

## Antimicrobial Stewardship in Pediatrics. Training, Prescribing and Surveillance: An Initiative in Outpatient Children

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### Abstract

Because of the spontaneous, incorrect or inappropriate use of Antibiotics, many infections have become resistant to treatment. The Antibiotic resistance represents a real global health emergency, which in Italy has the highest and most worrying rates in Europe.

To combat the antibiotic resistance a cultural change is necessary to which everyone is called Antibiotic Stewardship Programs (ASPs) focus on guiding paediatricians to use Antibiotic only when adequate evidence for Bacterial Respiratory Diseases (BRD) exist. The training and the correct prescription are indispensable for the success of the Antibiotic Stewardship Programs.

The purpose of this article is to highlight an initiative of Antimicrobial Stewardship in pediatrics in outpatient children and to disseminate knowledge of the appropriateness of Antibiotics prescription and of the pediatric Pharmacovigilance and to highlight the cultural and organizational difficulties for its implementation. The objectives are to promote the organization of specific training courses and research projects aimed at: 1) to improve the accuracy of BRD diagnosis, 2) to improve the appropriateness of prescribing drugs in children; 3) to highlight the antibiotic resistance increase; 4) to foster the culture of iatrogenic disease in pediatrics and the antibiotic resistance; 5) to encourage spontaneous reporting of ADRs in children; 6) to involve Paediatricians in Post-Authorization Safety Studies (PASS) according to GCP,GVP and ENCEPP Code of Conduct.

The study: "Active surveillance on the use of the Ab in children particularly in the age group from 0 to 2 years" conducted by the FP-MCRN on correct use of Antibiotics in children from 0 to 2 years showed a marked reduction in the prevalence of prescribed antibiotics, a reduction in health care costs and an improvement on prescriptive appropriateness after training courses for the FPs and continuous information to the families on the proper use, and on ADRs related to the abuse of Antibiotics in this age group.

**Keywords:** Children; Adverse Drug Reactions; Antibiotic Resistance; Pharmacovigilance; Post-Marketing Clinical Studies

### Abbreviations

ADRs: Adverse Drug Reactions; ASPs: Antibiotic Stewardship Programs; BRD: Bacterial Respiratory Diseases; GCP: Good Clinical Practice; GVP: Good Pharmacovigilance Practice; ENCEPP: European Network of Centres Pharmacoepidemiology and Pharmacovigilance; FPs: Family Pediatricians; FP-MCRN: Family Pediatricians - Medicines for Children Research Network; OsMed: Italian Observatory of Drugs; PASS: Post-Authorization Safety Studies

### Introduction

Antibiotics are the most prescribed drugs in pediatrics especially in the outpatients. Very often the prescriptions are inappropriate and unnecessary due to viral diseases that do not require antibiotic therapy. Incorrect use of Antibiotic exposes children to drug-related adverse events and favors the onset of drug-resistant bacteria pathogens [1].

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Because of the spontaneous, incorrect or inappropriate use of Antibiotics, many infections have become resistant to treatment. The Antibiotic resistance represents a real global health emergency, which in Italy has the highest and most worrying rates in Europe. Antimicrobial resistance is a public health problem. In fact the infections caused by resistant bacteria lead about 25,000 deaths each year in Europe. In children, a significant increase in the prevalence of this type of infection has occurred in the last two decades.

Since there are no new antibiotics available and the number of targeted studies on antibiotics in children is few, it become important to implement strategies to preserve the efficacy of existing antibiotics, especially in the extra-hospital setting [2].

Antimicrobial Stewardship Programs (ASPs) have been created in many hospitals in an effort to curtail and optimize antibiotic use.

In 2016, the guidelines for the implementation of ASPs by the Infectious Diseases Society of America were updated and defined as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration”. In recent years there have been efforts by both the American Academy of Pediatrics and the Pediatric Infectious Diseases Society to advance and implement pediatric ASPs within various health care settings. Pediatric-focused ASPs are necessary because of the differences in antimicrobial need and use among this patient population, unique considerations and dosing, vulnerability for resistance due to a lifetime of antibiotic exposure, and the increased risk of adverse events [3].

