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Decreased Antibiotic Prescription in an Italian Pediatric Population With Nonspecific and Persistent Upper Respiratory Tract Infections by Use of a Point-of-Care White Blood Cell Count, in Addition to Antibiotic Delayed Prescription Strategy

Luigi Cioffi, MD[1], Raffaele Limauro, MD[1], Roberto Sassi, MD[1], Antonio Boccazzi, MD[2], and Donatella del Gaizo, MD, PhD[1]

Abstract

The aim of this study was to test, in delayed antibiotic strategy, if the usages of a point-of-care leukocyte count would significantly decrease the prescription rate of antibiotics for children with nonspecific upper respiratory tract infections. A prospective clinical trial was performed in 23 primary care pediatric doctors' offices on children with nonspecific upper respiratory tract infection with fever for at least 48 hours. The children were randomized into 2 groups: one using a point-of-care white blood cell (WBC) count as guidance and the other prescribing antibiotics to all children, according to delayed antibiotics prescription strategy. A total of 792 patients participated. In the WBC group (n = 437), 56 patients had WBC >15 000/mm^3 and received antibiotics. At follow-up, an additional 44 children received antibiotics. In the control group (n = 355), antibiotics were prescribed to all children. The reduction of antibiotic usage was 77% between the groups. The decrease in antibiotic usage gave no influence on recovery, complications, or other medical outcome.

Keywords

general pediatrics, infectious diseases, allergy/immunology, medical education, critical care

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Introduction

In the United States, each year at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23 000 people die as a direct result of those infections.[1] Using antibiotics correctly is literally a matter of life and death.[2] Italy has one of the highest antibiotic prescription rates in Europe.[3] However, comparing statistics from 2010 showed similar prescription rate in the United States as in Italy.[3-5] Recent data from 2013 in the Italian pediatric population confirmed the overuse of antibiotics.[6] Common indications were acute infections of the respiratory tracts and acute infections of the lower urinary tracts.[6]

Upper respiratory tract infections (URTIs) are one of the most common reasons for consultation in pediatric primary care. Controlled studies have shown that antibiotic treatment does not change the prognosis, does not reduce the rate of complications, and side effects are more common in treated patients.[7] International comparisons clearly indicate that the rate of antibiotic resistance is strongly linked to the use of antibiotics in primary care.[3] In 2008, the National Institute for Health and Clinical Excellence in the United Kingdom reviewed the evidence and produced a practical guide for the prescription of

[1]Federazione Italiana Medici Pediatri, Naples, Italy
[2]IRCCS Policlinico Ca Granda, Milan, Italy

Corresponding Author:
Luigi Cioffi, Via Artiaco 1c, 80078 Pozzuoli (NA), Italy.
Email: lcioffi@libero.it

antibiotics for respiratory tract infections.[7] The Guideline Development Group recognized a concern of general practitioners and patients regarding the danger of developing complications. While most patients may be reassured that they are not at risk of major complications, the difficulty for prescribers lies in identifying the small number of patients who will suffer severe and/or prolonged illness or, more rarely, will develop complications.[7] Spurling et al showed that a strategy of delayed antibiotic prescription (prescription of antibiotics if fever and symptoms persist for more than 48-72 hours) reduces the consumption of antibiotics by 46% compared to a strategy of immediate prescription for adults and children with URTIs.[8] Similar recommendation exists today from the Centers for Disease Control and Prevention in the United States.[9] Even in accordance with all guidelines, it is the responsibility of the pediatrician to make the right decision for children with persistent illness to either prescribe antibiotic therapy or just treat the symptoms and offer additional observation.[10-12]

Another probable cause of inappropriate antibiotic prescription is that the family pediatrician does not have a tool in his office to identify patients at potential higher risk for a bacterial etiology. White blood cells (WBC) count has been used for this purpose.[13,14] In a study on 1956 children, Casey et al[14] showed a significant reduction of antibiotic use in URTIs and nonspecific febrile illnesses without adverse outcomes using a standardized procedure and selective WBC testing.

