

Considerations on Antibiotic Use for Outpatients

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Abstract

In ambulatory care, where the number of feasible tests is limited, it is not unusual for antibiotic therapy to be initiated without the result of the responsible organisms. However, careful attention is necessary to choose the appropriate antibiotics, to take into account the presence of resistant bacteria, and to prevent the increase of resistant bacteria in the community.

In cases of upper respiratory tract infection, it should be borne in mind that most cases of common cold are attributable to viruses and antibiotics therefore are useless, and that purulent secretions do not necessarily mean bacterial infection. It is also important not to overlook group A β -hemolytic streptococcal infection and abscess. In cases of lower respiratory tract infection, responsible organisms vary substantially according to the background of patients. It is therefore recommended that Gram stain and culture of sputum be carried out if possible even in the ambulatory care. If admission to hospital is indicated, two sets of blood culture should be obtained in the ambulatory care prior to hospitalization. In cases of urinary tract infection, excessive use of fluoroquinolone should be avoided in order to prevent the increase in fluoroquinolone-resistant bacteria.

Key words Antibiotics, Ambulatory care, Resistant bacteria, Appropriate antibiotic use

Introduction

In ambulatory care, where feasible tests tend to be limited, it is not unusual that the indication and kinds of antibiotic therapy should be determined without the result of the responsible organisms. However, careful attention is required to choose the appropriate antibiotics since the presence of resistant bacteria needs to be taken into account in the ambulatory care. On the other hand, prudence is required in prescribing antibiotics so as not to increase resistant bacteria, although benefit to the patient should be the first priority. Indications, types, and dosage of antibiotics will be described below about major infectious diseases.

Upper Respiratory Tract Infection

Common cold

First of all, it is important to clearly distinguish between common cold and acute pharyngitis caused by group A streptococcus. Most cases of common colds are caused by viruses. Although common colds attributable to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* do exist, such cases are infrequent.

Although purulent nasal discharge and sputum are commonly seen in patients with common cold, it is important to note that purulent secretions are very common in patients with viral infection. Secretions become purulent as a result of leukocytes and desquamated epithelial cells. In 37% of patients with viral infection, leukocyte counts in sputum exceed 10/HPF, creating a macroscopically purulent feature. On the other hand, it has

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1. Assign 1 point for each of the following clinical characteristics: (1) history of fever, (2) anterior cervical adenopathy, (3) tonsillar exudate, and (4) absence of cough.

2. Find the column that most closely matches the pretest probability of strep in the patient and look down the column to the row that matches the patient's number of points to determine the probability of strep.

Points, No.	Likelihood ratio	Pretest probability of strep throat (%)							
		5	10	15	20	25	40	50	
0	0.16	1	2	2	3	5	10	14	
1	0.3	2	3	5	7	9	17	23	
2	0.75	4	8	12	16	20	33	43	
3	2.1	10	19	27	34	41	58	68	
4	6.3	25	41	53	61	68	81	86	

(Cited from Ebell MH, et al. JAMA. 2000;284:2912–2918.)

Fig. 1 Centor clinical prediction rule for the diagnosis of strep throat in adults

been reported that bacteria are found in only 48% of cases with sputum containing 10/HPF or more leukocytes.¹

• Antibiotic therapy:

Most cases of common cold are attributable to viral infection, and therefore antibiotic therapy is useless. Clinical studies have shown that prophylactic administration of antibiotics does not decrease the incidence of bacterial complications.² Indiscriminate use of antibiotics is harmful rather than beneficial, in view of the adverse effects and selection of resistant bacteria.

Acute pharyngitis

About 90% of cases of acute pharyngitis are caused by viruses. Antibiotics are ineffective for viruses. Indications of antibiotic therapy are restricted to the following.

1. Acute pharyngitis due to group A β -hemolytic streptococcus

Acute pharyngitis due to group A β -hemolytic streptococcus accounts for 15–30% of pediatric pharyngitis cases, and 5–10% of adult cases. It is not difficult to distinguish this disease from common cold by history and physical examinations, and rapid tests are also useful. Determination of the Centor score by history and physical examinations (Fig. 1) helps to establish a diagnosis.³ Agreement in all four findings of the Centor score represents an approximately 75% possibility of

group A β -hemolytic streptococcal infection. The absence of rhinitis is a characteristic feature. On the other hand, purulent secretions in the tonsils are also common in cases of viral infection. Therefore, it is important that the diagnosis not be based only on the presence of exudate on the tonsil. Rapid tests are useful, showing sensitivity of 80–90% and specificity of 90% or more.

