatal Intensive Care Unit, PICU=Paediatric Intensive Care Unit*

Table 2 Antimicrobial stewardship programs according to the different settings

Discussion

We performed a rigorous systematic review of all published studies reporting ASPs on the pediatric population in both outpatient and in-hospital settings. Antimicrobial stewardship is a collection of strategies (including policies, guidelines, surveillance, education, and evaluation) that collectively result in optimization of antibiotic prescribing practices through defining principles for antimicrobial empiric and targeted therapy and focusing on selection of appropriate antimicrobial agent, dose, frequency and route of administration [32].

An ideal antimicrobial stewardship team should include infectious disease physicians, clinical pharmacists, clinical microbiologists, infection control professionals, hospital epidemiologists, and Information Technology specialists [32,35]. In adult populations, ASP has been proven to reduce inappropriate antimicrobial use and resistance, enhance patients' safety and lower drug costs.[36,37] Nevertheless only 82 studies over the last 10 years were performed in paediatric settings and data about the effect of ASPs in these settings are still limited.

Most of the studies we reviewed originated from the US while other ASPs experiences remain sparse.

ASPs are mainly based on two core strategies: prospective audit and feedback, which involves interaction and feedback between an infectious disease physician and the prescriber, or formulary restriction and preauthorization requirements for specific agents [32,35].

These core strategies in conjunction with supportive tools (education, decision support services, and treatment algorithms) ensure an efficient ASP. These strategies and supplemental components are not mutually exclusive and varied combinations are possible, depending on the setting, local resources, practices, and needs [33,38].

Most studies report a single-centre intervention and despite the two core strategies strongly recommended by the ASP guidelines, in our systematic review we found only 26/81 (31.7%) audit and feedback, 8/82 pre-authorization (9.8%) and 4.9% both (4/82).

Not surprisingly, core interventions were usually implemented in the US with only two programs implemented in Europe.

This could be due to the fact that guidelines published so far (IDSA/SHEA) [32,35] are designed for the US healthcare system and easily adopted in this setting, while the diversity of healthcare systems throughout Europe implies a wide range of approaches to the same problem. Second, across Europe we found a high variability of funding opportunities and specialists (infectious diseases, pharmacist, and microbiologist) with advance training in pediatrics, while resources in US are more easily accessible [39]. A recent survey of 38 children's hospitals in the US revealed that 16 had a formal

ASP, and 15 were planning to implement a program [40]. To meet the needs of European countries The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has formed the ESCMID study group for antibiotic Policies (ESGAP) to promote the development of ASP through available free tools (www.escmid.orh/esgap).

Moreover, facing the difficulties in building a solid system for monitoring antimicrobial consumption, in 2010 the Antibiotic Resistance and Prescribing in European Children project was launched by the European Society for Pediatric Infectious Diseases [41]. This project monitoring antimicrobial use and resistance in European children has proven to be a useful tool to assess the impact of antimicrobial stewardship activities in different countries [4].

Despite the slow implementation of the ASPs core strategies, minor interventions based on guidelines, clinical pathways along with educational programs have proven to be reasonable and feasible first steps for implementation, especially in settings where resources are limited [42,43]. A Clinical pathway is a task-oriented plan designed to support the implementation of clinical guidelines and protocols. Their use can change antibiotic prescribing behavior in primary care and inpatient settings without adversely affecting patient safety or outcomes [32,44,45]. However, guidelines and clinical pathways can affect only antibiotic prescriptions for the diseases they have been specifically designed for.

Indeed, the combination of different ASP is always suggested. The use of biomarker (e.g. procalcitonin) [46-49] or rapid microbiological tests [50-52] for targeting or shortening the duration of antibiotic therapy has shown to be cost-effective, and combined with the previous strategies could enhance overall AS effectiveness.

Four studies in our review (4.9%) focused on perioperative prophylaxis. Three of these studies showed an improvement of antimicrobial prescriptions after the implementation of perioperative guidelines [53-55]; Putnam et al. reported no improvement despite multiple interventions [56]. This represents important space for improvement for ASP on both side of Atlantic. While trends in surgical prophylaxis among adult patients are widely available, only a few studies include pediatric data. This limits the conclusions that can be drawn about efficacy and safety of these ASP strategies.

To date, pediatric ASPs have primarily targeted the inpatient setting, and there is a paucity of literature regarding antimicrobial stewardship strategies in the Emergency Department (ED) (6/82, 7.3%) despite the great number of children who receive antibiotics in this setting. Since ED are uniquely positioned at the interface of inpatient and outpatient settings, ED physicians have the opportunity to have a consistent impact on prescribing trends in both locations [57].

Identification of potential barriers to successful intervention remains crucial. In the ED setting, challenges are represented mainly by high turnover rates for both patients and practitioners and rapid decision-making, usually without microbiology support [58].

In order to build an ASP in the ED, at least one ED physician should be included in the antimicrobial stewardship committee, improving engagement with other ED physicians and collaborating with other physicians, infectious disease colleagues, pharmacists, microbiologists and epidemiologists [59].

Only 14.6% of ASPs in our review were implemented in outpatient settings. Despite the sparse data, these interventions seem effective in reducing antimicrobial prescriptions. Most of the interventions involve guidelines and the use of computerized decision support tools. Interestingly, two studies included parents in education activities, underling how they could be a key component of a successful ASP. Also in this case only one intervention originated from a European country [60-71].

Clearly, the possibility of accessing data from the daily activities of pediatric general practitioners and family pediatricians is a unique resource, both for studying individual diseases, as well the interactions between different areas of health care and population health. However, the creation of a network is more difficult in outpatient settings than in-hospital for lack of technical and human resources and the fragmentation of the primary care healthcare.

Pedianet is an example of an efficient pediatric outpatient network which collects specific data from computerised clinical files filled out by pediatricians during their daily professional activities. With more than 300 Italian pediatricians enrolled throughout the country, this network has been proven to be able to carry out epidemiological studies on major pediatric diseases or pharmacovigilance and would be a valuable resource for a pediatric outpatient AS network [72].

The IDSA guidelines recommend that ASPs should improve antimicrobial use leading a reductions in antimicrobial resistance, adverse drug events, cost, and rate of *C. difficile* infections. The most commonly reported outcome in the papers included in this study was the change in antimicrobial prescription with less emphasis on cost, safety and resistance [32].

Measurement of this outcome in children is more complex than adults. Dosages vary according to weight or body surface, making defined daily dose not applicable. To overcome this issue, some authors propose to measure the duration of therapy by days of therapy (DOT) and length of therapy (LOT). A single DOT is calculated for each antimicrobial administered to an individual subject within a 24 hour time period regardless of dose and frequency [73,74]. LOT is counted for each day a subject receives any systemic antimicrobial therapy, regardless of the number of agents, dose, or frequency of administration. LOT provides a more accurate measure of the duration of therapy and is often coupled with DOT [74].

Despite using different metrics, all the studies we reviewed evaluating antimicrobial consumption showed a significant reduction [46-49,51-55,59-71,76-118]. For the first time, one study described an ASP in a Paediatric HIV Clinic. This program through a comprehensive assessment tool for regimen simplification showed to be an effective strategy to improve clinical outcomes in pediatric HIV infected patients [67]. Only two studies included in this systematic review report a decrease in use of antifungals as part of an antimicrobial stewardship program. The first from the US showed the reduction in use of caspofungin after the implementation of audit and feedback strategy for selected antimicrobials [106]. The second form Japan reported a reduction of liposomal amphotericin B and fosfluconazole prescriptions of 85% and 44% respectively after the implementation of an ASP based on the combination of the two core strategies [92]. No antiviral or antifungal stewardship experience has been reported so far in European pediatric patients.

Twelve papers (14.6%) reported prescribing physician compliance as an outcome [56,70,76,87,99,119-125].

Compliance after ASP implementation was high, showing that ASP intervention are generally well tolerated despite theoretical concerns about prescriber opposition [126]. Moreover, as suggested by some authors, a successful AS strategy should include prescribers from the setting where the ASP is going to be implemented [127]. This can improve the acceptance rate, helping determine which metrics are meaningful to their colleagues and which interventions are preferred. At the same time, physicians may be more receptive to implementing changes in their practice if they are suggested by a colleague rather than other physicians external to the ward.

Ten of the included studies (12.2%) quantified cost savings related to the intervention [79,88,91,93,96,110,112,116,128,129]. Decrease in cost was most often due to lower drug administration rates. However, the cost saving of ASPs should also include the reduction due to intravenous to oral shift, the reduction in length of hospital stay and in rate of infections due to multidrug resistant bacteria. Indeed, the total cost of hospital care rather than antimicrobial cost saving alone would be the best metric for antimicrobial stewardship [130].

For this reason, formal economic studies are also needed in paediatrics to show how ASP implementation impacts all cost, not just costs of antibiotics.

None of the papers included in this systematic review analysed the cost of ASP development and implementation. As detailed above, despite the fact that the costs of implementation would be covered after few months of stewardship activities, set-up cost is still a limit for countries which suffer of lack from funding in this area.

Eight papers included in this review (9.8%) take into consideration change in antimicrobial resistance as an outcome [76,91,92,96,98,102,117,118]. In three cases, no changes were reported, while the

other five studies showed an increased susceptibility of the bacteria analysed. This outcome is less consistently reported in the paediatric population. No study assessed the rate of *C. difficile* infections after the implementation of a paediatric ASP. In this case, a fundamental supportive role could be played by the infection prevention and control team. It can assist the AS team in the evaluation of the outcomes of their strategies by monitoring all healthcare associated infections and trends of multi-drug resistant organisms and by providing advice to manage eventual outbreaks [32]. This systematic review has strengths and limitations. This is the first review that evaluates the effectiveness of ASPs in all different pediatric settings. Furthermore, since no MeSH term is provided for antimicrobial stewardship, a wide search term strategy was used to be sure to retrieve all studies with an intervention on antimicrobial use even if not explicitly defined as antimicrobial stewardship. The primary limitation of our study is that only two databases were searched and we may not have identified all paediatric stewardship studies. Secondly, we were limited to the available search indices and methods; unpublished, unreported data and case reports were not included.

CONCLUSIONS

This systematic review describes the impact of paediatric ASPs worldwide. Mirroring what has previously been reported for adults, paediatric ASPs can reduce antimicrobial utilization, increasing cost savings and having a positive effect on antimicrobial resistance. Despite these outstanding results, paediatric ASPs are spreading rapidly in the US, while their implementation in Europe is still challenging.

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Supporting information

Search strategy:

("Child"[Mesh] OR "Child, preschool"[Mesh] OR "Infant"[Mesh] OR child* OR children OR paediatr* OR pediatr* OR infant* OR infancy OR toddler* OR kid* OR baby OR babies OR neonat*) AND (("Guideline Adherence"[Mesh] OR (guideline*[tw] AND (adher*[tw] OR complian*[tw] OR concordan*[tw] OR according[tw]))) AND ("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR "Antifungal Agents"[Mesh] OR "Antifungal Agents" [Mesh] OR anti-bacterial* OR antibacterial* OR anti-mycobacterial* OR antimycobacterial* OR antibiotic* OR anti-infective OR antifungal OR anti-fungal OR bactericid* OR bacteriocid* OR antimicrobial* OR treatment* OR therap* OR prophyla* OR perioperative* OR stewardship NOT case reports[pt]) NOT ("HIV Infections"[Mesh] OR HIV[Mesh] OR HIV[ti] OR human immunodeficiency virus[ti]))

CHAPTER III

Antibiotics Prescriptions in the Neonatal Intensive Care Unit:
How to Overcome Everyday Challenges

Abstract

Antimicrobial prescriptions in neonatal intensive care units (NICUs) represent a point of concern for the emergence of MDROs and for morbidity associated with prolonged antibiotic exposure (e.g., invasive candidiasis, necrotizing enterocolitis, and late-onset sepsis). Antimicrobial stewardship programs (ASPs) have shown to be a valuable tool for the prevention of resistance with the goals of optimizing clinical outcomes while decreasing unnecessary prescribing. The most frequent ASP strategies include the correct collection and interpretation of microbiological specimens, prescription of the narrowest-spectrum antibiotic appropriate for a particular case, and de-escalation or discontinuation of therapy in defined situations. A robust ASP requires everyday multidisciplinary collaboration between ID physicians, neonatologist, clinical pharmacists, clinical microbiologists, infection control professionals, hospital epidemiologists, and information services specialists. Education and clinical pathways (e.g., sepsis or surgical prophylaxis pathways) are an excellent starting point if followed by proactive interventions such as prospective audits and feedback and formulary restriction with prior antimicrobial authorization. The current review outlines the problems faced in NICU antimicrobial prescribing and presents various solutions from the literature.

Antimicrobials are the most commonly prescribed drugs in both the community and in hospitals, especially among neonates [1]. Grohskopf et al, with a 2-day point prevalence survey of antimicrobial consumption in 29 U.S. NICUs, showed that 43.3% of infants received at least one antibiotic.[2] Hshieh et al performed a retrospective review (2005–2010) to provide an update on medication use in infants admitted to the neonatal intensive care unit (NICU) in the United States and found that antimicrobials were predominant [3].

Even more evidence suggests that major neonatal causes of morbidity such as invasive candidiasis, necrotizing enterocolitis (NEC), and late-onset sepsis (LOS) in infants admitted to the NICU could be associated to an altered neonatal microbiome pattern due to a prolonged antibiotic exposure, which is often unnecessary [4 -8].

It is known that although antimicrobial resistance occurs naturally or can be acquired through gene transferring, prolonged antimicrobial use promotes the selection of multidrug-resistant organisms (MDROs). The emergence of such pathogens and their rapid global spread have transformed resistance from a challenge to an effective prescription to an important global public health threat with a substantial impact on patient outcomes such as length of hospital stay and mortality, as well as on health care costs [9-12]. Furthermore, infants colonized or infected with MRDOs can cause poor outcome also in previously well infants through the horizontal transmission of those pathogens [13,14].

In the past, antimicrobial resistance has been overcome with the introduction of new, broad-spectrum agents, but this option is no longer viable given the difficulties in developing new molecules [15]. Indeed, the cost of pharmaceutical research (estimated to be $400–800 million per approved agent) represents the first barrier.[16] The aging of the population, resulting in a shift toward agents for the treatment of chronic medical conditions, and the large number of antimicrobials already approved make the development of new antimicrobials even less economically attractive [17,18].

Furthermore, few pharmacokinetic (PK) and clinical studies on efficacy of antibiotics have been performed in infants [19,20] although adverse drug events and excessive costs of treatment are major reasons of concern[21,22] in the first months of life. In a review including eight studies conducted in European and Australian neonatal wards, Lindell-Osuagwu et al showed that 80 to 93% of prescriptions were for off-label or unlicensed antimicrobials [23].

Therefore, the European Union had funded several projects to define PK of antibiotics and determine dosing recommendations in children and infants, especially for critically important antibiotics as vancomycin and meropenem. The first project, called NeoMero-1, is an open-label, randomized controlled superiority trial to compare the efficacy of meropenem with a predefined

standard of care (SOC) for the treatment of LOS in infants and infants aged < 90 days (inclusive) admitted to an NICU.[24] The second study, NeoVanc, is a multicenter randomized open-label phase IIb study to evaluate an optimized dosing regimen for vancomycin in infants aged < 3 months affected by late-onset bacterial sepsis [25].

For all the aforementioned reasons, during the MDROs-era the key point for limiting the emergence of resistance of antibiotics and minimizing adverse events in the NICU setting is represented by the judicious use of antimicrobials among neonates.

Antimicrobial stewardship (AS) was formally introduced in 2007 and, if used, properly has shown to be a valuable tool for the prevention of resistance with the goals of optimizing clinical outcomes while decreasing unnecessary prescribing. AS practices define principles for antimicrobial empiric therapy, targeted therapy, and prophylaxis, focusing on antimicrobial agent selection, dose, frequency, and route of administration [26].

A well-established AS program usually is built on proactive interventions such as prospective audits and feedback to prescribers and formulary restriction with prior antimicrobial authorization. Each has been shown to decrease unnecessary antimicrobial exposure, reduce costs, and improved patient outcomes [26].

An NICU AS ideal team should involve infectious disease (ID) physicians, neonatologist, nurse, clinical pharmacists, clinical microbiologists, infection control professionals, hospital epidemiologists, and information services specialists tracking antimicrobial resistance patterns and identifying nosocomial infections and outbreaks[26-28] (**Fig. 1**).
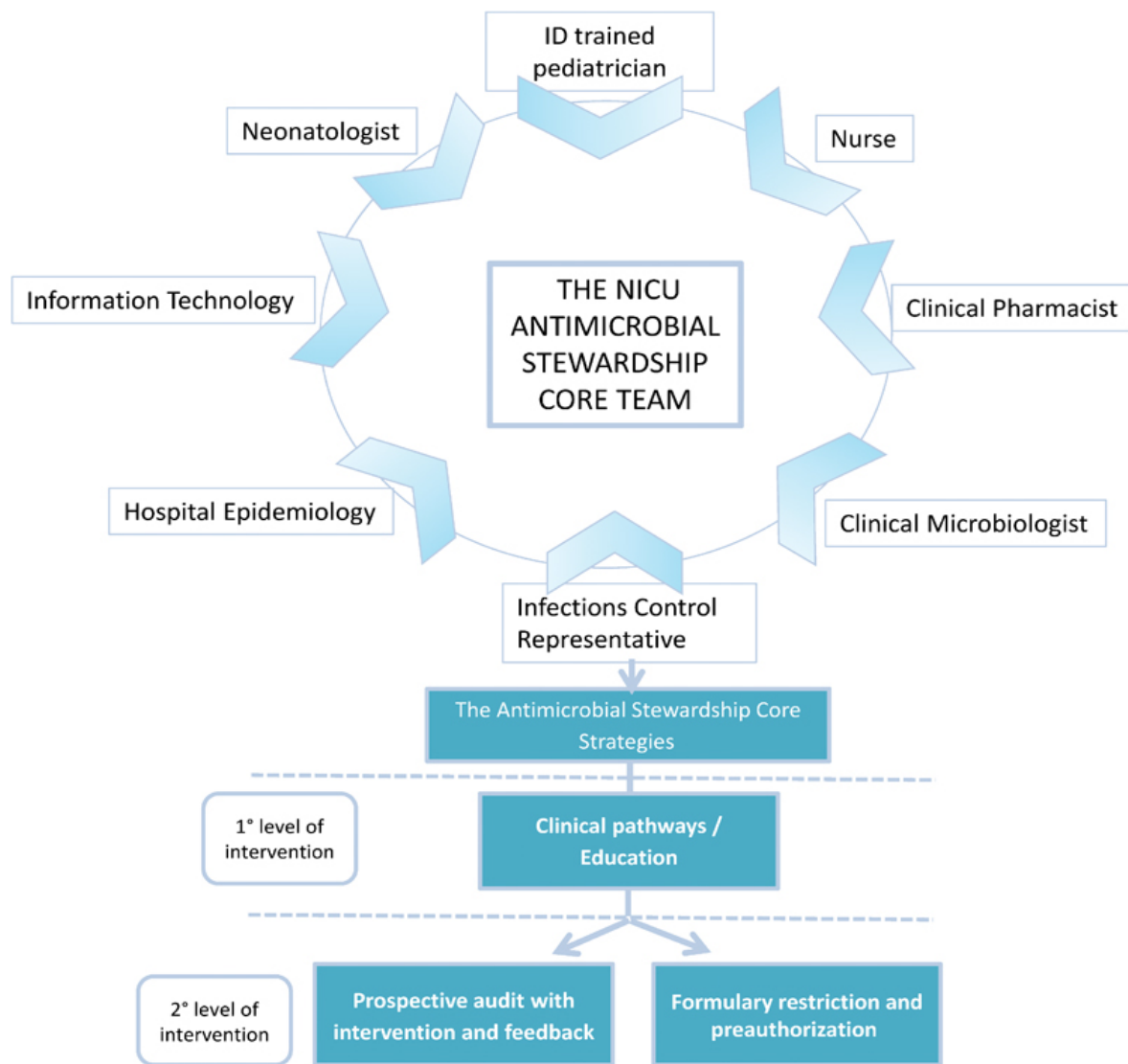
Figure 1. Antimicrobial stewardship strategies in the NICU. ID, infectious disease; NICU, neonatal intensive care unit.

In resource-limited settings where a robust AS team is hard to establish, clinical pathways represent a reasonable and feasible first step for AS implementation (**Fig. 1**). Clinical pathways are an effective means to change antibiotic prescribing behavior, standardizing care without adversely affecting patient safety [29-32].

Clinical pathways must be developed by a multidisciplinary team to guarantee the best quality and a high level of coordination of interventions. For instance, an infectious disease specialist could act in concert with a clinical pharmacist and a microbiologist to create specific clinical pathways, and, especially for NICUs, a neonatologist can play a key role in helping and monitoring their implementation. As suggested by Cantey and Patel, a neonatologist on the AS team can help determine which metrics are meaningful to their colleagues and which interventions are preferred.

At the same time, neonatologists may be more receptive to implementing changes in their practice if they are suggested by a colleague rather than other physicians external to the ward [33] ([Fig. 1]).

Challenges in Diagnosis

The major challenge in prescribing antibiotics in NICUs is that signs and symptoms of infection are not specific in the neonatal population. Indeed, septic infants can present with clinical findings that extensively overlap with noninfectious conditions such as apnea of prematurity, respiratory distress, hypotension, or temperature instability [34]. On the other hand, bacteremia could occur in the absence of clinical signs [35]. In a recent meta-analysis, Verstraete et al showed that even if signs such as lethargy and pallor and/or mottling for infants and apnea and/or bradycardia and poor peripheral perfusion for very low-birth-weight infants are the most powerful clinical signs for predicting sepsis, no prediction models should be considered as an absolute indicator due to their limited diagnostic accuracy [36].

Despite a wide variety of acute-phase reactants having been evaluated in infants with suspected sepsis and some of them have showed promising results (e.g., interleukin 8, urinary neutrophil gelatinase-associated lipocalin),[37,38] C-reactive protein (CRP) and procalcitonin (PCT) still are the most used inflammatory markers.

In the healthy adult, after an infectious episode, PCT increases within 2 hours, peaks at 12 hours, and normalizes within 2 to 3 days [39-41]. PCT does not pass through the placenta, and in the neonatal period its production depends on intestinal bacterial colonization. Therefore, PCT physiologic increase in the first 24 hours of life can give false-positive results in case of noninfectious conditions (e.g., neonatal respiratory distress syndrome, pneumothorax). Some authors pointed out the difficulty of interpreting this marker during the first 48 to 72 hour of life, which is the same period in which early-onset sepsis (EOS) diagnosis should be made [42,43]. Chiesa et al found that PCT shows 79% of sensitivity and 95% of specificity for neonatal EOS, but in the same publication authors identified age-dependent variations of CRP and PCT, thus making it difficult to establish any specific threshold.[42] A study regarding 2,151 newborns suspected of having EOS showed that umbilical cord PCT value, reflecting the antenatal infectious process, allows to distinguish infected infants from healthy ones with a cutoff value of 0.6 ng/mL.[44] The same authors also demonstrated that umbilical cord PCT at 6 hours of life had a specificity of 98.5% and a predictive negative value of 99% [45].

On the other hand, CRP concentration increases within 6 to 8 hours from an infectious episode in infants and peaks at 24 hours [46]; thus CRP sensitivity increases if its determination is made 6 to 12 hours after birth. Benitz et al have demonstrated that excluding a value at birth, two normal CRP

determinations (8–24 hours after birth and 24 hours later) have a negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis [47].

In a recent commentary, Benitz et al argue how currently available laboratory tests (e.g., blood cell counts, CRP, and PCT) are not sufficiently sensitive or specific to justify their use to decide whether to initiate or withhold empiric treatment of babies with clinical signs of illness; laboratory markers are more useful to support early discontinuation of empiric treatment in presence of a normal result for identification of infants without sepsis [48].

Some authors posit that vital signs can be helpful to assist in the early diagnosis of sepsis. Moorman et al observed abnormal heart rate characteristics (HRC), reduced variability, and transient decelerations in the hours to days prior to the clinical appearance of illness, and found that measurements of standard deviation, sample asymmetry, and sample entropy are highly related to imminent clinical illness [49].

Puopolo and Escobar developed a predictive model of sepsis risk among infants born at ≥ 34 weeks' gestation based on information available in the immediate perinatal period (maternal fever, use of epidural analgesia, prolonged premature rupture of membranes [ROM], intrapartum use of antibiotics). Use of this model can establish a prior probability of infection at the time of birth, which can aid the clinician in subsequent decisions regarding neonatal management and safely decrease the number of infants evaluated for infection [50].

According to the aforementioned findings, in 2010 an expert meeting organized by the European Medicines Agency (EMA) defined the diagnostic criteria of LOS for infants.[51] These criteria have been formulated in an effort to address several issues regarding clinical trials in the neonatal population with sepsis and have been tested in a clinical setting by Lutsar et al,[24] with a predictive value of 61% to identify patients with culture-proven LOS.

According to the experts' panel, clinical sepsis was defined for infants up to 44 weeks of postmenstrual age by the combination of at least two clinical symptoms (e.g., modified body temperature, cardiovascular instability, respiratory instability) and at least two laboratory signs (white blood cell count, CRP, or PCT).

The diagnosis becomes even more challenging when the blood cultures are negative, but a neonate shows clinical signs or laboratory values compatible with sepsis. This situation can represent two opposites: the cultures drawn are negative because the neonate does not have an infection or the cultures drawn are negative because they have not been appropriately collected.

As such, standardized best practices for blood culture collection are a useful AS tool. Optimizing blood cultures can improve use of antibiotics, because the detection of an organism can allow targeted antibiotic therapy [52].

The American Academy of Pediatrics' guidelines on the management of infants with suspected sepsis recommend obtaining a minimum of 1 mL of blood for culture when sepsis is suspected [39].

Although 0.5 mL has previously been considered acceptable, Schelonka et al demonstrated that 0.5 mL would not reliably detect low-level bacteremia (≤ 4 colony-forming units [CFU]/mL).[53] Furthermore, audits of NICU blood cultures showed that the median volumes are often too low [53, 54].

Challenges in Treatment

The problems related to determining the best antimicrobial therapy involve therapeutic agent selection, dosing, and duration of therapeutic treatment.

Despite advances in neonatal care, neonatal sepsis remains a major cause of mortality and morbidity in NICU [55]. This leads to the tendency to administer empiric therapy even when sepsis signs and symptoms are minimal. Because cultures often turn back positive after > 48 hours, immediate empiric treatment when appropriate is imperative; this represents a key point for AS policy implementation.[48] ID specialists and microbiologists should define the best empiric antibiotic therapy for each case based on guidelines and unit-specific resistance data from cumulative antibiograms and outbreak surveys, especially as outbreaks of methicillin-resistant Staphylococcus aureus (MRSA), ampicillin-resistant Escherichia coli, vancomycin-resistant enterococci, and multidrug-resistant gram-negative bacteria are increasingly reported from NICUs [56,57].

In a 2-year surveillance study conducted in the United States, > 90% of all blood isolates in infants admitted to NICU were susceptible to the combination therapy of ampicillin and aminoglycoside.[58] In one review from a single center [59], 90% of EOS were susceptible to the aforementioned combination therapy. Unfortunately, European data on antimicrobial resistance in NICU are missing. Data from the UK Health Protection Agency's national bacteremia survey in 2010 demonstrated that, in England and Wales, EOS organisms were susceptible in 94% of cases to the combination of penicillin plus gentamicin, 100% of cases to amoxicillin plus cefotaxime, and 96% of cases to monotherapy with cefotaxime.[58] To the best of our knowledge, combination of ampicillin and aminoglycoside still represents the first-line treatment for EOS [39], guaranteeing the best coverage for group B Streptococcus (GBS), E. coli, and Listeria monocytogenes. Third-generation cephalosporins (e.g., cefotaxime) could represent the best choice for proven MDROs and in case of suspected or proven meningitis because of its excellent CSF penetration [60]. However, its routinely use is not recommended because of the risk of rapid development of resistance [61] and the increased rates of invasive candidiasis, especially in low-birth-weight infants [62]. Ceftriaxone is not indicated in infants because it strongly binds to albumin and could displace bilirubin leading to a risk of kernicterus [39].

Whereas EOS is considered to be acquired at delivery, LOS is secondary to a postnatal exposure to organisms associated with nosocomial infections [63,64].

According to literature, all LOS organisms, with the exclusion of coagulase-negative staphylococci (CoNS), were still sensitive to semisynthetic penicillin combined with aminoglycoside, ampicillin, or third-generation cephalosporin [58,65].

A further prospective observational study conducted in 18 NICUs in five European countries reported that 90% of Enterobacteriaceae collected during LOS were susceptible to meropenem and about two-thirds to amikacin, ciprofloxacin, and cefotaxime plus gentamicin.[66] Approximately 95% of Enterobacteriaceae were resistant to ampicillin (median minimum inhibitory concentration [MIC] value of 32 g/mL), and MIC values for cefotaxime and gentamicin were relatively low (MIC 1 and 2 g/mL, respectively), as demonstrated in [**Table 1**].

Antibiotics	CoNS	Enterobacteriaceae		Nonfermentative gram-negatives	
	Resistant % (*n/N*)	Resistant % (*n/N*)		Resistant % (*n/N*)	
Ampicillin	100 (28/28)	95 (21/22)		NA	
Oxacillin	96 (27/28)	NA		NA	
Cefotaxime/ceftazidime	96 (27/28)	33 (7/21)		60 (3/5)	
Meropenem	96 (27/28)	10 (2/20)		50 (3/6)	
Piperacillin/tazobactam	NA	62 (13/21)		67 (4/6)	
Gentamicin	81 (22/27)	38 (8/21)		67 (4/6)	
Amikacin	100 (6/6)	24 (5/21)		60 (3/5)	
Ciprofloxacin	80 (4/5)	33 (6/18)		60 (3/5)	
Vancomycin	8 (2/26)	NA		NA	
Teicoplanin	26 (5/19)	NA		NA	
Ampicillin + gentamicin	81 (22/27)	38 (8/21)		67 (4/6)	
Cefotaxime + gentamicin	81 (22/27)	32 (7/22)		67 (4/6)	
		Escherichia coli	*Klebsiella, Serratia, Enterobacter Citrobacter*	*Pseudomonas*	*Acinetobacter*
Flucloxacillin + gentamicin	76 (100/132)	14 (5/36)	24 (17/72)	7 (1/14)	57 (4/7)
Amoxicillin + cefotaxime	100 (14/14)	16 (5/32)	34 (17/51)	0 (0/11)	86 (6/7)

Abbreviations: CoNS, coagulase-negative staphylococci; EUCAST, European Committee on Antimicrobial Susceptibility Testing; LOS, late-onset sepsis; NA, not available.

Table 1. LOS antimicrobial resistance (R) based on EUCAST criteria of Enterobacteriaceae, nonfermentative gram-negative microorganisms, and CoNS (Vergnano et al.[65]; Lusar et al.[66])

According to surveillance performed in NICUs of England and Wales, CoNS accounted for 22% of EOS and around 50% of LOS. Despite the fact that some authors have reported that > 50% of CoNS neonatal bacteremia were considered to be true infections [67]. CoNS are usually considered contaminants, especially when they are found during an EOS episode. Because of the presence of the mecA gene, most CoNS isolates are resistant to semisynthetic penicillins [68]. Therefore, many NICUs include vancomycin as empiric antibiotic regimen for LOS. Other NICUs, owing to low neonatal

mortality rate after CoNS infection,[69] have adopted a vancomycin-reduction protocol. This protocol includes a semisynthetic penicillin as empiric therapy with an eventual switch to vancomycin only in case of proven CoNS infection (more than two positive blood cultures for CoNS) or when MRSA is suspected [70].

Therefore, an LOS antibiotic first-line therapy including a semisynthetic penicillin combined with aminoglycoside is still reasonable. The use of vancomycin should be reserved for severely ill patients, if MRSA infection is suspected, or if CoNS is proven and stopped if cultures suggest a narrower-spectrum antibiotic could be used. A prompt interruption is advisable not only for stemming the growth of resistance but also for concerns regarding drug toxicity and the risk of gram-negative bacteria bloodstream infection due to the alteration of gastrointestinal tract flora by this agent [71]. In addition, when gram-negative organisms are suspected (e.g., previous colonization) or the course of sepsis is fulminant, anti-pseudomonal lactams such as penicillin with a β-lactamase inhibitor or cefepime could represent a reasonable choice [69].

Antimicrobial Stewardship Strategies Relevant to Antibiotic Prescription in the NICU

Optimization of antimicrobial dosing based on individual patient characteristics (gestational age, chronological age, and body weight), causative organism, site of infection, and PK and pharmacodynamic characteristics of the drug is an important part of AS [26,27].

Moreover, for certain antimicrobials, such as aminoglycosides and vancomycin, blood drug monitoring must be performed to detect efficacy and toxicity.

Aminoglycosides are concentration-dependent antibiotics, and thus peak and trough levels are necessary for monitoring. For gentamicin in patients with normal renal function receiving conventional aminoglycoside multiple-dose regimens, peak level could be collected 30 minutes after the end of infusion, with 6 to 10 µg/mL as expected value. Otherwise, trough samples should be collected at the steady state (before the fourth dose) with a recommended level of < 2 µg/mL [72].

Vancomycin peak levels are not recommended for monitoring because they lack correlation to efficacy; therefore, trough concentration is the most accurate method for vigilance of efficacy and toxicity. Current recommendations for vancomycin monitoring include checking trough concentration before the fourth dose. For therapeutic effect, blood concentration should be maintained at > 10 µg/mL, whereas for complicated infections secondary to S. aureus (bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia), trough concentration of 15 to 20 µg/mL is recommended to improve drug penetration and clinical outcome [72,73].

