

Use of Antimicrobial Agents for Upper Respiratory Tract Infections in Taiwanese Children

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Upper respiratory tract infections (URTIs) are mostly caused by viruses. Antibiotic misuse for viral URTIs in children is a serious problem that not only results in selection of resistant strains of bacteria but also wastes millions of dollars each year in Taiwan. Antibiotic resistance among common respiratory bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis* has become a major issue for public health. The common cold, acute pharyngotonsillitis, acute otitis media, acute sinusitis, acute bronchitis, influenza and acute epiglottitis are the most frequently encountered acute URTIs in out-patient clinics. This article recommends the judicious use of antimicrobial agents for these seven common pediatric URTIs, based on local epidemiological data and the recommendations of the Infectious Disease Society of Taiwan and the American Academy of Pediatrics. With education and behavior modification, practitioners will help to reduce antibiotic overuse, and the goal of reducing antimicrobial resistance may be accomplished. (*Chang Gung Med J* 2005;28:758-64)

Key words: upper respiratory tract infections, antibiotic, resistance, children, Taiwan.

The widespread use of antimicrobials has caused the emergence and spread of resistant bacteria to become a clinical problem, and physicians frequently encounter treatment dilemmas due to these resistant organisms. Hospital-acquired organisms, like vancomycin-resistant enterococci, multidrug-resistant tuberculosis and pan-drug resistant *Acinetobacter baumannii* etc. emerged recently in Taiwan and spread rapidly. The resistance rates of common community-acquired organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* to first-line antibiotics have also become greater in recent years. However, millions of courses of unnecessary antibiotics are given each year. Chang et al.⁽¹⁾ collected all prescriptions from 114~166 health stations with 40891~53992 physician visits per year in Taiwan, for 1 week in March each year from 1996 to 1999. Antibiotics were prescribed in 13.4% of total visits

and patients who were younger than 11 years of age had the highest percentage (38.2%) for receiving such prescriptions. The common cold was the most frequent diagnosis for antibiotic prescription and accounted for 32% of all antibiotic-containing prescriptions. Among the patients diagnosed with the common cold, antibiotics were prescribed for 31%, and the highest percentage (45.5%) was amongst those aged less than 16 years. Penicillins (35%), cephalosporins (27%) and macrolides (22%) were the antibiotics most commonly prescribed.

The antimicrobial resistance among respiratory pathogens in Taiwan is high. Hsueh et al.⁽²⁾ reported 60-80% of penicillin-nonsusceptible *S. pneumoniae*, 67-100% of erythromycin-resistant *S. pneumoniae*, 45-73% of ampicillin-resistant *H. influenzae*, 30-51% of erythromycin-resistant group A beta-hemolytic *Streptococcus* (GABHS), and 53-83% of

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methicillin-resistant *Staphylococcus aureus* (MRSA) in 12 major hospitals in Taiwan in 2000.

The common cold, acute pharyngotonsillitis, acute otitis media, acute sinusitis, acute epiglottitis, acute bronchitis and influenza are the most frequently encountered acute upper respiratory tract infections (URTIs) in out-patient clinics. Here we propose the principles of judicious use of antibiotics for these common URTIs for primary care physicians. The suggested antimicrobial agents, mainly in oral formulations, were limited to those marketed in Taiwan and based on local epidemiological data and antimicrobial resistance rates of common respiratory pathogens, as well as on the 2002 guidelines of the Infectious Disease Society of Taiwan⁽³⁾ and the practical guidelines from the American Academy of Pediatrics (AAP).

Common Cold

Common cold is an acute communicable viral disease characterized by nasal stuffiness, sneezing, coryza, throat irritation, with or without fever. Most children suffer from the common cold between three and eight times per year, more frequently if they attend school or day care centers. More than 200 serologically different viruses can cause the common cold. Close personal contact via nasal secretions, particularly nasal blowing and sneezing, is necessary for transmission.

Controlled trials of antimicrobial treatment for the common cold showed that antibiotic treatment did not change the clinical course or outcome.⁽⁴⁾ Further, there was no evidence of a protective effect from antibiotic treatment for URTI in preventing lower RTI in children.⁽⁵⁾ Mucopurulent rhinitis usually accompanies the common cold and is more appropriately considered part of the natural history of viral rhinosinusitis than a bacterial disease. Therefore, mucopurulent rhinitis is not an indication for antimicrobial therapy unless it persists without improvement for more than 10 to 14 days.⁽⁴⁾

It is apparent that antimicrobials should not be prescribed for the common cold but antibiotics were prescribed in more than 45% of pediatric patient visits in Taiwan between 1996 and 1999.⁽¹⁾

