Advs Exp. Medicine, Biology - Neuroscience and Respiration (2016) 20: 25–31
DOI 10.1007/5584_2015_198

Published online: 23 January 2016

Antibiotic Prescription Practices Among Children with Influenza

A. Nitsch-Osuch, E. Gyrczuk, A. Wardyn, K. Życinska, and L. Brydak

Abstract

The important factor in the development of resistance to antibiotics is their overuse, especially for viral respiratory infections. The aim of the study was to find out the frequency of the antibiotic therapy administrated to children with influenza. A total of 114 children younger than 59 months seeking care for the acute respiratory tract infection was enrolled into the study. The patients had influenza-like symptoms: fever $>$ 38 °C, cough, and sore throat of less than 4 days duration. Nasal and pharyngeal swabs were tested for influenza A and B virus with a real-time PCR. Thirty six cases of influenza were diagnosed: 34 of influenza A (H3N2) and 2 of influenza B. The rate of influenza infection was 32 % in the study group. The antibiotic therapy was ordered for 58 % patients with influenza. Antibiotics were given less frequently in the outpatient setting (33 %) compared with the hospitalized patients (93 %) ($p < 0.05$). The most often administrated antibiotics were amoxicillin with clavulanic acid, cefuroxime, and amoxicillin. None of the patients received oseltamivir. Antibiotics were overused, while antivirals were underused among children with influenza. To improve health care quality, more efforts in the diagnosis of influenza and the appropriate use of antimicrobials and antivirals are required.

Keywords

Antibiotics • Antimicrobials • Antivirals • Children • Infection • Influenza • Neuraminidase inhibitors • Resistance • Respiratory tract

A. Nitsch-Osuch (✉), E. Gyrczuk, A. Wardyn, and K. Życinska
Department of Family Medicine, Medical University of Warsaw, 1a Banacha St., 02-097 Warsaw, Poland
e-mail: anitsch@wum.edu.pl

L. Brydak
National Influenza Center, National Institute of Public Health – National Institute of Hygiene, Warsaw, Poland

1 Introduction

The antibiotic resistance to bacteria is an emerging threat to the public health. An important factor in the development of this resistance is overuse of antibiotics, especially for treatment of viral respiratory infections and influenza-like illness (ILI). It is estimated that 38 % of patients with the sole diagnosis of influenza received antibiotic prescriptions (Ciesla et al. 2004). Studies limited to children have demonstrated even higher rates of antibiotic treatment in patients diagnosed with viral infections, including influenza (Wilkes et al. 2009). One of the prime factors leading to the inappropriate prescription of antibiotics in children with influenza is a difficulty in making a reliable diagnosis. A misuse of antibiotic treatment for influenza infections and subsequent emergence of bacterial resistance can be reduced by limiting a viral spread through the hand hygiene and vaccination, using laboratory tests for confirmation of influenza cases, judicious use of antivirals, and by expanding the knowledge of physicians and parents regarding the appropriate use of antibiotics (Friedman et al. 2011). The aim of the present our study was to define the frequency and appropriateness of the antibiotic therapy administrated to children with a laboratory-confirmed influenza. This is one of first studies describing this problem in Central Europe where influenza vaccination rates are low, influenza incidence is underestimated and simultaneously the problem of overuse of antibiotics is increasing (Brydak and Nitsch-Osuch 2014; Skoczyńska et al. 2007).

2 Methods

The legal guardians of eligible children provided a written consent for the study participation. The study procedures, consent documents, and data collection sheets were reviewed and approved by the Ethics Committee of the Warsaw Medical University in Warsaw, Poland.