Concerning the duration of therapy, recent neonatal guidelines suggest a 10-day therapy for bacteremia without an identifiable focus of infection, a minimum of 14 days for uncomplicated

meningitis attributable to GBS and minimum of 21 days for gram-negative meningitis. In the latter case, the optimal empiric treatment option should include both a third-generation cephalosporin and an aminoglycoside until the results of susceptibility testing are known [39, 74].

Every institution, according to their capacity, should implement an AS program for guiding physicians through everyday challenges in diagnosis and treatment. This process could be established also in resource-limited settings, applying as a first step one or more of the supplemental strategies described previously.

The duration of antimicrobial therapy in infants with negative blood cultures is still controversial. In this situation, the decision should be based on the consideration of benefits and risks associated with a longer course of antibiotic. Even more challenging is to define the best therapy duration for infants born to mothers with chorioamnionitis. Maternal chorioamnionitis is a recognized risk factor for EOS, but, at present, there is a lack of studies defining the management of well-appearing infants whose mothers received inadequate intrapartum antibiotic prophylaxis [39,75]. Neonatal guidelines recommend continuing antimicrobial therapy as long as blood culture and laboratory data result negative. At present, antibiotic therapy could be avoided only in well-appearing infants at risk of group B streptococcal infection because of prematurity or prolonged rupture of membranes. In this case, evaluation should be limited to a blood culture, markers of infections, and complete blood count with differential and platelet count [75]. Furthermore, even more reports have suggested an association with prolonged administration of antimicrobial agents (> 5 days) in infants with suspected EOS (and negative blood cultures) with death and NEC [6,7,39]. Benitz et al recently reviewed data concerning risk of EOS in asymptomatic late-preterm and term infants born to a mother diagnosed with chorioamnionitis prior to delivery, leading to the conclusion that it is time to abandon the policy of treating well-appearing infants [3] 34 weeks' gestation because of chorioamnionitis alone.[48] Some authors show that routine antibiotic use for prophylaxis for invasive neonatal management (e.g., indwelling catheters, invasive mechanical ventilation) does not appear to have any protective effect [76, 77]. The most concerning aspect of this situation is that even more evidence in the literature has shown that a prolonged perioperative antibiotic prophylaxis does not prevent bacterial infection but could increase the risk of MRDO [78,79]. The editing of surgical procedure clinical pathways could reduce interprofessional variation optimizing the perioperative antimicrobial administration.

Toward Effective Antibiotic Stewardship

AS programs can guide the neonatologist to the best antimicrobial choice, avoiding overlapping spectrum antibiotic combinations and unnecessary prolonged treatment [26,27]. The use of

antimicrobial order forms where neonatologists have to justify the antibiotics requested, dosage and duration of therapy can be an effective component of AS and these strategies have been demonstrated to facilitate implementation of practice clinical pathways [80].

The microbiology report with antibiotic susceptibility testing is an essential tool to define the best treatment.

A supplemental AS strategy based on streamlining or de-escalating of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy has shown satisfying results.[26,27] In a study by Briceland et al, the review by a pharmacist and an ID physician of patients' antimicrobial therapy led to streamlining recommendations in 54% of antimicrobial courses over 7 months [81].

An AS program should help neonatologists go through these really simple but efficient considerations.[82] Antimicrobial therapy should be discontinued if all cultures turn back negative by 48 hours and the child's clinical conditions are improving [39]:

- The timing of the report is important, because growth of cultures after 48 hours is more likely to be contaminated [83]. If cultures from a nonsterile body site turn back positive, a complete reevaluation must be done to be sure to treat an infection and not a colonization. Recently Messacar et al evaluated the clinical impact and provider acceptability of implementing real-time AS decision support for children with positive blood culture results according to the FilmArray blood culture identification panel and found that among children with blood cultures that contained true pathogens, the time to effective antimicrobial therapy decreased significantly; moreover, unnecessary antibiotic initiation for children with a culture that contained organisms considered to be contaminants decreased from 76 to 26% [84].

- When susceptibility result is ready, clinicians must reevaluate the ongoing antimicrobial therapy switching to a narrow-spectrum one, if possible.

- AS programs must indicate the most appropriate antibiotic and dosage based on MIC. Physicians must pay attention because antimicrobials do not achieve the same concentration at any body site, so antimicrobial with MICs near the clinical breakpoint would not be recommended or should be recommended with a nonconventional dosage.

Conclusion

Infants represent a vulnerable population at high risk for infections. Antimicrobial prescriptions in NICUs still represent a point of concern for the emergence of MDROs and difficult area of implementation.

Correct collection and interpretation of microbiological specimen, prescription of narrowest-spectrum antibiotic, and de-escalation or discontinuation of therapy represent important areas for quality improvement.

A robust AS program requires everyday multidisciplinary collaboration between ID physicians, neonatologist, clinical pharmacists, clinical microbiologists, infection control professionals, hospital epidemiologists, and information services specialists. Everyone plays a key role in building a stewardship team. Education and clinical pathways (e.g., sepsis or surgical prophylaxis pathways) are excellent starting points if followed by proactive interventions of AS program such as prospective audits and feedback and formulary restriction with prior antimicrobial authorization.

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CHAPTER IV

The impact of Clinical Pathways on antibiotic prescribing for Acute Otitis Media and Pharyngitis in the Emergency Department

Background

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 US, 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].

Since 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.

Since PED 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.

MATERIAL AND METHODS

Study Design

CPs were implemented from 1 October 2015 through 15 October 2015. We conducted a pre-post quasi-experimental study to assess changes in antibiotic prescribing during the 6-month period prior to CP implementation (pre-intervention: 15 October 2014 through 15 April 2015) and during the 6 months after intervention (post-intervention: 15 October 2015 through 15 April 2016). The same months have been analyzed in each period to control for effects 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 (see Figures, **Supplemental Digital Content 1 and Supplemental Digital Content 2**). CPs were delivered as laminated pocket cards and three 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.

Study population

All patients aged 2 months to 15 years with an *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code or descriptive diagnosis of AOM or pharyngitis at the PED in Padua during the pre- and post-intervention 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.

Considering admissions numbers in 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 post-implementation 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 post-implementation 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 two conditions.

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

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

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

Two different authors independently collect the data (MB, GB). 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. An informed consent form was sent to the families, and follow-up data were included only when authorized.

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; 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, two formulations were considered: oral suspension and tablets. Oral suspension was used for children less than 40kg and tablets for those 40kg 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 pre-packaged in specific quantities.

Data analysis:

Data were analyzed using STATA®13 and QI macros 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. post-intervention period were conducted with chi-square or Fisher's 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 pre-intervention period, 13,262 children were seen in the PED, in comparison to 12,335 children during the 6-month post-intervention period.

During the pre-intervention 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 post-intervention period (332/12,335 (2.7%), p=0.4). The study population pre- and post-intervention is shown in **Supplemental Digital Content 3**.

The two 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 (**Supplemental Digital Content 4**).

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 to 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**).

	ACUTE OTITIS MEDIA (AOM)					GAS PHARYNGITIS				
	Pre-intervention period		Post-intervention period		p value	Pre-intervention period		Post-intervention period		p value
Patients included	295		278			298		366		
	n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
TREATMENT										
"Wait and see" for AOM or no antibiotic treatment for GAS pharyngitis	64	21.7	92	33.1	p<0.01	147	49.3	200	54.6	p=0.17
Antibiotic therapy	231	78.3	186	66.9	p<0.01	151	50.7	166	45.4	p=0.17
TYPE OF ANTIBIOTICS										
Amoxicillin	74	32.0	96	51.6	p<0.001	81	53.6	155	93.4	p<0.001
Broad spectrum (amoxi-clavulanate +cephalosporins+ macrolides)	157	68.0	90	48.4	p<0.001	70	46.4	11	6.6	p<0.001
Amoxicillin-clavulanate	106	45.9	70	37.6	p=0.09	60	39.7	5	3.0	p<0.001
Cephalosporins	47	20.3	16	8.6	p<0.001	10	6.6	6	3.6	p=0.28
Macrolides	4	1.7	4	2.2	p=0.76	-	-	-	-	-

Abbreviations: n=indicates the number of patient for each category; AOM=Acute Otitis Media; GAS Pharyngitis=Group A Streptococcus Pharyngitis

Table 1. Treatment option of Acute Otitis Media and GAS pharyngitis

A significant and stable difference in antibiotic prescribing for AOM between pre- and post-intervention groups was reported (**Figure 1A**), especially for uncomplicated AOM (AOM without otorrhea) (**Figure 1B**).
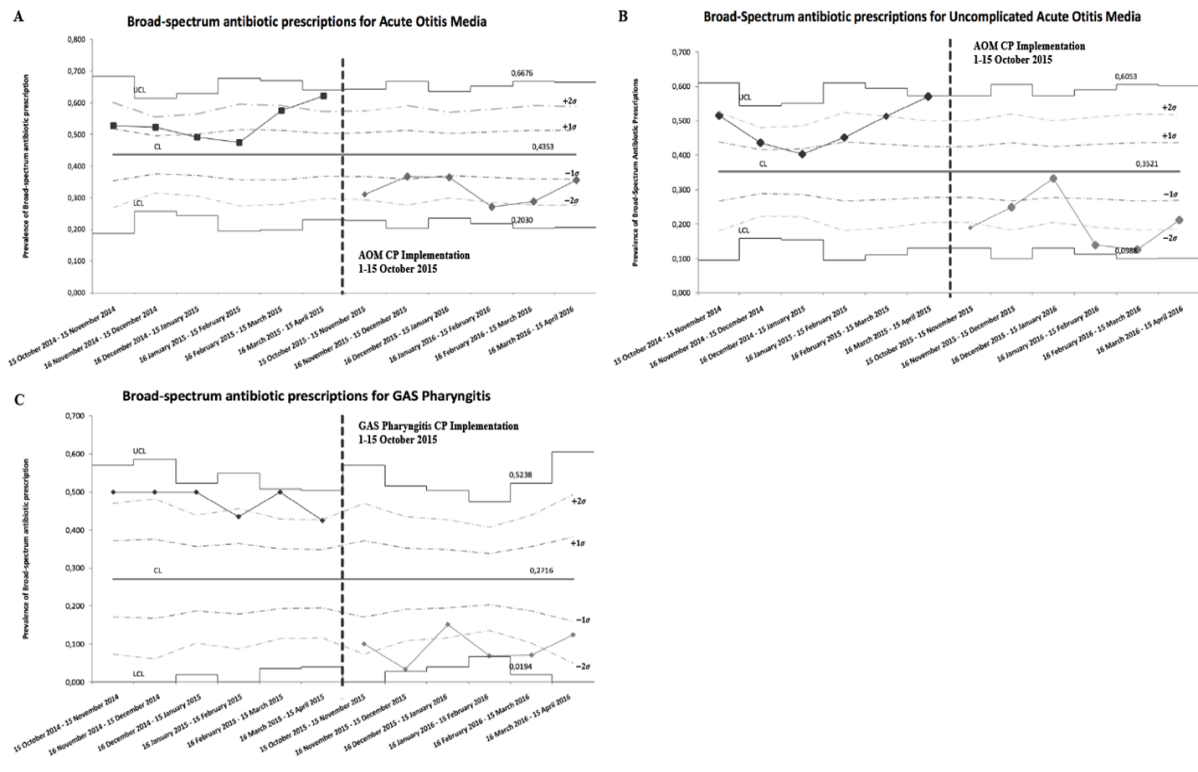
Abbreviations: UCL= Upper Control Limit; CL=Control Limit; LCL=Low Control Limit; σ =the standard deviation of the sample data; AOM=Acute Otitis Media; CP=Clinical Pathway; GAS Pharyngitis= Group A Streptococcus Pharyngitis.

Figure 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.

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 post-intervention 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 one month post CP implementation and remained stable during the 6-month post-intervention period (**Supplemental Digital Content 5**).

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.

In children <2 years old, median DOT fluctuated between 8 and 10 for the first three months after CP implementation and then met the recommended duration of 10 days in the last three months both for uncomplicated and complicated AOM. Wilcoxon rank sum test comparing pre- and post-intervention median DOTs found a significant increase (p<0.001) in the post intervention group (**Figure 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 two months of the post-implementation period. The difference between median DOT in the two periods was statistically significant (p<0.001) (**Figure 2B**).

For children ≥2 years old with complicated AOM, median DOT was in line with recommended treatment duration in both pre- and post-intervention periods, with no significant difference over time (**Figure 2C**).
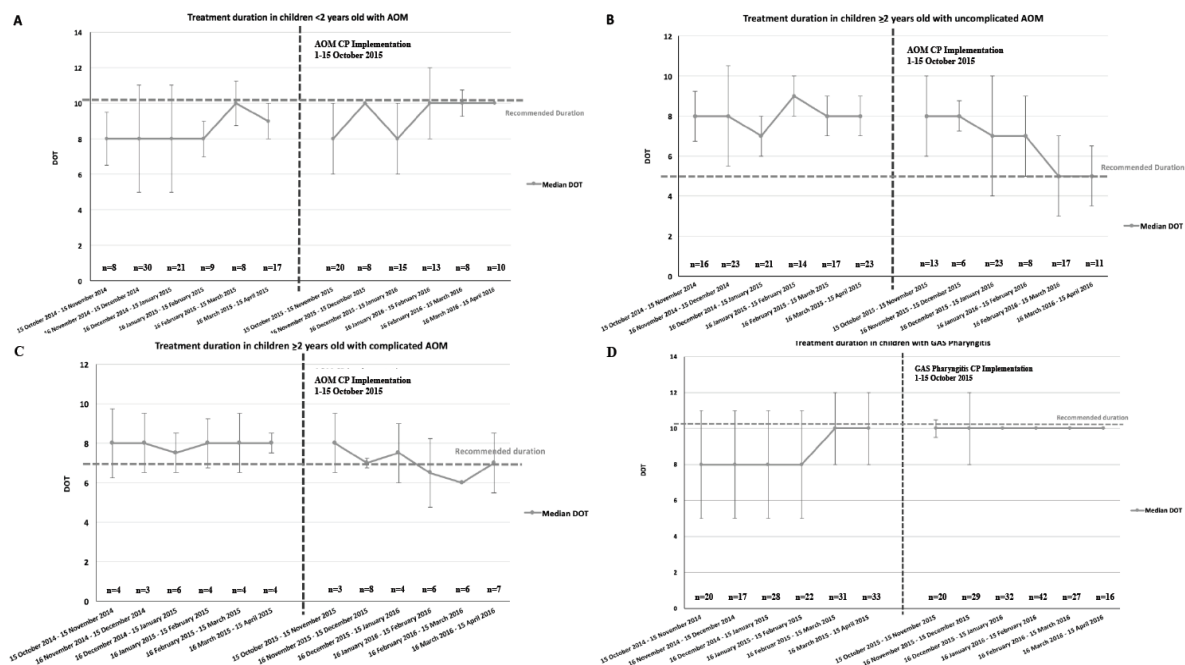
Abbreviations: CP=Clinical Pathways; DOT=Days of Therapy; AOM=Acute Otitis Media; GAS Pharyngitis=Group A Streptococcus Pharyngitis; n=the sample size

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).

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During the pre-intervention period, 388 patients were evaluated for pharyngitis, accounting for 2.9% (388/13,262) of total PED visits, while in the post-intervention period patient were 448/12,335, (3.6%), p<0.002. (**Supplemental Digital Content 6**).

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 (**Supplemental Digital Content 7**).

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 post-intervention period (**Figure 1C**).

Antibiotic dosage for GAS pharyngitis

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

Treatment duration for GAS pharyngitis

Median DOT for GAS pharyngitis met the recommended 10 days in the last two months of the pre-implementation period and remained stable in the post-implementation period (**Figure 2D**). Wilcoxon rank sum test comparing overall pre-and post-intervention median DOT found a significant increase post-intervention (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 post-intervention periods, respectively. The sub-groups 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 post-intervention 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**).

	ACUTE OTITIS MEDIA (AOM)					GAS PHARYNGITIS				
	Pre-intervention Period		Post-intervention Period		p-value	Pre-intervention Period		Post-intervention Period		p-value
Patients available for follow-up	214 (72.5% of total AOM)		206 (74.1% of total AOM)			98 (64.9% of GAS pharyngitis)		118 (71.1% of GAS pharyngitis)		
	n	%	n	%		n	%	n	%	
TREATMENT										
Wait and see	48	22.4	66	32.0	p<0.05					
Antibiotic therapy	166	77.6	140	68.0	p<0.05					
TYPE OF ANTIBIOTICS										
Amoxicillin	55	25.7	73	35.4	p<0.05	52	53.1	109	92.4	p<0.001
Broad spectrum (amoxi-clavulanate+cephalosporins +macrolides)	111	51.9	67	32.5	p<0.001	46	46.9	9	7.6	p<0.001
Amoxicillin+clavulanate	78	36.5	50	24.3	p<0.01	40	40.8	3	2.5	p<0.001
Cephalosporins	30	14.0	14	6.8	p<0.05	6	6.1	6	5.1	p=0.97
Macrolides	3	1.4	3	1.5	p=0.96	-	-	-	-	-
TREATMENT FAILURES	**26**	**12.1**	**23**	**11.2**	**p=0.75**	**6**	**6.1**	**8**	**6.8**	**p=0.93**
Changed antibiotic for persistence or worsening of symptoms	12	5.6	5	2.4	p=0.10	2	2.0	3	2.5	p=0.83
Changed antibiotic for side effects	3	1.4	4	1.9	p=0.96	2	2.0	2	1.7	p=0.75
Antibiotic prescriptions for another AOM episode within 30 days after discharge	4	1.9	1	0.5	p=0.39	2	2.0	3	2.5	p=0.83
Antibiotic prescription after "wait and see"	7	3.3	13	6.3	p=0.14					

Abbreviations: n=the number of patient for each category; AOM=Acute Otitis Media; GAS Pharyngitis=Group A Streptococcus Pharyngitis

Table 2. Treatment and treatment failure during follow-up of patients with AOM and GAS Pharyngitis

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 post-intervention periods, respectively.

Also for GAS pharyngitis, sub-groups 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 post-intervention 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 prior to CP implementation, AOM antibiotics cost per 1000 PD was 8,033.08€, with 7,014.20€ (87.3% of total antibiotics costs) for broad-spectrum. Following CP implementation, total cost per 1000PD reduced to 5,878.30€, with 4,382.67€ for broad-spectrum antibiotics (**Table 3**).

	ACUTE OTITIS MEDIA (AOM)									GAS PHARYNGITIS								
Total Patient	Pre-intervention period 295				Post-intervention period 278				p value	Pre-intervention period 151				Post-intervention period 166				p value
	Prescription		Expenditure/ 1000PD		Prescription		Expenditure/ 1000PD			Prescription		Expenditure/ 1000PD		Prescription		Expenditure/ 1000PD		
	n	%	€	%	n	%	€	%		n	%	€	%	n	%	€	%	
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	p<0.001	81	53.6	2,599.07	27.8	155	93.4	5,186.45	83.0	p<0.001
Broad spectrum (amoxi-clavulanate +cephalosporins+ macrolides)	157	68.0	7,014.20	87.3	90	48.4	4,382.67	74.6	p<0.001	70	46.4	6,738.61	72.2	11	6.6	1,060.78	17.0	p<0.001
Amoxicillin-clavulanate	106	45.9	3,965.36	49.4	70	37.6	3,441.81	58.6	p<0.001	60	39.7	5,752.58	61.6	5	3.0	531.45	8.5	p<0.001
Cephalosporins	47	20.3	2,921.05	36.4	16	8.6	794.51	13.5	p<0.001	10	6.6	986.03	10.6	6	3.6	529.34	8.5	p<0.001
Macrolides	4	1.7	128.80	1.6	4	2.2	146.35	2.5	p=0.002									

Abbreviations: n=indicates the number of patient for each category; GAS Pharyngitis=Group A Streptococcus Pharyngitis; PD=Patient Day

Table 3. Antibiotic prescription indication, type and expenditure per 1000 Patient-Days for AOM and GAS pharyngitis

The proportion of total antibiotics costs for cephalosporins, which represented an important part of broad spectrum costs in the pre-intervention period, decreased dramatically in the post-intervention (2,921.05€ (36.4%) vs. 794.51€ (13.5%), p<0.001), with a concurrent increase in the proportion of antibiotics costs for amoxicillin-clavulanate (3,965.36€ (49.4%) vs. 3,441.81€ (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 (**Supplemental Digital Content 8**).

Total cost for pharyngitis

Prior to CP implementation, antibiotics for pharyngitis cost per 1000 PD amounted to 9,337.68€, with 6,738.61€ (72.2%) for broad-spectrum antibiotics. During the post-implementation period, the total cost decreased to 6,247.23€, with a dramatic reduction in the proportion of antibiotics costs from broad-spectrum antibiotics (1,060.78€) (**Table 3**).

By drug, the proportion of antibiotics costs from amoxicillin-clavulanate reduced dramatically (5,752.58€ (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 (**Supplemental Digital Content 9**).

Discussion

Our study showed sustained changes in physician prescribing behaviors for AOM after implementation of a clinical pathway. 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 et al. [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 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. Indeed, according to epidemiology and resistance data, 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 showed maximum eradication rate only at high doses of amoxicillin administered in three 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 gastro-intestinal side effects. However, despite the increase in dosage post-implementation, no difference in terms of side effects were observed between pre- and post-intervention groups.

In contrast with rapid adoption of the recommended therapy duration of 10 days for children < 2 years old in the post-implementation period, recommended treatment duration for children > 2 years old with uncomplicated AOM of 5 days was slower to catch on after CP implementation, with higher adherence rates observed only after 3-4 months. Although we don't 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. 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 indication in the pre-intervention 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 post-intervention 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 post-intervention group, adverse events did not increase.

Regarding costs per 1000PD, after AOM CP implementation there was a significant reduction in total expense per 1000PD, 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 5,500€ and a tenfold 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 three 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 keep the results achieved, as reported by Potocky 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 clinical pathways 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 clinical pathways 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 ICD-9 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 post-implementation 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 two groups. Moreover, only two 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. Since Italian pharmacies sell only pre-established 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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Supplemental Digital Content 3. Figure

Supplemental Digital Content 4. Table

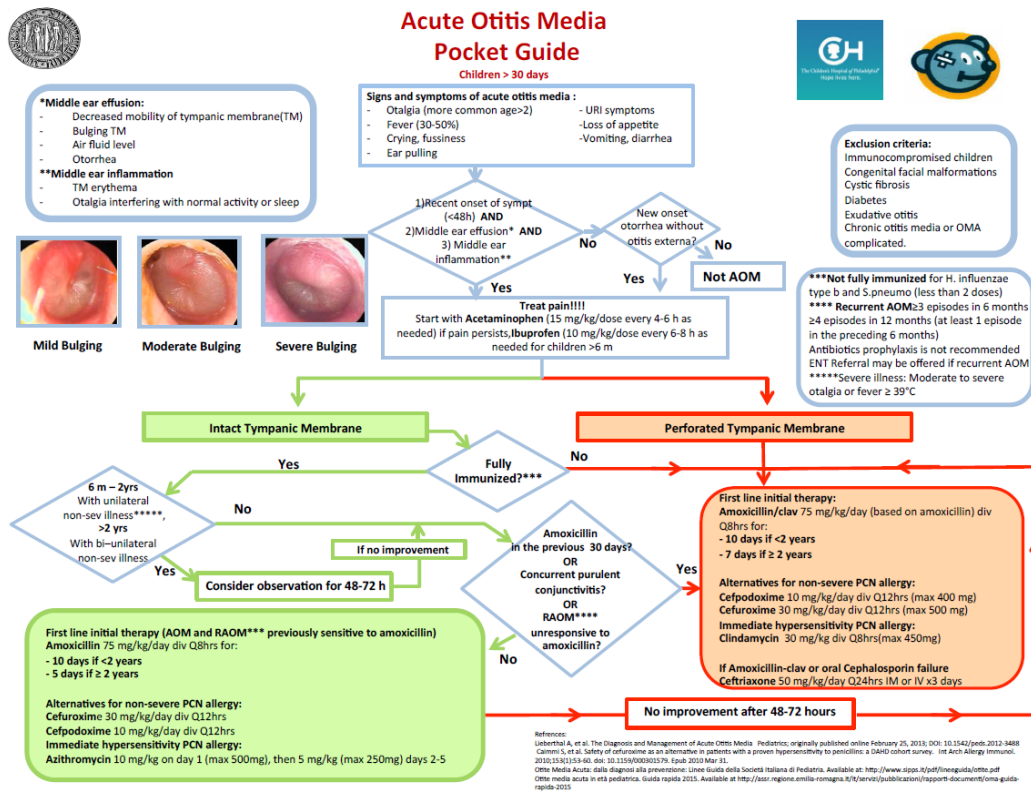Supplemental Digital Content 5. Figure

Supplemental Digital Content 6. Figure

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Acute Otitis Media
Pocket Guide
Children > 30 days

*Middle ear effusion:
- Decreased mobility of tympanic membrane(TM)
- Bulging TM
- Air fluid level
- Otorrhea
**Middle ear inflammation
- TM erythema
- Otalgia interfering with normal activity or sleep

Mild Bulging   **Moderate Bulging**   **Severe Bulging**

Signs and symptoms of acute otitis media :
- Otalgia (more common age>2)   - URI symptoms
- Fever (30-50%)   -Loss of appetite
- Crying, fussiness   -Vomiting, diarrhea
- Ear pulling

Exclusion criteria:
Immunocompromised children
Congenital facial malformations
Cystic fibrosis
Diabetes
Exudative otitis
Chronic otitis media or OMA
complicated.

1)Recent onset of sympt (<48h) **AND**
2)Middle ear effusion* **AND**
3) Middle ear inflammation**

New onset otorrhea without otitis externa?

No   **Yes**   **No**   **Not AOM**

Yes

***Not fully immunized for H. influenzae type b and S.pneumo (less than 2 doses)
**** Recurrent AOM≥3 episodes in 6 months ≥4 episodes in 12 months (at least 1 episode in the preceding 6 months)
Antibiotics prophylaxis is not recommended
ENT Referral may be offered if recurrent AOM
*****Severe illness: Moderate to severe otalgia or fever ≥ 39°C

Treat pain!!!!
Start with **Acetaminophen** (15 mg/kg/dose every 4-6 h as needed) if pain persists,**Ibuprofen** (10 mg/kg/dose every 6-8 h as needed for children >6 m

Intact Tympanic Membrane

Yes

Perforated Tympanic Membrane

No

Fully Immunized?*

6 m – 2yrs
With unilateral non-sev illness*****,
>2 yrs
With bi–unilateral non-sev illness

No

Yes

If no improvement

Amoxicillin in the previous 30 days?
OR
Concurrent purulent conjunctivitis?
OR
RAOM**** unresponsive to amoxicillin?

Yes

No

Consider observation for 48-72 h

First line initial therapy:
Amoxicillin/clav 75 mg/kg/day (based on amoxicillin) div Q8hrs for:
- 10 days if <2 years
- 7 days if ≥ 2 years

Alternatives for non-severe PCN allergy:
Cefpodoxime 10 mg/kg/day div Q12hrs (max 400 mg)
Cefuroxime 30 mg/kg/day div Q12hrs (max 500 mg)
Immediate hypersensitivity PCN allergy:
Clindamycin 30 mg/kg div Q8hrs(max 450mg)

If Amoxicillin-clav or oral Cephalosporin failure
Ceftriaxone 50 mg/kg/day Q24hrs IM or IV x3 days

First line initial therapy (AOM and RAOM* previously sensitive to amoxicillin)**
Amoxicillin 75 mg/kg/day div Q8hrs for:
- 10 days if <2 years
- 5 days if ≥ 2 years

Alternatives for non-severe PCN allergy:
Cefuroxime 30 mg/kg/day div Q12hrs
Cefpodoxime 10 mg/kg/day div Q12hrs
Immediate hypersensitivity PCN allergy:
Azithromycin 10 mg/kg on day 1 (max 500mg), then 5 mg/kg (max 250mg) days 2-5

No improvement after 48-72 hours

Refrences:
Lieberthal A, et al. The Diagnosis and Management of Acute Otitis Media Pediatrics; originally published online February 25, 2013; DOI: 10.1542/peds.2012-3488
Caimmi S, et al. Safety of cefuroxime as an alternative in patients with a proven hypersensitivity to penicillins: a DAHD cohort survey. Int Arch Allergy Immunol. 2010;153(1):53-60. doi: 10.1159/000301579. Epub 2010 Mar 31.
Otite Media Acuta: dalla diagnosi alla prevenzione: Linee Guida della Società Italiana di Pediatria. Available at: http://www.sipps.it/pdf/lineeguida/otite.pdf
Otite media acuta in età pediatrica. Guida rapida 2015. Available at http://assr.regione.emilia-romagna.it/it/servizi/pubblicazioni/rapporti-documenti/oma-guida-rapida-2015

Supplemental Digital Content 2. Figure

Acute Pharyngitis Pocket Guide
Children > 30 days

McIsaac Score	Point
Fever (≥ 38 C)	1
Tonsillar swelling or exudates	1
Tender anterior cervical lymph nodes	1
Absence of cough, conjunctivitis, diarrhea	1
Age 3-14 years	1

What is McIsaac score?

Exclusion criteria:
Immunodeficiency or immunosuppressive therapy
Previous tonsillectomy

0-2

Viral etiology likely

Viral etiology most common (60-80%)! Associated with: conjunctivitis, rhinitis, hoarseness, cough, diarrhea and rash

ANTIBIOTIC THERAPY NOT INDICATED !!

3-4

Perform RAD test

Negative

Positive

5

ANTIBIOTIC THERAPY

Treat pain!!!!
Start with **Acetaminophen** (15 mg/kg/dose every 4-6 h as needed) if pain persists, **Ibuprofen** (10 mg/kg/dose every 6-8 h as needed for children >6 m

GAS pharyngitis diagnosed in the previous 30 days? — YES / No

Is GAS pharyngitis strongly likely ? McIsaac score 4-5 — YES / No

First-line therapy:
Amoxicillin 50 mg/kg/day div Q12hrs for 10 days

Not IgE mediated reaction:
Cefuroxime axetile 20-30 mg/Kg/day div Q12hrs for 5 days
Cefaclor 40-50 mg/ kg/day div Q12hrs for 5 days
IgE mediated reaction: (think about CULTURE to test sensibility or strict follow-up)
Azithromycin 12 mg/Kg/day for 5 days

THINK ABOUT IT!
Patients with recurrent pharyngitis and laboratory evidence of group A streptococcus may be chronic carriers who are having repeated viral infections. Antibiotics are not generally recommended!!