Starting in January 2017, the requirements for the new ASPs, have been made effective. This standard provides specifics with regard to elements, including accountability, leadership, education, and core elements, that will be required. The opportunity for expansion is clear, because ASPs are crucial to the improvement of clinical outcomes and patient safety by combating antibiotic resistance, improving the appropriate use of antimicrobials, and reducing adverse events [3].

### **Antibiotic Stewardship Programs**

To combat antibiotic resistance a cultural change is necessary to which everyone is called Antibiotic Stewardship Programs focus on guiding pediatricians to use Antibiotic only when adequate evidence for Bacterial Infectious Diseases exist. The training and the correct prescription are indispensable for the success of the Antibiotic Stewardship Programs [1-4]. Furthermore there is a need for rapid diagnostic tests for the correct diagnosis of bacterial infectious diseases [5].

Successfully ASPs have a significant impact on the reduction of antibiotic use in children, on costs and on prescription errors, without negative impacts on patient safety, and consequently better results for this fragile population. Pediatric ASPs should not be limited to the hospital and should be effective in reducing antibiotic abuse especially in community settings [2].

In the United States each year at least 23,000 people die each year from infections caused by resistant bacteria. Italian data of 2016 confirmed the excessive use of antibiotics in the pediatric population [1,2]. Furthermore, it is clear that the antibiotic resistance rate is strongly linked to the use of antibiotics in primary care [6].

The National Institute for Health Research (NIH) in the UK reviewed the evidence and produced a practical guide for the prescription of Antibiotics for respiratory tract infections.

Spurling, *et al.* have shown that a delayed prescription of antibiotics (prescription of antibiotics if the fever and symptoms persist for more than 48 - 72 hours) reduces the consumption of antibiotics by 46% compared to an immediate prescription strategy in children with URTI. Therefore it is the pediatrician's responsibility to prescribe antibiotic therapy or simply treat the symptoms and offer further observation [7-9].

From the OsMed in the last four years (2012-2016) despite the campaigns undertaken by AIFA there is an increase in the consumption, drug spending and prescription unsuitability for Antibiotic in children [OsMed 2016- beta-lactamic inhibitor: 8.7 DDD/1000/ab die; macrolides 3.7 DDD/1000/ab die; fluorochinolonic 2.8 DDD/1000/ab die] with an increase of ADRs related to them. After the vaccines, in fact, Antibiotics are the class of medications with higher incidences of ADRs, especially skin and allergic type, with manifestations of hypersensitivity of variable intensity, to serious reactions such as anaphylactic shock. In this class of medication, from the numerous reports of oral formulation, cefaclor and amoxicillin/clavulanate are prominent while among injectable forms, ceftriaxone is the most noted [10-12].

The risk of adverse drug reactions (ADRs) in children has become a public health concern. In paediatric populations the problem is enhanced by the fact that ADRs are rarely represented in Randomized Controlled Clinical Trials (RCCTs). The differences such as pharmacokinetics, pharmacodynamics, epidemiology and co-medication between children and adults in general as well as between children of different age groups, the adverse event and ADR profiles may be different in children and adults. In addition most genetic and rare disease have a childhood onset which adds to the diversity of this population from the adult one [10-13].

Pediatricians should be aware that inappropriate use of drugs increases the risk of adverse reactions and should be much more careful when administering antibiotics to their patients [14-17].

To address the issue of off-label and unlicensed prescribing in children, European regulations were issued with the scope of obliging pharmaceutical companies willing to register new compounds, or indications and formulations, for paediatric use, to submit "paediatric investigation plans" from January 2007 [18].