Children younger than 59 months seeking care for the acute respiratory tract infection (ARTI) in both inpatient and outpatient settings in the capital city of Warsaw were enrolled into the study. The patients were eligible for the study if they reported influenza-like illness (ILI) with fever $>$ 38 °C and cough or sore throat of less than 4 days duration. The enrollment took place when there was a confirmation of the presence of the influenza season in the period of January-March 2015. Respiratory specimens, one nasal and one pharyngeal swab, were taken and tested for influenza A and B virus with the real-time reverse transcription polymerase chain reaction (real-time PCR), described in detail elsewhere (Nitsch-Osuch et al. 2013b). The PCR results were not immediately available to clinicians, but collectively after all the samples were tested. Nonetheless, physicians had access to rapid influenza diagnostic tests, mainly for outpatients, or to other tests, such as X-ray examination, blood tests, and cultures, available mainly for inpatients. The patients' demographical data, symptoms, co-morbidities, and the information regarding antibiotic prescriptions were obtained from medical records. Statistical analysis was conducted using a statistical calculator available on www.medcalc3000.com. Categorical data were analyzed with a χ^2 test or Fisher's exact test when there were fewer than 10 cases. A p-value <0.05 was considered statistically significant. Odds ratio (OR) and 95 % confidence intervals (CI) were calculated using the Wald method.

3 Results

A total of 114 patients were enrolled into the study, 52 (45 %) inpatients and 62 (55 %) outpatients. There were 36 cases of influenza diagnosed; 34 cases of influenza A (H3N2) and 2 cases of influenza B virus infections. The prevalence of influenza in the study group was 32 %. There were 15 cases (42 %) of influenza diagnosed in the hospitalized children and 21 cases (58 %) diagnosed in ambulatory outpatients. Antibiotic therapy was prescribed for 21 (58 %) patients with influenza. The therapy was more frequently administered in the

hospitalized children than in those under ambulatory outpatient care (93 % *vs.* 33 % patients), while symptomatic treatment was more frequently conducted in the outpatients; the difference in the treatment mode between the two groups of patients was significant ($p < 0.05$; Table 1).

The most often administrated antibiotics for children with diagnosed influenza were amoxicillin with clavulanic acid, cefuroxime, and amoxicillin (Fig. 1). Amoxicillin alone was used only among ambulatory treated children (Table 2). Lower tract respiratory infections, including pneumonia (diagnosed in 12/21, 57 % patients), bronchitis (diagnosed in 4/21, 19 % patients), and otitis media (diagnosed in 5/21, 24 % patients) were the main reasons for administration of antibiotics. Pneumonia was a significantly reason of the introduction of antimicrobials in hospitalized children, while otitis media occurred mainly in children under ambulatory care ($p < 0.05$; Table 2).

Although we identified children with predisposing factors for a severe and complicated course of influenza, none of them received oseltamivir. Dehydration and decreased daily activity occurred statistically more often in the hospitalized children compared with the ambulatory treated ones ($p < 0.05$, Table 3). None of the children in this study group were vaccinated against influenza during the current season.

4 Discussion

In the present study, 58 % of children with a laboratory confirmed influenza received antibiotic therapy. The therapy was conducted mainly in the hospital setting. The crucial questions which should be addressed are the following. Is antibiotic therapy overused for children with influenza and how to increase the appropriateness of prescribing antibiotics for patients with influenza? Mazzaglia et al. (2003) have reported that 44 % of patients with influenza received antibiotics, while Ochoa et al. (2000) have shown that even more than 70 % cases of influenza found at the emergency department are treated with antibiotics. The present findings showing frequent prescribing of antibiotics for influenza treatment are in line with other studies. Interestingly, a majority of antibiotic courses was administrated to the hospitalized but not ambulatory treated children. A possible explanation for this finding may be a more frequent use of rapid influenza diagnostic tests (RIDTs) in ambulatory care settings, and not at hospital emergency units in Poland. Although RIDTs have both advantages and disadvantages, their use is recommended by WHO and CDC (Brydak et al. 2013). It has been previously shown that the use of RIDTs may lead to decreased use of antibiotics, even in up to 50 % of cases (Bonner et al. 2003). RIDTs can detect influenza A and influenza B antigens within 30 min, the tests are of variable sensitivity (median 70–75 %) and high specificity (90–95 %) (Nitsch-Osuch et al. 2013a). Significant false negative results have been reported (Wang et al. 2014). Nevertheless, RIDTs provide additional support for the initial diagnosis and may promote the rational use of antibiotics. Other popular tests, such as complete blood count and C-reactive protein measurements, may help recognize bacterial coinfections, secondary to primary viral infection, so that their results should be carefully taken under consideration while proscribing antibiotics for children with ARTI (Dugas et al. 2015; Friedman et al. 2011).