After 48 are symptoms improving? — No / YES

COMPLETE ANTIBIOTIC THERAPY

References:
- Alan L et al, Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis available at: http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Strep.pdf
- Regoli M et al, Update on the management of acute pharyngitis in children. Ital J Pediatr. 2011 Jan 31;37:10. doi: 10.1186/1824-7288-37-10. Review.
- Farringite in età pediatrica. Guida rapida 2015. Available at http://assr.regione.emilia-romagna.it/it/servizi/pubblicazioni/rapporti-documenti/oma-guida-rapida-2015

Supplemental Digital Content 3. Figure

Flowchart of children with Acute Otitis Media enrolled during pre and post-intervention period.
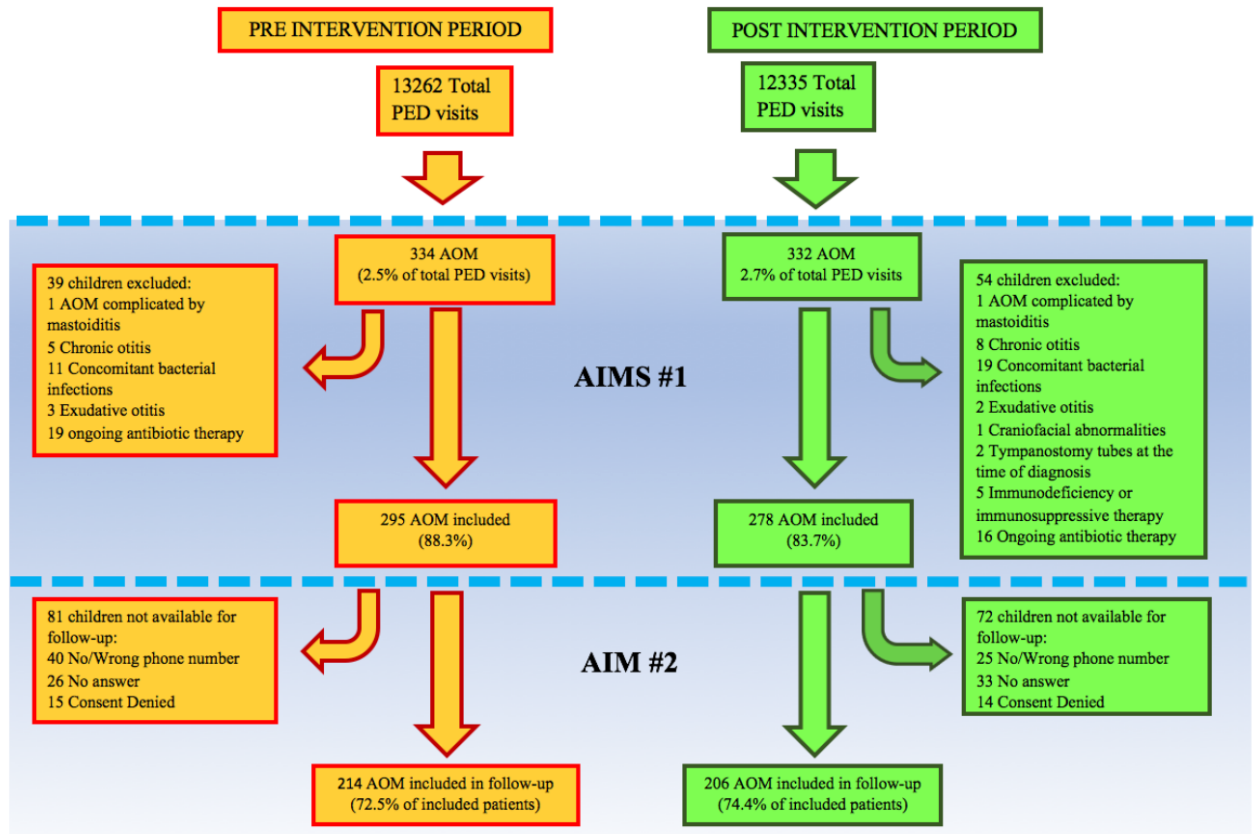
Abbreviations: PED visits=Pediatric visits; AOM=Acute Otitis Media
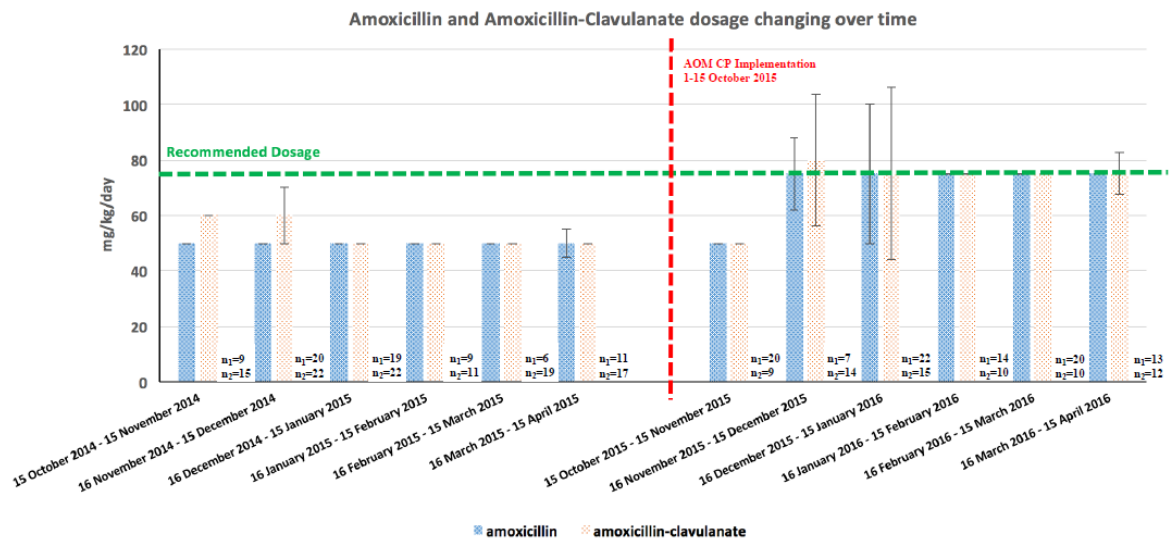
Supplemental Digital Content 4. Table

Characteristics of Study Population with AOM

	Pre intervention Period				Post intervention Period				p value for included patients
Total PED visits	13262				12335				
AOM PED visits	334 (2.5% of total ED visits)				332 (2.7% of total ED visits)				p=0.4
	Patients excluded n=39, 11.7%		**Patients included n=295, 88.3%**		**Patients excluded n=54, 16.3%**		**Patients included n=278, 83.7%**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Male	25	64.1	183	62.0	26	48.1	157	56.5	p=0.18
AGE									
2 mo – 2 yr	14	35.9	109	36.9	13	24.1	85	30.6	p=0.11
2 yr – 5 yr	13	33.3	115	39.0	18	33.3	127	45.7	p=0.10
5 yr– 15 yr	12	30.8	71	24.1	23	42.6	66	23.7	p=0.9
Complicated AOM (AOM with otorrhea)	3	7.7	46	15.6	2	3.7	61	21.9	p=0.05

Abbreviations: PED visits=Pediatric Emergency Department visits; AOM=Acute Otitis Media; ED=Emergency Department; n= the number of patient for each category

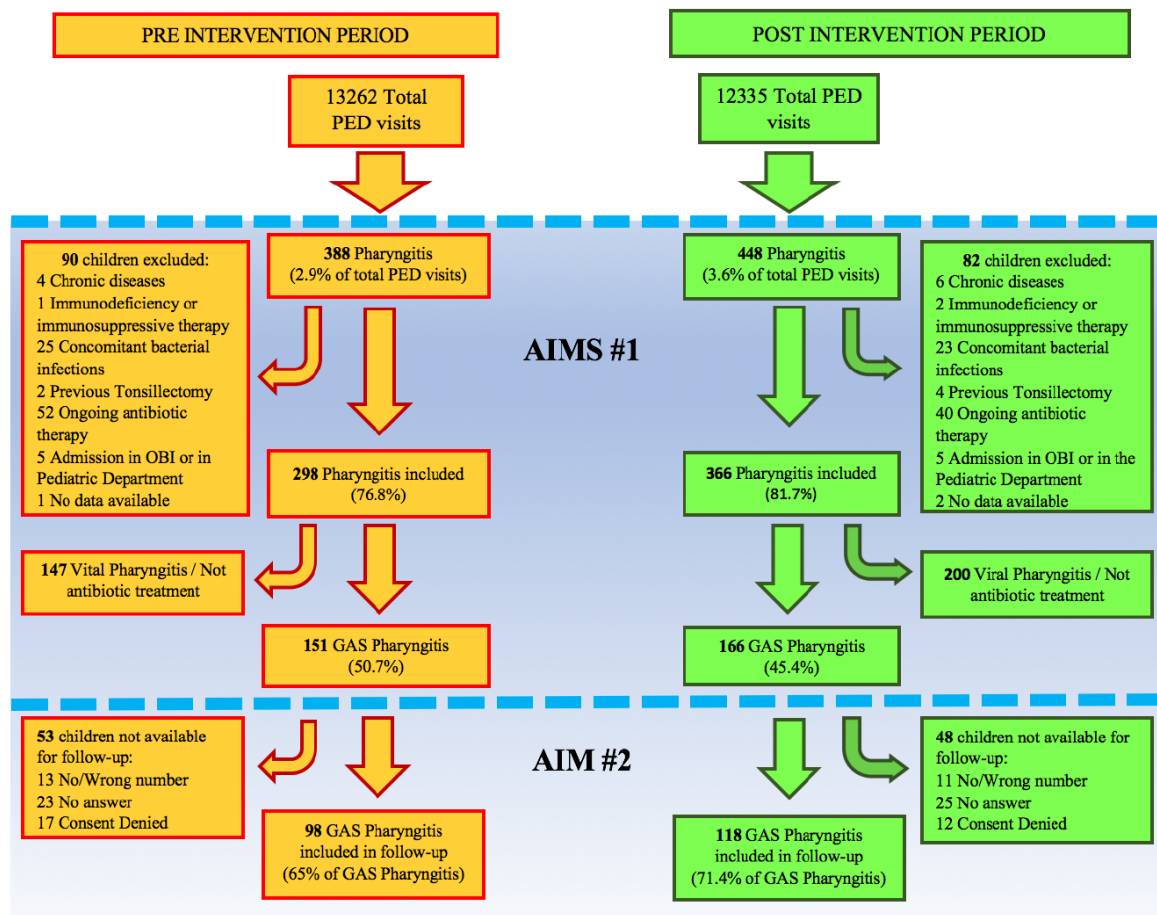**Supplemental Digital Content 5. Figure**

Amoxicillin and Amoxicillin-clavulanate dosage for Acute Otitis Media and interquartile range changing over time.

Abbreviations: AOM=Acute Otitis Media; CP=Clinical Pathways; n1=the sample size of amoxicillin group; n2=the sample size of amoxicillin-clavulanate group.

Supplemental Digital Content 6. Figure

Flowchart of children enrolled for Pharyngitis during pre- and post-intervention period.

Abbreviations: PED visits=Paediatric Visits; GAS Pharyngitis=Group A Streptococcus Pharyngitis

Supplemental Digital Content 7. Table

Characteristics of Study Population with GAS Pharyngitis

	Pre intervention Period				Post intervention Period				p value for included patients
Total PED visits	13262				12335				
Pharyngitis PED visits	388 (2.9% of total ED visits)				448 (3.6% of total ED visits)				p<0.002
	Patients excluded n=90, 23.2%		Patients included n=298, 76.8%		Patients excluded n=82, 18.3%		Patients included n=366, 81.7%		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Male	58	64.4	168	56.4	42	51.2	214	58.5	p=0.58
AGE									
2 mo – 3 yr	31	34.4	108	36.2	32	39.0	146	39.9	p=0.34
3 yr – 15 yr	59	65.6	190	63.8	50	61.0	220	60.1	p=0.34

Abbreviations: PED visits=Pediatric Emergency Department visits; ED=Emergency Department; GAS Pharyngitis=Group A Streptococcus Pharyngitis; n=the number of children for each category
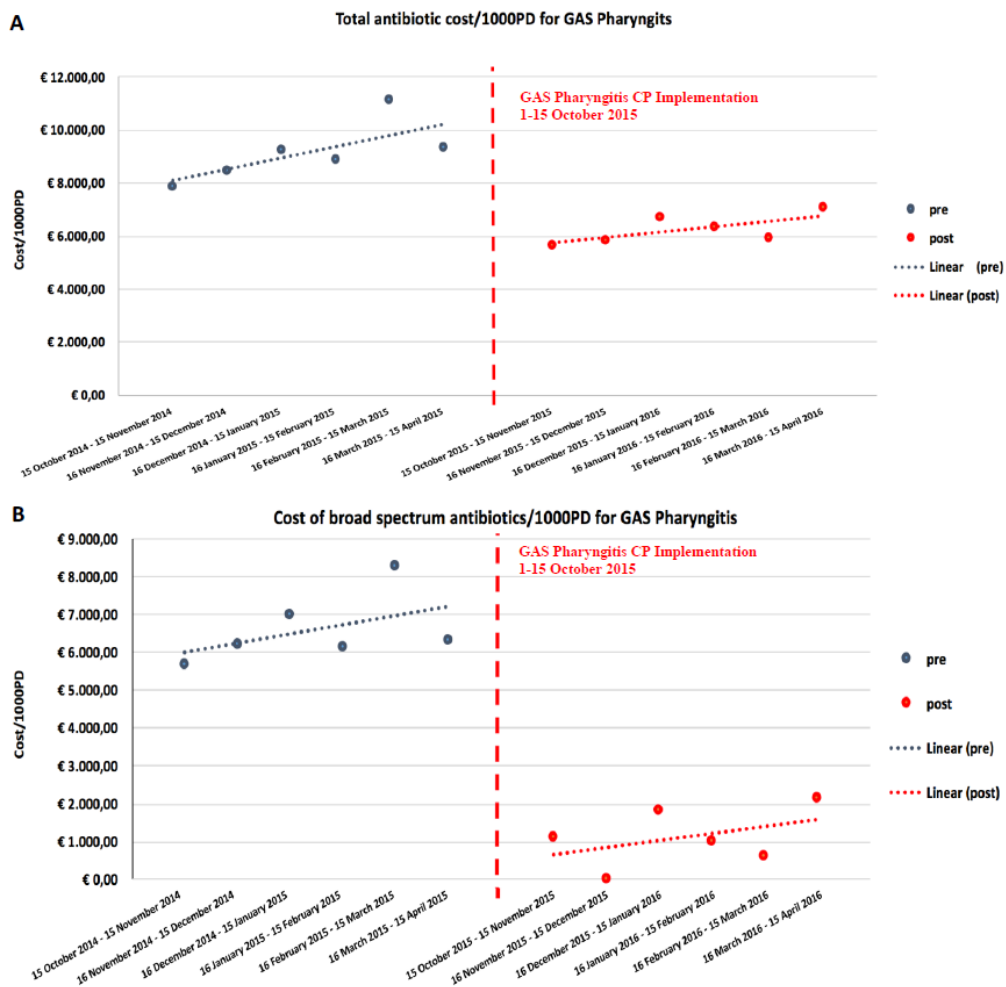
Supplemental Digital Content 8. Figure

AOM total cost per 1000PD for overall antibiotic (A) and for broad-spectrum ones (B) for each month.
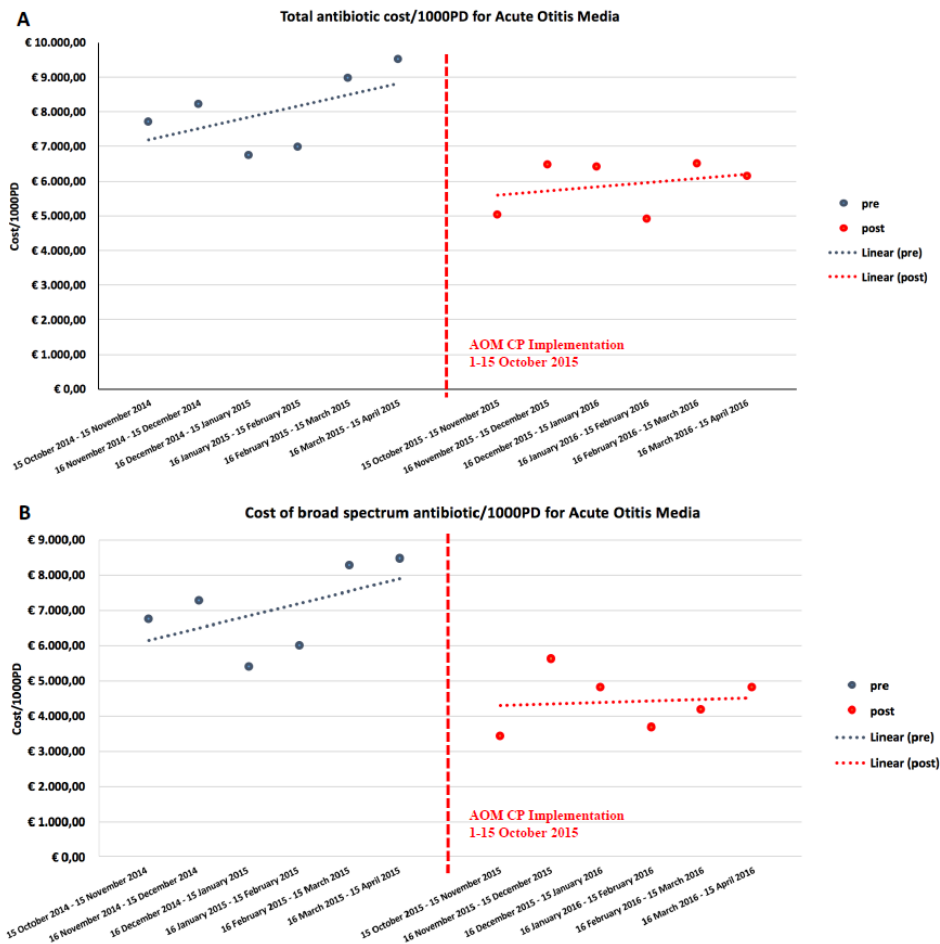
Abbreviations: PD= Patient Day; circle=data; the dashed line=the linear trend line

Supplemental Digital Content 9. Figure

GAS Pharyngitis total cost per 1000 PD for overall antibiotic (A) and for broad-spectrum ones (B) for each month.

Abbreviations: PD= Patient Day; GAS Pharyngitis=Group A Streptococcus Pharyngitis; circle = data; dashed line= the linear trend line

CHAPTER V

Treatment of Community-Acquired Pneumonia: Are All Countries Treating Children in the Same Way?
A Literature Review

Abstract

Background. Pneumonia represents an important threat to children's health in both developed and developing countries. In the last 10 years, many national and international guidelines on the treatment of pediatric CAP have been published, in order to optimize the prescription of antibiotics and limit their cost and side effects. However, the practical implementation of these guidelines is still limited. Main Text. We analyzed the current recommendations for the therapy of pediatric community-acquired pneumonia (CAP) that all converge on the identification of aminopenicillins and beta-lactams as the optimal treatment for CAP. We also conducted a review of the current literature on antibiotic regimens used for pediatric CAP to identify the current state of guidelines implementation in different settings. We selected 37 studies published from 2010 to 2016, including both retrospective and prospective studies, mainly cross-sectional and hospital based. The results show a global heterogeneity in the antibiotics prescription for pediatric CAP, with application of guidelines varying from 0% to more than 91% and with important differences even within the same country. Conclusions. Our review has demonstrated that the implementation of the guidelines is still limited but also that achieving the optimal prescription is possible and can be done in both developed and developing countries.

Introduction

Pneumonia is the single greatest cause of death in children worldwide, with an estimated 1.3 million deaths in 2011 and more than 90% occurring in developing countries [1–3]. It is responsible for 4% of deaths in newborns and 14% of deaths in pediatric patients [4]. The incidence of CAP is lower in developed countries: in the US it is about 35–40/1000/person-years in children < 5 years old, 20/1000 person-years in children 5–10 years old, and 10/1000 person-years in children > 10 years old. Despite this, approximately 50% of children with CAP < 5 years old, 20% between 5–10 years old, and 10% of children > 10 years old need to be hospitalized [5]. These numbers demonstrate the burden that CAP represents for society and for economic healthcare resources.

Materials and Methods

In the first part of the study, we compared the latest national and international guidelines on pediatric CAP, including all those who were published since 2005 to 2016, focusing on their recommendations for first-line therapies.

Then we performed a search on PubMed and Scopus databases, looking for studies published from 2010 to 2016 about CAP antimicrobial therapy in children, trying to get data from as many different countries as possible. We also performed hand-search of references of relevant articles. Our search included both retrospective and prospective studies, mainly cross-sectional and hospital based, including both inpatients and outpatients. All of them except for one [6] included pediatric patients only.

To get a more extensive review of CAP prescribing behaviour, for those countries where specific studies on antimicrobial prescriptions for CAP were not available, a search for articles on antimicrobial prescriptions in pediatric age groups was performed. All articles including CAP as reason for treatment were included.

Results and Discussion

Different Countries, Same Pathogens

Organisms responsible for CAP vary stratifying children by age because of the developing immune system and age-related exposures: viruses or mixed infections are more common amongst younger patients (children under 5 years of age), while exclusive bacterial origin and atypical etiology (mainly Mycoplasma pneumoniae and Chlamydophila pneumoniae) are more often identified in older children [7, 8]. S. pneumoniae and Haemophilus influenzae are the commonest bacterial pathogens isolated in children under five years with CAP accounting for 30%–50% and 10%–30%, respectively [9]. Around 50% of deaths due to pneumonia are attributable to these organisms [10].

Viral etiology has been documented in up to 80% of CAP cases in children younger than 2 years and much less in older children (10–16 years). The most frequently identified viral pathogen in younger children is Respiratory Syncytial Virus (RSV), rarely detected in older children. Less frequent are Adenoviruses, Bocavirus, Human Metapneumovirus, Influenza A and B Viruses, Parainfluenza Viruses, Coronaviruses, and Rhinovirus. Up to 33% of hospitalized children are simultaneously infected by 2 or more viruses. Mixed infections (both of viral and bacterial etiology) have been documented in 2–50% of children with CAP, more frequently in inpatients, which are more seriously ill than outpatients [3, 11].

Atypical pneumonia caused by different pathogens is characterized by a different clinical course: slowly progressing, with malaise, sore throat, low-grade fever, and cough developing over 3–5 days. The main organisms responsible for atypical pneumonia are M. pneumoniae in older children and C. pneumoniae in infants. Legionella species are rarely identified in children [8, 12, 13].

The etiologic definition is difficult for many reasons, such as low yield of blood cultures, difficulty in obtaining adequate sputum specimens from younger children, frequent specimen contaminations by upper airways bacterial flora and invasiveness of pulmonary biopsy, lung aspiration, and bronchoalveolar lavage which are rarely performed [13]. However, over the last 10 years, there have been improvements in PCR techniques for viral identification on nasopharyngeal aspirates or secretion, and molecular assays are now commonly used in Europe and in the US.

Vaccines are the most effective strategy for prevention of pediatric CAP. Haemophilus influenzae type B (HiB) conjugate vaccine and 7-valent pneumococcal conjugate vaccines (PCV7) dramatically decreased the incidence of bacterial CAP after introduction of universal vaccination campaigns [14, 15]. PCVs have been included for some years in the immunization schedules of children in their first year of life in many countries and they have completely modified the burden of pneumococcal diseases among these children and their unvaccinated contacts of any age [16]. Currently, the

polyvalent pneumococcal vaccine (PCV13) confers immunity to approximately 85% of serotypes responsible for most invasive pneumococcal diseases [17].

Same Pathogens, Same Treatment: International CAP Recommendations

Since its introduction during the 20th century, antibiotic therapy, along with vaccines, has decreased CAP mortality of 97% in developed countries [14]. Most of the time the choice of an antimicrobial agent is empirical and based on the most common etiologies for each age group, on the local prevalence of causative organisms, and on the presence of risk factors for atypical or resistant bacteria [18].

During the last 10 years, many guidelines have defined the best antimicrobial regimen for CAP in children considering spectrum of activity, antimicrobial susceptibility, tolerability, bioavailability, safety, and cost [19, 20]. As already highlighted by other authors, these guidelines present some differences in treatment strategies, but almost all agree on the first-line therapy to administer in case of CAP (Figure 1) [19].
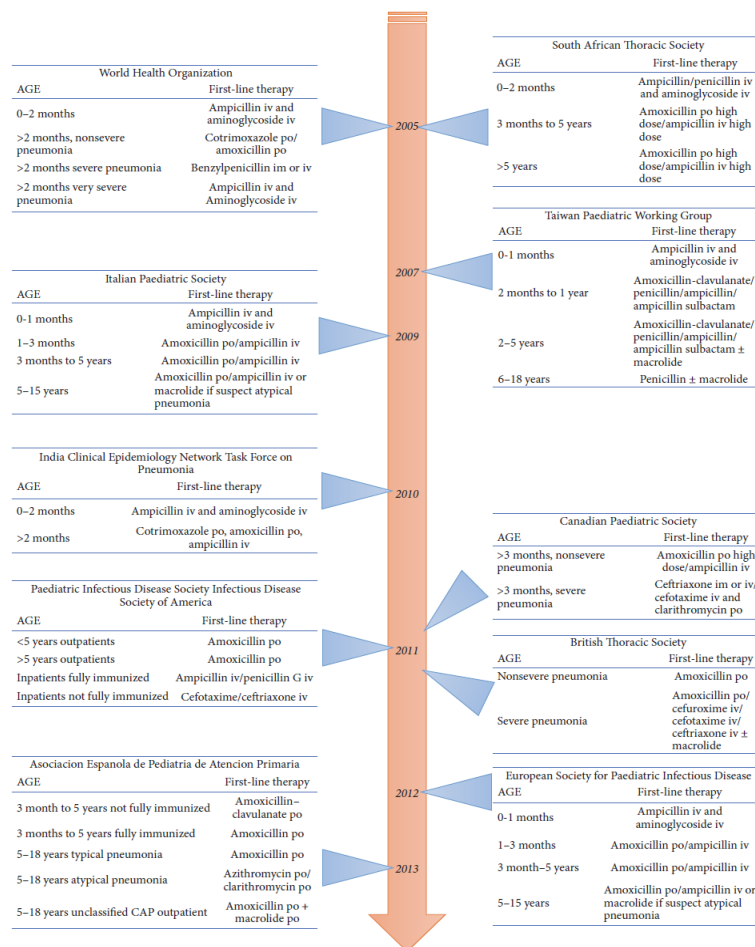

Figure 1: Pediatric CAP guidelines timeline [adapted by Berti et al., 2013 [19]].

For infants < 2 months of age, the association with ampicillin and aminoglycosides is the most suggested therapy, ensuring coverage for Group B streptococci and Gram-negatives. In case of atypical pneumonia, in this period of life, because of the possibility of Chlamydia trachomatis infection, macrolides are recommended [3, 19, 21–23].

For all children > 3 months of age, the narrowest regimen with S. pneumoniae activity is suggested worldwide. Penicillin is the ideal first-line therapy, being a narrow-spectrum agent achieving therapeutic concentrations for S. pneumoniae in the lung up to MIC of 4 mg/ml [24]. However, due to its limited bioavailability, oral amoxicillin is reported as an equivalent and more feasible option [24, 25].

Despite general agreement on the agent, differences in dose and posology have been reported, varying according to pneumococcal resistance [19]. Indeed, beta-lactam effectiveness is time dependent and S. pneumoniae does not develop resistance through β-lactamase enzyme production, but through the alteration of the cell wall's antimicrobial targets (penicillin-binding proteins) [26]. Thus, in the setting of resistant S. pneumoniae serotype, higher concentration at the infection site is needed in order to saturate penicillin-binding proteins and to overcome resistance [27].

A study of children with pulmonary pneumococcal infection [28] provided data to develop a model for describing amoxicillin pharmacokinetics administered with different patterns: 50 mg/kg/day in two or three administrations daily. The resulting curve, integrated with S. pneumoniae MIC for amoxicillin, showed that, for intermediate resistant S. pneumoniae (MIC 4 mg/ml) CAP, the amoxicillin plasma concentration remained above the pneumococcal MIC level for about 4 hours. Therefore, amoxicillin administered every 8 hours maintains blood and lung concentrations that are above S. pneumoniae MIC for enough time to allow S. pneumoniae eradication. A longer interval between administrations (every 12 hours), in case of intermediate resistant serotypes, would not permit having a sufficient antimicrobial plasma concentration [28]. Similarly, penicillin G needs more frequent administrations than other beta-lactams, because of its shorter half-life [13].

Beta-lactam dose is the other key factor for pathogen eradication. Through the different guidelines, amoxicillin daily dose varies from 40–50 mg/kg to 90–100 mg/kg, with higher dosage recommended in areas with higher risk for antibiotic-resistant serotype, as in the US [13, 19]. In the same way, for inpatient parenteral therapy, higher doses of penicillin G or ampicillin are recommended [13].

The only two guidelines which suggest an aminopenicillin plus beta-lactamase inhibitor as first line are the Taiwan Pediatric Working Group and Asociacion Espanola de Pediatria de Atencion Primaria [29, 30]. Unlike the first one, in which aminopenicillin plus beta-lactamase inhibitor (e.g., amoxicillin-clavulanate) is suggested as first-line therapy for all children treated as outpatient, the Spanish

guidelines recommend coamoxiclav only for children who are not fully immunized with conjugate vaccines for *type B H. influenzae* and for *S. pneumoniae*. Indeed, this population is at increased risk to develop a CAP by aggressive S. pneumoniae serotypes and other less common organisms, as H. influenza. Unlike Pneumococcus, type B and nontypeable *H. influenzae* became resistant to penicillin through the production of β-lactamase. Therefore, treatment with the association of amoxicillin with a β-lactamase inhibitor ensures a broader coverage [30]. It should be noted that the addition of a β-lactamase inhibitor does not change the amoxicillin kinetic curve; as a consequence, in order to treat a pneumococcal infection with the association of amoxicillin with clavulanate, the therapy should be administered every 8 hours [26].

The WHO guidelines are the only one suggesting cotrimoxazole as alternative to amoxicillin in outpatient treatment. This recommendation derived from evidence of no difference in treatment failure rates between amoxicillin and cotrimoxazole [31–33]. Despite concerns about the increase of S. pneumoniae and H. influenzae resistant to cotrimoxazole, as demonstrated by some authors [34], the reason for this indication is mainly attributable to economic factors. Indeed, for children <10 kg, the cost of a five-day treatment with amoxicillin is higher than the same duration on cotrimoxazole [35–37].

No guidelines recommend oral cephalosporins as first-line therapy. Indeed, pharmacokinetic and pharmacodynamic studies showed that none of the available oral cephalosporins is able to exceed the pneumococcal MIC for more than 50% of the time between two administrations [26]. Moreover, recent US data on S. pneumoniae susceptibility to cefdinir and cefuroxime indicated only 70% to 80% efficacy, compared with 84% to 92% amoxicillin efficacy [38, 39].

The only cephalosporin that has been demonstrated superior to penicillin in S. pneumoniae eradication, even if resistant, is ceftriaxone [40]. No microbiologic failures have been reported for S. pneumoniae with ceftriaxone MIC of 4.0 mg/mL [13, 41]. Thus, ceftriaxone or cefotaxime in standard doses is suggested by all guidelines as alternatives in case of first-line treatment failure, severe clinical conditions, or not fully immunized children [3, 7, 13, 21–23, 29, 30, 41].

Due to high prevalence of macrolide resistance circulating strains of S. pneumoniae, macrolides are not recommended as empiric therapy for CAP. Their use is suggested only when atypical etiology is suspected or in case of persistence of symptoms despite beta-lactams administration [7, 13, 42]. This strict indication for macrolides use derives from the evidence that Mycoplasma lower respiratory tract infection (LRTI) has a high rate of spontaneous clinical remission and the use of azithromycin has been associated with the selection of resistant organisms because of its prolonged serum elimination half-life [13]. Moreover, no significant benefits of antibiotic treatment in M. pneumonia infection have been documented [37].

For complicated pneumonia (i.e., moderate parapneumonic effusion and necrotizing pneumonia), antimicrobial therapy must be broadened to cover less common but highly aggressive pathogens as Streptococcus pyogenes and S. aureus. As for S. pneumoniae, macrolides cannot be considered an effective empiric therapy because of the high level of resistance [13].

Despite the fact that no penicillin or cephalosporin resistance has been reported for S. pyogenes, some authors suggest that, in case of concomitant symptoms attributable to toxic shock syndrome, combination therapy with clindamycin decreases the severity of symptoms [43]. In fact, since clindamycin inhibits protein synthesis (by binding the 50S subunit of the bacterial ribosome), it inhibits the production of S. aureus toxins, resulting in a lower inflammatory reaction. Clindamycin may be bacteriostatic or bactericidal depending on the organism and drug concentration and is indicated by US guidelines as a good option for both methicillin susceptible S. aureus (MSSA) and community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains [13].

Nowadays almost all MSSA have penicillin resistance which can be overcome with the addition of a β-lactamase inhibitor or through penicillinase-resistant beta-lactams, such as oxacillin or first-generation cephalosporins. MRSA strains have mecA gene that encodes penicillin-binding protein 2a, an enzyme that has low affinity for beta-lactams, leading to resistance to all antibiotics active against MSSA. During the last decade, both community-associated and hospital-acquired infections with MRSA have increased. MRSA, accounting for 20%–40% of all hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), have demonstrated a rapid increase as cause of pneumonia even in patients without exposure to the healthcare system [44]. This CA-MRSA has become an important cause of CAP complicated by empyema and necrosis [45].

Since erythromycin resistance predicts inducible clindamycin resistance in many isolates, a D-test to assess clindamycin susceptibility should always be performed. In case of D-test positivity, the use of clindamycin should be avoided, since it is highly possible that the organism will become resistant during the infectious process, especially in high-inoculum infections such as empyema [45]. On the other hand, all CA-MRSA strains are susceptible to vancomycin, which is considered by all guidelines as the drug of choice if MRSA is suspected [7, 13]. Although linezolid has been recently demonstrated as efficient as vancomycin for the treatment of MRSA pneumonia, its use should be considered as a second-line treatment for cost consideration (linezolid costs >10 times more than vancomycin) and because linezolid-resistant MRSA has already been described [46, 47].

Different Countries, Same Treatment?

A worldwide review about CAP antimicrobial therapy in children includes 37 studies about antibiotics prescriptions in 50 countries published since 2010. The results are shown in Table 1 and Figure 2.

TABLE 1: Papers on CAP antibiotic treatment in children from 2010 to 2016.