Pharyngotonsillitis

Acute pharyngotonsillitis is a common URTI in children and usually presents with a sore throat due

to erythema, exudates or ulceration involving the nasopharynx, uvula, soft palate or tonsils. The common causes of pharyngotonsillitis include viruses such as adenoviruses, enteroviruses, influenza viruses, and Epstein-Barr virus and GABHS. GABHS is the only pathogen for which antibiotic therapy is definitely indicated. However, only a small percentage of acute pharyngitis is caused by GABHS. In a prospective study conducted by Chi et al. in Taipei,⁽⁶⁾ GABHS accounted for less than 2% of 416 children with acute pharyngitis treated at the out-patient department of a medical center. It is apparent that it is unnecessary to prescribe antibiotics for most children with this illness.

Differentiating streptococcal pharyngitis from viral infection is important. Clinical features of a streptococcal pharyngitis include acute onset sore throat, swollen tonsils, anterior cervical lymphadenopathy, scarlatiniform rash with less cough, rhinorrhea and conjunctivitis. Though suggestive, the positive predictive values of these features for group A streptococcal infection were less than 50%:⁽⁷⁾ the clinical features of viral and group A streptococcal pharyngitis are largely overlapping. A laboratory test, such as the rapid antigen-detection test, and/or throat swab culture is indicated when group A streptococcal pharyngitis is suspected.⁽⁸⁾

Penicillin and its congeners are usually recommended for 10 days as the drugs of choice for group A streptococcal pharyngitis.⁽⁹⁾ However, a recent meta-analysis of treatment of group A streptococcal pharyngitis in children indicated that cephalosporins had a higher bacteriological cure rate (odds ratio (OR), 3.02; 95% confidence interval (CI) 2.49-3.67) as well as a higher clinical cure rate (OR 2.33; 95% CI 1.84-2.97) than penicillin.⁽¹⁰⁾ They also found a trend for diminishing bacteriological cure with penicillin over time.

Pichichero et al.⁽¹¹⁾ retrospectively analyzed 2,140 episodes of childhood group A streptococcal pharyngitis and found 20.5% recurrence was noted within 30 days and 30.2% recurrence within 60 days. They also found that recurrent group A streptococcal pharyngitis was more frequent in the 1990s than in the 1970s, in children younger than eight years of age than in adolescents, and after penicillin treatment (21.8% of 1,581) than after other alternative antibiotic therapy (cephalosporins 8.6% of 254, macrolides 14% of 143).

We recommend the rapid antigen detection test or throat culture for patients with clinical manifestations suggestive of group A streptococcal pharyngitis. No antimicrobials should be given in the absence of laboratory-confirmed streptococcal infection. Penicillin V or benzathine penicillin intramuscular (IM) is still the drug of choice for children. First generation cephalosporins and clindamycin are appropriate alternatives. However, due to the high resistance rate of GABHS,⁽²⁾ erythromycin and other macrolides are not suitable for GABHS pharyngitis in Taiwan at present. Routine bacteriological follow-up after treatment or testing asymptomatic household contacts is not recommended. For recurrent cases, clindamycin or amoxicillin-clavulanic acid for 10 days or one dose of benzathine penicillin G with/without oral rifampin for four days are suggested regimens.⁽⁸⁾

Acute Otitis Media

Acute otitis media (AOM) is an extremely common illness in children and almost every child has one or more episodes up to the age of four years. The peak incidence is between six to eighteen months of age. AOM should be differentiated from otitis media with effusion (OME) because antibacterial agents are unnecessary for OME unless the effusion persists for more than three months.⁽¹²⁾ A diagnosis of AOM requires acute onset of symptoms/signs of middle-ear inflammation (either distinct erythema of the tympanic membrane or distinct otalgia) and middle ear effusion (MEE). The common pathogens of AOM include *S. pneumoniae*, nontypable *H. influenzae*, and *Moraxella catarrhalis*. *S. pneumoniae* is still the most common pathogen for persistent otitis media, followed by *H. influenzae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The increasing drug resistance of these pathogens creates a treatment dilemma, and this is a very serious problem in Taiwan. A recent study conducted by Li et al.⁽¹³⁾ in Taipei showed that 96% of 96 *S. pneumoniae* isolates, from ear fluids of children with severe AOM or with unsatisfactory response to initial antibiotic therapy for AOM, were penicillin nonsusceptible, and only 11% of 45 *H. influenzae* isolates were sensitive to ampicillin.