In the present study, a majority of hospitalized children with influenza had an admission diagnosis of pneumonia, which could explain

Table 1 Prevalence of antibiotic and symptomatic treatments in children with laboratory confirmed influenza

No. of influenza patients:	Ambulatory treatment	Hospital treatment	OR; 95 % CI
Symptomatic treatment	14	1[a]	0.04; 0.001–0.37
Antibiotic therapy	7	14[a]	28.00; 2.70–698.10

[a]$p < 0.05$ between the two treatment modes
OR odds ratio, *95 % CI* confidence intervals

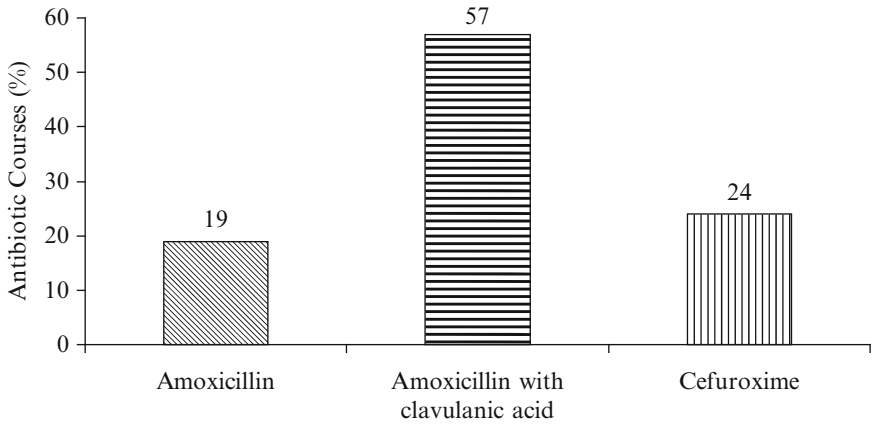

Fig. 1 Antibiotics prescribed for children with influenza

Table 2 Antibiotic therapy in hospitalized and ambulatory treated children with influenza

	Ambulatory treatment	Hospital treatment	OR; 95 % CI
Antibiotic therapy			
Amoxicillin	4	0[a]	3.28; 3.25–28.12
Amoxicillin + Clavulanate	2	10[a]	0.16; 0.02–1.08
Cefuroxime	1	4[a]	0.41; 0.05–3.72
Diagnosis			
Pneumonia	1	11[a]	0.05; 0.01–0.44
Bronchitis	2	2	2.40; 0.32–18.27
Otitis Media	4	1[a]	2.27; 2.27–27.13

[a]$p < 0.05$ between the two treatment modes; *OR*, odds ratio; *95 % CI*, confidence intervals
OR odds ratio, *95 % CI* confidence intervals

Table 3 Predictors of a severe and complicated course of influenza in children

	Ambulatory treatment (n = 21)	Hospital treatment (n = 15)	OR; 95%CI
Age < 24 months	12	12	0.33; 0.07–1.46
Comorbidities:	3	4	0.92; 0.17–4.79
Bronchial Asthma	2	4	
Obesity	1	0	
Feeding difficulties	1	4	0.13; 0.29–1.08
Dehydration	1	8[a]	0.44; 0.06–0.34
Breathing difficulties	1	2	0.35; 0.04–2.80
Decreased daily activity	1	5[a]	0.10; 0.01–0.77
Rapid symptomatic deterioration	1	3	0.20; 0.03–1.62
Neurological symptoms (convulsions)	1	1	0.70; 0.07–7.26

[a]$p < 0.05$ between the two treatment modes
OR odds ratio; *95 % CI* confidence intervals