	Authors year of publication [ref.]	Country	Study design	Treated infections (% of pneumonia)	Population: age in/outpatient	Most prescribed antibiotics (%)
(1)	Amadeo et al. (2010) [48]	Europe	Multicenter, 2-day PPS on abx prescriptions	Various (respiratory tract infection: 30%)	<18 y inpatients	Third-generation cephalosporins (18%)
(2)	Ceyhan et al. (2010) [49]	Turkey	Multicenter, cross-sectional, 1-day PPS	Various (29.4%)	<18 y inpatients	Cephalosporins (22.1%), Penicillin (20.5%) 56% inappropriate prescriptions
(3)	Younis (2010) [50]	Iraq	6-month, multicenter, prospective, observational study	Various (20%)	6m–16y inpatients	Ampicloxacillin (50%)
(4)	Mohajer et al. (2011) [51]	Saudi Arabia	1-month, retrospective, cross-sectional study on pharmacy prescriptions	Various (16.2%)	<12 y inpatients	Cephalosporin <1yr (44.6%), coamoxiclav 1–5 years (35.4%), and 5–12 years (35.8%)
(5)	Bergicho et al. (2012) [52]	Ethiopia	1-month, single-center observational retrospective study on abx prescriptions	Various (9.27%)	<18 y inpatients	Cotrimoxazole (18.87%) Amoxicillin (14.5%)
(6)	Borrás Novell et al. (2013) [53]	Spain	A 1-year, prospective multicenter study including patients seen in PED on day 14 of each month who required hospitalization with systemic abx	Various (29.4%)	<18 y inpatients	Cefotaxime (27.8%), coamoxiclav (23.4%)
(7)	Brogan et al. (2012) [54]	USA	5-year, multicenter, retrospective cohort study from the Pediatric Health Information System (PHIS)	100%	1–18 y inpatients	Cephalosporins (40.4%)
(8)	Fossum et al. (2013) [55]	Norway	1-year, observational study primary care records	All respiratory tract infection (2.4%)	<6 y outpatients	Macrolides (44%)
(9)	Gwimile et al. (2012) [56]	Tanzania	7-month, single-center, cross-sectional descriptive hospital based study	Various (41%)	1m–5 y inpatients	Penicillin (47.9%)
(10)	Moinuddin et al. (2012) [57]	India	9-month, prospective treatment charts review	100%	<18 y inpatients	Third-generation cephalosporins (57.2%)
(11)	Choudry and Bezbaruah (2013) [58]	India	1-month, single-center observational prospective study on abx prescriptions	Various (17%)	<12 y inpatients	Coamoxiclav (35%) Ceftriaxone (29%)
(12)	De Sá Del Fiol et al. (2013) [59]	Brazil	12-month, cross-sectional study on questionnaire on abx prescriptions in two Primary Health Centres	Various (3.13%)	<9 y outpatients	Penicillin (73.13%)
(13)	Dorj et al. (2013) [6]	Mongolia	10-week observational prospective study on written abx prescriptions of community pharmacies in rural and urban areas	100%	Adults and children outpatients	Aminopenicillins (16%)
(14)	Feleke et al. (2013) [60]	Ethiopia	6-month, prospective, cross-sectional study on patients charts	Various (56.3%)	<10 y inpatients	Ceftriaxone (43.50%)
(15)	Neuman et al. (2013) [61]	USA	Data were obtained from the National Hospital Ambulatory Medical Care Survey (NHAMCS) for ED visits from 2001 through 2009 for children with CAP	100%	Adults and children outpatients	Cephalosporin (35%) Macrolides (36%)

TABLE 1: Continued

	Authors year of publication [ref.]	Country	Study design	Treated infections (% of pneumonia)	Population: age in/outpatient	Most prescribed antibiotics (%)
(16)	Alakhali and Shaik-Mohammad (2014) [62]	Saudi Arabia	2-month, observational, retrospective study on abx prescriptions	Various (9.7%)	<12 y inpatients	Cephalosporin (52%)
(17)	Dubos et al. (2014) [63]	France	A phone survey with a standardized questionnaire submitted randomly to GPs, pediatricians, and pediatric fellows	100%	<18 y outpatients	Coamoxiclav 54% Amoxicillin 29%
(18)	Maltezou et al. (2014) [64]	Greece	A standardized questionnaire distributed to 520 private-practice pediatricians	100%	<18 y outpatients	Compliance with the first-line recommended antibiotic was 30.6% for CAP
(19)	Mishra et al. (2014) [65]	India	Single-center, prospective, interventional study	Various (LRTI: 17.9%)	1 m–16 y outpatient	Amoxicillin (44%)
(20)	Osowicki et al. (2015) [66]	Australia	Multicentre, single-day, hospital-wide PPS	Various (LRTI: 22%)	<18 y inpatients	Narrow-spectrum penicillin (18%) β-lactam–β-lactamase inhibitor combinations (15%)
(21)	Salih et al. (2014) [67]	Sudan	12-month, cross-sectional study on abx prescriptions	100% (severe)	2 m–5 y inpatients	Coamoxiclav (22.1%) Cephalosporins: (i) Ceftriaxone (20.2%) (ii) Cefuroxime (19.7%)
(22)	Sviestina et al. (2014) [68]	France, Latvia, and UK	Multicenter, 1-day PPS on abx prescriptions ##	Various: LRTI Latvia (26.2%), France (11.8%), UK (9.3%)	<18 y inpatients	UK: piperacillin/tazobactam (32%), coamoxiclav (26%) Latvia: amoxicillin (30%), ceftriaxone (21%) France: coamoxiclav (21%), amoxicillin (17%)
(23)	Awor et al. (2015) [69]	Uganda	All drug shops in the intervention area were included and all child visits in 8 months were analyzed	Various (45%)	<7 y outpatients	Amoxicillin (91%)
(24)	Fadare et al. (2015) [70]	Nigeria	7-month, cross-sectional study using medical records	Various (respiratory tract infections: 53.7%)	<5 y outpatients	Amoxicillin (52.4%) Coamoxiclav (19%)
(25)	Iroh Tam et al. (2015) [71]	USA	Multicenter, retrospective study (six hospitals) on medical records with pneumonia	100%	2 m–18 y inpatients	Third-generation cephalosporins (72%)
(26)	Milner et al. (2015) [72]	USA	2-year multicenter retrospective cohort study	100%	3 m–18 y	Emergency department providers prescribed narrow-spectrum therapy 27% of the time
(27)	Thapaliya et al. (2013) [73]	Nepal	6-month, single center, retrospective study on medical charts	Various (22.5%)	<13 y inpatients	Cephalosporins (ceftriaxone 49.3%, cefotaxime 26.2%)
(28)	Williams et al. (2015) [74]	USA	6-month multicenter, prospective, population-based, active surveillance of CAP hospitalizations among children pre: 1–9%, post: 15.2%	100%	3 m–18 y inpatients	Cephalosporins pre (52.8%)

TABLE 1: Continued.

	Authors year of publication [ref.]	Country	Study design	Treated infections (% of pneumonia)	Population: age in/outpatient	Most prescribed antibiotics (%)
(29)	Fonseca Lima et al. (2016) [75]	Brazil	3-year, single-center, cross-sectional study	100%	1 m–5 y inpatients	Ampicillin 62.17%
(30)	De Luca et al. (2016) [76]	Italy	1-day PPS on abx prescriptions ##	Various (LRTI: 22.1% of children, 2.3% of neonates)	<18 y inpatients	Cephalosporins (43.3%)
(31)	Ivanovska et al. (2016) [77]	Netherlands	3-year, retrospective, observational study; deriving data on diagnoses and prescriptions from the electronic health records-based NIVEL Primary Care Database	Respiratory tract infection (pneumonia 5.8–7.1%)	<18 y outpatients	Amoxicillin: 2010 (60.4%), 2011 (66.9%), and 2012 (63%)
(32)	Launay et al. (2016) [78]	France	Multicenter, prospective two-period study using data from the French pneumonia network	100%	1 m–15 y inpatients	First period: amoxicillin 58.1% Second period: amoxicillin 71.0%
(33)	Sharma et al. (2016) [79]	Guyana	1-year, retrospective chart review of pediatric patients seen in the emergency department	Various (RTI: 19.5%)	1 m–13 y outpatients	Amoxicillin 33.6%
(34)	Thomson et al. (2015) [80]	USA	15-month, single-center, retrospective cohort study	100%	3 m–18 y inpatients	Aminopenicillins (63.6%) Third-generation cephalosporins (16.8%)
(35)	Usonis et al. (2016) [81]	Europe	Snapshot prospective study based on a questionnaire developed and distributed by the CAP Paediatric Research Initiative (CAP-PRI) working group and distributed across Europe	100%	<18 y inpatients and outpatients	Inpatients: amoxicillin (32%), ampicillin (37%) Outpatients: amoxicillin (84%)
(36)	Vesporten et al. (2016) [82]	Africa, Asia, Oceania, Latina America, North America and Europe	1-day PPS on abx prescriptions ##	Various (LRTI 18.7%)	<18 y inpatients	Third-generation cephalosporins: Eastern Europe (37.5%) and Asia (28.6%), fourth-generation cephalosporins in North America (13.3%). Narrow-spectrum (b-lactamase sensitive penicillin 11% in Africa and 4.3% in Northern Europe)
(37)	Zec et al. (2016) [83]	Serbia	Single-center, 6-month, retrospective study on medical charts	100%	1 m–6 y inpatients	Cephalosporins (cefazolin 40.4%, third-generation cephalosporins 31.7%)

Data from Antibiotic Resistance and Prescribing in European Children (ARPEC) project.

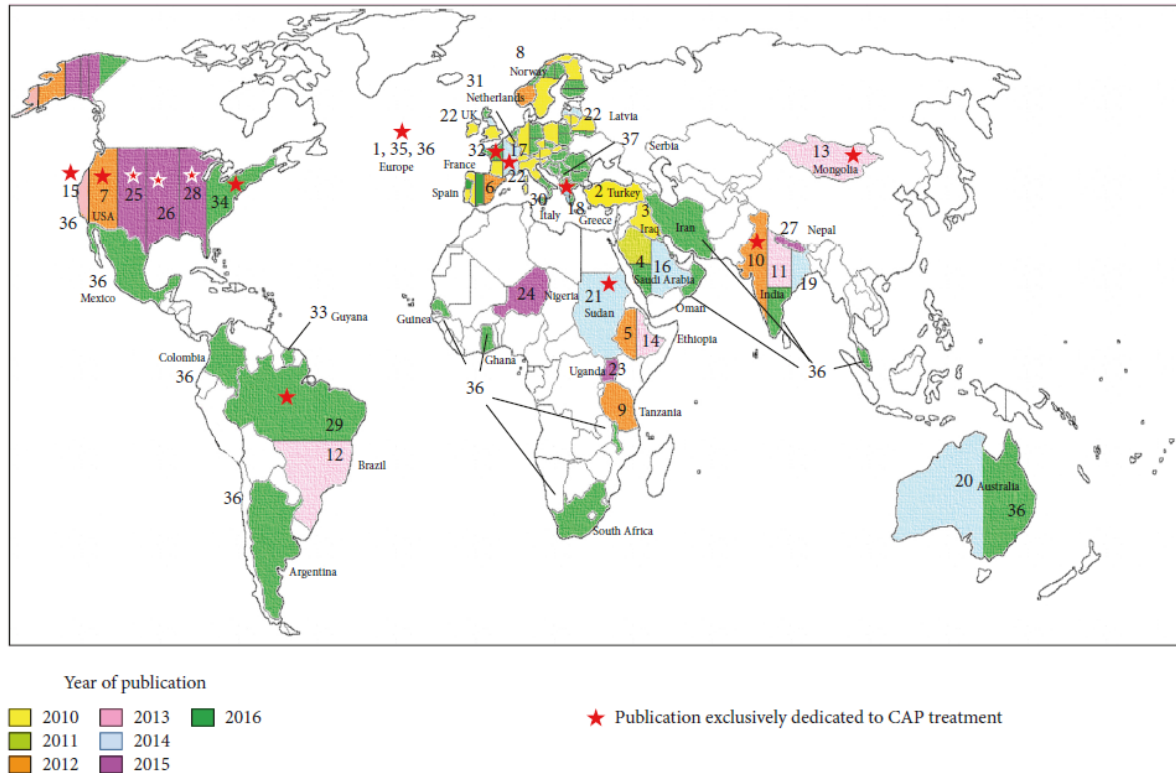**Table 1: Papers on CAP antibiotic treatment in children from 2010 to 2016**.

Figure 2: World map of papers on CAP treatment in children stratified by year of publication.

Even if the studies were different in design and study population, their results give a good picture of the antibiotic prescription patterns in different environments, and they show the global heterogeneity in the application of the guidelines for the treatment of childhood pneumonia.

In fact, the first important result of our review is that the correct implementation of the guidelines is not confined to specific areas but may be variable even inside the same country. For example, Iroh Tam et al., through a 2-year retrospective study on hospitalized children with CAP in six US centres, showed that the most used antibiotics were third-generation cephalosporins (73%), and only 1% of the patients received amoxicillin. These findings during the first 2 years after US guidelines publication led the authors to recommend more strategies for educating healthcare providers [71]. On the other hand, Thomson et al. in another retrospective study set in an US hospital, with the same population (hospitalized children between 3 months old and 18 years old) in a 15-month period (May 2011–July 2012), had an opposite result, reporting that 63,6% of the pediatric CAP were treated with aminopenicillins and only 16.8% with third-generation cephalosporins [80].

We found a similar situation comparing studies from France [63, 78] and India [57, 65].

Interestingly, in France our data about CAP prescriptions derive from two different settings. Launay and colleagues investigated antimicrobial prescriptions and recommendations adherence in a French Emergency Pediatrics Department through a prospective two-period study, including all children

aged one month to 15 years. The results were encouraging, with an increase of recommendation compliance from 18.8% to 48% between 2009 and 2012, and a consequent increase of amoxicillin monotherapy prescription from 54.2% to 71% [78]. Dubos et al., on the other hand, give us a picture of CAP antimicrobial prescriptions through general practitioners (GPs), private pediatricians, and pediatric fellows. The results of the standardized questionnaire submitted to every participant showed that CAP guidelines were insufficiently followed, with high rate of amoxicillin/clavulanate prescriptions (amoxicillin in monotherapy was prescribed in only 29% of cases, for 54% of cases associated with clavulanic acid) [63].

In India, in addition, we found some of the lowest rates of prescription on aminopenicillins as single therapy. Choudry and Bezbaruah, in a prospective observational study based in a university hospital in Assam, including inpatients up to 12 years, reported 0% use of penicillin as single therapy in cases of pediatric pneumonia. The therapy mostly used (54% of cases) was the combination of amoxicillin/clavulanate [58]. Another prospective study by Moinuddin et al. was conducted over 9 months in 2012, in two hospitals in Bangalore. The most widely used therapy was amoxicillin + clavulanate (43,8%), with third-generation cephalosporins as the most prescribed class (ceftriaxone 36.2%, cefotaxime 21%). Penicillin in single therapy accounted only for 1% of prescriptions [57].

Cephalosporins were often reported to be the class with higher rates of prescription for CAP treatment, as reported by many centres in different countries, like Ethiopia [60], Saudi Arabia [62], Nepal [73], Serbia [83], Sudan [67], US [54, 71, 74], Italy [76], and other European countries [48, 82]. Feleke and colleagues conducted their 5-month prospective study in a large government hospital in Ethiopia. The study includes all children admitted in that period and CAP accounted for 56.3% of all drug prescriptions. Ceftriaxone was the most prescribed drug (43.5%) followed by gentamicin (25.6%), and penicillin and ampicillin ranked the third and fourth place [62]. In a retrospective study by Zec et al., during a 6-month period in 2014, first- and third-generation cephalosporins were given to children with CAP in 40.4% and 31.7% of cases, respectively. Penicillin was used in 25% of cases [83]. In an Italian 1-day point-prevalence survey on antimicrobial use in hospitalized neonates and children in 2012, the main indication for treatment in children was LRTI (34%), with higher prevalence of third-generation cephalosporins (43.3%) followed by macrolides accounting for 26.8%. No ampicillin/amoxicillin prescription was reported [76].

Association of aminopenicillins was found to be often prescribed: amoxicillin + clavulanate was reported to be the most used therapy by studies conducted in Saudi Arabia [51], France [63], and India [58], and a study conducted in Iraq, by Younis, reported that ampicillin + cloxacillin, alone and in combination, accounted for 50% of the antibiotic prescriptions for the children with respiratory tract infections [50].

One study, in particular, reported a high rate of prescriptions of macrolides. It was conducted in Norway, by Fossum and colleagues, and included the prescriptions of general practitioners in case of respiratory tract infections in patients < 6 years. They found that macrolides were prescribed in 44% of the cases of pneumonia, more than penicillin V, which was used in 31%, and that extended spectrum penicillin accounted for 24% of the prescriptions [55].

Studies on the appropriateness of prescriptions or prescriber behavior were also found. In addition to the aforementioned French study, Maltezou et al. showed how Greek private-practice pediatricians guidelines compliance is only around 30.6% [64]. Moreover, Ceyhan et al., in a multicenter point-prevalence survey with respiratory infection as main diagnosis, showed how cephalosporins and penicillin (most of the time combined with b-lactamase inhibitors) were improperly prescribed in 36.1% and 43.7% of cases, respectively. These analyses highlighted how, even now, adherence to guidelines is still low. On the other hand, Usonis and colleagues through a questionnaire developed and distributed by the CAP Pediatric Research Initiative (CAP-PRI) working group and distributed across Europe showed high adherence to CAP guidelines, with a high prescription rate of narrow-spectrum penicillin for inpatients (amoxicillin (32%) and ampicillin (37%)) and outpatients (amoxicillin (84%)) [81].

An encouraging result is that almost a half (15/38) of the studies included in this review reported high rates of single therapy aminopenicillin or penicillin prescriptions. These studies were conducted in Brasil [75], Guyana [79], India [65], Mongolia [6], Nigeria [70], Tanzania [56], USA [80], Uganda [69], and France [78], showing that the current guidelines are applied in both developed and developing countries. The study by Awor et al. in Uganda in 2015 offers an important cause for reflection, since it shows that adherence to guidelines may be successfully implemented even in a nonhospital environment. In their 8-month quasi-experimental analysis, they investigated the visits and the prescriptions made by drug shop sellers, underlining how this class of health workers plays an important role in providing healthcare to populations in rural areas. Their result is that 91% of the children with pneumonia that were visited by drug shop sellers received amoxicillin, the highest rate of its prescription among all the studies included in this review [69].

Some data of antimicrobial prescriptions have been derived from point-prevalence surveys (PPS), including Australia [66, 82], Mexico, Colombia, Argentina, Singapore, and European countries [48, 49, 81, 82]. CAP was not the only analyzed disease, but the LRTI category was the most represented. Even though antimicrobial prescriptions were not specific only to CAP, PPS data were similar to the results of those other studies that were performed in the same country, but specifically designed for CAP.

Another interesting result is that the development of a local antimicrobial stewardship program could reduce inappropriate antimicrobial use and bacterial resistance, enhance patients' safety, and lower drug costs [84]. Moreover, global PPS could be a reliable and feasible tool for monitoring antimicrobial prescriptions all over the world.

Finally, it is also worthy of notice how data from certain countries were not available despite interest in the improvement of antibiotic prescription. For example, we did not find any report about pediatric CAP antibiotic treatment in Canada, even extending the research to 2005–2010. Likewise, we did not find any study set in other important countries, like China and Russia. It is worth remembering that the reduction of antimicrobial therapy and of microbial resistance is a global issue, and global effort is required in order to improve antibiotic prescription and administration practice.

Conclusions

In the last 10 years, many guidelines on the optimal treatment for childhood CAP have been published, with the aim of optimizing pediatric CAP antibiotic prescriptions. Our review demonstrates that the implementation of these guidelines is still limited but also that achieving the optimal prescription is possible and can be done in both developed and developing countries.

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CHAPTER VI

Effects of a clinical pathway on antibiotic prescriptions for pediatric community-acquired pneumonia

Abstract

Background: Italian pediatric antimicrobial prescription rates are among the highest in Europe. As a first step in an Antimicrobial Stewardship Program, we implemented a Clinical Pathway (CP) for Community Acquired Pneumonia with the aim of decreasing overall prescription of antibiotics, especially broad-spectrum.

Materials and methods: The CP was implemented on 10/01/2015. We collected antibiotic prescribing and outcomes data from children aged 3 months-15 years diagnosed with CAP from 10/15/2014 to 04/15/2015 (pre-intervention period) and from 10/15/2015 to 04/15/2016 (post-intervention period).

We assessed antibiotic prescription differences pre- and post-CP including rates, breadth of spectrum, and duration of therapy. As balancing measures, we determined length of hospital stay for inpatients and treatment failure for inpatients and outpatients. Chi-square and Fisher's exact test were used to compare categorical variables and Wilcoxon rank sum test was used to compare quantitative outcomes.

Results: 120 pre- and 86 post-intervention clinic visits were identified with a diagnosis of CAP. In outpatients, we observed a decrease in broad-spectrum regimens (50% pre-CP vs. 26.8% post-CP, p=0.02), in particular macrolides, and an increase in narrow-spectrum (amoxicillin) post-CP. Post-CP children received fewer antibiotic courses (median DOT from 10 pre-CP to 8 post-CP, p<0.0001) for fewer days (median LOT from 10 pre-CP to 8 post-CP, p<0.0001) than their pre-CP counterparts. Physicians prescribed narrow-spectrum monotherapy more frequently than broad-spectrum combination therapy (DOT/LOT ratio 1.157 pre-CP vs. 1.065 post-CP). No difference in treatment failure was reported before and after implementation (2.3% pre-CP vs. 11.8% post-CP, p=0.29). Among inpatients we also noted a decrease in broad-spectrum regimens (100% pre-CP vs. 66.7% post-CP, p=0.02) and the introduction of narrow-spectrum regimens (0% pre-CP vs. 33.3% post-CP, p=0.02) post-CP. Hospitalized patients received fewer antibiotic courses post-CP (median DOT from 18.5 pre-CP to 10 post-CP, p=0.004), while there was no statistical difference in length of therapy (median LOT from 11 pre-CP to 10 post-CP, p=0.06). In particular, days of broad-spectrum therapy were notably lower post-CP (median bsDOT from 17 pre-CP to 4.5 post-CP, p <0.0001). No difference in treatment failure was reported before and after CP implementation (16.7% pre-CP vs. 15.4% post-CP, p = 1).

Conclusions: Introduction of a CP for CAP in a Pediatric Emergency Department led to reduction of broad-spectrum antibiotic prescriptions, of combination therapy and of duration of treatment both for outpatients and inpatients.

Background

Pneumonia is the single greatest cause of death in children worldwide: 1-4% of the pediatric population is treated every year for community acquired pneumonia (CAP) and 0.1-2% of those children are hospitalized [1-3].

Inpatient healthcare costs associated with CAP are estimated to be more than one billion dollars per year [4].

Inappropriate antibiotic prescribing for CAP has been frequently reported, as many patients receive antibiotics for viral pneumonia or broad-spectrum antibiotics for uncomplicated bacterial pneumonia [5]. The Italian antimicrobial prescription rate is one of highest in the EU (52%) [6], and antibiotic resistance has become a serious health threat with high social costs and severe consequences including prolonged illness, increased length of hospitalization and mortality [6]. Increasing penicillin and macrolide resistance of *Streptococcus pneumoniae* strains pose an important threat to effective treatment [7]. There is also widespread β-lactamase production in *Haemophilus influenzae* and macrolide resistance in *Streptococcus pyogenes* [8].

Thus, it is imperative to reduce improper use of these drugs. Clinical Pathways (CPs) along with educational programs have shown to be a reasonable and feasible first step for Antimicrobial Stewardship Program (ASP) implementation by reducing antibiotic prescriptions in both community and in-hospital settings [9-13].

To date, ASPs have primarily targeted the inpatient setting, and there is a paucity of literature regarding antimicrobial stewardship strategies in the Pediatric Emergency Department (PED), despite the substantial proportion of antibiotics prescribed to children in this setting [14-17]. Since PEDs are uniquely positioned at the interface of inpatient and outpatient settings, PED physicians could have a consistent impact on prescribing trends in both locations.

In the PED setting, challenges include high turnover rates for both patients and practitioners, the need for rapid decision-making, and diagnostic uncertainty in empiric prescription [18].

Since CPs have been effective in reducing antibiotic prescriptions in primary care and in hospital settings, we hypothesized that their implementation in the PED could decrease overall prescription of antibiotics, especially broad-spectrum, for common infectious diseases such as CAP [9-13].

The primary aim of this study was to assess changes in antibiotic prescription before and after CP implementation for CAP in a large Italian PED. Secondary aims were to compare treatment failures before and after CP implementation.

Materials and methods

Study design

The study was set at the PED of the Department for Women and Children Health at Padua University Hospital. Our Children's Hospital provides primary and secondary care for a metropolitan area of 350,000 people (45,000 younger than 15 years) and tertiary care for a regional and extra-regional population, with approximately 26,000 PED visits per year and an overall hospital admission rate from PED of around 7 out of 100 visits.

From the PED, children with moderate-severe CAP are usually admitted to the Pediatric Acute Care Unit (PACU), an acute care unit near the emergency department, which shares the same medical staff.

This is a pre-post quasi-experimental study that assesses the changes in antibiotic prescribing for CAP during a 6-month period preceding CP implementation (pre-intervention, from 15 October 2014 to 15 April 2015) and during the six months after CP implementation (post intervention, from 15 October 2015 to 15 April 2016). The decision to analyse the same period in different years was made in order to limit the effects of seasonality.

Intervention

On 1 October 2015 CPs for the management of CAP were implemented.

The CP is a one-page decision support algorithm designed to assist providers in determining whether an antibiotic should be prescribed, and if so, the optimal agent and duration of therapy.

The CP summarizes international guidelines [1,8] for the diagnosis and treatment of the clinical condition and was developed by the Division of Pediatric Infectious Diseases and Pediatric Emergency Department of Padua in collaboration with the Division of Pediatric Infectious Diseases of the Children's Hospital of Philadelphia.

Three CP training sessions (two during the first weeks of October and one during the first week of November) were presented to PED and Pediatric Acute Care Unit (PACU) physicians and residents along with an overview of the guidelines, the rationale behind the treatment.

Study population

All patients aged between 3 months and 15 years with *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes 485 and 486 at discharge diagnosis or descriptive diagnosis of CAP were included.

Exclusion criteria were: cystic fibrosis or other chronic pulmonary diseases (except for asthma), immunodeficiency or immunosuppressive therapy, sickle cell disease, tracheostomy, patients at risk for aspiration pneumonia, hospitalization during previous 30 days, concomitant infections, ongoing antibiotic therapy.

Participating patients were divided in two groups:

- **Outpatients**: patients evaluated at the PED and discharged;
- **Inpatients**: patients admitted to the PACU.

Data source

All patients with a clinical diagnosis of pneumonia (medical progress notes) or documentation of a chest infiltrate (radiology notes) were included. All clinical, demographic, diagnostic and antimicrobial data were manually collected from electronic medical records, using a password protected REDCap® data collection form and stored in the secure server at the University of Padua.

We considered treatment based on amoxicillin or ampicillin alone narrow-spectrum. Broad-spectrum antimicrobials were defined as: β-lactam and β-lactamase inhibitor combinations, second- and third-generation cephalosporins, clindamycin, glycopeptides, fluoroquinolones and macrolides. Therapeutic regimens including at least one broad-spectrum prescription, despite the association with amoxicillin, were considered broad-spectrum. In line with expert consensus CAP guidelines [1], our CP suggested a dosage of amoxicillin of 90 mg/kg/day divided every 8 hours.

Amoxicillin *per os* rather than penicillin G is recommended due to its better gastrointestinal absorption and higher levels in blood and lung parenchyma [1,19].

Privacy was guaranteed in two ways: a unique, study specific survey number was assigned to each patient and no personally identifying data were collected.

To evaluate the effectiveness and safety of the intervention, follow up phone calls to the family were made within 30 days to assess for treatment failure, defined as new admission, prescription of a new antibiotic for persistence or relapse of symptoms or for drug side effects (eg rash, diarrhea) within 30 days after discharge, and/or side effects.

Admissions for CAP in the same patient occurring greater than 30 days apart were analysed as separate events.

This study was approved by the Institutional Review Board of Department for Woman and Child Health at the University of Padua.

Determination of outcomes

Primary outcome

The following aspects of antibiotic prescriptions for CAP were assessed every month over the six months before and the six months after CP implementation:

- Prevalence of antimicrobial prescriptions by active agent;
- Duration of therapy expressed in Days of therapy (DOT) and Length of Therapy (LOT) [20-22], DOT/LOT ratio, median DOTs of broad-spectrum antibiotics (bsDOTs) and bsDOT/DOT ratio.
- Dosage of the most frequently prescribed antibiotics, expressed in mg/kg/day;
- Length of hospital stay (LOS) for inpatients.

Secondary outcome

Thirty day treatment failures investigated through a phone call, defined as: changes in antibiotic prescription for persistence or worsening of symptoms; treatment changes for antibiotic side effects or new antibiotic prescriptions within 30 days from discharge date for relapse of symptoms and mortality.

Data analysis

Results are summarized as frequencies and proportions for categorical variables and as median and range for quantitative variables.

Comparisons of categorical and quantitative variables were conducted with chi-square or Fisher's exact test and Wilcoxon rank sum test respectively, since the data were not normally distributed (Shapiro-Wilk test). Statistical significance was declared for $p \leq 0.05$. Statistical analysis was conducted with SAS 9.2 (SAS Institute, Inc., Cary, NC) for Windows.

Results

Over the 6-month pre-intervention period, 13,262 children were evaluated in the PED and 12,335 children were seen during the 6-month post-intervention period.

During the pre-intervention period, 120 patients were diagnosed with CAP, accounting for 0.90% (120/13,262) of total PED visits. In the post-intervention period 86/12,335 (0.70%) children were evaluated for CAP. Of these, 70/120 (58.3%) children and 59/86 (68.6%) met the inclusion criteria in the two analysed periods of time (Fig 1).
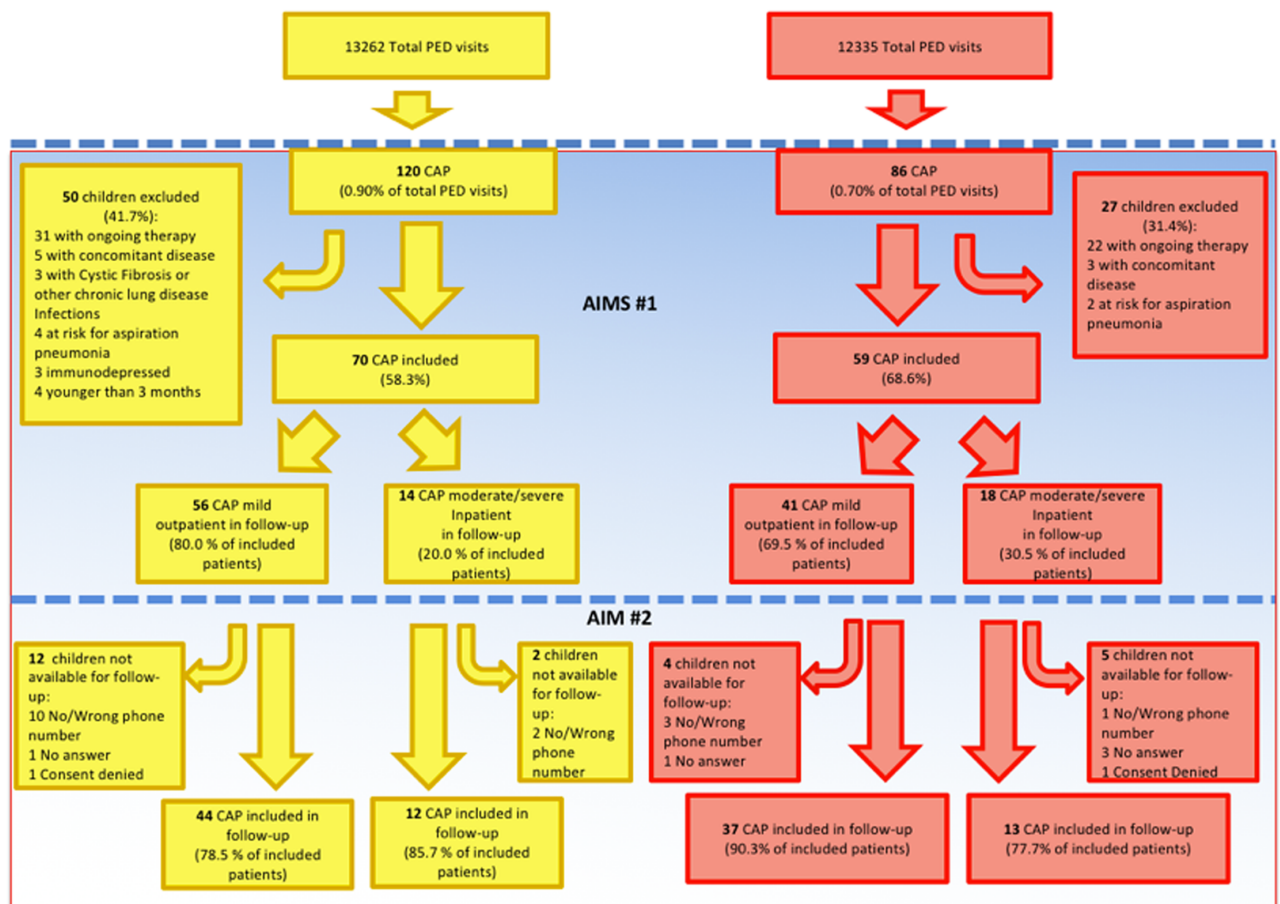

Fig 1. Flowchart of children enrolled during the pre and post-intervention period.

Characteristics of the studied population

Variables including sex, age, severity and time of disease were assessed in pre- and post-CP populations. The two groups were similar with respect to sex (p=0.76): 50.0% (35/70) females pre-intervention and 54.2% (28/59) post-intervention.

Age was stratified into three age ranges: 3 months-2 years, 2 years-5 years and 5 years-15 years. In both groups, the highest prevalence of CAP was reported in the 2-5 years group with 55.7% (39/70) pre and 61.0% (36/59) post-intervention respectively (p=0.44). The same analysis was performed also for excluded patients with similar results.

To describe prescription trends over time, both groups were divided in four sub-periods of 45 days each.

For both the inpatient and outpatient groups, there was no statistically significant difference in frequency or proportion of patients diagnosed with *Mycoplasma pneumoniae* by serology. Proportion of inpatients presenting with hypoxemia and with pleural effusion were similar in the pre- and post-CP groups (**Table 1** and **2**).

		Pre-Intervention Period		Post-Intervention Period		p value
Included Patients		70		59		
Included 0utpatients		56 (80.0% of included patients)		41 (69.5% of included patients)		
		N	%	N	%	
Sex	m	24	42.9	19	46.3	0.73
	f	32	57.1	22	53.7	
Age	3 mo - 2 yr	12	21.4	9	22.0	0.10
	2 yr - 5 yr	31	55.4	29	70.7	
	5 yr - 15 yr	13	23.2	3	7.3	
Period	15 Oct - 30 Nov	0	0	6	14.6	<0.0001
	1 Dec - 15 Jan	25	44.6	17	41.5	
	16 Jan - 28/29 Feb	14	25.0	18	43.9	
	1 Mar - 15 Apr	17	30.4	0	0	
Mycoplasma Pneumoniae IgM test	performed	1	1.8	3	7.3	0.31
	not performed	55	98.2	38	92.7	
Number of M. Pneumoniae IgM positive test/number of test performed		1	100	0	0	0.40

Table 1. Characteristics of Outpatients Population.