We performed a randomized and controlled study in pediatric patients with persistent fever in nonspecific URTIs to assess whether the use of a point-of-care test (POCT) for WBC count, as a complement to the clinical investigation, would be safe and effective to additionally reduce antibiotic therapy without adverse differences in clinical outcome. Such a system is available from HemoCue AB (Ängelholm, Sweden). The HemoCue WBC System provides a reliable count in 3 minutes from a capillary sample. The system has previously been evaluated in a pediatric population showing perfect correlation with a large laboratory cell counter.[15]

Materials and Methods

A prospective randomized clinical trial on children with nonspecific URTIs in primary care pediatric doctor's offices was performed from October 2012 to April 2013. Twenty-three pediatricians on 23 different sites, well distributed in the region of Campania, Italy, participated in the study. The inclusion criteria were patients with nonspecific URTIs, observed for the first time having fever for at least 48 hours together with symptoms of coughing, sneezing, muscle pain, runny mucus, or purulent mucous (lasting less than 10 days), a finding of hyperemia of the pharynx and/or eardrums, and normal breath sounds.

Excluded in the enrollment were children with congenital or acquired immunodeficiency, chronic lung diseases (cystic fibrosis, ciliary dyskinesia, bronchodisplasie, chronic bronchiectasis, congenital or acquired), and leukemia, as well as children with a clear diagnose of acute otitis media, acute sinusitis, group A β-hemolytic streptococcus (positive rapid Strep A test), and lower respiratory tract infections (LRTIs). Otitis media was based on fever and/or otalgia, bulging, and hyperemia of the tympanum. For acute sinusitis the considered symptoms were fever, purulent rhinorrhea, postnasal drip, cough lasting more than 10 days or worsening after the clinical symptoms improving period. LRTIs were diagnosed in children with cough, abnormal breath sounds, wheezes, and crackles.

The enrolled children were randomized into 2 groups: the experimental group using the point-of-care WBC count as part of the clinical investigation (Leukocyte group) and the control group getting antibiotic treatment according to delayed antibiotics prescription strategy (Control group).[7,8] The enrollment was carried out after obtaining parental consent.

During the 6 months of observation, each pediatrician performed clinical evaluations of 60 patients, all reported in real time. The patients with nonspecific URTIs were divided into 3 age groups: 2 to 4 years, 4 to 8 years, and 8 to 14 years, with 20 patients in each age group.

The pediatrician first opened a randomized sealed envelope and assigned the child to his group. Information regarding age of the child, sex, birth weight, breastfeeding, parental smoking, school attendance, parental atopy, recurrence of URTI together with the records of the clinical evaluation was noted in the data acquisition card. Presence of fever and presence or absence of pharyngeal hyperemia, myalgia, hyperemia of eardrums, rhinorrhea or postnasal drip, coughing, and normal breath sounds were recorded. The children in the Control group were offered antibiotic treatment.

In the Leukocyte group, the WBC count was measured immediately in the doctor's office with the HemoCue WBC system. Children with a WBC count $<15\,000/mm^3$ were symptomatically treated. Pediatricians were given the choice whether or not to prescribe antibiotics for children with a WBC count $>15\,000/mm^3$. A WBC count of $15\,000/mm^3$ was used as cutoff for antibiotic prescription as already reported by other authors.[14,15]

All children were followed-up after 48 hours from the first visit, either with an office visit or a telephone contact, investigating if patients had become afebrile,

Table 1. Characteristics of Symptoms in the Leukocyte Group and the Control Group.

	Leukocyte Group	Control Group
N	437	355
Mean age, years	5.92	5.91
Minimum age, years	2	2
Maximum age, years	14	13.9
Mean duration of symptoms, days	3.28	3.27
Fever (°C)		
37.5-38.5	131	111
38.5-39.5	260	204
>39.5	46	40
Cough	385	336
Pharyngeal hyperemia	331	291
Pains/myalgia	242	165
Ear drum hyperemic	104	113
Purulent rhinorrhea	11	14
Chest sounds	149	127

eventual complications, and if visit to emergency room or hospitalization had occurred. In the Leukocyte group, the patients feeling worse or still febrile were given antibiotics.

On the seventh day a final doctors' office visit was carried out for all the patients in both groups. In this follow-up, recovery, complications, and any side effects of antibiotic therapy were investigated and noted in the data acquisition card. Recovery was defined as absence of fever, absence of pharyngeal hyperemia, absence of rhinorrhea and sneezing, decreased coughing, and normal breath sounds.