According to the clinical practice guidelines of AAP and the American Academy of Family Physicians (AAFP) published in 2004,⁽¹⁴⁾ observation without antibacterial agents (deferred for 48-72

hours) for uncomplicated AOM is an option for selected children, based on diagnostic certainty, age, illness severity and assurance of follow-up. If antibacterial agents are warranted, a 10-day course of high dose amoxicillin 80-90mg/kg/day for younger patients (less than 2 years of age) or for severe diseases is recommended, and a 5- to 7-day course is recommended for children six years of age and older with mild to moderate disease. If patients fail to respond to initial management within 48-72 hours, physicians should reassess to confirm the diagnosis of AOM and exclude other causes. The guidelines also encourage prevention of AOM through reducing the risk factors, such as altering child care attendance patterns, breastfeeding for at least six months, avoiding supine bottle feeding, reducing or eliminating pacifier use in the second six months of life, eliminating exposure to environmental tobacco smoke and immunoprophylaxis with inactivated flu vaccine.

We recommend that antimicrobial agents are indicated in the treatment of diagnosed AOM and high dose amoxicillin (80-90mg/kg/day) in 2-3 divided doses is the drug of choice for children. For patients with severe illness, who need additional coverage for beta-lactamase-producing bacteria, and for patients with a poor response to initial amoxicillin therapy, high-dose amoxicillin-clavulanate (in 2-3 divided doses) is recommended. If this fails, a 3-day course of ceftriaxone can be used.

Acute Sinusitis

Acute bacterial sinusitis is most often preceded by a viral URTI. Since radiological sinus changes do not correlate well with clinical signs and symptoms, acute sinusitis is usually a disease diagnosed clinically. In general, a diagnosis of bacterial sinusitis may be made in children suffering from prolonged non-specific upper respiratory signs and symptoms such as nasal congestion, nasal discharge and cough without improvement for more than 10 to 14 days, or with severe upper respiratory tract signs and symptoms such as fever $\geq 39^{\circ}\text{C}$, facial swelling and facial pain.⁽¹⁵⁾ As with AOM, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* are the predominant pathogens associated with acute bacterial rhinosinusitis in children.⁽¹⁶⁾ However, there have been no comprehensive studies regarding the etiologies of acute bacterial sinusitis for children in Taiwan.

Based on AAP clinical practice guidelines,

image studies are not necessary for confirming the diagnosis of acute bacterial sinusitis in children less than six years of age, and high dose amoxicillin or amoxicillin-clavulanate (90mg/6.4mg/kg per day) are the recommended treatments, achieving a more rapid clinical cure.⁽¹⁷⁾ Once there are confirmed or suspected complications, such as involvement of the orbit and/or central nervous system, immediate referral to an otolaryngologist, infectious disease specialist, ophthalmologist or neurosurgeon should follow because detrimental sequelae or even death could occur if the appropriate treatment is not promptly administered.

We recommend a 10- to 14- day course of high dose amoxicillin 80-90mg/kg/day for acute sinusitis in children. Amoxicillin-clavulanate and second generation cephalosporins are alternative agents.

Cough Illness/Bronchitis

Technically, bronchitis can be defined as inflammation of the bronchial respiratory mucosa resulting in a productive cough. However, clinical definition of bronchitis is not well established and there is a lack of a standard definition. Usually a diagnosis is made when the patient presents with a chronic cough, with or without fever or sputum production. Bronchitis is usually self-limited, and most commonly caused by viral pathogens such as parainfluenza virus, respiratory syncytial virus and influenza virus.

The majority of prolonged cough illnesses are allergic, postinfectious or viral in nature. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Bordetella pertussis* are occasionally recognized pathogens in children more than five years of age. Sputum production and character, and fever are not predictive of a bacterial etiology. Nasopharyngeal cultures are poor predictors of true bacterial pathogens.

No benefit was found in four clinical studies regarding antibiotic treatment of children with bronchitis.⁽¹⁵⁾ There is no evidence to support use of antibiotics to prevent bacterial complications or to decrease the severity following viral respiratory tract infections.⁽¹⁸⁾ However, antimicrobial therapy may be of benefit to children with underlying chronic pulmonary diseases (i.e. cystic fibrosis, bronchopulmonary dysplasia, ciliary dyskinesia, chronic aspiration) during acute exacerbation, and for prolonged cough (> 10 days) caused by *Bordetella pertussis*,

Mycoplasma pneumoniae, or *Chlamydia pneumoniae*.

Antimicrobial treatment is not recommended for bronchitis/cough illness in children without an underlying lung disease. Even though antimicrobial treatment for chronic cough, of more than 10 days duration, may be indicated occasionally for *pertussis* or *Mycoplasma pneumoniae* infection, a macrolide has minimal effect on shortening the duration of the cough.