			Pre-Intervention Period		Post-Intervention Period		p value
Included Patients			70		59		
Included Inpatients			14 (20.0% of included patients)		18 (30.5% of included patients)		
			N	%	N	%	
Sex		m	11	78.6	8	44.4	0.11
		f	3	21.4	10	55.6	
Age		3 mo – 2 yr	4	28.6	7	38.9	0.87
		2 yr – 5 yr	8	57.2	7	38.9	
		5 yr – 15 yr	2	14.2	4	22.2	
Period		15 Oct – 30 Nov	1	7.1	2	11.1	0.02
		1 Dec – 15 Jan	2	14.2	6	33.3	
		16 Jan – 28/29 Feb	5	35.7	10	55.6	
		1 Mar – 15 Apr	6	43.0	0	0	
Mycoplasma Pneumoniae IgM test		performed	8	57.1	13	72.2	0.47
		not performed	6	42.9	5	27.8	
Number of *M. pneumoniae* IgM positive test/number of test performed			3	37.5	2	15.4	0.33
Hypoxia			8	57.1	11	72.2	1
Pleural effusion			4	28.6	3	16.7	0.67
Chest Drainage			1	7.1	0	0	0.44

Table 2. Characteristics of inpatient population

Antibiotic prescription in outpatients

Changes in prevalence of antibiotic prescriptions for CAP

Before implementation 50% of children (28/56) received exclusively amoxicillin, compared with 73.2% (30/41) after CP release; prescriptions for broad-spectrum antibiotics also decreased. Due to the high prevalence of combination therapy, further analysis on antibiotic prescriptions were performed using Days of Therapy (DOTs) for each patient. The median DOT for the pre-intervention period was 10 (range, 5-26), the median DOT for the post-intervention period was 8 (range, 5-20) (p<0.0001).

The median DOT was calculated for every sub-period of observation (**Figs 2a and 2b**).

DOTs analysis for each antimicrobial reflected the prescriptions prevalence. Statistically significant increase in use of amoxicillin (54.5% pre-CP vs. 71.1% post-CP, p <0.0001) and decrease in use of macrolides (21.3% pre-CP vs. 6.4% post-CP, p <0.0001) was observed. Cephalosporins and amoxicillin-clavulanate use decreased as well (9.7% and 14.5% pre-CP vs. 8.5% and 14.0% post-CP), but the difference was not statistically significant.

Changes in prevalence of broad-spectrum antibiotic prescriptions for CAP

In the pre-intervention period the median bsDOT was 10 (range 1-25) and in the post-intervention period 8 (range 4-14), with a significant and stable difference in prescribing between pre- and post-intervention groups reported for each sub-period in the time series (Fig 3). As a result pre-intervention bsDOT/DOT was 0,45, while in post-intervention it was 0.29.

Changes in duration of therapy

For treating mild CAP our clinical pathway recommends a 7-day antibiotic therapy.

Pre-intervention median LOT was 10 (range 3-15), while post-intervention median LOT was 8 (range 5-10) (p<0.0001) according to the pathway, with a decreasing trend over all sub-periods after implementation.

DOT/LOT ratio indicates use of combination therapy and the length of therapy: pre-intervention DOT/LOT was 1.16, post-intervention 1.07. Specifically, during the related sub-periods, pre-CP DOT/LOT was included between 1.25 and 1.08, post-CP ratio, instead, ranged from 1.19 to 1.04 (Figs 2c and 2d).
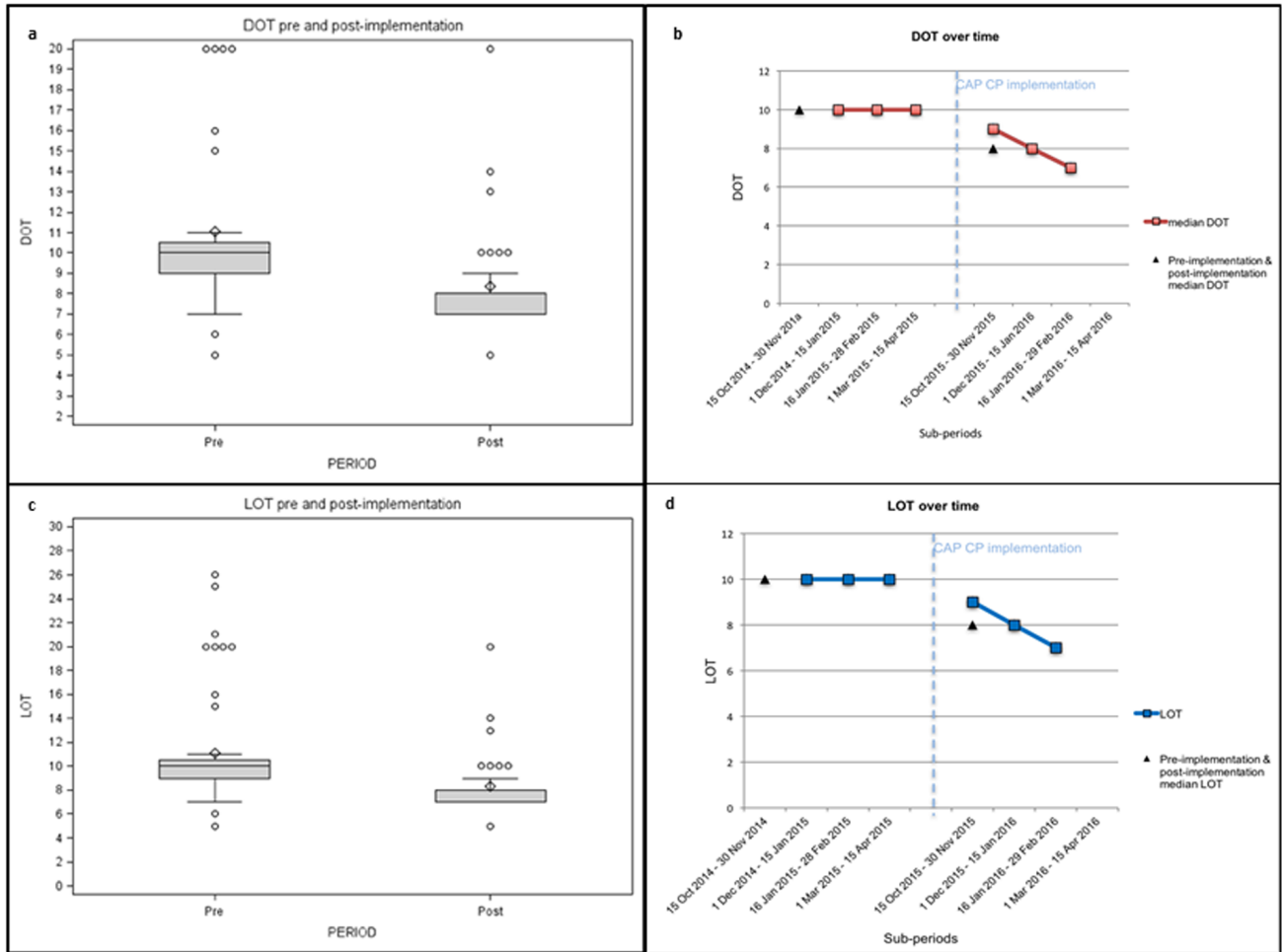
Fig 2a. Median DOT pre and post-implementation for outpatients; 2b. DOT over time for outpatients; Median LOT pre and post-implementation for outpatients; 2d. LOT over time for outpatients.
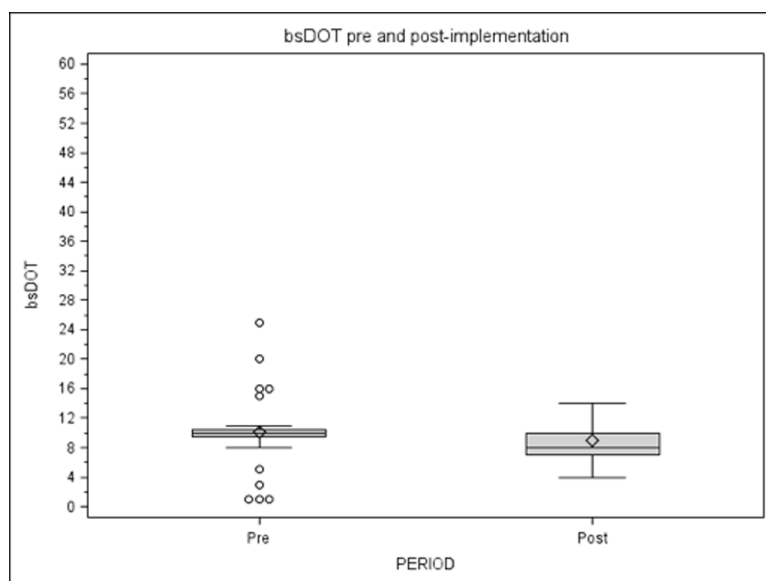

Fig 3. bsDOT/DOT for outpatients.

Changes in dosage for the most commonly prescribed antibiotic for CAP

The most commonly prescribed antibiotic for outpatients with CAP was amoxicillin. Pre-intervention median dosage corresponds to 82.9mg/kg/day (range 28.6-102). Post-intervention median dosage was 88.15mg/kg/day (range 64-95.5) (p=0.03) according to the pathway (Fig 4).
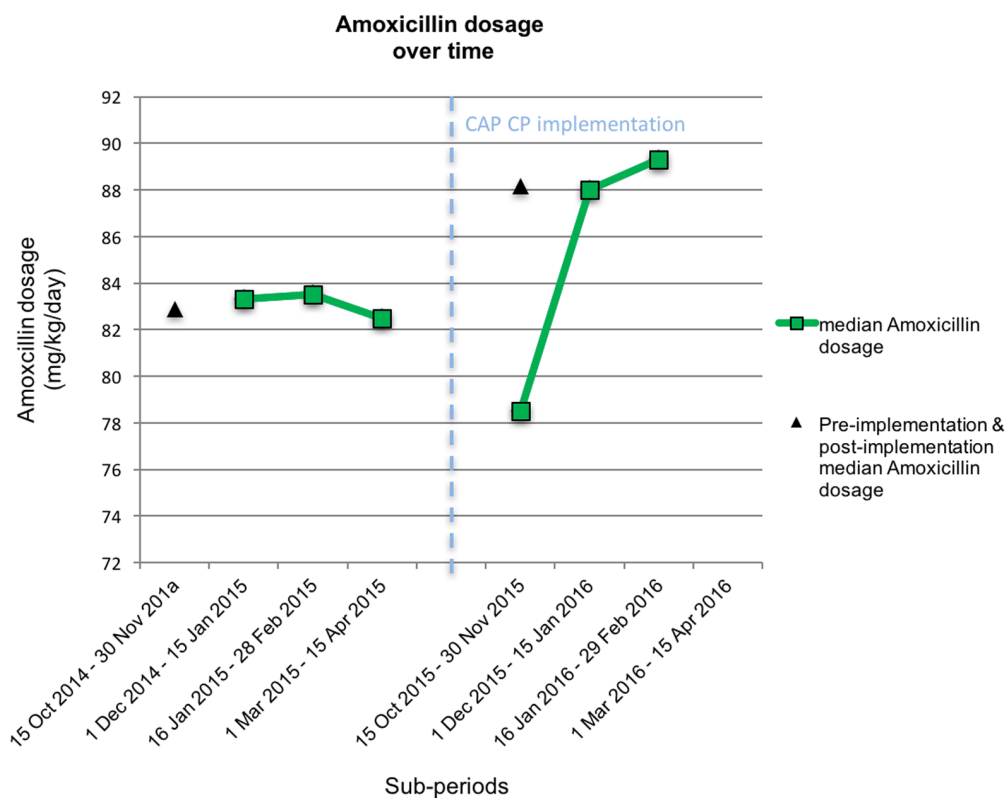
Fig 4. Median amoxicillin dosage over time.

Antibiotic prescription in inpatients

Changes in prevalence of antibiotic prescriptions for CAP in inpatients

We observed an increase in narrow-spectrum regimens prescribed in the post-CP period: 6/18 children (33.3%) after CP implementation received exclusively narrow-spectrum antibiotics in contrast with 0% in the pre-intervention period (p=0.02). Broad-spectrum antibiotics also showed a decreasing trend (14/14 pre-CP, 12/18 post-CP).

Median DOT for the pre-intervention period was 18.5 days (range 11-32), for the post-intervention it was 10 (range 3-26) (p=0.004) (Table 3).

We reported a statistically significant increase in use of ampicillin and amoxicillin and a concomitant decrease in use of cephalosporins and macrolides. Furthermore, use of amoxicillin-clavulanate, ampicillin-sulbactam, carbapenems and glycopeptides was abandoned. Clindamycin was prescribed only in the post-CP period.

	Pre-intervention period		Post-intervention period		
Number of inpatients	14		18		p value
Total DOT	295		200		
	N	% of DOT	N	% of DOT	
Ampicillin	0	0	15	7.5	<0.0001
Amoxicillin	33	11.2	98	49.0	<0.0001
Cephalosporins	89	30.2	43	21.5	0.03
Macrolides	80	27.1	32	16.0	0.004
Amoxicillin-clavulanate	14	4.7	0	0	0.002
Ampicillin-sulbactam	15	5.1	0	0	0.001
Carbapenems	29	9.8	0	0	<0.0001
Glycopeptide	35	11.9	0	0	<0.0001
Clindamycin	0	0	12	6	<0.0001

Table 3. Total DOT for each type of antibiotic prescribed.

Changes in prevalence of broad-spectrum antibiotic prescriptions for CAP

Broad-spectrum antibiotic use was assessed through median bsDOTs: pre-intervention median bsDOT was 17 (range 11-24) and it decreased to 4.5 (range 1-23) in the post-intervention period ($p<0.0001$).

Broad-spectrum in relation to overall antibiotic use evaluated through bsDOT/DOT ratio decreased from 0.83 in the pre-CP to 0.41 in the post-CP period ($p<0.0001$).

Changes in duration of therapy and length of stay

Pre-CP median LOT was 11 days (range 5-17), while post-CP LOT was 10 days (range 3-15) (p=0.06). Pre-intervention ratio of DOT/LOT, which measures the quantity of antibiotics prescribed per day,, was 1.70, while post-intervention DOT/LOT was 1.26.

Median LOS in the pre-CP period was 5 days (range 3-16) and in the post-CP period, 4 days (range 2-14) (p=0.23).

Changes in dosage for the most commonly prescribed antibiotics for CAP

The CAP CP developed for this study recommends ampicillin dosage of 200-300 mg/kg/day. In the pre-CP period, there were no ampicillin prescriptions. In the post-intervention period, 6/18 (16.7%) patients received ampicillin with median dosage of 200 mg/kg/day (range 200-307.7).

The recommended dosage of ceftriaxone in our CAP CP is 50-100 mg/kg/day. Ceftriaxone was prescribed in 8/14 (57.1%) pre-CP patients and 8/18 (44.4%) post-CP. The median dosage was 75 mg/kg/day both pre-intervention (range 38.5-100) and post-intervention (range 75-100).

Treatment failure in outpatients

As a balancing measure, we assessed treatment failure: 44/56 (78.5%) children were available for CAP follow-up in the baseline period, in comparison with 37/41 (90.3%) in post-intervention period.

The two groups were compared for prevalence of prescriptions: amoxicillin and broad spectrum antibiotic prescriptions did not show significant differences before and after CP implementation, though trends for all antibiotics indicated improvement post-intervention (Table 4).

In the pre-CP period, treatment failure occurred in 2.3% (1/44) of cases, while 11.8% (4/34) failed treatment in the post-CP period (p=0.29) (Fig 5). All these cases consist of change of antibiotic for persistence or worsening of symptoms.

	Pre-intervention period		Post-intervention period		p value
Number of outpatients available for follow-up	44		34		
Number of prescriptions	56		39		
Prescriptions/patients ratio	1.3		1.1		
	N	%	N	%	
Amoxicillin	28	50	25	64.1	0.17
Cephalosporins	9	16.1	4	10.3	0.42
Macrolides	10	17.8	3	7.7	0.16
Amoxicillin-clavulanate	9	16.1	7	17.9	0.97

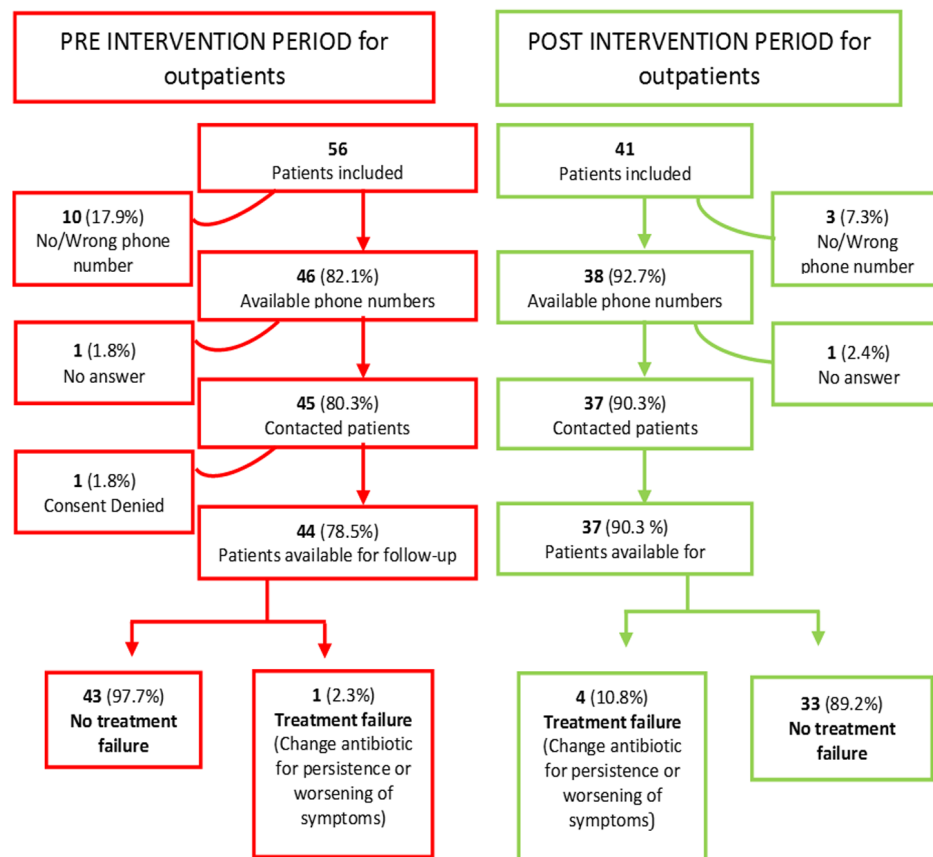**Table 4. Antibiotics prescriptions for follow-up outpatients.**

Fig 5. Outpatients treatment failure flow-chart.

Treatment failure in inpatients

Twelve out of 14 (85.7%) parents were available for a follow-up call in the pre-intervention period and 13/18 (72.2%) in the post-intervention period (p=0.36). In the pre-CP period 83.3% (10/12) of prescribed therapy was effective, with 2/12 cases of antibiotic change during hospitalization for persistence or worsening of symptoms. There was no significant change in the post-CP period, where 84.6% (11/13) of prescribed therapies was effective and for 2/13 patients' antibiotics were changed for persistence of symptoms (Fig 6; Table 5).

Table 5. Antibiotics prescriptions for inpatients follow-up

	Pre-intervention period		Post-intervention period		
Number of inpatients available for follow-up	12		13		
Number of prescriptions	34		25		**p value**
Prescriptions/Patients ratio	2.8		1.9		
	N	% of prescriptions	N	% of prescriptions	
Ampicillin	0	0	3	12	0.07
Amoxicillin	4	11.8	11	44	0.01
Cephalosporins	13	38.3	7	28	0.41
Macrolides	7	20.6	3	12	0.49
Amoxicillin-clavulanate	1	2.9	0	0	1
Ampicillin-sulbactam	3	8.8	0	0	0.25
Carbapenems	2	5.8	0	0	0.50
Glycopeptide	4	11.8	0	0	0.13
Clindamycin	0	0	1	4	0.03

Inpatients treatment failure flow-chart

PRE INTERVENTION PERIOD for inpatients

14
Patients included in the follow-up

2 (14.3%)
No/Wrong phone

12 (85.7%)
Available phone

12 (85.7%)
Contacted patients

12 (85.7%)
Patients available for

10 (83.3%)
No treatment failure

2 (16.7%)
Antibiotic change for persistence or worsening of symptoms during hospitalization

POST INTERVENTION PERIOD for inpatients

18
Patients included in the follow-up

1 (5.6%)
No/Wrong phone

17 (94.4%)
Available phone

3 (16.7%)
No answer

14 (77.7%)
Contacted patients

1 (5.6%)
Consent Denied

13 (77.7%)
Patients available for

2 (15.4%)
Antibiotic change for persistence or worsening of symptoms during hospitalization
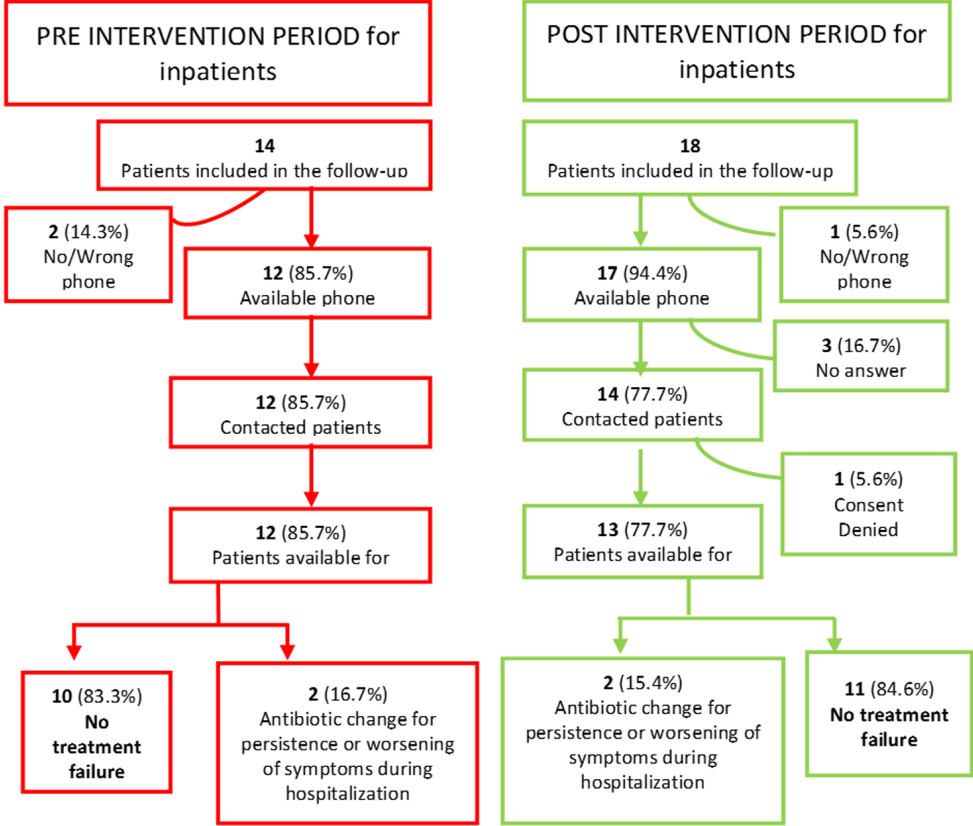
11 (84.6%)
No treatment failure

Fig 6. Inpatients treatment failure flow-chart.

Discussion

In accordance with the literature, the highest prevalence of CAP was observed in children between 2-5 years of age in our population [23].

Children treated as outpatients were all patients evaluated at the PED for mild CAP and discharged home. The two groups, before and after implementation, both had a higher prevalence of females and 2-5 year olds.

Current recommendations, reflected in our CAP CP, indicate that children with a clinical diagnosis of pneumonia should receive antibiotics, as bacterial and viral pneumonia cannot be reliably distinguished from each other [8]. Narrow-spectrum monotherapy (amoxicillin) is the first option for mild CAP in fully immunized children, as *S. pneumoniae* accounts for 21-44% of disease [24-29].

Adding β-lactamase inhibitors (amoxicillin-clavulanate) is suggested in case of β-lactamase producing bacteria (*H. influenzae* type B and *S. aureus*), lack of immunization or children with amoxicillin treatment in the previous 30 days [1,8]. Use of macrolides is only appropriate if atypical bacterial ethology is suspected, as the use of azithromycin has been associated with the selection of resistant organisms because of its prolonged serum elimination half–life [1,8].

Our study showed relevant changes in physicians' prescribing behaviours for outpatients immediately after CP implementation and after 6 months, in contrast to findings of delayed effects of CPs in other settings where significant effects were achieved only during the second year of the intervention [11].

We documented an increase in use of narrow-spectrum antibiotics and concomitant decrease of broad-spectrum ones after intervention, as single DOT analysis for amoxicillin and macrolides confirms, with also a significant decrease in overall median DOT from 10 to 8. This trend of lower bsDOTs continues throughout the post-intervention period.

LOT evaluation showed a statistically significant decrease from 10 to 8 in the post-CP period, approaching 7 days of therapy which is the current recommendation by the IDSA [1]. This indicates that during the post-intervention period more narrow-spectrum regimens were prescribed for fewer days.

In our population, macrolide over-prescription in the pre-CP period may have resulted from the perception that two antimicrobials were more reliable, as only one patient was actually infected with *Mycoplasma pneumoniae* in this period. Indeed, the pre and post populations were similar in terms of number of tests performed to detect *M. pneumoniae* infection and positive tests (only one in the pre-CP period). All inpatients were admitted to the PACU for an episode of moderate CAP.

No statistical difference was reported between the two groups before and after implementation with regard to sex, age, symptoms onset time, *M. pneumoniae* IgM serology positivity and presence of complications (hypoxia, pleural effusion, necrotizing pneumonia).

After CAP CP implementation, prescription of narrow-spectrum regimens (ampicillin or amoxicillin) among inpatients decreased significantly, with a concomitant significant decrease of broad-spectrum antibiotics. This is in line with most recent recommendations, which recommend high doses of narrow-spectrum β-lactams as the first-line parenteral therapy for moderate CAP if the child is fully immunized or is not admitted for a previous amoxicillin treatment failure. Alternatively, parenteral third generation cephalosporins are recommended [1] when these criteria are not med.

Median DOTs showed a substantial decrease from 18.5 to 10 days in pre- versus post-CP periods, indicating a decrease in the prevalence of antibiotic prescriptions. We also saw a significant increase in use of ampicillin and amoxicillin and decrease in cephalosporins and macrolides. This was in line with the CAP CP developed for this study, which recommended parenteral third-generation cephalosporins in case of penicillin treatment failure, since ceftriaxone or cefotaxime are more active *in vitro* against penicillin-resistant strains [1]. Indeed, wide-spread cephalosporin use can lead to an increase in multi-drug resistant pathogens (e.g. third-generation cephalosporin-resistant *E. coli*) [31,32].

Furthermore, use of broad-spectrum antibiotics like amoxicillin-clavulanate, ampicillin-sulbactam, carbapenems and glycopeptides were abandoned after CP implementation in our centre, while clindamycin was prescribed in the post-CP period only in case of complicated pneumonia (parapneumonic effusion, necrotizing pneumonia).

Carbapenems are one of the β-lactams with the broadest antibacterial spectrum currently available, with a relatively low rate of adverse effects. They are recommended as "last-line agents" for severe infections or resistant bacteria, since carbapenems are not destroyed by most β-lactamases [33]. From this study, it emerged that their empiric use was not exclusively for severe nosocomial infections in critically ill patients, but was prescribed as drug of choice for moderate CAP during pre-intervention period, as also reported by other authors [34]. The wide use of these lifesaving drugs is problematic due to the emergence of carbapenem-resistant bacteria which cause severe infections [35-40].

The dramatic change in antimicrobial choices is attributable to the shift in suggested first-line therapy for CAP and, since the starting therapy is established for both outpatients and inpatients by the PED, improvements in PED prescriptions determine improvements in PACU prescriptions, even because the two wards share the same medical staff.

Indeed, starting with penicillin (amoxicillin/ampicillin) gives physicians the possibility to observe children for 48-96 hours and, in case of persistence of symptoms, to switch to a third-generation cephalosporin. On the other hand, physicians starting with ceftriaxone are more prone to change to a broader spectrum antibiotic such as carbapenem.

Furthermore, the introduction of clindamycin recommendations for complicated moderate CAP gave the opportunity to avoid glycopeptides, hence reducing their use.

DOT, LOT and DOT/LOT ratio analysis was performed to describe inpatient prescriptions. Our intervention resulted in a statistically significant decrease in overall median DOT (narrow and broad-spectrum) from 18.5 to 10, as well as bsDOT from 17 to 4.5. LOT median did not significant decrease, despite CAP guidelines recommending 7 days of therapy in case of uncomplicated CAP and 14 days if complicated (parapneumonic effusion, necrotizing pneumonia). This suggests pediatricians are more inclined to change their attitude towards the choice of antibiotic prescribed rather than the duration of therapy.

The increased use of ampicillin/amoxicillin also resulted in a decrease of the median LOS after CP implementation. Indeed, a rapid and uneventful improvement during the first 24-48 hours after ampicillin administration has a favourable impact on switch to oral antibiotic and early discharge [41].

Changes in antibiotic dosage were analysed for the most prescribed antibiotics (ampicillin and ceftriaxone) in inpatients.

The median dosage of ampicillin in the post-implementation period was 200 mg/kg/day, in line with recommend dose of 200-300 mg/kg/day in the CAP CP developed for this study. This is an important achievement for inpatients: before the CP implementation physicians didn't even consider ampicillin for moderate CAP treatment in our centre.

Alternatively, therapy can be provided with ceftriaxone in standard, non-meningitis dosages which is documented to be effective with CAP caused by strains previously considered resistant to ceftriaxone [1,42]. Ceftriaxone dosage was stable with a median value of 75 mg/kg/day both pre- and post-CP implementation.

For both outpatient and inpatient populations, no differences in treatment failure were reported despite a remarkable decrease in broad-spectrum antibiotic prescription. During the post-CP period, an increase in treatment failure was reported in outpatients but it was not statistically significant. This may be due to relatively low sample sizes and to the very low occurrence of treatment failure overall, even in the pre-CP period. Continuing surveillance is needed to confirm this trend.

This study has strengths and limitations. It is the first study that evaluates the effectiveness of ASP through CPs in an Italian hospital. This intervention was designed to be feasible and was developed by a multidisciplinary team to guarantee a high quality and level of coordination, with cooperation between the Infectious Diseases and PED teams. Furthermore, following CP presentation a prominent educational campaign included lectures and distribution of handy pocket cards and posters.

This is the first study with a phone call follow-up to assess antimicrobial stewardship in the PED context, allowing evaluation of antibiotic changes for persistence of symptoms or side effects.

Limitations include the retrospective nature of the analysis, its single-centre setting, the short period of observation and the inability to assess appropriateness of single antimicrobial prescriptions.

Thus, a longer term follow up study evaluating the longevity of observed changes in antimicrobial prescription is warranted to analyse further improvements, as well as expanding to include other Italian PED for validation of this tools.

Conclusions

This study provides evidence that clinical pathway implementation in an Italian PED setting is an effective tool for antimicrobial stewardship, appearing to be associated with the kind of treatment children receive.

An evidence-based CP supplemented by educational and explanatory lectures was associated with significant changes in prescribing habits of physicians at our centre, decreasing the use of broad-spectrum antibiotics in favour of narrow-spectrum, and reducing the length of therapy without increasing treatment failure both for outpatients and inpatients.

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List of Supplemental Digital Content:

Supplemental Digital Content 1. Figure
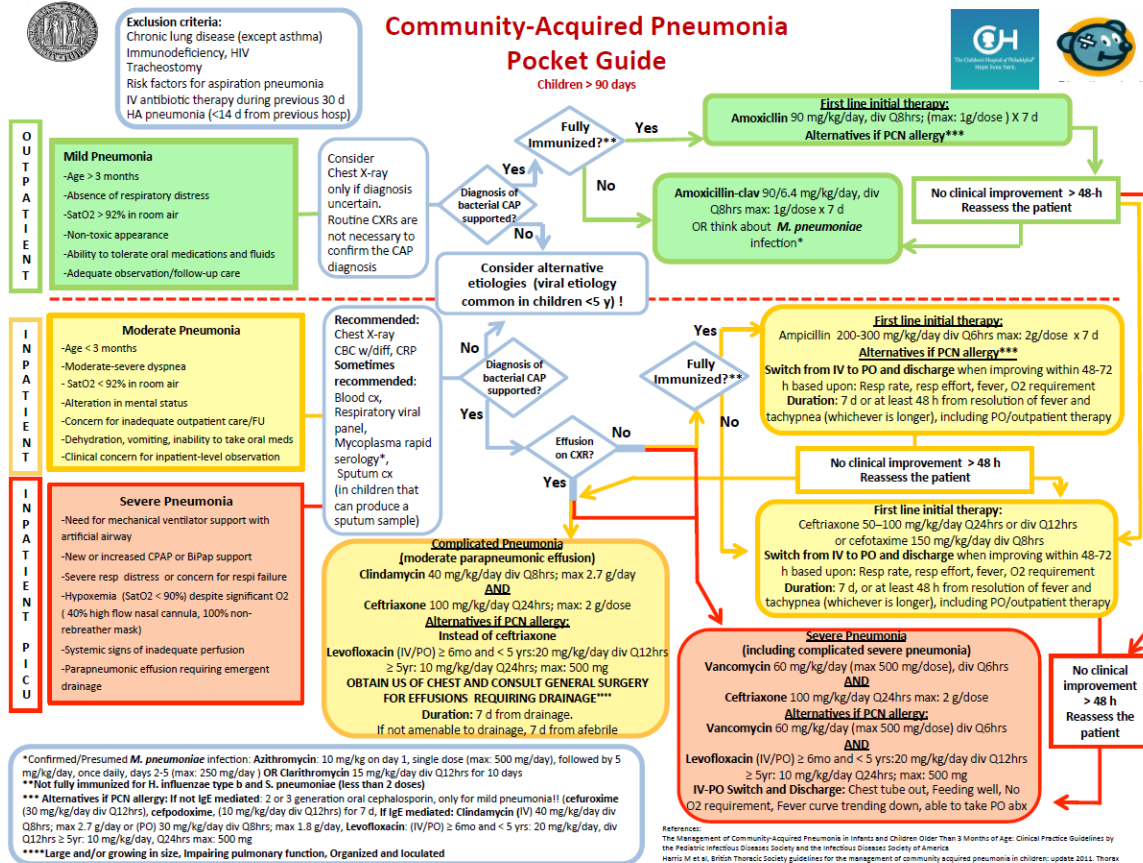
CAP clinical pathway

CHAPTER VII

The Sustainability of an Antimicrobial Stewardship Program based on Clinical Pathways in the Emergency Department

ABSTRACT

Background. Antimicrobial resistance has become a global problem. Italian pediatric antimicrobial prescription rates are among the highest in Europe (EU). As a first step for antimicrobial stewardship (AS) implementation, clinical pathways (CP) outlining standard of care for acute otitis media (AOM), and group A streptococcus (GAS) pharyngitis and community-acquired pneumonia (CAP) were developed and implemented in our pediatric emergency department (PED) in collaboration with Children's Hospital of Philadelphia.