EpiInfo version 7 (Centers for Diseases Control and Prevention, Atlanta, GA) was used as support for the randomization to guarantee there was no impact on study outcome by study population's anamnestic and clinical factors. Each age group was subdivided into 2 groups of 10 patients, generated randomly by a computer. At the start of the study, participant randomization was sent to each pediatrician in sealed envelopes. Sample size was statistically calculated using EpiInfo for cohort studies by calculating an average population of 23 000 children and average prevalence of 23% of respiratory tract infection. In order to have a study with a confidence interval of 95% and a power of 80%, at least 250 participants should be included in each study group.

The Family Pediatricians Medicines for Children Research Network Scientific Study Center performed statistical analysis and quality control. Comparisons between the 2 groups (Leukocyte group and Control group) were performed by Student's *t* tests and relative risk using MedCalc version 13 (2014; Ostend, Belgium). A *P* value of <.05 was considered significant.

Results

Twenty-three primary care pediatricians from the district of Campania in Italy participated in this prospective randomized study. A total of 990 children with symptoms of nonspecific URTIs were first enrolled during a period of 6 months. A total of 198 of those were excluded because they did not meet the enrollment criteria. Of those, 185 patients visited the pediatrician before the third day (before 48 hours) of fever and 13 children had a clear indication of a severe bacterial infection. A general scheme is presented in Figure 1 (available online at http://gph.sagepub.com/supplemental).

A total of 792 children aged between 2 and 14 years were finally enrolled. A total of 437 patients were enrolled in the Leukocyte group and 355 in the Control group. There was no difference in the anamnestic risk or in the clinical evaluation, and both groups had similar distribution of age and fever (Table 1). The distribution of the leukocyte (WBC) count for the Leukocyte group is presented in Figure 2 (available online at http://gph.sagepub.com/supplemental).

In the Leukocyte group, 381 of 437 children had a WBC count of <15 000/mm^3. They were all treated symptomatically at the first visit.

At the 48-hour follow-up, 336 of 381 children (88%) had become afebrile and 45 of the 381 children (12%) still had a fever. Eight of the afebrile children were still symptomatic for URTIs. Of the still febrile children, 44 received antibiotic therapy.

On the seventh day follow-up 328 patients (86%) were considered recovered. Remarkable to note is that as many as 37 of the 44 patients receiving antibiotic therapy were not considered recovered. Eight patients

Table 2. Summary of Outcomes.

	Leukocyte Group		Control Group	
Leukocyte count	<15 000/mm^3		—	
N	381		355	
Afebrile after 48 hours	338	89%	329	93%
Recovery after 7 days	328	86%	312	88%
Not recovered after 7 days	53	14%	43	12%
Hospitalization	6	1.6%	2	0.6%

from the 44 receiving antibiotics reported complications: 4 with acute otitis media, 3 with pneumonia, and 1 with sinusitis. Of those 3 with pneumonia, 1 was hospitalized. Totally, 6 of 381 patients were hospitalized, 1 of 337 (no antibiotic) for asthma and 5 of 44 (antibiotic) for high temperature including the one with pneumonia. Nine children had side effects, mainly diarrhea, related to antibiotic therapy. A summary of the clinical outcomes is provided in Table 2.

Fifty-six of 437 children (13%) had a WBC count >15 000/mm^3. Those 56 patients were treated with antibiotics as they were considered at higher risk of bacterial infection.[14,15] They were included in the antibiotic statistics, but they were excluded from the outcome statistics because they were treated "medically" as the control group. After 48 hours, 50 of those (89%) had become afebrile and after 7 days 41 (73%) children had recovered. One child was hospitalized (1.8%). Two of the patients (3.6%) experienced diarrhea during the antibiotic therapy.

Finally, of the 437 children of the experimental Leukocyte group, antibiotic was given to a total of 100 childrens, 56 with a WBC count >15 000/mm^3 and 44 with WBC count <15 000/mm^3 (48-hour follow-up). Totally, in the experimental Leukocyte group, only 23% received antibiotic treatment.