• Antibiotic therapy:

To prevent rheumatic fever (which occurs in 0.3–3% of untreated patients), antibiotic therapy should be continued for 10 days. Since the presence of penicillin G (PCG)-resistant strains has not been reported, first-line therapy should be penicillin antibiotic.

(1) Ordinary cases

Penicillin G, 800,000 units qid, for 10 days

Amoxicillin, 500 mg tid or qid, for 10 days

(2) If oral therapy is not indicated because of pharyngeal pain

Ceftriaxone, 2 g qd, i.v. or i.m. (intramuscular administration is not covered by insurance)

(3) Patients allergic to penicillin

Clarithromycin, 200 mg bid, for 10 days

Azithromycin, 500 mg qd, for 3 days

When aminopenicillins are given to patients with infectious mononucleosis due to EB virus, eruptions occur almost invariably. Routine use of these agents should be avoided when the diagnosis is not made.

2. Peritonsillar abscess

Most cases of peritonsillar abscess are secondary to pharyngitis due to group A β -hemolytic streptococcus, and are accompanied by infection with oral anaerobic bacteria at onset. Surgical drainage is necessary, and brief hospitalization is usually indicated. Patients should be referred to secondary care facilities.

Acute otitis media

Most cases of acute otitis media are caused by infection via the auditory canal. Therefore, Gram stain and culture of epipharyngeal fluid are useful for identifying the responsible organisms for acute otitis media. Three major causative bacteria are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Otitis media cures spontaneously in 80% of patients. Since it is extremely rare (0.5%) that the condition becomes severe within 3 days of onset, the standard policy for mild cases is to observe them for the initial 3 days without antibiotic therapy. Antibiotics

Table 1 Responsible organisms as determined from various items of history-taking

COPD, bronchiectasis	<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Pseudomonas aeruginosa</i>
Diabetes mellitus, alcoholism, liver disease	<i>Klebsiella pneumoniae</i> , <i>Staphylococcus aureus</i>
Neurologic disorder, caries, bed rest	Anaerobes
Antecedent viral infection	<i>S. pneumoniae</i> , <i>S. aureus</i>
Pet animals	<i>Chlamydia</i> , <i>Rickettsia</i> , <i>Cryptococcus</i>
Traveling, hot spring use, digging grounds	<i>Legionella</i>
HIV	<i>Pneumocystis jiroveci</i> , TB, MAC, CMV
Close contact to people with the same symptoms (within a few days)	Viruses such as influenza virus
Close contact to people with the same symptoms (within 10–14 days)	<i>Mycoplasma</i>
Repeated dosing of antibiotics	<i>P. aeruginosa</i> , other resistant bacteria
Recent history of hospitalization	Various Gram-negative bacilli, MRSA

(Adapted from Fujimoto T. Manual of Infectious Diseases for Residents. Tokyo: Igaku-Shoin Ltd.; 2004.)

are used for patients with unimproved course of milder cases or a severer condition.

• **Antibiotic therapy:**

Even now, when penicillin-resistant *S. pneumoniae* (PRSP), β -lactamase-negative ampicillin-resistant (BLNAR) *H. influenzae* are increasing, amoxicillin remains the first-line drug for mild to moderate disease.⁴ Imprudent use of cephem antibiotics should be avoided.

For patients with severe disease, high-dose amoxicillin, amoxicillin clavulanate (14:1 preparation), or high-dose cefditoren pivoxil is used in combination with tympanostomy.⁴

Amoxicillin, usual dose: 30 mg/kg/day, in
3 divided doses*²

high dose: 60 mg/kg/day, in
3 divided doses*²

Amoxicillin clavulanate (14:1 preparation),
96.4 mg/kg/day, in 2 divided doses

Cefditoren pivoxil, high dose: 12 mg/kg/day,
in 2 divided doses

Acute sinusitis

Contrary to general assumption, acute sinusitis is more frequently viral than bacterial. Transient thickening of paranasal sinus mucosa and accumulation of effusion are found in about 80% of patients with common cold. On the other hand,

common cold is accompanied by bacterial sinusitis at a frequency of 0.5–5%. In cases of bacterial infection, the responsible organism is similar to that in acute otitis media.

• **Antibiotic therapy:**

Amoxicillin, 500 mg tid or qid

Sultamicillin, 375 mg tid or qid

Clarithromycin, 200 mg bid

Lower Respiratory Tract Infection

Acute bronchitis

Like common cold purulent sputum does not necessarily denote bacterial infection. Cases of viral origin are more frequent than those of bacterial origin.

• **Antibiotic therapy:**

In most cases, antibiotic therapy is unnecessary. If antibiotics are to be used, they should be prescribed in the following manner.