In Italy regulatory authorities have increased efforts to enhance awareness of health professionals about the importance of their reporting of ADRs as a significant contribution towards the process of pediatric Pharmacovigilance. Post-authorization safety studies (PASS) guarantee much more reliable value of the risk of ADR than those resulting from spontaneous reports [19-26].

Most (70 - 80%) of respiratory tract infections cases have a viral cause and not bacterial, thus Antibiotics are not effective for treating them. Therefore, the high Antibiotic prescriptions in the pediatric population for respiratory diseases such as sore throat, cough and cold mainly caused by viruses is a recognized indicator of inappropriate prescribing [27-30].

It is more worrying that approximately 50% of Antibiotic prescriptions for children given by primary care physicians are not necessary [6]. The link between Antibiotic use and bacterial resistance is well known thus antibiotic over prescribing has a significant impact on public health [6].

The purpose of this article is to highlight an initiative of Antimicrobial Stewardship in pediatrics in outpatient children and to disseminate knowledge of the appropriateness of Antibiotics prescription and of the pediatric Pharmacovigilance and to highlight the cultural and organizational difficulties for its implementation. The objectives are to promote the organization of specific training courses and research projects aimed at: 1) to improve the accuracy of BRD diagnosis, 2) to improve the appropriateness of prescribing drugs in children; 3) to highlight the antibiotic resistance increase; 4) to foster the culture of iatrogenic disease in pediatrics; 5) to encourage spontaneous reporting of ADRs in children; 6) to involve Paediatricians in Post-Authorization Safety Studies (PASS) according to GCP, GVP and ENCEPP Code of Conduct.

In this context relevant proactive roles are being played by the FP-MCRN (Family Paediatricians-Medicines for Children Research Network) to develop new methodological approaches and optimise use of available resources, to enable the system to recognise as early as possible issues of efficacy and safety reducing the health risks for such fragile populations as children [11-16].

The FP-MCRN, member of ENPREMA and of ENCEPP, has become an expert in pediatric pharmacovigilance studies, with an improvement in both training and research methodology. Through specific training (TRAINING AND EDUCATIONAL COURSES) Family Pediatricians (FPs) acquire in fact a correct research methodology according to GCP and GVP (Module VIII of the Good Pharmacovigilance Practices on Post-Authorization Safety Studies) standards, to the Ethical Consideration and to the Code of Conduct of ENCePP for the conduct of clinical studies on children. Family Pediatricians (FPs) have a close involvement with children and their families so it becomes easier both the capacity to involve outpatients in clinical trials and to give more accurate information on the correct use of pediatric drugs [11-16].

### **Post-Authorization Safety Studies (PASS)**

PAS studies are useful as they give estimates of the incidence of ADR that cannot be obtained from spontaneous reports. In these studies a significant role can be played by the FPs [11-16].

A project conceived, structured and implemented by the family pediatricians was approved by the AIFA and financed through the regional funds (Molise) available for the years 2008 and 2009 [31,32].

From the OsMed data emerges a “over-prescription” of antibiotics, especially in the age group between 0 and 2 years an increase in ADRs.

Hence the need for a research project, Phase IV, managed and coordinated in full for the first time with the Family Pediatrician, that can foresee on one hand training and information regarding the prescription appropriateness, the proper use of antibiotics in children and possible iatrogenic pathologies caused by their improper use, the other to constitute a territorial survey in the prescriptive appropriateness and safety of these drugs in children aimed at evaluating the risk-benefit balance on usage. The study exceeded the limits of OsMed data both for diagnosis and for the evaluation of prescriptions in the various pediatric age groups (especially 0-2 years) [32-34].

### Material and Method

The study conducted by 37 Family Pediatricians consisted of three phases:

1. In the first phase (retrospective) we assessed the prevalence of antibiotic prescriptions in the 0 to 2 years age group, the type of antibiotic used and any ADRs;
2. The second phase was that of training/information to the FPs and families on prescriptive appropriateness and proper use;
3. In the third phase the Prevalence of prescriptions has been reassessed and the type of antibiotic used and the possible ADRs (after the training phase). These data had been compared to the data of prevalence of the first phase [32-35].