Aims. The primary aim of this study was to assess changes in antibiotic prescription one year after the CP implementation for AOM, GAS pharyngitis and CAP; secondary aim was to compare treatment failure before and after CPs implementation.

Methods. CPs were implemented at the Department for Woman and Child Health of Padua on October 1st 2015. The first before/after quasi-experimental study has been conducted between the Pre-intervention period (from 15/10/2014 to 15/04/2015), Post-intervention period (from 15/10/2015 to 15/04/2016) and 1-Year post intervention period (from 15/10/2016 to 15/04/2017). ITS was used to determine the effect of the intervention, chi squared test to define the treatment failure and Kruskal Wallis test to compare antibiotic dosages and durations.

Results. AOM: after CP implementation there was an increase in "wait and see" (21.7% vs. 33.1% vs. 28.9%, p=0.08) and in the use of amoxicillin as first line therapy (25.1% vs. 34.5%, p<0.001), with a decrease from 53.2% to 32.4% (p<0.001) in overall prescription of broad-spectrum antibiotics. Amoxicillin prescriptions increased (32% Pre vs. 51.6% Post and 52.8% 1-Year Post, p<0,001) with a decrease in overall prescription of broad-spectrum antibiotics. Among fully immunized with no complicated OMA, broad-spectrum antibiotics were prescribed in only 4.7% of cases (29.8%, Pre vs. 7.2% Post, p<0.001). Pharyngitis: During 1-year Post intervention period 63.2% of patients received a diagnosis Goup A Steptococcus pharyngitis (50.7% Pre vs 45.4% Post), reflecting the increasing age of the population examined (more patients aged 3-15 years). Amoxicillin was the choice for 93.2% of patients (53.6% Pre and 93.4% Post). CAP: prescriptions/patients rate has decreased to 1.02 (1.3 Pre, 1.12 Post) reflecting an increase use of monotherapy. 82.5% of patients received amoxicillin (52.1% Pre vs. 69.9% Post, p<0.001) and macrolide prescriptions decreased to 2.1% (19.7 Pre vs. 6.5% Post). No statistically significant difference in treatment failure was seen for all the pathologies examined.

Conclusions. A reduction in broad-spectrum antibiotic prescriptions for AOM. Gas pharyngitis and CAP without compromising clinical outcomes indicates effectiveness of CPs in this setting. Furthermore their effects after more than one year suggests CPs are useful and suitable tool.

Background

Antibiotics are the most commonly prescribed drugs in the pediatric population, especially in preschool age[1]. Moreover, it has been estimated that half of the prescriptions are unnecessary[1–4].

Although resistance can occur naturally or can be acquired through gene transfer, antibiotic overuse plays a key role in the selection of multi-drug resistant organisms[5]. The emergence of such pathogens and their rapid global spread has transformed resistance into an important global public health[6–9].

In response to this frightful situation, in 2007 IDSA emphasized the concept of an antimicrobial stewardship program (ASP) as a key component of programs designed to reduce inappropriate antimicrobial use, prevent resistance, enhance patients' safety and lower drug costs[10]. Despite prospective pre-authorization or audit and feedback represent the main ASP core strategies, Clinical Pathways (CPs) are a reasonable first step for ASP implementation, especially in setting where funding are limited[10–14].

Although prudent antibiotic prescribing has been a high priority in the EU, focused, organized efforts to improve prescribing are lacking. Italy is still one of the European countries with the highest prescription rate, with an overuse of third generation cephalosporins and penicillin plus beta-lactamase inhibitors[15].

Since CPs have proven a promising tool to reduce antibiotic prescription in the Pediatric Emergency Department (PED) (**Chapter IV** and **VI**), we hypothesized the positive results on antimicrobial prescriptions would remain stable also one year after CPs implementation.

The primary aim of this study was to assess changes in antibiotic prescriptions one year post CP implementation for acute otitis media (AOM), Pharyngitis and Community-acquired pneumonia (CAP).

The secondary aim was to compare treatment failures pre, post and one year post CP implementation.

Material and methods

Study design

On 1 October 2015 CPs for the management of AOM, Pharyngitis and CAP were implemented in the PED of the Department for Woman and Child Health of Padua University Hospital. The CPs summarize national and international guidelines for the diagnosis and treatment of the three clinical conditions and have been developed by the Division of Pediatric Infectious Diseases and Pediatric Emergency Department of Padua in collaboration with the Division of Pediatric Infectious Diseases of the Children's Hospital of Philadelphia.

This is a pre-post quasi-experimental study to assess changes in antibiotic prescribing during the 6 months period prior to CP implementation (pre-intervention: 15 October 2014 through 15 April 2015), the 6 months after intervention (post-intervention: 15 October 2015 through 15 April 2016) and other 6 months after one year from the intervention (1-year post-intervention: 15 October 2016 through 15 April 2017). The same months have been analyzed in each period to control for effects of seasonality (**Figure 1**).

Three educational lectures were presented to physicians and residents in October 2015 and one recall lecture was given in January 2017. CPs were delivered as laminated pocket cards to all physicians and CPs posters were also hung in the PED.

This study was approved by Institution 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.
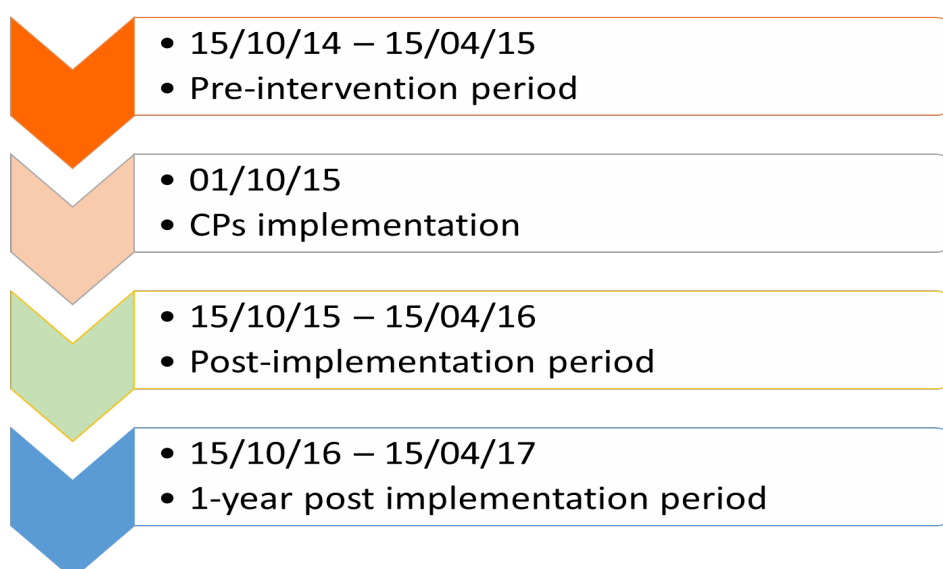
- 15/10/14 – 15/04/15
- Pre-intervention period

- 01/10/15
- CPs implementation

- 15/10/15 – 15/04/16
- Post-implementation period

- 15/10/16 – 15/04/17
- 1-year post implementation period

Figure 1. Study design

Study population

In the study were included all patients aged 2 months to 15 years with an *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code or descriptive diagnosis of AOM, GAS pharyngitis and all patients aged 3 months to 15 years with a ICD-9 code or descriptive diagnosis of CAP.

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

Pharyngitis exclusion criteria were: immunodeficiency or immunosuppressive therapy, pharyngitis with an ongoing antibiotic therapy at the time of admission, concomitant bacterial infections involving other sites or systemic bacterial infection, previous tonsillectomy, chronic disease included PFAPA and admission to the Pediatric Department.

CAP exclusion criteria were: cystic fibrosis or other chronic lung diseases (except asthma), immunodeficiency or immunosuppressive therapy, pneumonia with an ongoing antibiotic therapy at the time of admission, concomitant bacterial infectious involving other sites or systemic bacterial infection, tracheostomy, risk factors for aspiration pneumonia, IV antibiotic therapy during previous 30 days, hospital acquired pneumonia (<14 day from previous admission) and admission to the Pediatric Department.

Data source

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

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

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

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

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.

Outcomes:

Primary outcomes

The following aspects of antibiotic prescriptions for AOM, GAS pharyngitis and CAP 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, 4) duration of therapy, expressed in days of therapy (DOTs) and Length of Therapy (LOT), DOT/LOT ratio (LOT and DOT/LOT ratio only for CAP).

A DOT represents any dose of antibiotic administered during a 24 hour-period. Instead, the LOT is the total number of treatment days, irrespective of the number of different antibiotics. DOT/LOT ratio allows to evaluate how many combination therapies were prescribed compared to monotherapy[16].

Secondary outcomes

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

Data analysis

Data were analyzed using STATA®13. Results were summarized as frequencies and percentages for categorical variables and as median, minimum and maximum for continuous variables. Comparison of categorical variables in pre- vs. post- vs. 1-year post-intervention period were conducted with chi square test. Continuous variables were compared with Kruskal-Wallis test. Interrupted Time Series (ITS) were used to compare the prescription rate[17]. Each of the three periods were divided in 6 different sub-periods of 1 month each for AOM e GAS pharyngitis and in 4 different sub-periods of 45 days each for CAP.

Results

Primary Aim

Over the 6-month of 1-year post intervention period, 13,082 children attended the PED, in comparison to 13,262 children in the pre and 12,335 children in the post intervention period.

AOM population

During 1-year post intervention period 370 patients were discharged with a diagnosis of AOM, accounting for 2.8% (370/13,082) of total PED visits. The same proportion was observed in pre-intervention period (334/13,262, 2.5%) and in post-intervention period (332/12,335, 2.7%) (p=0.3). Three hundred and one children were included in the study for 1-year post intervention period, 295 for pre-intervention and 278 for post-intervention period. The study population pre-, post- and 1-year post intervention period is shown in **table 1**.

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value (for included patients)
Total PED admissions	13262		12335		13082		
AOM admissions	334 (2.5% of total admissions)		332 (2.7% of total admissions)		370 (2.8% of total admissions)		p=0.30
	Excluded patients	Included patients	Excluded patients	Included patients	Excluded patients	Included patients	
	n=39 11.7%	n=295 88.3%	n=54 16.3%	n=278 83.7%	n=69 18.6%	n=301 81.4%	
	n	%	n	%	n	%	n	%	n	%	n	%	
Male	25	64.1	183	62.0	26	48.1	157	56.5	41	59.5	158	52.5	p=0.06
AGE													
2 mo – 2 yr	14	35.9	109	36.9	13	24.1	85	30.6	33	47.8	91	30.2	p=0.15
2 yr – 5 yr	13	33.3	115	39.0	18	33.3	127	45.7	23	33.4	141	46.8	p=0.12
5 yr – 15 yr	12	30.8	71	24.1	23	42.6	66	23.7	13	18.8	69	22.9	p=0.94
Complicated AOM (AOM with otorrhea)	3	7.7	46	15.6	2	3.7	61	21.9	5	7.2	70	23.3	p=0.05
6 mo – 2 yr with unilateral not severe illness, >2 yr with mono/bilateral not severe illness			142	48.1			134	48.2			115	38.2	p=0.21

Abbreviations: PED=Pediatric Emergency Department; AOM=Acute Otitis Media; n=the number of patient for each category

Table 1. Characteristics of Study population with AOM

The three 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. The percentage of complicated AOM remains stable during the three different periods (pre 15.6% (46/295), post 21.9% (61/278), 1-year post 23.3% (70/301), p=0.05), as well as the percentage of children eligible for wait and see approach (pre 48.1% (142/295), post 48.2% (134/278), 1-year post 38.2% (115/301), p=0.21).

Antimicrobial prescription rate for AOM

During 1-year post intervention period there was an increase of 'wait and see' approach as compared to pre-CP period (pre 21.7% (64/292), post 33.1% (92/278), 1-year post 28.9%, p=0.008) and a decrease in antibiotic prescriptions, especially for broad spectrum ones (pre 68.0% (157/231), post 48.4% (90/186), 1-year post 47.2% (101/214), p<0.001) (**Table 2**). This result is further highlighted by the ITS analysis in **figure 2**. The decrease in broad-spectrum antibiotics was even greater considering only those children for whom this class of antibiotics were strictly recommended (not fully immunized, with complicated AOM and treated with amoxicillin in the previous 30 days) (pre 29.8% (88/295), post 7.2% (20/278), 1 year post 4.7% (14/301)) (**figure 3**).

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients included	295		278		301		
Treatment	n	%	n	%	n	%	
Wait and see	64	21.7	92	33.1	87	28.9	p=0.008
Antibiotic Treatment	231	78.3	186	66.9	214	71.1	p=0.008
ANTIBIOTICS							
Amoxicillin	74	32.0	96	51.6	113	52.8	p<0.001
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides + quinolones)	157	68.0	90	48.4	101	47.2	p<0.001
Amoxicillin-clavulanate	106	45.9	70	37.6	83	38.7	p=0.17
Cephalosporins	47	20.3	16	8.6	16	7.5	p<0.001
Macrolides	4	1.7	4	2.2	1	0.5	p=0.33
Quinolones	0	0	0	0	1	0.5	p=0.38
Broad spectrum with exclusion of complicated AOM, not fully immunized, and patients who had received amoxicillin within the previous 30 days	88	29.8	20	7.2	14	4.7	p<0.001

Abbreviations: n= indicates the number of patient for each category; AOM= acute otitis media

Table 2. Treatment option of Acute Otitis Media

Antibiotics dosage for AOM

Dosage comparison was conducted only for the most prescribed antibiotics: amoxicillin and amoxicillin-clavulanate. Kruskal-Wallis test comparing overall pre, post and 1-year post intervention found a significant increase in the median dose for both drugs (p<0.001). The trend analysis showed the optimal dosage recommended by the AOM CP, reached within the post implementation period, remained stable in 1-year post intervention period (**Figure 4**).

Figure 2. ITS analysis of broad-spectrum antibiotic prescription for AOM
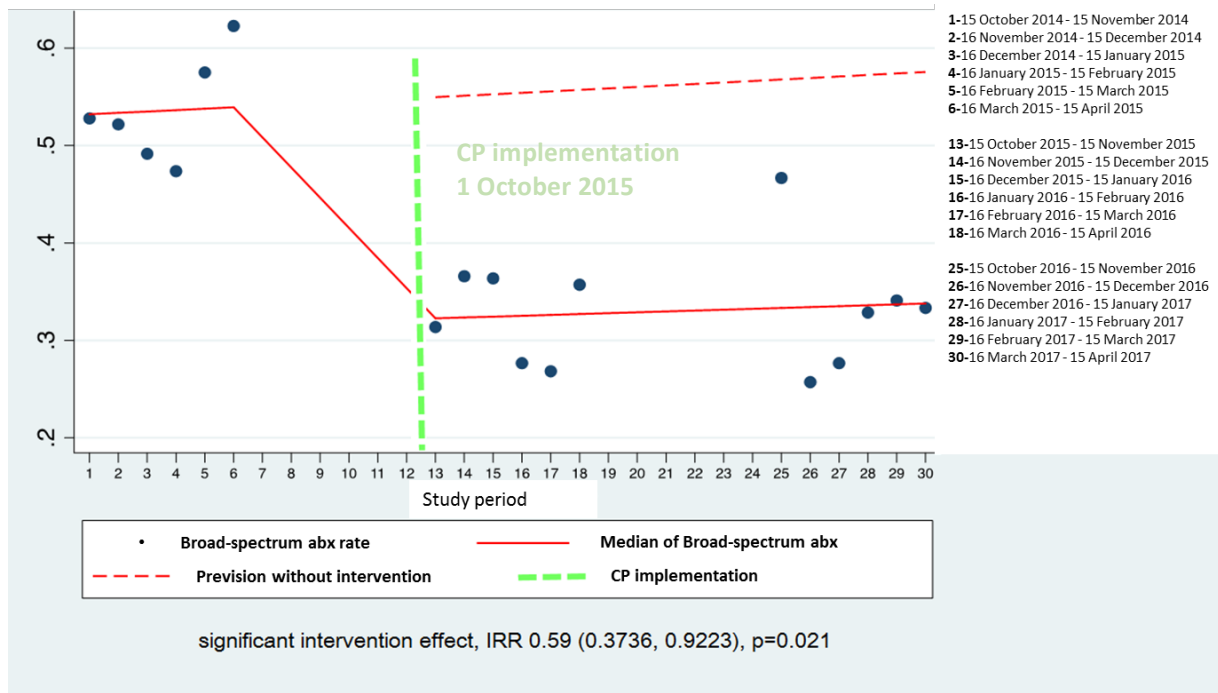
Abbreviations: AOM=Acute Otitis Media; Abx=antibiotics; CP=Clinical Pathway

Figure 2. ITS analysis of broad-spectrum antibiotic prescription for AOM
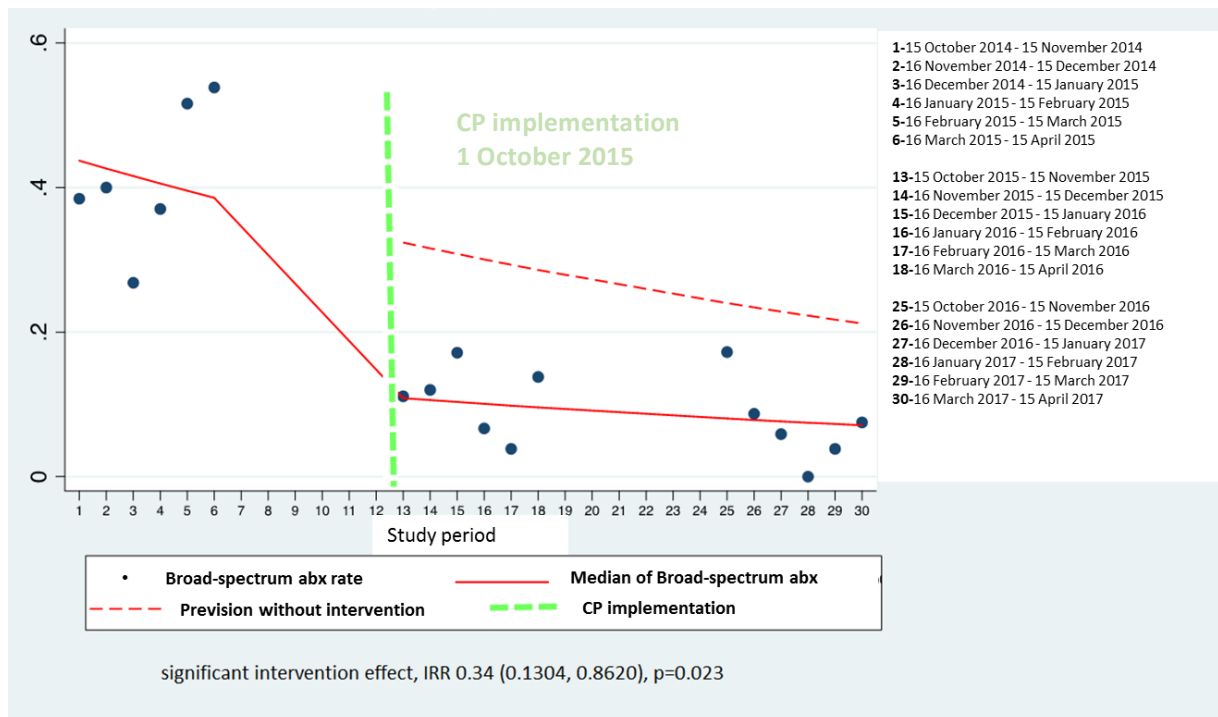
Abbreviations: AOM=Acute Otitis Media; Abx=antibiotics; CP=Clinical Pathway

Figure 3. ITS analysis of broad-spectrum antibiotic prescriptions for AOM in children fully immunized, with uncomplicated AOM and who have not received amoxicillin within the previous 30 days

Abbreviations: AOM=Acute Otitis Media; CP=Clinical Pathway

Figure 4. Amoxicillin and Amoxicillin-Clavulanate dosage for AOM and interquartile range changing over time.

Treatment duration for AOM

Treatment duration was analyzed stratifying the population by age (<2 years old, ≥2 years old) and disease severity (complicated vs. uncomplicated), independently from the oral agent prescribed.
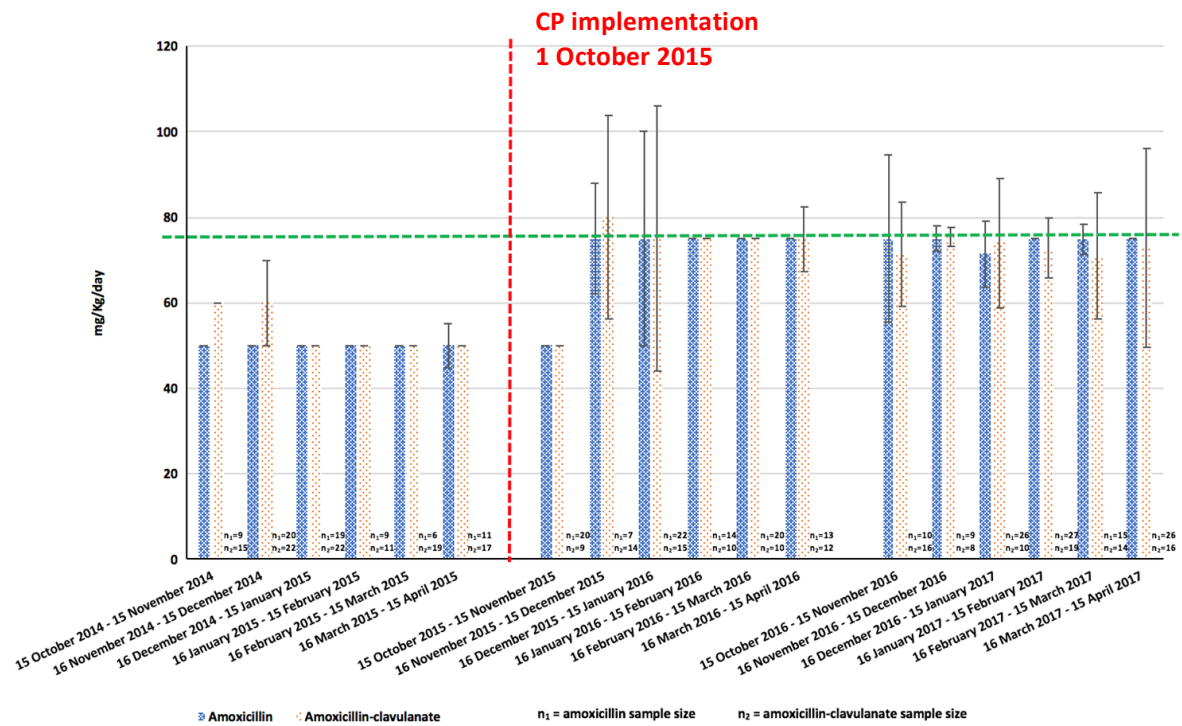
In children <2 years old and in children ≥2 years old not fully immunized or with complicated AOM, median DOT met the recommended duration of 10 days and 7 days respectively. The difference between median DOT in the three periods was statistically significant (p<0.001) (**Figure 5** and **Figure 6**).

In children ≥2 years old, fully immunized and with uncomplicated AOM, median DOT fails to reach the recommended duration of 5 days despite in the last forth months of 1-year post intervention period never exceeds the duration of 6 days. The difference between media DOT in the three periods was statistically significant (p<0.001) (**Figure 7**).

Figure 5. Duration of therapy in median DOT and interquartile range each month in pre-, post- and 1 year post period for children <2 years old with AOM.

Figure 6. Duration of therapy in median DOT and interquartile range each month in pre-, post- and 1 year post period for children ≥ 2 years old not fully immunized or with complicated acute otitis media
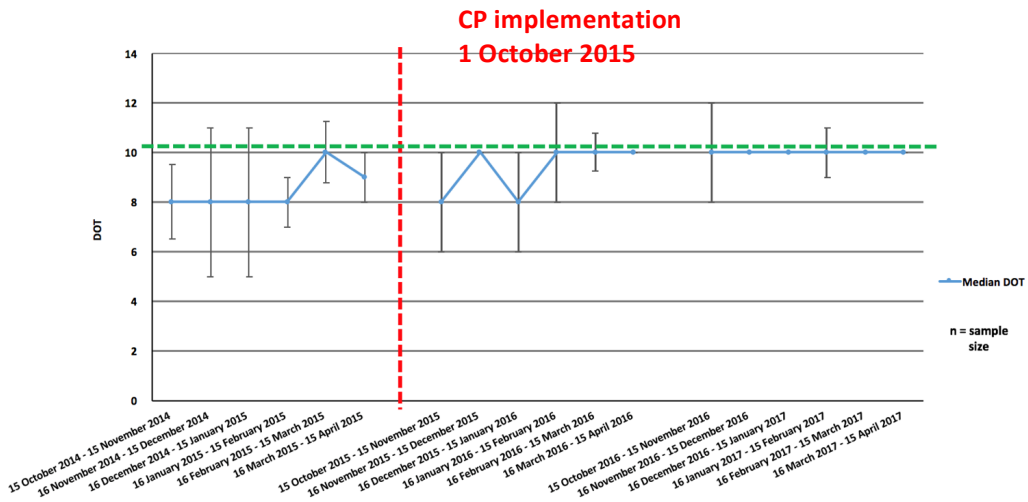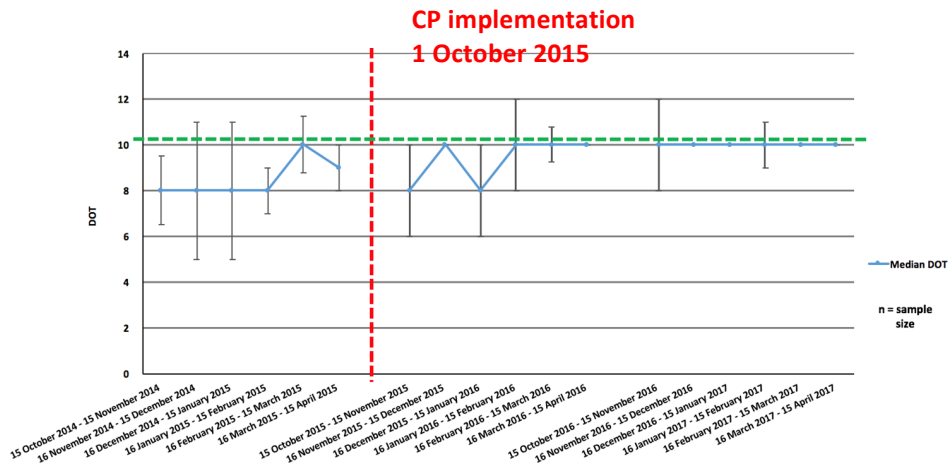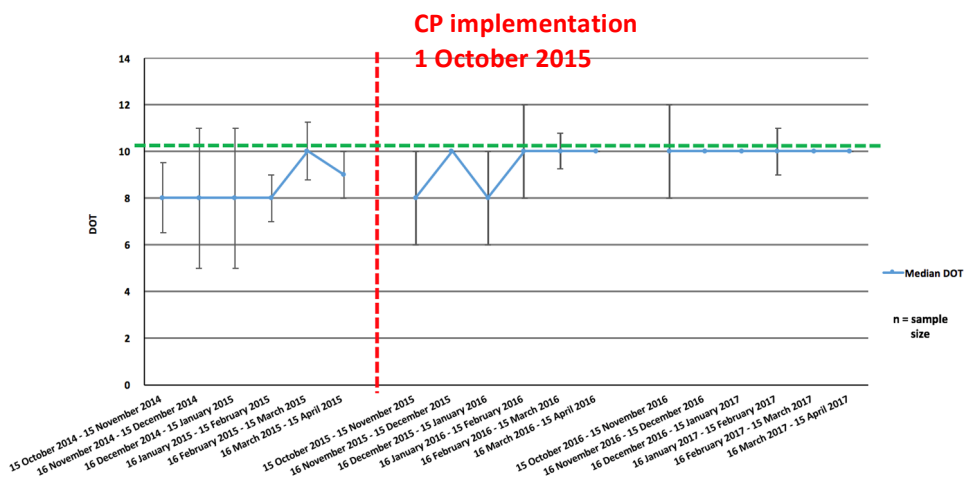

Figure 7. Duration of therapy in median DOT and interquartile range each month in pre-, post- and 1 year post period for children ≥ 2 years old fully immunized with uncomplicated acute otitis media

Pharyngitis population

During 1-year post intervention-period, 417 patients were evaluated for pharyngitis, accounting for 3.2% (417/13,082) of total PED visits. The same proportion was observed in pre-intervention period (388/13,262, 2.9%) and in post-intervention period (448/12,335, 3.6%) (p=0.005). Three hundred and twenty-six children were included in the study for 1-year post, 298 for pre-intervention and 366 for post-intervention period. The study population is shown in **Table 3**.

	Pre-intervention period				Post-intervention period				1 year post intervention period				p-value (for included patients)
Total PED admissions	13262				12335				13082				
Pharyngitis admissions	388 (2.9% of total admissions)				448 (3.6% of total admissions)				417 (3.2% of total admissions)				p=0.005
	Excluded patients		Included patients		Excluded patients		Included patients		Excluded patients		Included patients		
	n=90 23.2%		n=298 76.8%		n=82 18.3%		n=366 81.7%		n=91 21.8%		n=326 78.2%		
	n	%	n	%	n	%	n	%	n	%	n	%	
Male	58	64.4	168	56.4	42	51.2	214	58.5	54	59.3	172	52.8	p=0.31
AGE													
2 mo – 3 yr	31	34.4	108	36.2	32	39.0	146	39.9	34	37.3	87	26.7	p=0.0009
3 yr – 15 yr	59	65.6	190	63.8	50	61.0	220	60.1	57	62.7	239	73.3	p=0.0009

Abbreviations: PED=Pediatric Emergency department; GAS pharyngitis=Group A Streptococcus Pharyngitis; n=the number of children for each category

Table 3. Characteristics of Study population with GAS pharyngitis

The three populations were similar in terms of sex, with a slight male predominance. Although in all three populations the incidence was higher among older children. In 1-year post intervention period the percentage of children between 3 and 15 years increased compared to other analyzed periods (pre 63.8% (190/298), post 60.1% (220/366), 1-year post 73.3% (239/326), p<0.001). For this reason, a higher number of GAS pharyngitis was diagnosed in 1-year post-intervention period (pre 50.7% (151/298), post 45.4% (166/366), 1-year post 63.2% (206/326), p<0.001).

Antimicrobial prescription rate for pharyngitis

During 1-year post intervention period there was an increase in amoxicillin prescription rate as was observed in post-implementation group in comparison to pre-implementation (Pre 53.6% (81/151), Post 93.4% (155/166), 1-year post 93.2% (192/206), p<0.001) with a concomitant decrease in broad-spectrum antibiotic prescription, especially amoxicillin-clavulanate prescription rate (Pre 39.7% (60/151), Post 3% (5/166), 1 year post 4.4% (9/206), p<0.001). Stratifying prescriptions by age (<3

years old, 3-15 years old), the majority were administered to children older than 3 years (pre 74.2% (112/151), post 78.3% (130/166), 1 year post 81.6% (168/206), p=0.25) (**Table 4**).

Analyzing the GAS pharyngitis prescriptions trend for each month in time series, a remarkable and stable reduction in broad-spectrum antibiotic prescriptions was reported (**figure 8**).