1. When *S. pneumoniae*, *H. influenzae*, or *Moraxella catarrhalis* is suspected:

Amoxicillin clavulanate, 375 mg tid or qid

Sultamicillin, 375 mg tid or qid

2. When *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* is suspected:

Clarithromycin, 200 mg bid

Azithromycin, 500 mg qd (for 3 days)

*² Some experts advocate that the usual dose and high dose of amoxicillin be 60 mg/kg/day (in 3 divided doses) and 90 mg/kg/day (in 3 divided doses), respectively.

Table 2 Point scoring system for step 2 of the prediction rule for assignment to risk classes II, III, IV, and V

Characteristic	Points assigned*
Demographic factor	
Age	
Men	Age (yr)
Women	Age (yr) – 10
Nursing home resident	+10
Coexisting illnesses**	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical-examination findings	
Altered mental status***	+20
Respiratory rate ≥ 30 /min	+20
Systolic blood pressure < 90 mmHg	+20
Temperature $< 35^\circ\text{C}$ or $\geq 40^\circ\text{C}$	+15
Pulse ≥ 125 /min	+10
Laboratory and radiographic findings	
Arterial pH < 7.35	+30
Blood urea nitrogen ≥ 30 mg/dl (11 mmol/liter)	+20
Sodium < 130 mmol/liter	+20
Glucose ≥ 250 mg/dl (14 mmol/liter)	+10
Hematocrit $< 30\%$	+10
Partial pressure of arterial oxygen < 60 mmHg****	+10
Pleural effusion	+10

* A total point score for a given patient is obtained by summing the patient's age in years (age minus 10 for women) and the points for each applicable characteristic. The points assigned to each predictor variable were based on coefficients obtained from the logistic-regression model used in step 2 of the prediction rule (see the Methods section).

** Neoplastic disease is defined as any cancer except basal- or squamous-cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.

*** Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.

**** In the Pneumonia PORT cohort study, an oxygen saturation of less than 90 percent on pulse oximetry or intubation before admission was also considered abnormal.

(Cited from Fine MJ, et al. *N Engl J Med.* 1997;336:243–250.)

Community-acquired pneumonia

The organisms responsible for community-acquired pneumonia vary widely according to the background of the patient, and therefore history taking is important (Table 1).⁵ In cases of pneumonia, it is preferable that Gram stain of sputum be carried out if possible, even in the ambulatory care. Sputum cultures should not be omitted; they need to be submitted prior to the initiation of antibiotic therapy. If hospital admission seems to be indicated, two sets of blood culture should be submitted in the ambulatory care prior to hospitalization.

• Classification of the severity of pneumonia:

Patients are subjected to either ambulatory care or hospitalization depending on the results of the severity evaluation. Severity of pneumonia is rated by the risk calculation system proposed by the Pneumonia Patient Outcomes Research Team (PORT) study (Table 2),⁶ and the Confusion, Urea nitrogen, Respiratory rate, Blood pressure (CURB)-65 criteria, etc. Risk is classified according to five grades as follows, based on the sum of PORT scores: grade I, age 50 or younger, no comorbidity, and no abnormal vital signs; grade II, score 70 or less; grade III, score 71–90; grade IV, score 91–130; grade V, score 131 or more. Patients who are classified as grade I or II are amenable to ambulatory care. Those of grade IV or V are hospitalized. Those of grade III are followed and later allocated to outpatient or inpatient. However, these criteria serve as an aid at the time of evaluation, and poor appearance based on a clinician's impression should not necessarily be disregarded. It may also be practical to consider hospitalization for some patients of grade I or II to ensure safety.

• Antibiotic therapy:

Gram stain is also recommended in the ambulatory care. It is unfortunate that US guidelines do not attach much weight to the Gram stain of sputum.⁷ If Gram stain of sputum is not feasible, empirical treatment is an alternative.

Cautions for empirical treatment are given below.

1. Avoid imprudent use of fluoroquinolones

The prevalence of fluoroquinolone-resistant *S. pneumoniae* strains has been reported to be about 2%. New respiratory quinolones represent a powerful card for penicillin-resistant *S. pneumoniae*, and should be used only in cases of

Table 3 Indications of antibiotic therapy for non-typhoidal *Salmonella* enteritis

- Severe cases accompanied by bacteremia
- Children age 1 year or younger
- Patients with aortic aneurysm or valvular heart disease
- Patients with an artificial femoral head or prosthetic valve
- Patients with HIV infection or transplant patients

(Cited from Fujimoto T. Manual of Infectious Diseases for Residents. Tokyo: Igaku-Shoin, Ltd.; 2004)

necessity.

2. Avoid heavy reliance on β -lactam antibiotics

More than a few cases of community-acquired pneumonia are non-responsive to β -lactam antibiotics.