### Clinical Signs

We suggest these clinical signs for the diagnosis of Bacterial Respiratory Diseases (BRD) in children in the extra hospital setting and the Pediatric Treatment Recommendations for their treatment.

Children with a clear diagnosis of BRD will be enrolled, according to clinical signs: acute otitis media, acute sinusitis, pharyngotonsillitis [group A beta-hemolytic streptococcus (positive rapid Strep A test)], lower respiratory tract infections (LRTIs), etc. Pharyngotonsillitis (beta-hemolytic streptococcus group a) will be based on sore throat, trouble or painful swallowing, enlarged, painful neck glands, fever, change in voice, headache.

Otitis media will be diagnosed in children with fever and/or otalgia, bulging, and hyperemia of the tympanum.

Acute sinusitis will be based on fever, purulent rhinorrhea, postnasal drip, cough lasting more than 10 days.

LRTIs will be diagnosed in children with cough, abnormal breath sounds, wheezes, and crackles.

Diagnosis of pneumonia will be based on clinical findings (fever or cough, tachypnea, dyspnea or respiratory distress, and breathing with grunting or wheezing with rales) and confirmed by chest radiography (infiltration or consolidation).

Presence of fever and presence or absence of pharyngeal hyperemia, myalgia, hyperemia of eardrums, rhinorrhea or postnasal drip, coughing, and normal breath sounds will be recorded.

### Pediatric Treatment Recommendations (PTR)

Bacterial Infectious Disease diagnosis and Antibiotic treatment must be done according to International GLs, Pediatric Treatment Recommendations (PTR) CDC.

International and National GL for the Institute of Health and Clinical Excellence (NICE), 2008 - affirmed that:

- In the case of a child with a sore throat, though there are other signs of infection concomitant respiratory tract (nasal discharge, cough) it is certainly a viral disease.
- All available guidelines support antibiotic therapy only for strep throat infection associated with beta-hemolytic streptococcus group A (SBEA).
- In children “at risk” of complications due to the presence of a pre-existing co-morbidities, in which antibiotics are to be used for the treatment of each type of fever, suffering from: heart, lung, kidney or liver pad, diseases neuromuscular, immunosuppression, cystic fibrosis, prematurity.

New NICE 2015 Guidelines: Antibiotic Stewardship: systems and processes for effective antimicrobial medicines use [NG15] recommend the effective and rational use of antibiotics in children, youth and adults.

They also suggest that physicians devote time to discussions with patients about the nature of their likely illness, on the benefits and risks of an immediate antimicrobial prescription, on alternative options such as watchful waiting and/or a delayed prescription and on the reasons why prescription an antibiotic may not be the best option for them - for example, if they have a self-limiting respiratory tract infection”.

It is therefore necessary that parents should consult their pediatricians before administering drugs to their children.

### **Acute rhinosinusitis (Rh)**

If a bacterial infection is established: Amoxicillin or amoxicillin/clavulanate remain first-line therapy. Recommendations for treatment of children with a history of type I hypersensitivity to penicillin vary. In children who are vomiting or who cannot tolerate oral medication, a single dose of ceftriaxone can be used.

### **Acute otitis media (AOM)**

Mild cases with unilateral symptoms in children 6 - 23 months of age or unilateral or bilateral symptoms in children > 2 years may be appropriate for alertness.

Amoxicillin remains first line therapy for children who have not received amoxicillin within the past 30 days. Amoxicillin/clavulanate is recommended if amoxicillin has been taken within the past 30 days, if the child has a history of recurrent AOM unresponsive to amoxicillin. For children with a hypersensitivity to penicillin: cefuroxime, cefpodoxime, or ceftriaxone.