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients included	298		366		326		
Patients not treated with antibiotics	147	49.3	200	54.6	120	36.8	p<0.001
	n	%	n	%	n	%	
Males	82	55.8	117	58.5	59	49.2	p=0.26
Age							
2 mo – 3 yr	69	46.9	110	55.0	49	40.8	p=0.04
3 yr – 15 yr	78	53.1	90	45.0	71	59.2	p=0.04
Patients treated with antibiotics (GAS pharyingits)	151	50.7	166	45.4	206	63.2	p<0.001
	n	%	n	%	n	%	
Males	86	57.0	97	58.4	113	54.9	p=0.78
Age							
2 mo – 3 yr	39	25.8	36	21.7	38	18.4	p=0.25
3 yr – 15 yr	112	74.2	130	78.3	168	81.6	p=0.25
Antibiotics							
Amoxicillin	81	53.6	155	93.4	192	93.2	p<0.001
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides)	70	46.4	11	6.6	14	6.8	p<0.001
Amoxicillin-clavulanate	60	39.7	5	3.0	9	4.4	p<0.001
Cephalosporins	10	6.6	6	3.6	4	1.9	p=0.07
Macrolides	0	0	0	0	1	0.5	p=0.46

Abbreviations: n=the number of patient for each category; GAS pharyngitis=Group A Streptococcal Pharyngitis

Table 4. Treatment option of GAS pharyngitis
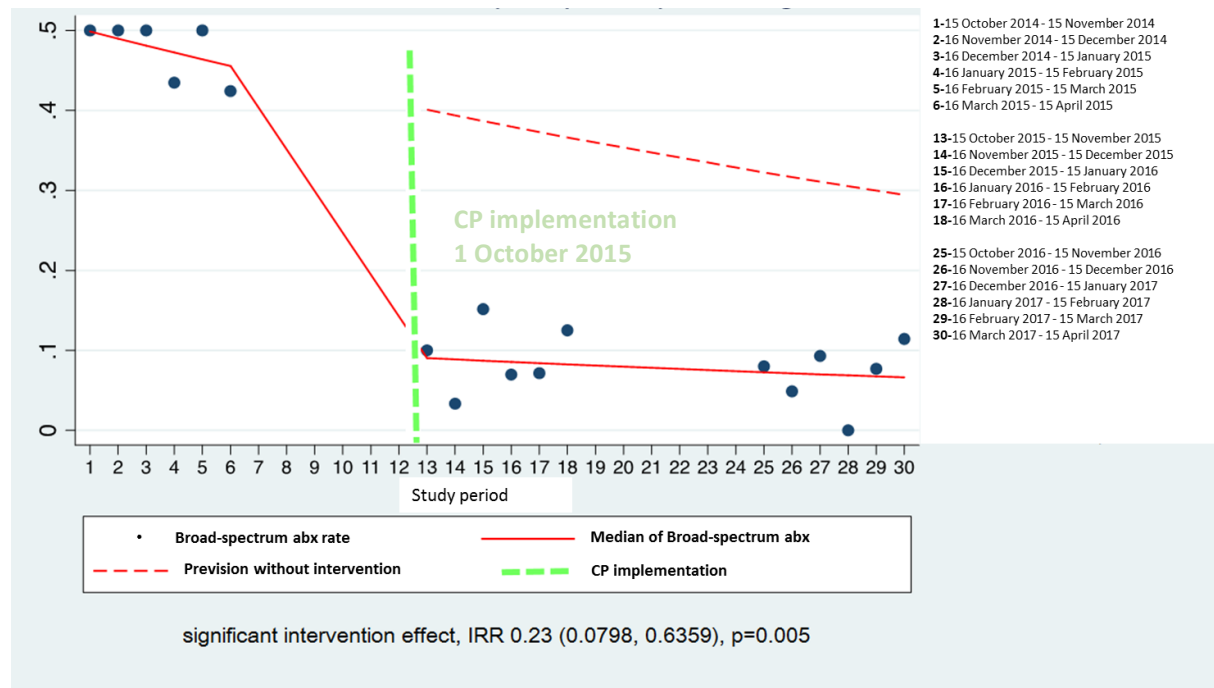
Abbreviations: GAS pharyngitis=Group A Streptococcus Pharyngitis; Abx=antibiotics; CP=Clinical Pathway

Figure 8. ITS analysis of broad-spectrum antibiotic prescription for GAS pharyngitis

Antibiotic dosage and treatment duration for GAS pharyngitis

Changes in dosage over time were assessed only for amoxicillin, as amoxicillin-clavulanate. Dose remained stable during the three analyzed periods, in line with CP's recommendations (**Figure 9**).

In 1-year post intervention period, median DOT met the recommended 10 days for all the 6 months, as was observed for post-intervention period. Kruskal Wallis test comparing overall pre-, post- and 1 year post-intervention median DOT found a significant increase ($p < 0.001$) (**Figure 10**).
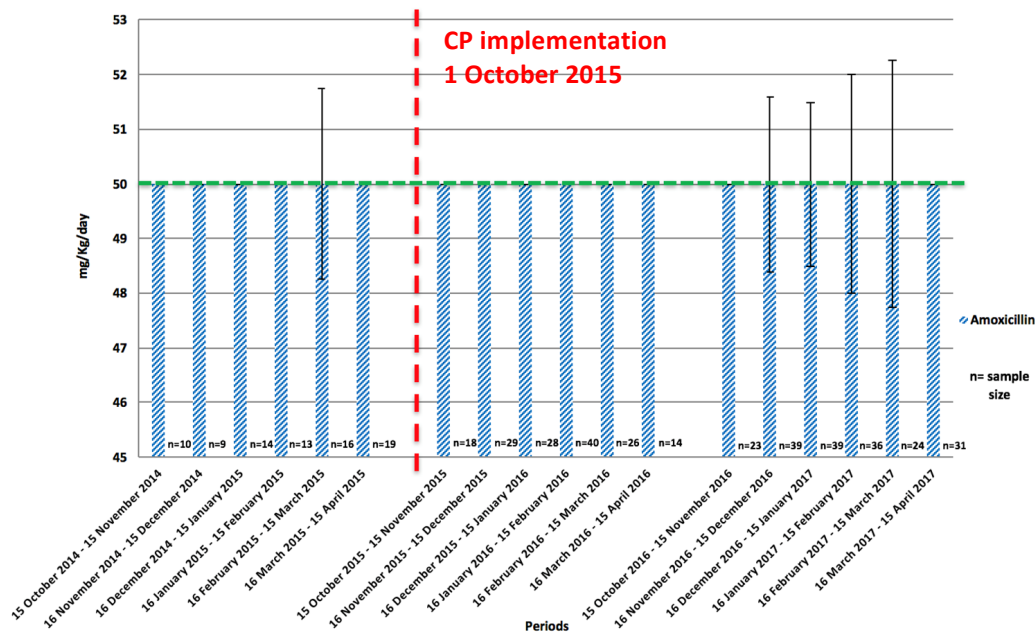
Abbreviations: GAS pharyngitis=Group A Streptococcus pharyngitis; CP=Clinical Pathway.

Figure 9. Amoxicillin dosage for GAS pharyngitis and interquartile range changing over time.
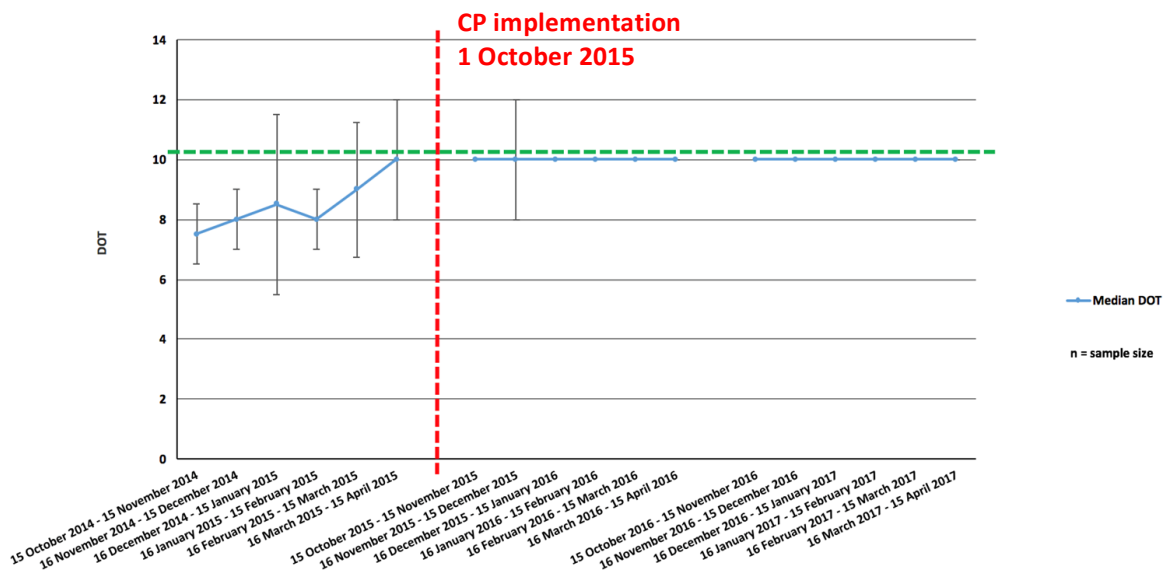
Abbreviations: GAS pharyngitis = Group A Streptococcus pharyngitis; CP = Clinical Pathway; DOT= Days of therapy.

Figure 10. Duration of therapy in median DOT and interquartile range each month in pre-, post- and 1 year post period for children with GAS pharyngitis

CAP population

During 1-year post intervention period there was an increase in the number of patients evaluated for CAP in comparison to other periods (Pre 120/13,262, 0.9%, Post 86/12,335, 0.7%, 1-year post 181/13,082, 1.38%, p=0.03). Ninety-five children were included in the study for 1-year post intervention period, 56 for pre-intervention and 41 for post-intervention period. The study population pre-, post- and 1-year post intervention period is shown in **Table 5**.

The three populations were similar with respect to age, with an increased incidence among children between 2 and 5 years old (Pre 55.4% (31/56), Post 70.7% (29/41), 1-year post 52.6% (50/95), p=0.14).

	Pre-intervention period				Post-intervention period				1 year post intervention period				p-value (for included patients)
Total PED admissions	13262				12335				13082				
CAP admissions	120 (0.90% of total admissions)				86 (0.70% of total admissions)				181 (1.38% of total admissions)				p=0.03
	Excluded patients		Included patients		Excluded patients		Included patients		Excluded patients		Included patients		
	n=64 53.3%		n=56 46.7%		n=45 52.3%		n=41 47.7%		n=86 47.5%		n=95 52.5%		
	n	%	n	%	n	%	n	%	n	%	n	%	
Male	37	57.8	24	42.9	23	51.1	19	46.3	51	59.3	52	54.7	p=0.33
AGE													
3 mo – 2 yr (or less than 3 months for excluded patients)	21	32.8	12	21.4	18	40.0	9	22.0	30	34.9	22	23.2	p=0.97
2 yr – 5 yr	25	39.1	31	55.4	15	33.3	29	70.7	33	38.4	50	52.6	p=0.14
5 yr – 15 yr	18	28.1	13	23.2	12	26.7	3	7.3	23	26.7	23	24.2	p=0.07

Abbreviations: PED=Pediatric Emergency department; CAP=community acquired pneumonia; n=the number of children for each category

Table 5. Characteristics of Study population with CAP

Antimicrobial prescription rate for CAP

During 1-year post-intervention period 97 prescriptions were made by the PED physicians. The prescriptions/patients ratio decreased compared to pre and post-intervention period (prescriptions/patients ratio: Pre 1.3, Post 1.12; 1 year post 1.02 prescriptions/patients ratio). Considering the number of prescriptions for the different molecules, there was an increase of amoxicillin prescriptions (Pre 52.1% (37/71), Post 69.6% (32/46), 1 year post 82.5% (80/97), p=0.0001) with a concomitant decrease in broad-spectrum antibiotics prescription, especially for macrolides (pre: 19.7% (14/71), Post 6.5% (3/46), 1 year post 2.1% (2/97), p=0.003) (**Table 6**).

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients included	56		41		95		
Total number of prescriptions	71		46		97		
Prescriptions/patients ratio	1.3		1.12		1.02		
TYPE OF ANTIBIOTICS	n	% of total prescriptions	n	% of total prescriptions	n	% of total prescriptions	
Amoxicillin	37	52.1	32	69.6	80	82.5	p=0.0001
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides + quinolones)	34	47.9	14	30.4	17	17.5	p=0.0001
Amoxicillin-clavulanate	9	12.7	7	15.2	9	9.3	p=0.56
Cephalosporins	11	15.5	4	8.7	6	6.2	p=0.13
Macrolides	14	19.7	3	6.5	2	2.1	p=0.003

Abbreviations: n=the number of patient for each category; CAP=community acquired pneumonia

Table 6. Treatment option of CAP

The reduction in broad-spectrum antibiotic prescription rate is showed in **figure 11**.
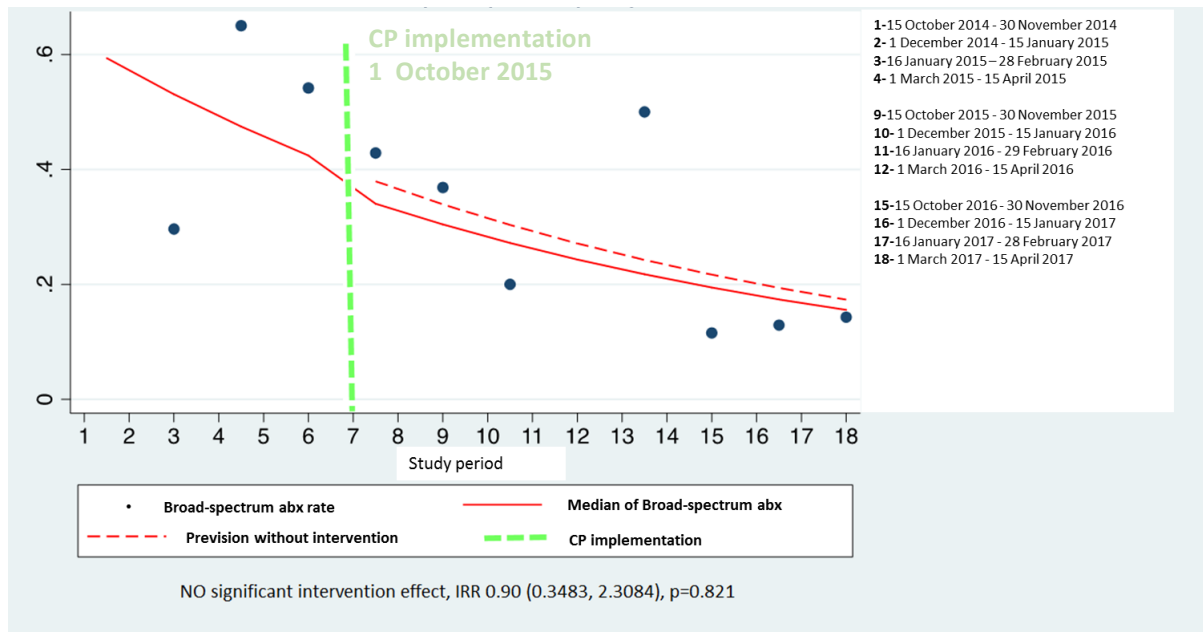
Abbreviations: CAP=Community Acquired Pneumonia; Abx=antibiotics; CP=Clinical Pathway

Figure 11. ITS analysis of broad-spectrum antibiotic prescription for CAP

Antibiotics dosage for CAP

Amoxicillin dose increased in 1-year post intervention period; reaching the recommended dose (90 mg/kg/day). The difference between median dose in the three different periods was statistically significant ($p<0.001$) (**Figure 12**).
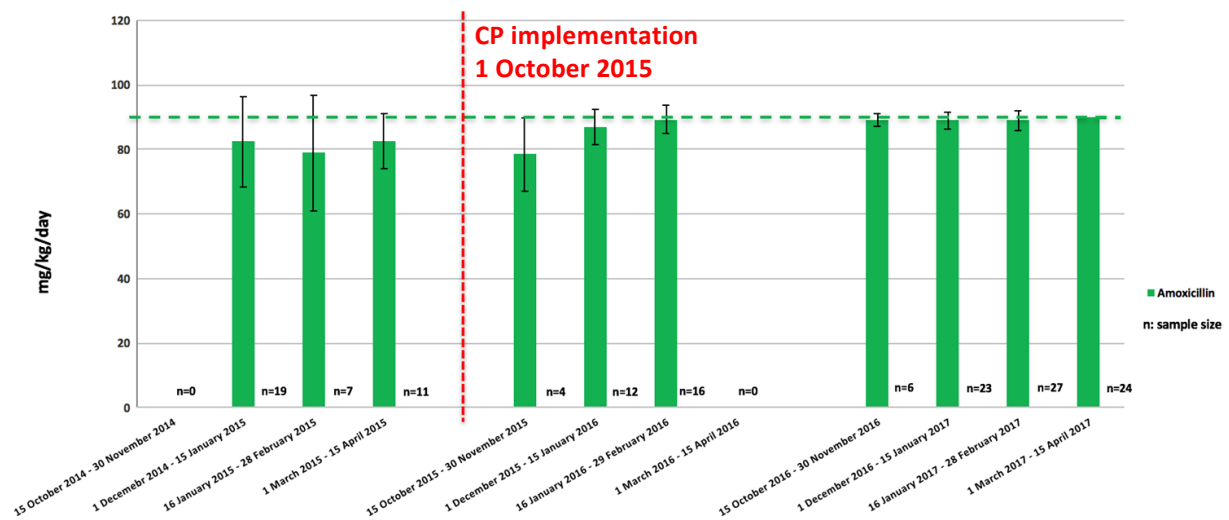
Abbreviations: CAP=Community Acquired Pneumonia; CP=Clinical Pathway

Figure 12. Amoxicillin dosage for CAP and interquartile range changing over time.

Treatment duration for CAP

Median DOT for CAP decreased from the 10 days of pre- intervention period to the recommended duration of 7 days. The difference between median DOT in the three periods was statistically significant ($p<0.001$) (**Figure 13**). Median LOT reflected median DOT and the difference between the three periods was statistically significant ($p<0.001$) (**Figure 14**).

DOT/LOT ratio decreased in 1-year post implementation period and reached the value of 1 in comparison to 1.2 in pre-intervention and 1.1 in post-intervention period (**figure 15**).
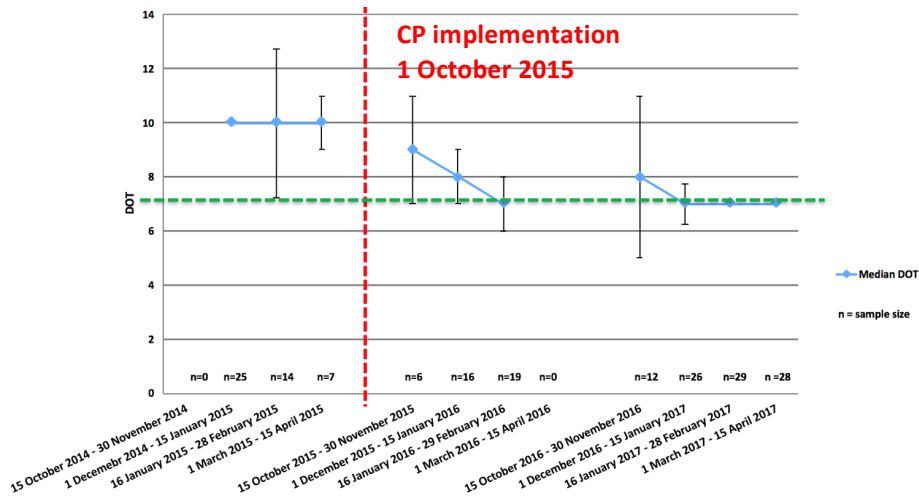
Abbreviations: CAP=Community Acquired Pneumonia; CP=Clinical Pathway, DOT=days of therapy

Figure 13. Duration of therapy in median DOT and interquartile range in pre-, post- and 1 year post period for children with CAP
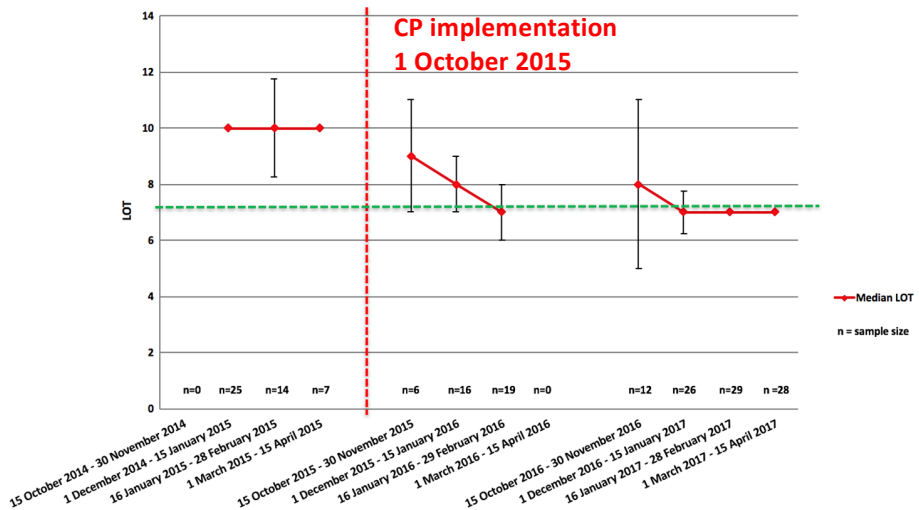
Abbreviations: CAP=Community Acquired Pneumonia; CP=Clinical Pathway, LOT=length of therapy

Figure 14. Duration of therapy in median LOT and interquartile range in pre-, post- and 1 year post period for children with CAP
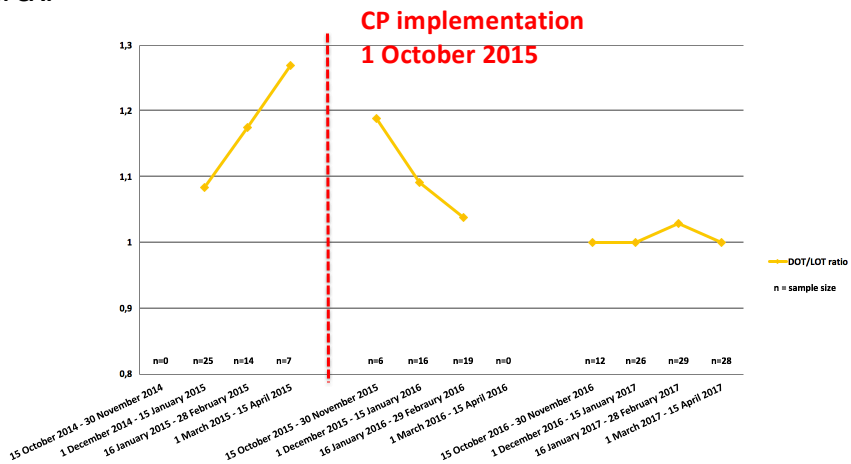
Abbreviations: CAP=Community Acquired Pneumonia; CP=Clinical Pathway, DOT/LOT ratio Day of therapy/Length of therapy ratio

Figure 15. DOT/LOT ratio in pre-, post- and 1 year post period for children with CAP

Secondary aim

AOM treatment failure

In 1-year post intervention period 207/301 (68.8%) children were available for AOM follow-up, in comparison to 214/295 (72.5%) and 206/278 (74.1%) children in pre and post-intervention period respectively (**Table 7**).

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients available for follow-up	214 (72.5% of total AOM)		206 (74.1% of total AOM)		207 (68.7% of total AOM)		
Treatment	n	%	n	%	n	%	
Wait and see	48	22.4	66	30.6	59	28.5	p=0.08
Antibiotic Treatment	166	77.6	140	68	148	71.5	p=0.08
Amoxicillin	55	33.1	73	35.4	77	37.2	p=0.003
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides + quinolones)	111	66.7	68	48.2	71	34.3	p<0.001
Amoxicillin-clavulanate	78	36.4	50	24.3	58	28.0	p=0.02
Cephalosporins	30	14.1	14	6.8	12	5.8	p=0.005
Macrolides	3	2.7	3	4.3	1	0.5	p=0.6
Quinolones	0	0	0	0	0	0	
Treatment failure	26	12.1	23	11.2	30	14.5	p=0.31
Change in antibiotic regimen for persistence of symptoms	12	5.6	5	2.4	9	4.3	p=0.26
Change in antibiotic regimens for adverse drug events	3	1.4	4	1.9	2	1.0	p=0.71
New antibiotics prescriptions in case of "wait and see" was the first line therapeutic choice	7	3.3	13	6.3	16	7.7	p=0.13
Relapse of symptoms within 30 days from discharge date with new antibiotic prescription	4	1.7	1	0.5	3	1.4	p=0.43

Abbreviations: n = the number of patient for each category; AOM = Acute Otitis Media

Table 7. Treatment and treatment failure during follow-up of patients with AOM

During 1-year post intervention period only 14.5% (30/207) of patient presents a treatment failure, in line with the previous periods (Pre 12.1% (26/214), Post 11.2% (23/206), p=0.31). The difference between the treatment failure was not statistically significant both in the group treated with antibiotics (p=0.26) and in the 'wait and see' group (p=0.13).

Pharyngitis treatment failure

Only patients with a diagnosis of GAS pharyngitis were followed-up. In 1-year post implementation period 142/206 (68.9%) children were contacted (**Table 8**).

The difference between overall treatment failure rates in pre, post and 1-year post intervention groups was not statistically significant (6.9% (7/102), 6.7 (8/120), 6.3% (9/142) p=0.98).

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients available for follow-up	98 (64.9% of total GAS pharyngitis)		118 (71.1% of total GAS pharyngitis)		142 (68.9% of total GAS pharyngitis)		
Treatment	n	%	n	%	n	%	
Amoxicillin	52	53.1	109	90.8	135	95.1	p<0.001
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides)	46	46.9	9	7.6	7	4.9	p<0.001
Amoxicillin-clavulanate	40	40.8	3	2.5	5	3.5	p<0.001
Cephalosporins	6	6.1	6	5.1	1	0.7	p=0.051
Macrolides	0	0	0	0	1	0.7	p=0.47
Treatment failure	6	6.1	8	6.7	9	6.3	p=0.98
Change in antibiotic regimen for persistence of symptoms	2	2.0	3	2.5	5	3.5	p=0.78
Change in antibiotic regimens for adverse drug events	2	2.0	2	1.7	1	0.7	p=0.65
Relapse of symptoms within 30 days from discharge date with new antibiotic prescription	2	2.0	3	2.5	3	2.1	p=0.96

Abbreviations: n = the number of patient for each category; GAS pharyngitis = Group A Streptococcus Pharyngitis

Table 8. Treatment and treatment failure during follow-up of patients with GAS pharyngitis

CAP treatment failure

CAP follow-up was available for 70/95 (73.7%) children in the 1-year post intervention period, in comparison to 44/56 (78.6%) and 37/39 (90.3%) children in pre- and post-intervention period respectively (**Table 9**).

During 1-year post intervention period only 14.3% (10/70) of patient had a treatment failure, with no significant change compared to the previous periods (Pre 2.3% (1/44), Post 10.8% (4/37), p=0.11). All treatment failures were represented by the need to change antibiotics for the persistence of symptoms.

	Pre-intervention period		Post-intervention period		1 year post intervention period		p-value
Patients available for follow-up	44 (78.6% of total CAP)		37 (902% of total CAP)		70 (73.7% of total CAP)		
Number of prescriptions	56		39		71		
Treatment	n	%	n	%	n	%	
Amoxicillin	28	50.0	25	64.1	58	81.7	p<0.001
Broad spectrum (amoxicillin-clavulanate + cephalosporins + macrolides)	28	50.0	14	35.9	13	18.3	p<0.001
Amoxicillin-clavulanate	9	16.1	7	17.9	7	9.9	p=0.42
Cephalosporins	9	16.1	4	10.3	6	8.5	p=0.39
Macrolides	10	17.8	4	10.3	6	8.5	p<0.001
Treatment failure	1	2.3	4	10.8	10	14.3	p=0.11
Change in antibiotic regimen for persistence of symptoms	1	2.3	4	10.8	10	14.3	p=0.11
Change in antibiotic regimens for adverse drug events	/	/	/	/	/	/	/
Relapse of symptoms within 30 days from discharge date with new antibiotic prescription	/	/	/	/	/	/	/

Abbreviations: n=the number of patient for each category; CAP=community acquired pneumonia

Table 9. Treatment and treatment failure during follow-up of patients with CAP

Discussion

An antimicrobial stewardship program (ASP) based on CPs was implemented on October 1st 2015 at the PED of Padua.

Afterwards, data on antibiotic prescriptions, including timing of prescription, breadth of spectrum prescribed, dose, duration of therapy and outcomes were assessed for AOM, GAS pharyngitis and CAP.

As already reported by other authors, also in our case, CPs have been proven a useful tool to reduce antibiotic prescriptions for common illnesses[11–13,18–20]. However, only few authors have reported data on the sustainability of an ASP long after its implementation[21].

Regarding AOM, the results obtained were in line with those obtained in post-intervention period with a reduction in antibiotic prescription rate and an increase in 'wait and see' approach. This strategy was encouraged since AOM could be caused by viruses or bacteria with a high spontaneous eradication rate, such as *Moraxella Catharralis* and *Haemophilus Influenzae* (80% and 50% respectively). For this reason, this became the first option for all immunized children 6 months to 2 years old with unilateral non-severe illness and for those >2 year old with bi–unilateral AOM[22].

Streptococcus pneumoniae, responsible for at least 50% of AOM episodes[23], has a spontaneous eradication rate around 10%; for this reason it should be considered the first target of antibiotic therapy. Currently, the polyvalent pneumococcal vaccine (PCV13) confers immunity to approximately 85% of serotypes responsible for most invasive pneumococcal diseases[24]. Data from an Italian survey[25] showed that *S. Pneumoniae* amoxicillin resistance rate is still around 11.3% with only 4.8% representing high resistance isolates. Since *S. pneumoniae* does not develop resistance to beta-lactams through β-lactamase enzymes production but through the alteration of the cell wall's antimicrobial target (penicillin-binding protein)[26] the addition of β-lactamase inhibitors has no rational support. For all of these reasons amoxicillin was the first recommended choice for uncomplicated AOM in fully immunized children[22,27–30]. Penicillins with β- lactamase inhibitors (amoxicillin-clavulanate) were suggested only for complicated AOM or when β-lactamase producing bacteria could be more likely, such as in cases of lack of immunization, children with amoxicillin treatment in the previous 30 days or concurrent purulent conjunctivitis[22,27,30].

The change in dosage obtained in the post implementation period was confirmed in 1-year post implementation period both for amoxicillin and amoxicillin-clavulanate.

Regarding treatment duration, the results obtained in 1-year post implementation were excellent for children < 2 years old and for children ≥ 2 years old with complicated AOM. In both cases treatment duration met CP recommendations. On the contrary, treatment duration for children ≥ 2 years old with uncomplicated AOM was not so easy to reach. This confirm the physicians' discomfort in

prescribing a AOM short-course treatment already reported in post-intervention period (**Chapter IV**).

Compared to pre-intervention period, in 1-year post intervention period there was a slightly increase in treatment failure that resulted not statistically significant. This changing is almost entirely due to the increase of treatment failure after 'wait and see' approach. In fact, despite the remarkable decrease of broad spectrum prescription rate, the proportion of patients who need to change the antibiotic for persistence or worsening of symptoms was lower in 1 year post implementation period than in pre-intervention period.

Regarding pharyngitis, in 1-year post intervention period there was an increase in GAS pharyngitis diagnosis compared to the two previous periods. This may be related to the increase in the proportion of children between 3 and 15 years of age in the 1-year post-intervention. Indeed, as reported by literature, GAS pharyngitis is more common between school children[31].

Our CP follows the US and Italian guidelines which suggest calculating a McIsaac score using previous clinical evaluation and through that score to recognize children eligible for RAD testing. Moreover, a further stratification was proposed as suggested in the Emilia Romagna guidelines[32]. According to CP, children presenting with pharyngitis and McIsaac score of 3 or 4 should receive a RAD test to confirm GAS etiology. In case of McIsaac score of 5, the physician could reasonably skip the RAD test and directly prescribe antimicrobial therapy. In case of a McIsaac score below 3 suggestive of viral pharyngitis antimicrobials should be avoided.

Amoxicillin was always the first antibiotic treatment choice, given the high susceptibility of GAS to penicillin, while oral cephalosporins were accepted only in case of non-severe beta-lactam allergy, both because of the higher cost compared to penicillin and the risk of selection of multi-drug resistant organism[33]. As for *S.pneumoniae,* macrolides are no longer indicated as first-line due to GAS high resistance rates[33]. Amoxicillin-clavulanate was never considered suitable for acute GAS pharyngitis because *S. pyogenes* does not produce beta-lactamase and the use of clavulanate would only increase related side effects. According to GAS pharyngitis CP, the most prescribed antibiotic was amoxicillin. This result is in line with the one obtained in post-intervention period.

The change in treatment duration and dose obtained in post intervention period was confirmed also in 1-year post implementation period.

Despite the dramatic decrease in broad spectrum antibiotic use, no difference in treatment failure was observed between 1-year post intervention period and pre-intervention period.

Regarding CAP, the number of patients evaluated in PED for this pathology has doubled in 1-year post intervention period in comparison to the other two periods.

According to guidelines all children with a clear clinical diagnosis of pneumonia should receive antibiotics as bacterial and viral pneumonia cannot be reliably distinguished from each other[34]. Narrow-spectrum regimen, defined as a prescription of amoxicillin in monotherapy, was encouraged since *S pneumoniae* accounts for 21-44% of disease[35–37].

Currently, the polyvalent pneumococcal vaccine (PCV13) confers immunity to approximately 85% of serotypes responsible for most invasive pneumococcal diseases[24]. Data from an Italian survey showed that *S. Pneumoniae* amoxicillin resistance rate is still around to 11.3% with only 4.8% of high resistant isolates[25]. Since *S. pneumoniae* does not develop resistance to β-lactamases through β-lactamase enzymes production but through the alteration of the cell wall's antimicrobial target (penicillin-binding protein) the addition of β-lactamase inhibitors has no rational support[26].

For this reason, amoxicillin monotherapy became the first option for mild CAP in fully immunized children. Penicillins with β-lactamase inhibitors (amoxicillin-clavulanate) were suggested only when β-lactamase producing bacteria (*H. influenzae* type B (HiB), and *S. aureus*) could be more likely as: lack of immunization, children with amoxicillin treatment in the previous 30 days[34,38]. *Mycoplasma pneumoniae* is more frequent in school-aged children and adults. According to CP, use of macrolides is accepted only if atypical etiology is suspected. Their strict indications derives from the evidence that *Mycoplasma* low-tract respiratory infections (LTRI) have an high rate of spontaneous clinical remission and the use of azithromycin has been associated with the selection of resistant organisms because of its prolonged serum elimination half–life[34].