The following four policies are useful and practical:

- (1) When atypical pneumonia is suspected
Clarithromycin, 400 mg bid, or
Azithromycin, 500 mg qd (for 3 days)
- (2) When bacterial origin is suspected, and *Pseudomonas aeruginosa* is excluded
Amoxicillin clavulanate, 375 mg tid or qid
Sultamicillin, 375 mg tid or qid
- (3) Whether to apply regimen (1) or (2) is unclear
Both regimens (1) and (2) should be employed.
- (4) When bacterial origin is suspected, and *P. aeruginosa* is probable (e.g., in cases where hospitalization and discharge are repeated due to COPD, *P. aeruginosa* is already isolated, etc.)
Levofloxacin, 400 mg qd (although once-daily dosing is not covered by insurance)

Urinary Tract Infection

Uncomplicated cystitis

About 80% of uncomplicated cystitis is attributable to *Escherichia coli*.

• Antibiotic therapy:

First-line therapy should be first- or second-generation cephem antibiotics for 3–5 days.

Cephalexin, 500 mg qid

Cefuroxime axetil, 250–500 mg tid

Fluoroquinolone antibiotics are precious broad-spectrum antibiotics and should be held in reserve if possible.

Uncomplicated acute pyelonephritis

It is highly likely that patients with acute pyelonephritis will be subjected to hospitalization. Urine culture and blood culture should be carried

out. These cultures are indispensable, particularly when chills and shaking are present. Although the fundamental policy is hospitalization, ambulatory treatment is possible in mild cases as long as there is no underlying disease.

• Antibiotic therapy:

(1) Mild cases

Levofloxacin, 400 mg qd (although once-daily dosing is not covered by insurance)

(2) Moderate cases

Ceftriaxone, 2 g qd (in the ambulatory care)

The isolation rates for extended-spectrum β -lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* are increasing in Japan. The third-generation cephem antibiotic ceftriaxone may be indicated for outpatients because this drug allows single daily dosing. However, ESBL-producing organisms are resistant to this drug, and thus caution is necessary.

Ambulatory Treatment for Infectious Diarrhea

Three major organisms responsible for infectious diarrhea cases in the community are *Vibrio parahaemolyticus*, *Salmonella* spp., and *Campylobacter* spp. Viral infectious diarrhea is also common, accounting for 30–40% of all cases. There are two types of disease: small-bowel type and large-bowel type. Most cases of bacterial infectious diarrhea are of the large-bowel type, and are characterized by lower abdominal pain, tenesmus, and bloody stools. Most viral cases are of the small-bowel type, and are characterized by upper gastrointestinal symptoms such as nausea and vomiting, vague pain in the mid-abdomen, and watery and profuse diarrhea.

• Antibiotic therapy:

The vast majority of cases require only rest and supplementation of water, electrolytes, and carbohydrate. The need for antibiotic therapy is restricted to the following cases.

1. *Salmonella* spp.

Basically, no antibiotics are indicated for non-typhoidal *Salmonella* enteritis. This is because antibiotic therapy increases the carrier rate (0.3–0.6%), rather than reducing symptoms or duration of bacterial shedding. Antibiotic therapy is indicated only for the cases listed in Table 3. When blood culture is positive, antibiotic therapy should be continued for 10–14 days.

Levofloxacin, 400 mg qd, for 3–5 days

(although once-daily dosing is not covered by insurance)

Ceftriaxone, 1–2 g bid, for 3–5 days

2. *Campylobacter* spp.

Antibiotic therapy is given only to severe cases.

Clarithromycin, 200 mg bid, for 5 days

3. Shigellosis (bacillary dysentery)

About 600 cases of bacillary dysentery occur annually in Japan.

Levofloxacin, 400 mg qd, for 3 days (although once-daily dosing is not covered by insurance)

4. Enterohemorrhagic *E. coli* (EHEC)

Although the propriety of antibiotic therapy for this condition remains controversial, many experts are against risking the use of antibiotics. Some prospective and retrospective studies have shown that the use of antibiotics increases the incidence

of hemolytic-uremic syndrome (HUS).^{8,9} On the other hand, it has been reported that a low incidence of HUS was associated with the use of fosfomycin within 2 days of EHEC onset.¹⁰ No conclusion as to this issue was drawn from the huge outbreak in Sakai City, Japan. Antibiotics do not contribute to a reduction in the duration of enteritis symptoms.

Conclusion

In the ambulatory treatment of infectious diseases, it is desirable to take a cautious attitude toward the overuse of broad-spectrum antibiotics in order not to increase community-acquired resistant strains.

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