### **Pharyngitis (Ph)**

Amoxicillin and penicillin V remain first-line therapy (recommended treatment is 10 days). For children with hypersensitivity to penicillin: clarithromycin, or azithromycin are recommended.

### **Bronchitis (Br), Bronchopneumonia (BPn), Bacterial Pneumonia (Pn)**

Amoxicillin remain first-line therapy (30 - 90 mg/kg/die in 2 - 3 doses for 7 - 10 days).

### **Atypical pneumonia (APn)**

Clarithromycin remain first-line therapy (15 mg/kg/die in 2 doses for 7 - 14 days).

### **Common cold or non-specific upper respiratory tract infection (URI) and Bronchiolitis (Brc)**

Antibiotic should be not prescribed for these conditions.

## **Results and Discussion**

The study showed, in the first phase, that the prevalence of antibiotics prescribed by 37 FP from 0 - 2 years old (4060 children) was 83% (the number of children with at least one prescription was 3339) with a number of prescriptions of 7114 (the number of items prescribed was 8367).

After the training phase, in the third phase was detected a 56% prevalence (the number of children was 4116. The number of children treated was 2327) with a significant decrease (-27%) compared to 83% in the first phase. In addition there has been a reduction of 2938 prescriptions (the number of prescriptions was 4176) and a reduction of 2975 prescribed items (the number of items prescribed was 5392) with savings of € 18,854.23 (60950.15 EUR in the first phase and 42095.92 EUR in the second phase).

Finally there was also an improvement in the appropriateness of prescriptions according to the Guide lines: Amoxicillin (38%), followed by Amoxi/clavulanate (29.3%), Macrolides (16.3%), and Cephalosporins (15.2%). There were no ADRs in the two reference years.

In light of the results before mentioned, there was a clear necessity to undertake an information campaign on the appropriate use of this class of medication, either through the organization of training/information events, and through the dissemination of national and international guidelines on the correct antibiotic use in therapy.

As it is known, in fact, an inappropriate use of antibiotics is a potential risk not only for individual health, with an increase in exposure to the risk of adverse reactions, but also for public health resulting in development of resistance, and the problem of costs to the National Health Service.

Among the main unjustified use of antibiotics, highlighted is the fact of the high use of this class of medication for the treatment of colds, flu and other respiratory infections, which for 80% of cases are due to viral and not bacterial, especially in the 0 to 2 years age group, and therefore antibiotics are not effective for treating them.

The high prescription of antibiotics in the pediatric population for childhood respiratory diseases such as strep throat, acute cough, cold, mainly caused by viruses is a recognized indicator of inappropriate prescribing. It then proceeded to give relief to these aspects of inappropriateness prescriptive disseminating the main aspects of national and international guidelines for pediatricians. In particular, it was forwarded, as shown in the international guidelines (NICE 2008 -2015), in the case of a child with a sore throat, though there are other signs of infection concomitant respiratory tract (nasal discharge, cough) is certainly a viral disease.

The Antibiotic resistance represents a real global health emergency, which in Italy has the highest and most worrying rates in Europe. To combat this threat, a cultural change is necessary to which everyone is called: using Antibiotic well is the responsibility of the individual towards his own health, to always have effective drugs available for his pathology, and it is also a collective responsibility, since encouraging the development of resistance puts the health of the community seriously at risk.

The ASPs are mainly used to guide pediatricians to use antibiotics only when there is clear evidence for the diagnosis of BRD. The training and the correct prescription are indispensable for the success of the Antibiotic Stewardship Programs [1-4]. Furthermore there is a need for rapid diagnostic tests for the correct diagnosis of bacterial infectious diseases [5].

The aim of this study was to implement strategies to optimize the use of Antibiotics therapy in extra hospital settings to reduce the Antibiotic resistance (reduction of relapses) and ADRs. Through our study we only wanted to provide appropriate and valid support for diagnostic accuracy to FPs. All aimed at reducing the prevalence of Antibiotic prescriptions in out-patients children and offering a ASPs model for Italian FPs that, in addition to providing training and information (FPs and families), can be considered a valid support for the management of BRD.