Influenza

Influenza, caused by influenza viruses type A and B, and rarely C, is characterized by abrupt onset constitutional and respiratory signs and symptoms including fever, myalgia, headache, malaise, nonproductive cough, sore throat and rhinitis. The incubation period for influenza is one to four days, with an average of two days. Influenza can cause significant morbidity in children. During a four and a half year period, Wang et al.⁽¹⁹⁾ identified 84 children with influenza A virus infection requiring hospitalization at a children's hospital in Taiwan, and found that lower respiratory tract infection (63%) was the most common clinical manifestation, occurring predominantly in children less than five years of age (92%), while encephalitis/encephalopathy was noted in 26 (31%) predominantly older children (69%). Myositis was more commonly seen in children with influenza B infection.

For children with influenza but without bacterial complications, no benefit can be found from treatment with antibiotics. However, antibiotics were prescribed in 52.2% of influenza-related patient visits (children < 15 years of age) in Taiwan.⁽¹⁾ Physicians should recognize the possibility of influenza during epidemics and avoid unnecessary use of antibiotics. In fact, antiviral agents should be administered within the first 24 to 48 hours of onset for patients with significant risk of morbidity and mortality, including those with chronic obstructive airway disease, cardiovascular disease, those who are immunocompromized, health care workers, and the elderly. Amantadine (for influenza A only) and oseltamivir are the drugs of choice. Influenza vaccination is the primary method used for preventing influenza and its severe complications. Children aged six to 23 months are included in the target population for vaccination in Taiwan since the 2004-5 season.

Acute Epiglottitis

Acute epiglottitis is rare in Taiwan.⁽²⁰⁾ Acute epiglottitis is characterized by a rapid onset and progression of airway obstruction, which presents with stridor, drooling, dyspnea and high fever, and is a disease of emergency in children. *H. influenzae* type b is the most common pathogen. Prompt airway establishment and appropriate antibiotic treatment are critical for management of this disease. The prevalence of ampicillin-resistant *H. influenzae* was 45~73% in Taiwan.⁽²⁾ Amoxicillin/clavulanate, ampicillin/sulbactam, and second or third generation cephalosporins, preferably in intravenous form, are recommended.

Conclusion

Viruses are frequent causes of URTIs in children and antibiotics are usually not needed for their treatment. Prudent use of antimicrobials for distinct bacterial diseases can reduce selection and spread of resistant bacterial pathogens, and is beneficial for both individuals and the community. The recommendations for antimicrobial use for URTIs in Taiwanese children are summarized in Table 1.

Table 1. Antimicrobial Therapy Guidelines for Upper Respiratory Tract Infections in Children in Taiwan (modified from reference 3)

Diagnosis	Drug of Choice	Alternative
Common cold	No antimicrobials	
Acute pharyngotonsillitis*	Penicillin V Benzathine penicillin (IM)	Clindamycin 1° Cephalosporins
Acute otitis media	Amoxicillin (high dose)†	Amoxicillin/clavulanate 2° or 3° Cephalosporins
Acute sinusitis	Amoxicillin (high dose)†	Amoxicillin/clavulanate 2° or 3° Cephalosporins
Acute bronchitis	No antimicrobials	
Influenza	Amantadine (Influenza A only) Oseltamivir	
Acute epiglottitis‡	Amoxicillin/clavulanate Ampicillin/sulbactam 2° or 3° Cephalosporins	Aztreonam

* No antimicrobial treatment except for documented streptococcal pharyngitis.

† 80-90mg/kg/day in 2-3 divided doses.

‡ Intravenous formulations.

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台灣兒童上呼吸道感染之抗生素使用建議

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病毒是造成上呼吸道感染的主要致病原。然而在台灣，就兒童的上呼吸道感染而言，抗生素的不當使用已造成嚴重問題，不但導致細菌的抗藥性增加，也浪費許多健保經費。常見的呼吸道細菌，譬如肺炎雙球菌 (*Streptococcus pneumoniae*)，嗜血桿菌 (*Haemophilus influenzae*)，金黃色葡萄球菌 (*Staphylococcus aureus*)，和布魯氏菌 (*Moraxella catarrhalis*) 等的抗藥性已經變成全球健康主要課題。一般感冒，急性咽炎，急性中耳炎，急性鼻竇炎，急性支氣管炎，流行性感冒，和急性會厭炎是門診常見的急性上呼吸道感染。這篇文章將探討如何審慎使用抗生素於這七種兒童常見的上呼吸道感染，並參考本土流行病學資料，中華民國感染症醫學會的建議和美國小兒科醫學會的建議而提出抗生素使用規範，以供臨床醫師參考。希望藉由不斷再教育和行為改造，我們相信一定會達成減少抗生素濫用和降低細菌抗藥性的目標。(長庚醫誌 2005;28:758-64)

關鍵詞：上呼吸道感染，抗生素，抗藥性，兒童，台灣。

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