administration of antibiotic therapy. However, several predisposing factors for influenza complications, predominantly young age of less than 5 years, were also present in our patients. We might expect that an earlier influenza diagnosis and oseltamivir treatment, a neuraminidase inhibitor, could have prevented some complications and antibiotic treatment. Whitley et al. (2001) have shown that the use of oseltamivir for children with influenza reduces the incidence of complications requiring antibiotics by 40 %, compared with placebo, and reduces the relative risk of otitis media by 44 %. Although there remains a possibility of triggering the development of resistant viral strains with antiviral treatment, the risk is much lower than that of the generation of resistance in bacteria following the use of antibiotics. The antiviral treatment benefits clearly outweigh the risk of bacterial resistance (Low 2008). The present study shows that antiviral therapy for influenza is not administrated frequently enough due to a lack of influenza diagnosis. The problem of the underuse of antivirals for influenza has also been reported by Havers et al. (2014) who show that only 16 % of influenza patients receive antivirals, while 30 % of them receive one of the three common antibiotics (amoxicillin, amoxicillin-clavulanate, or azithromycin). A neuraminidase inhibitor is recommended for patients who are at risk for influenza complications, including those who are younger than 2 years or older than 65 years of age, or have a chronic medical condition. The treatment should commence within two days after illness onset if possible, but a later treatment beginning also can help (Grohskopf et al. 2015).

In the present study, the main reason for administration of antibiotic therapy with penicillins or cephalosporins were the lower respiratory tract infections, such as pneumonia and bronchitis, in hospitalized children, and otitis media in children under ambulatory care. Although prescribing of antibiotics for pneumonia is justified, as we know that bacterial complications of influenza are present in 80 % of cases and only 20 % are of the primary viral origin (Crott et al. 2014), a need for antibiotic therapy for children with bronchitis is debatable, especially that the majority of them are hospitalized due mainly to feeding difficulties or dehydration. No benefit has been reported regarding antibiotic treatment for children with bronchitis. There is no evidence to support the use of antibiotics to prevent bacterial complications of influenza or to decrease the severity of persisting viral respiratory tract infections. On the other side, antimicrobial therapy is beneficial to children with underlying chronic pulmonary diseases such as cystic fibrosis, bronchopulmonary dysplasia, or ciliary dyskinesia (O'Brien et al. 1998).

Otitis media is the most common influenza complication among children, occurring in one third of cases. Acute otitis media (AOM) should be differentiated from otitis media with effusion (OME), since antimicrobial agents are not required for the latter unless the effusion persists for more than 3 months (Gisselsson-Solen 2015). The common pathogens of AOM include *Streptoococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*; an increasing drug resistance to these pathogens creates a treatment dilemma (Short et al. 2013). An observational approach, without introducing antibacterial agents, lasting for 48–72 h, for uncomplicated AOM is an option for selected children, which should be based on diagnostic certainty, age, illness severity, and assurance of follow-up (Gisselsson-Solen 2015). This approach for AOM is worthy of consideration in view of the antibiotic resistance data in Poland, showing that 30 % of *Streptococcus pneumoniae* isolates are resistant to pencilllin (Skoczyńska et al. 2007).

The choice of antibiotics in the present study seemed rational and according the national recommendations. It also is in agreement with other researchers (Huang and Huang 2005). However, we should emphasize that the national guidelines encourage prevention of some infections, including influenza and its complications, by immune prophylaxis with vaccines. Kwong et al. (2009) have reported that after 10 years of universal influenza vaccination, there has been a 64 % decline in the

antibiotic prescribing practices. A need for vaccination against influenza should be underlined in Poland, where the coverage rate among the general population stands very low at 3.5 % (Brydak and Nitsch-Osuch 2014). Indeed, none of our patients with influenza was vaccinated during the current season.

We conclude that there are three following ways of responding to the challenge posed by influenza infections and the misuse of antibiotics: firstly, more common employment of laboratory diagnostic tests, including PCR and RIDTs, to identify patients with influenza; secondly employment of neuraminidase inhibitors, a causative treatment for influenza; and thirdly, prevention of influenza by vaccination. The first proposition is crucial, albeit pricey, the second one may be successfully introduced only when laboratory diagnosis is available and conducted, while the third one seems to be the most simple and effective. This complex approach could reduce the overuse of antibacterials and lead to more effective treatment of influenza and its complications.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

References

Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW (2003) *Impact of the rapid diagnosis of influenza on physician decision-making and patient* management in the pediatric emergency department: results of a randomized, prospective, controlled trial. Pediatrics 112:363–367

Brydak LB, Nitsch-Osuch A (2014) Prevention of influenza infection – a Polish perspective. Adv Hyg Exp Med 68:137–144