Through the results of this study, we'd like to suggest a diagnostic/therapeutic pathways that optimize the efficacy and cost-effectiveness of the use of Antibiotics in outpatient children. Clinical symptoms, compared with the reference GLs, will always be at the base for a better diagnostic accuracy as a model for the management of BRD in children in the extra hospital setting.

We had suggest on the one hand, training courses for FPs and informational activities directed to families about the correct use of Antibiotics and any iatrogenic illness caused by their improper use will provided, on the other hand the study represented a territorial survey on the prescriptive appropriateness and safety of Antibiotics in children, aimed at evaluating the risk-benefit balance on usage.

The event has paid particular attention to the importance of promoting research and pharmacological trial culture, by building an even higher skill aimed especially at protecting the most vulnerable as the pediatric population, and its attention to the culture of iatrogenic disease for a careful analysis of the risk/benefit ratio of medication for use in children. Also pediatricians colleagues were stimulated to major reporting of adverse reactions in children.

The aims of this pilot project were illustrated and announced, first the data of the pediatric antibiotic prescriptions, promoting awareness on appropriateness of prescription through the communication of the above mentioned national and international guidelines.

Finally it highlights the information/ training work done by Family Pediatricians with the families of their patients to stress the concept of the proper use of medicines in children, and in particular of antibiotics in the most vulnerable age group, avoiding the “do it yourself” by families, that expose children to the risk of adverse symptoms.

### Conclusions

The rationale of the study was to generate a diagnostic/therapeutic pathway that can be a model for all Italian FPs through a determinant analysis and formulate a valid model for a correct management of BRD in children in the extra-hospital setting to reduce the Antibiotic resistance and ADRs.

This study contributed to overcome the limits of the inadequate assessment of prescriptions in the various pediatric age groups, especially in 0-2 year age group.

The possible impact on the studied population (children):

- 1) A considerable translational relevance improving the prescriptions appropriateness by ensuring an increased knowledge and facilitating the transfer of the best scientific evidence to the professional practice
- 2) An improvement of a correct FP management of BRD ensuring adequate regulatory effects through an improving of:
  - a. The prescription appropriateness after specific training courses for FPs according to the GLs requirements for a correct diagnosis and therapy
  - b. A therapeutic adherence in term of exact dosage, timing and duration of administration (therapeutic appropriateness)
- 3) A reduction of the Antibiotic resistance (reduction of relapses) that has become a public health emergence
- 4) An improved Family Communication (FC) with a reduction of Antibiotic self prescriptions
- 5) A reduction of the possible number of ADRs associated with Antibiotic administrations
- 6) A reduction of the government spending by decreasing prescriptions and inappropriate Hospital admissions.

Therefore it becomes very important to conduct the research in pediatric ambulatories in which the FP of the area has a more adequate opportunity compared to hospital / university to carry out results of the research especially regarding some illnesses in some categories of medicines that do not require hospital admittance especially in children. Another innovation is that the study will directly involve families who must learn to know the proper use of Antibiotics and to contact the FPs before administering Antibiotics to their children [32-35].

The main objective of Family Pediatricians should be to appropriate the research aspect in order to ensure greater knowledge and better decision-making. The FP-MCRN must be ready for specific training so that it can answer with competence for independent research. Quality and ethics of research are becoming fundamental for territorial pediatrics and important end points for the correct treatment of BRD in the pediatric age groups [32-35].

Overall, the importance of proper training is clear for pediatrician's appropriateness of prescribing antibiotics for this vulnerable class of children, correct information for families on knowledge and experience of pediatric drugs and the importance of always consulting the pediatrician before "misuse" of medication that do not resolve the clinical solution but rather expose these young patients at risk [32-35].

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### **Conflict of Interest**

The authors declare that they have no competing interests.

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