The prescription/patient ratio decreased compared to the previous periods, reaching a value very close to 1. This value indicates that clinicians had preferred monotherapy, instead of combination therapy. Furthermore, in 1-year post intervention period there was a dramatic increase in the choice of amoxicillin as first line therapy. Broad-spectrum prescription rate decreased, especially for macrolides prescription with a ten-fold reduction compared to pre intervention period. Indeed, use of macrolides is acceptable only if atypical etiology is suspected.

In 1-year post intervention period, the amoxicillin dosage met the 90 mg/kg/day recommended by the CP improving the result obtained in post implementation period.

Despite the fewer overall broad-spectrum antibiotic prescriptions, the number of treatment failure slightly increase without statistical significance. All treatment failure was due to persistence or worsening of symptoms as happened in the two previous periods.

In summary, our study shows that the results obtained after CPs implementation remain stable over time.

This study has strengths and limitation.

First of all, this is the first study which evaluated the sustainability of ASP with CPs. Second, this study had a phone call follow-up to collect information about treatment failure directly speaking to the families. Third, all patients with ongoing therapy were excluded in order to avoid the influences in treatment choices by other physicians.

The primary limitation of our study is the retrospective nature of the analysis. Furthermore, this was a single center study, so further validation of this tool should include other Italian PEDs. Third, our analysis of treatment failure was underestimated due to the high number of children lost to follow-up for wrong or no available for number or for consensus denied.

Conclusion

This study confirms that CPs represent a reasonable first step of ASP implementation. Evidence-based CP supported by adequate provider education have been proven a promising, efficient and sustainable tool that can effectively influence prescribing practices without compromising clinical outcomes.

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CHAPTER VII

The Effects of a Clinical Pathway on Perioperative Antibiotic Prophylaxis in pediatrics

Abstract

Background. SSI is the second most common healthcare-associated infection. It represents more than 16% in adults and 17-18% in children of all hospital-acquired infections. While trends in surgical prophylaxis among adult patients are widely available, only a few studies include pediatric data.

The aim of this study is to determine the effectiveness of an Antimicrobial Stewardship Program based on a Clinical Pathway (CP) to improve the adherence to perioperative antibiotic prophylaxis (PAP) guidelines [9]. Secondary aim is to evaluate the effect CP implementation on SSIs.

Materials and methods. This is a pre-post quasi-experimental study to assess the changes in PAP appropriateness during a 6-month period preceding CP implementation (per-intervention, from 1 February 2016 to 31 July 2016) and during the six months after CP implementation (post intervention, from 1 February 2017 to 31 July 2017). On 31 January 2017 the CP for PAP was implemented. All patients aged between 1 months and 15 years subjected to one or more surgical procedures were eligible to be included in our study.

Results. 810 children were included in the study, 412 in pre-intervention period and 385 in post-intervention period. Two hundred and two (202/412, 49.0%) and 166/385 (43.1%) patients received a PAP during pre and post-intervention period respectively (p=0.09).
The majority of patient receiving an antibiotic prophylaxis gad an indication for PAP in both periods (170/202 (84.6%) vs 145/166 (87.3%), p=0.38). In the post-intervention period, there was an increasing of correct PAP with 90/202 (44.6 %) in pre and 93 (56.0 %) in post intervention period (p=0.03). Indeed, we found that the selection of the appropriate antibiotic for prophylaxis improved in the post intervention period, both for monotherapy (111 (81.0%) for pre vs 114 (91.9%) for post, p=0.02) and combination therapy (31 (47.7 %) for pre vs 29 (69.0%) fro post, p=0.03) . Also the duration of prophylaxis decreased during the post intervention period, with an increase of PAP discontinuation from 83/202 (41.0 %) in the pre-intervention period to 102 (61.4%) (<0.001). Despite the higher use of narrow-spectrum antibiotic for fewer days, there was no increase in treatment failures between the two analysed periods (16 (3.9 %) pre vs 10 (2.6%) post, p=0.3).

Conclusions. CPs with a proper educational intervention can be a useful tool to improve the choice of first-line antibiotic and the duration of PAP in pediatric patients.

Background

SSI is the second most common healthcare-associated infection [1] and CDC showed that it complicates approximately 5% [2] of surgical operations each year.

It represents more than 16% [3] in adults and 17-18% [4,5] in children of all hospital-acquired infections recorded in the National Healthcare Surveillance Safety Network of the Centres for Disease Control and Prevention (CDC) and 38% of nosocomial infections in surgical patients [2]. While trends in surgical prophylaxis among adult patients are widely available, only a few studies include pediatric data [3,6-8].

The aim of this study is to determine the effectiveness of an Antimicrobial Stewardship Program based on a Clinical Pathway (CP) to improve the adherence to perioperative antibiotic prophylaxis (PAP) guidelines [9]. Secondary aim is to evaluate the effect CP implementation on SSIs.

Materials and methods

Study design

This is a pre-post quasi-experimental study to assess the changes in PAP appropriateness during a 6-month period preceding CP implementation (per-intervention, from 1 February 2016 to 31 July 2016) and during the six months after CP implementation (post intervention, from 1 February 2017 to 31 July 2017) (figure 1).

The study was set at the Surgical Paediatric Unit of the Department for Women and Children Health at Padua University Hospital.

Pre-interventio period
01/02/16 -31/07/16

Intervention
31 January 2017

Post-interventio period
01/02/17 -31/07/17
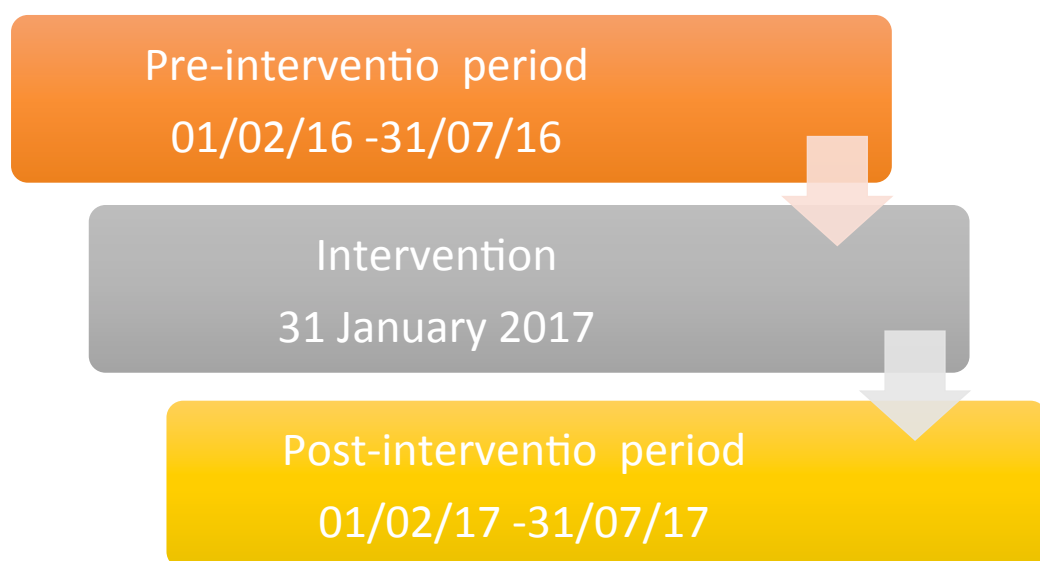
Figure 1. Study design

Intervention

On 31 January 2017 the CP for PAP was implemented (figure 2,3,4,5).

On the same day, an educational lecture was presented. This meeting provided a review of the clinical guidelines for PAP and the potential benefits of a correct PAP, discussed the rationale for the guideline recommendations and highlighted situations where local practice in the pediatric surgery department diverged from guideline recommendations.

Following the lecture, a pocket card was delivered to all participants and, on the same day, to all other physicians and residents who were unable to attend the seminar.

The clinical pathway was developed by a multidisciplinary group (paediatric infectious disease, microbiology and paediatric surgery) based on international clinical guidelines [9] with the supervision of the paediatric infectious diseases team of Philadelphia Children's hospital.

Study population

All patients aged between 1 months and 15 years subjected to one or more surgical procedures were eligible to be included in our study.

Exclusion criteria were: concomitant infections, ongoing antibiotic therapy, immunodeficiency, immunosuppressive therapy, patients who underwent neurosurgical, vascular, ORL, and ocular procedures.

Data Source

All clinical, demographic, diagnostic and antimicrobial data were manually collected from electronic (*Galileo system*) or paper medical records. We used a password-protected REDCap® data collection form and we stored them in the secure server at the University of Padua. Surgical procedures were recorded using the international classification of disease, 9th revision and clinical modification (ICD 9 CM).

For every patient were recorded:

1) *preoperative data* including gender, age, weight ;

2) *procedure data* including type of procedure (divided for major categories, according to *the* ICD-9-CM, wound class (Clean, Clean-Contaminated, Contaminated), duration of surgical procedure, urgency of procedure and length of hospital stay

3) *perioperative PAP data* such as need for PAP, received PAP, indication for PAP among those received PAP, correct PAP (both agent and duration), correct antimicrobial agent, correct time of antibiotic discontinuing.

4) *postprocedure data* including date of medical evaluation for SSI.

PAP was defined appropriated only if the correct antimicrobial agent for the specific surgical procedures performed had been discotniued within 24 h after completion of surgery, according to Clinical practice guidelines for antimicrobial prophylaxis in surgery [9].

To evaluate the effectiveness and safety of the intervention, medical records follow-up was performed to assess for SSIs within 3 months after discharge.

Privacy was guaranteed in two ways: a unique, study-specific survey number was assigned to each patient and no personally identifying data were collected.

This study was approved by the Research Ethics Committee of Department for Woman and Child Health at the University of Padua.

Data analysis

The data was analyzed with SAS 9.4 program (SAS Institute Inc., Cary, NC, USA) for Windows.

Patient's demographic and clinical data was analysed in a descriptive way, reporting the number and percentage of patients in every category for: qualitative variables, median, minimum and maximum for quantitative variables considering that their distribution wasn't Normal (Shapiro-Wilks test).

Association between the two periods was performed with Chi-square test or Fisher test for qualitative variables, with Rank-sum Wilcoxon test for quantitative variables.

Logistic regression analysis was performed to evaluate the efficacy of the intervention on appropriate PAP overall, appropriate selection of PAP antibiotic agent and appropriate administration time of PAP.

We conducted stratified analyses to assess if the effectiveness of intervention was affected by the surgical characteristics such as type of procedure, urgent surgical procedure, length of hospital stay, duration of hospital stay.

Statistical significance was $p < 0.05$.
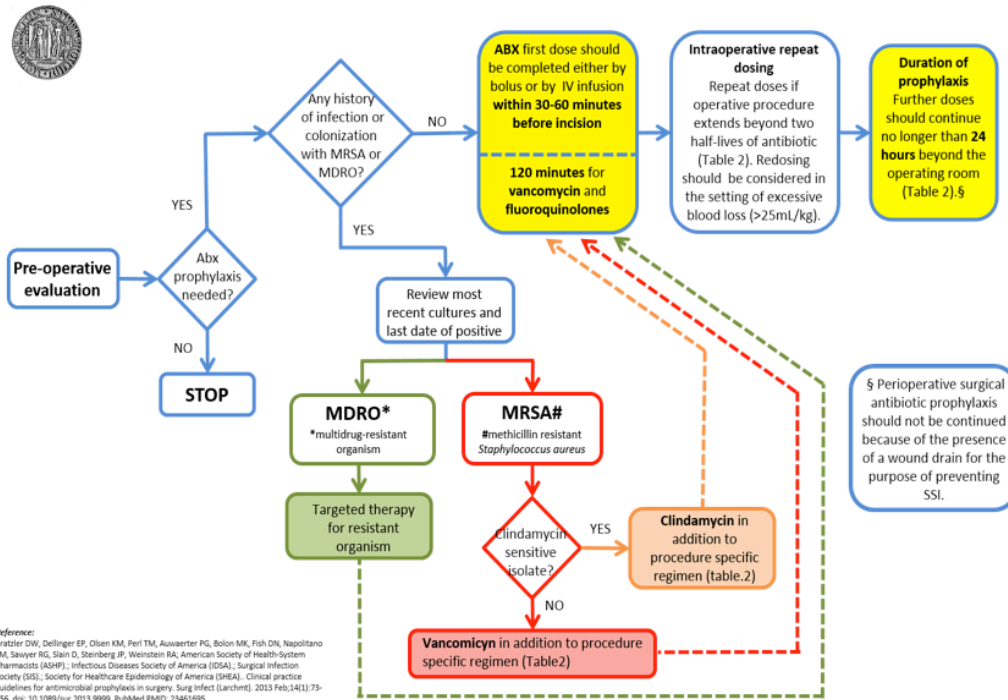
Perioperative Antibiotic prophylaxis

Pre-operative evaluation

Abx prophylaxis needed?

YES → Any history of infection or colonization with MRSA or MDRO?

NO → STOP

NO → ABX first dose should be completed either by bolus or by IV infusion **within 30-60 minutes** before incision

120 minutes for vancomycin and fluoroquinolones

YES → Review most recent cultures and last date of positive

MDRO* *multidrug-resistant organism

MRSA# #methicillin resistant *Staphylococcus aureus*

Targeted therapy for resistant organism

Clindamycin sensitive isolate?

YES → **Clindamycin** in addition to procedure specific regimen (table.2)

NO → **Vancomicyn** in addition to procedure specific regimen (Table2)

Intraoperative repeat dosing
Repeat doses if operative procedure extends beyond two half-lives of antibiotic (Table 2). Redosing should be considered in the setting of excessive blood loss (>25mL/kg).

Duration of prophylaxis Further doses should continue no longer than **24 hours** beyond the operating room (Table 2).§

§ Perioperative surgical antibiotic prophylaxis should not be continued because of the presence of a wound drain for the purpose of preventing SSI.

Reference:
Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists (ASHP).; Infectious Diseases Society of America (IDSA).; Surgical Infection Society (SIS).; Society for Healthcare Epidemiology of America (SHEA). . Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013 Feb;14(1):73-156. doi: 10.1089/sur.2013.9999. PubMed PMID: 23461695.

Figure 2 Perioperative Antibiotic Prophylaxis CP (page 1)

Surgery	Infective pathogen	Antibiotic	Alternative for Penicillin and/or Cephalosporin Allergy
Gastrointestinal			
ESOPHAGEAL, NON OBSTRUCTED GASTRODUODENAL AND JEJUNAL	gram negative bacilli, gram positive cocci	CEFAZOLIN	CLINDAMYCIN + GENTAMICIN
OBSTRUCTED GASTRODUODENAL AND JEJUNAL	gram negative bacilli, gram positive cocci and anaerobes	CEFAZOLIN + METRONIDAZOLE / AMPI/SULBACTAM	CLINDAMYCIN + GENTAMICIN
UNCOMPLICATED APPENDECTOMY	gram negative bacilli and anaerobes	CEFAZOLIN + METRONIDAZOLE / AMPI/SULBACTAM	CIPROFLOXACIN + METRONIDAZOLE
ILEAL AND COLORECTAL	gram negative bacilli, Enterococci and anerobes	CEFAZOLIN + METRONIDAZOLE	CIPROFLOXACIN + METRONIDAZOLE
Biliary tract			
OPEN AND LAPAROSCOPIC PROCEDURES	gram negative bacilli, gram positive cocci	CEFAZOLIN	CLINDAMYCIN + GENTAMICIN
BILIARY PROCEDURES WITH POSSIBLE MANIPULATION (PTC, ERCP)	gram negative bacilli, gram positive cocci, anaerobes	CEFAZOLIN + METRONIDAZOLE	CIPROFLOXACIN + METRONIDAZOLE
Head and Neck			
CLEAN		None	None
WITH PLACEMENT OF PROSTHESIS	gram negative bacilli, gram positive cocci	CEFAZOLIN	CLINDAMYCIN + GENTAMICIN
CLEAN-CONTAMINATED	gram negative bacilli, gram positive cocci	CEFAZOLIN	CLINDAMYCIN + GENTAMICIN
Urologic			
CYSTOURETHROSCOPY		Targeted therapy	Targeted therapy
OPEN SURGERIES OR LAPAROSCOPY (INCLUDING NEPHROSTOMY TUBE PLACEMENT IF INFECTED OR WITH STONES)	gram negative bacilli, gram positive cocci	CEFAZOLIN	CLINDAMYCIN + GENTAMICIN

Figure 3 Perioperative Antibiotic Prophylaxis CP (page 2)

CEFAZOLIN: Maximum concentration – 100 mg/ml; (IVP) infuse over 3-5 minutes.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates ≤7 days or ≤2 Kg	20 mg/kg/dose	8 hours	2
Neonates >7 days or >2 Kg	20 mg/kg/dose	4 hours	3
Infants > 1 month, children, adolescents and adults	30 mg/kg/dose (maximum 2 grams)	4 hours	3

METRONIDAZOLE: Maximum concentration – 5 mg/ml; (IVSS) infuse over 30 minutes.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates 0-4 weeks AND <1.2 kg, Neonates ≤ 7 days AND 1.2-2 Kg	7.5 mg/kg/dose	No redose	No additional dose required
Neonates ≤ 7 days AND >2 Kg, Neonates > 7 days AND 1.2-2 kg	7.5 mg/kg/dose	12 hours	2
Neonates > 7 days AND > 2 kg	15 mg/kg/dose	12 hours	2
Infants, children, adolescents and adults	7.5 mg/kg/dose (maximum dose 500 mg)	6 hours	4
Adults (colorectal)	15 mg/kg/dose (maximum dose 1 gram)	6 hours with 7.5 mg/kg/dose (maximum dose 500 mg)	4

AMPICILLIN/SULBACTAM: Maximum concentration – 30 mg/ml;

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates < 14 days	50 mg/kg/dose	8 hours	2
Neonates ≥ 14 days	50 mg/kg/dose	8 hours	2
Infants > 1 month, children, adolescent and adults	50 mg/kg/dose (maximum dose 2 grams)	4 hours	2

CLINDAMYCIN: Maximum concentration – 20 mg/ml; (IVSS) infuse over at least 10-60 minutes, at a rate not to exceed 30 mg/minute

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates ≤7 days or ≤2 Kg	5 mg/kg/dose	12 hours	2
Neonates >7 days or >2 Kg	5 mg/kg/dose	6 hours	3
Infants > 1 month, children, adolescents and adults	10 mg/kg/dose (maximum 900 mg)	6 hours	3

VANCOMYCIN: Maximum concentration – 5 mg/ml; (IVSS) infuse over 1 hour

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonate < 7 days AND 1000-2000 grams, Neonate ≥ 7 days AND < 1000 grams	15 mg/kg/dose	No redose	No additional dose required
Neonate < 7 days AND > 2000 grams, Neonate ≥ 7 days AND 1000-2000 grams	15 mg/kg/dose	12 hours	2
Neonates ≥7 days AND ≥2000 grams	15 mg/kg/dose	8 hours	3
Infants > 1 month, children≤ 50 kg	15 mg/kg/dose (maximum 750 mg)	6 hours	4
Children > 50 kg and adults	1000 mg	8 hours	3

CIPROFLOXACIN: Maximum concentration – 2mg/ml; (IVSS) infuse over 1 hour.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Children (≤ 40 kg)	10 mg/kg/dose (maximum dose 400 mg)	5 hours	2
Adults (>40 kg)	400 mg	8 hours	2

Figure 4 Perioperative Antibiotic Prophylaxis CP (page 3)

GENTAMICIN: Maximum concentration – 10 mg/ml; (IVSS) infuse over 30 minutes. *No redose for urologic procedures
**Dosage should be based on Adjusted Body Weight. **Contact Infectious Diseases for doses > 200 mg for verification.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates	4 mg/kg/dose	No redose	No additional dose required
Infants > 1 month, children≤ 10 years	2.5 mg/kg/dose**	6 hours*	3
Children > 10 years, adolescents and adults	2.5 mg/kg/dose**	6 hours*	3

CEFTRIAXONE: Maximum concentration – 40mg/ml; (IVP) infuse over 2-4 minutes.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
Neonates	Use cefotaxime in neonate	-	-
Infants, children, adolescents and adults	75 mg/kg/dose (maximum dose 2 grams)	12 hours	1

PIPERACILLIN/TAZOBACTAM: Maximum concentration – 60mg/ml (60 mg piperacillin component); IV intermittent infusion: infuse over 20-30 min.

Age/Weight	Dosing	Time for Redose (OR only)	Number of Postop Doses
GA <32 weeks and PNA < 14 days	80 mg/kg/dose of piperacillin component	8 hours	3
GA <32 weeks and PNA ≥ 14 days, GA ≥ 32 weeks and PNA < 14 days	80 mg/kg/dose of piperacillin component	4 hours	3
GA ≥ 32 weeks and PNA ≥ 14 days	100 mg/kg/dose of piperacillin component	4 hours	3
Infants> 28 days to 2 months	100 mg/kg/dose of piperacillin component	3 hours	4
Infants ≥ 2 months to 9 months	80 mg/kg/dose of piperacillin component	3 hours	4
Infants > 9 months, children, adolescents and adults	100 mg/kg/dose of piperacillin component (maximum dose 3 grams)	2 hours	4

Figure 5 Perioperative Antibiotic Prophylaxis CP (page 3)

Results

During the study period, 842 children underwent surgery. Of 430 children in pre-intervention period, 11 were excluded because admitted to an intensive care ward (PICU/NICU) and seven had an ongoing infectious process. For post-intervention period population, 13 were excluded because admitted in the PICU/NICU and 13 because receiving antibiotics for an infection.   Indeed, 797 children were included in the study, 412 in pre-intervention period and 385 in post-intervention period.

The two populations were similar in terms of sex and age, with an overall female predominance.

No difference between the different wound classes was reported between the two study populations: clean 300 (72.8%) in pre and 299 (78.1%) in post, clean contaminated 64 (15.5%) in pre and 52 (13.6%) in post and contaminated 49 (11.9%) in pre and 32 (8.4%) in post.

No difference in the type of surgical procedures was shown in the pre and post-intervention period.

Table 1 presents the baseline patient and procedure characteristics for patients enrolled in pre and post intervention period.

Patient's characteristics	Pre intervention	Post intervention	p-value
Gender			0.47
Male	132 (32%)	118 (30.6%)	
Female	280 (68%)	267 (69.4%)	
Median age (min-max)	5 (0- 17)	5,1 (0-17)	0.92
Body weight (kg)	20 (2.3-74)	19 (2.1-72)	0.9
Wound class			0.089
Clean (C)	300 (72.8%)	299 (78.1%)	
Clean contaminated (CC)	64 (15.5%)	52 (13.6%)	
Contaminated (CO)	49 (11.9%)	32 (8.4%)	
Type of procedure			0.12
Appendectomy	38 (9.2%)	28 (7.3%)	
Gastrointestinal/liver-biliary tract	47 (10.7%)	37 (9.6%)	
Head and neck	52 (12.6%)	71 (18.4%)	
Inguinal/scrotum	69 (16.7%)	57 (14.8%)	
Paediatric Gynaecology	6 (1.5%)	9 (2.3%)	

Table 1. Patient and preoperative data pre and post intervention

Two hundred and two (202/412, 49.0%) and 166/385 (43.1%) patients received a PAP during pre and post-intervention period respectively (p=0.09).

The majority of patient receiving an antibiotic prophylaxis gad an indication for PAP in both periods (170/202 (84.6%) vs 145/166 (87.3%), p=0.38) (**table 2**).

Indication for PAP	PRE (n=412)	POST (n=385)	p-value
PAP administered	202 (49.0%)	166 (43.1%)	0.09
PAP not administered	210 (51.0%)	219 (56.9%)	0.09
Indication for PAP (in those received PAP)	PRE (n=202)	POST (n=166)	
As recommended by guidelines	170 (84.6%)	145 (87.3%)	0.38
Not as recommended	32 (15.8%)	21 (12.7%)	0.38

Table 2. PAP comparison

In the post-intervention period, there was an increasing of correct PAP with 90/202 (44.6 %) in pre and 93 (56.0 %) in post intervention period (p=0.03) (**table 3**).

In the post intervention period, there was an increase of cefazolin use (159 (78.7%) pre vs 146 (88.0%) post, p=0.0001) with a decrease of ampicillin/sulbactam (41 (20.3%) pre vs 9 (5.4%), p=0.003) as suggested by the CPs (**table 3**). Indeed, we found that the selection of the appropriate antibiotic for prophylaxis improved in the post intervention period, both for monotherapy (111 (81.0%) for pre vs 114 (91.9%) for post, p=0.02) and combination therapy (31 (47.7 %) for pre vs 29 (69.0%) fro post, p=0.03) (**table 4**).

Correct PAP (both agent and duration)	PRE (n=202)	POST (n=166)	p-value
Yes	90 (44.6 %)	93 (56.0 %)	0.03
No	112 (55.4%)	59 (35.5 %)	0.03
Antibiotic consumption	PRE (n=202)	POST (n=166)	
Cefazolin	159 (78.7%)	146 (88.0%)	0.0001
Metronidazole	63 (31.2%)	46 (27.7%)	0.99
Amoxicillin/clavulanic acid	37 (18.3%)	21 (12.7%)	0.36
Ampicillin sulbactam	41 (20.3%)	9 (5.4%)	0.0003
Gentamicin	23 (11.4%)	11 (6.6%)	0.15
Other	7 (3.5%)	6 (3.6%)	0.7

Table 3 Correct PAP and most prescribed antibiotics in pre and post intervention periods

Also the duration of prophylaxis decreased during the post intervention period, with an increase of PAP discontinuation from 83/202 (41.0 %) in the pre-intervention period to 102 (61.4%) (<0.001) (**table 4**).

The stratification of the population by type and characteristics of the surgical procedures showed how CP was effective especially on emergent procedure and all surgical procedures involving Head/neck and thorax (**table 5**).

SSIs rate assessment showed no difference between the two analysed periods (16/412 (3.9 %) pre vs 10/385 (2.6%) post, p=0.3).

Choose of antibiotic for prophylaxis	PRE (tot=202)	POST (tot=166)	p-value
Monotherapy	**n=137**	**n=166**	
Correct	111 (81.0%)	114 (91.9%)	0.02
Not correct	26 (19.0%)	10 (8.1%)	0.02
Too broad coverage	25 (96.2%)	9 (90%)	
Not optimal for the procedure	1 (3.8%)	1 (10%)	
Combination therapy	**n=65**	**n=42**	
Correct	31 (47.7 %)	29 (69.0%)	0.03
Not correct	34 (52.3 %)	13 (31.0%)	0.03
Too broad coverage	34 (100 %)	13 (100 %)	
Not adequate for the procedure	/	/	
Discontinuation within 24 hours	**PRE (n=202)**	**POST (n=166)**	
Yes	83 (41.0 %)	102 (61.4%)	<0.001
No	119 (58.9%)	64 (38.6%)	<0.001
Treatment failure	**16 (3.9 %)**	**10 (2.6%)**	**0.30**

Table 4 Choose of antibiotic for PAP and timing of PAP discontinuation

	Pre intervention appropriate PAP (n=90)	Post intervention appropriate PAP (n=93)	p-value
Wound class			0.3
Clean (C)	48	57	
Clean contaminated (CC)	24	22	
Contaminated (CO)	18	14	
Emergent procedure	8	21	0.02
Type of procedure			
Appendectomy	16	16	0.9
Gastrointestinal/liver biliary tract	24	16	0.12
Head and neck	2	10	0.02
Inguinal/scrotum	10	5	0.15
Paediatric Gynaecology	1	4	0.18
Skin/soft tissue	11	9	0.75
Thoracic	1	9	0.03
Urologic	6	7	0.95
other	19	17	0.93

Table 5 Stratification by type and characteristics of the surgical procedures

Discussion

Perioperative antibiotic prophylaxis is the most effective intervention to prevent SSIs [1]. The most recent guidelines [9] define procedures requiring PAP, recommending narrow spectrum antibiotics as first choice for less than 24 hours for all procedures (with the exception of cardiac surgery). So far, few studies developed an antimicrobial stewardship program in children to improve antibiotic prescriptions on PAP. Three of these studies showed an improvement of antimicrobial prescriptions after the implementation of perioperative guidelines [3,6,7] while Putnam et al. reported no improvement despite multiple interventions [8].

Despite the availability of consensus guidelines designed to facilitate the appropriate use of PAP, a significant variation in this practice for the most commonly performed operations in pediatric surgery has been found [11].

On 31 January 2017 the CP (figure 2,3,4,5) for PAP was implemented and on the same day, an educational lecture was presented. Following the lecture, a pocket card was delivered to all participants. Step by step the CP details all the actions needed for administering a proper PAP. The first step to take into account for antibiotic administration is the surgical procedure; depending on the type, the site and the risk of developing surgical site infection based on CDC wound classification, an antibiotic will or will not be given to the patient.

The second step suggested is to collect medical history, looking for any infection or colonization by MRSA or other Multi-drug Resistant Organism (MDRO). The therapy in this case will be targeted for the resistant organisms isolated [9,11]. If the medical history is negative for MDRO, an empiric antibiotic regimen should be administered according the type of surgical procedure. Dose and prophylaxis duration must follow the indications detail the CP.

The drug of choice for all surgical interventions is a first generation cephalosporin alone. The association with metronidazole is recommended for surgical procedure with high risk for anaerobic bacteria contamination. Other molecules as clindamycin, gentamicin and ciprofloxacin must be reserved for patient with proven allergy to beta-lactams antibiotic.

Antibiotic first dose should be administered within 30-60 minutes before incision with the exception of vancomycin and ciprofloxacin. Due to the longer half-life they should be administered 120 minutes before the incision. An intraoperative re-dosing should be performed if the operative procedure extends beyond two half-lives of antibiotic and it should be considered in the setting of excessive blood loss (>25 mL/kg).

Further doses of antibiotics should be administered no longer than 24 hours after the end of surgical procedure. Another important aspect of this CP is that the antibiotic prophylaxis should not be continued because of the presence of a wound drain or prosthetic implant [12].

As reported by the studies mentioned above [3,6,7], in our Centre the compliance to PAP guideline improved after CP implementation. Correct PAP significantly increased from 44.6 % in pre intervention period to 56.0 %, with a change in both antibiotic first choice and duration of prophylaxis.

The choice of correct monotherapy was 81 % in pre-intervention period reaching 91.9% after CP dissemination. Cefazolin, the most prescribed antibiotic in both periods, definitely became the first choice in post intervention period with a concomitant decrease of ampicillin/sulbactam.   This change affected especially head/neck and thorax procedures. For both ampicillin/sulbactam was the drug of choice before the intervention. Indeed, PAP CP suggests cefazolin as the first-line antibiotic for all the procedures due to its activity against *S. aureus (MSSA)* and Gram-negative bacteria, its narrow-spectrum and the low cost. Ampicillin/sulbactam should be considered only an alternative for its broader spectrum [9].

Moreover, the use of correct combination therapy increased. Also, in this case, an important contribution was given by the reduction of ampicillin/sulbactam prescriptions especially in association with metronidazole. Indeed, this combination should be avoided due to their overlapping spectrum of activity against anaerobic bacteria. In the post intervention period, the combination of choice was cefazolin and metronidazole, sometimes combined with an aminoglycoside (gentamicin). The use of an aminoglycoside for surgical prophylaxis still presents room for improvement. St. Peter at al, in a prospective randomized trial, showed how a once daily dosing with the 2-drug regimen (ceftriaxone plus metronidazole) offers a more efficient, cost-effective antibiotic management in children with perforated appendicitis without compromising infection control when compared to a traditional 3-drug regimen (which includes gentamicin) [13].

Also the number of patients with a PAP stopped in 24 hours increase from 83/202 (41.0 %) in pre-intervention period to 102 (61.4%) during post intervention period.

The kind of procedures which have benefitted most from the intervention were emergent procedures. Usually, patients who undergo emergent surgical evaluation are a severely ill and for this reason surgeons are more prone to exceed the 24 hours. Indeed, this represents one of the most difficult points of implementation for an antimicrobial stewardship program. Many are the barriers identified in stopping PAP. The complexity and duration of surgical procedure, diagnostic uncertainty, inexperienced clinicians, extend in-hospital stay, patient preferences or the fear of SSIs are the most common [3,10]. The persistence of urinary catheter represents another point of

discussion. Though all the guidelines recommend stopping PAP despite the presence of a urinary catheter, many surgeons are still reluctant. This could be the reason why we have not seen, for urologic procedures, the same improvement we seen for others. However, many of the current guidelines and specialty-specific recommendations used for the pediatric population are based on old adult clinical data. It is possible that physicians may not find those guidelines relevant to their pediatric patients. Finally, confusion may exist when indication from adult guidelines are not in line with pediatric observational studies (eg inguinal hernia repair) [10].

For a further improvement in PAP compliance rate some authors [3] suggested to enforce guidelines' effect with and periodic audit by a surgeon trained in antimicrobial stewardship. This physician would monitor the choice, time and dose of PAP administration and would ensure the guidelines adherence.

Moreover, Prado et al [14] demonstrated how hospital pharmacist could have a key role participating in education activities as part of the discussion groups and in managerial actions that optimized the process of ordering, dispensing, administering, and documenting the perioperative antibiotic prophylaxis.

Despite the higher use of narrow-spectrum antibiotic for fewer days, there was no increase in treatment failures between the two analysed periods.

This study has strengths and limitations. This is the first study that evaluates the effectiveness of antimicrobial stewardship through clinical pathways 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.

The primary limitation of our study is the retrospective nature of the analysis.

Another limit was the analysis of treatment failure. We collected SSIs trough electronic medical records of our centre. If a patient had been admitted to another one we would be miss that information.

Conclusion

CPs with a proper educational intervention can be a useful tool to improve the choice of first-line antibiotic and the duration of PAP in pediatric patients.

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