Brydak LB, Wozniak-Kosek A, Nitsch-Osuch A (2013) Influenza diagnosis and vaccination in Poland. Respir Physiol Neurobiol 187:88–93

Ciesla G, Leader S, Stoddard J (2004) Antibiotic prescribing rates in the US ambulatory care setting for patients diagnosed with influenza, 1997–2001. Respir Med 98:1093–1101

Crott R, Pouplier I, Roch I, Chen YC, Closon MC (2014) Pneumonia and influenza, and respiratory and circulatory hospital admissions in Belgium: a retrospective database study. Arch Pub Heal 72:33

Dugas AF, Valsamakis A, Atreya MR, Thind K, Alarcon P, Faisal A, Gaydos CA, Rothman RE (2015) Clinical diagnosis of influenza in the ED. Am J Emerg Med 33:770–775

Friedman B, Schwabe-Warf D, Goldman R (2011) Reducing inappropriate antibiotic use among children with influenza infection. Can Fam Physician 57:41–43

Gisselsson-Solen M (2015) Acute otitis media in children-current treatment and prevention. Curr Infect Dis Rep 17:476–487

Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA (2015) prevention and control of influenza with vaccines: recommendations of the advisory committee on immunization practices, United States, 2015–16 influenza season. Morb Mortal Wkly Rep 7:818–825

Havers F, Thaker S, Cliappard J (2014) Use of influenza antiviral agents by ambulatory care clinicians during the 2012–2013 influenza season. Clin Infect Dis 59:774–782

Huang Y, Huang Y (2005) Use of antimicrobial agents for upper respiratory tract infections in Taiwanese children. Chang Gung Med J 28:758–764

Kwong J, Maaten S, Upshur R, Patrick D, Marra F (2009) The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. Clin Infect Dis 49:750–754

Low D (2008) Reducing antibiotic use in influenza: challenges and rewards. Clin Microbiol Infect 14:298–306

Mazzaglia G, Caputi A, Rossi A (2003) Exploring patient- and doctor-related variables associated with antibiotic prescribing for respiratory infections in primary care. Eur J Clin Pharmacol 59:651–657

Nitsch-Osuch A, Wozniak-Kosek A, Korzeniewski K, Zycinska K, Wardyn K, Brydak LB (2013a) Clinical features and outcomes of influenza A and B infections in children. Adv Exp Med Biol 788:89–96

Nitsch-Osuch A, Wozniak-Kosek A, Korzeniewski K, Zycinska K, Wardyn K, Brydak LB (2013b) Accuracy of rapid influenza detection test in diagnosis of influenza A and B viruses in children less than 59 months old. Adv Exp Med Biol 788:71–76

O'Brien KL, Dowell SF, Schartz B, Marcy SM, Philips WR, Gerber MA (1998) Cough illness/bronchitis-principles of judicious use of antimicrobial agents. Pediatrics 101:178–181

Ochoa C, Eiros JM, Inglada L, Vallano A, Guerra L (2000) Assessment of antibiotic prescription in acute respiratory infections in adults. The Spanish Study Group on Antibiotic Treatments. J Infect 41:73–83

Short KR, Reading PC, Brown LE, Pedersen J, Gilbertson B, Job ER, Edenborough KM, Habets MN, Zomer A, Hermans PW, Diavatopoulos DA, Wijburg OL (2013) Influenza-induced inflammation drives pneumococcal otitis media. Infect Immun 81:645–652

Skoczyńska A, Kadłubowski M, Waśko I, Fiett J, Hryniewicz W (2007) Resistance pattern of selected

respiratory tract pathogens. Clin Microbiol Infect 13:377–382

Wang L, Chang LS, Lee IK, Tang KS, Li CC, Eng HL, You HL, Yang KD (2014) Clinical diagnosis of pandemic A(H1N1) 2009 influenza in children with negative rapid influenza diagnostic test by lymphopenia and lower C-reactive protein levels. Influenza Other Respi Viruses 8:91–98

Whitley RJ, Hayden FG, Reisinger KS (2001) Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 20:127–133

Wilkes JJ, Leckerman K, Coffin SE, Keren R, Metigan TA, Hodinka LR (2009) Use of antibiotics in children hospitalized with community-acquired. Laboratory-confirmed influenza. J Pediatrics 154:447–449