In the Control group (n = 355), all patients (100%) received antibiotic treatment according to the delayed antibiotics prescription strategy.[7,8] A total of 329 (93%) patients were found to be afebrile at the 48-hour follow-up. On the seventh day follow-up, 312 (88%) had recovered. Two patients, both afebrile and with no complications, were hospitalized (0.6%). Eight children showed complications: 4 with acute otitis media (2 afebrile) and 4 had pneumonia (with fever). Thirteen patients (3.7%) experienced side effects related to the antibiotic therapy.

In pediatric patients with nonspecific URTIs and with the help of the POCT WBC count, a 77% reduction of antibiotic prescription was observed compared to the Control group.

No difference in recovery ($P = .5$, relative risk 0.98) or in the number of patients becoming afebrile ($P = .1$, relative risk 0.96) was observed between the Leukocyte group (<15 000/mm^3) and the Control group. A small increase in hospitalization from 2 to 6 individuals between the 2 groups was found but no statistical difference was proven ($P = .2$, relative risk 0.98).

In summary, by adding a point-of-care WBC count to the ordinary clinical investigation together with a 48-hour follow-up by phone or office revisit, prescription of antibiotics could substantially be reduced without any significant difference in terms of recovery, complications, or hospitalization.

Discussion

This is one of the first prospective randomized studies on children with nonspecific URTIs that found a significant decrease in antibiotic prescription rate using delayed antibiotic therapy as a Control group. Usage of a point-of-care WBC count as a complement to the clinical investigation substantially reduces antibiotic prescription. The most important finding was no adverse consequences on recovery and outcome for the patient compared to the Control group where all children received antibiotics.

Many attempts have been made to reduce antibiotic prescription. Guidelines and campaigns have been established in order to obtain a shift in clinical practice and the antibiotic prescription pattern. A decline of 36% in antibiotic use for young children with acute respiratory tract infections over a decade has been reached.[16] However, despite guidelines, information, and campaigns there is still an overuse of antibiotics.

As a complement to the clinical investigation the use of diagnostic markers such as WBC, C-reactive protein, and other inflammation markers could serve as an aid to distinguish between bacterial and viral infections.[17] A European study showed that physicians with access to C-reactive protein tests significantly reduced antibiotic prescription in patients with rhinosinusitis.[18] We decided to use the WBC count because of ease of use and cost. Earlier, Casey et al[14] showed that with a leukocyte count there is a significant reduction of prescription of

antibiotics for children with infections of the upper respiratory tract. The present study not only confirmed the mentioned results but also introduced a standardized method to be used at doctors' offices.

On children with URTIs, usage of a point-of-care WBC count can help identifying the high bacterial infection risk patients. The reduction of the prescription rate was 77% compared to existing practice.[3,7,9] A reduction of incongruous antibiotic prescription would lead to a potential decrease of antimicrobial resistance and also lead to a reduction of pharmaceutical spending.

It can always be discussed if it was appropriate to prescribe antibiotics to all patients in our Control group. The main reason was that we wanted to show that the reductions of prescription were safe and effective for the patients giving no adverse differences in clinical outcome. Prescribing antibiotics after fever >48 to 72 hours in children with persistent URTIs is a common practice in Italy, but it is also an event reported in other studies.[8]

We could have used other inflammation markers but decided to use the HemoCue WBC System because it is easy to handle, cheap, and gives a result within 3 minutes, and in addition, a WBC count is a well-known marker to all clinicians. The study showed the efficacy of using the WBC POCT method directly at the pediatricians' offices to additionally reduce the antibiotic prescription in delayed antibiotic therapy.

Conclusions

Reduction of inappropriate use of antibiotics is important in avoiding antibiotic resistance. This study in pediatric primary care has highlighted the inappropriateness of antibiotic therapy in patients with persistent URTIs. By adding a point-of-care WBC count as a part of the clinical investigation on children having fever and symptoms for at least 48 hours, the prescription of antibiotics in a pediatric setting could be significantly reduced. The decrease in antibiotic usage gave no influence on recovery, complications, or other medical outcomes.

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Author Contributions

LC: contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
RL: contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
RS: contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
AB: contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
DG: contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy

Declaration of Conflicting Interests

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