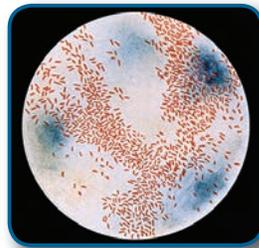


# JUDICIOUS USE OF ANTIBIOTICS

A Guide for Oregon Clinicians - Third Edition



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## INTRODUCTION

Since the Alliance Working for Antibiotic Resistance Education (AWARE) last published guidelines in 2005, new consensus guidelines have been published for the management of community-acquired pneumonia (CAP), sinusitis, pharyngitis and acute otitis media (AOM).<sup>1-5</sup> In general, the guidelines continue to emphasize strict criteria for diagnosis, while limiting use of antibiotics to those infections that have a high probability of a bacterial etiology. When an antibiotic is prescribed, preference should be given to a narrow spectrum agent unless drug susceptibilities are already known and dictate otherwise.

What has changed since our last edition, however, is the evolving epidemiology of *Streptococcus pneumoniae* (SP) in the post-conjugate pneumococcal vaccine era, which has had a positive impact on resistance patterns in Oregon and nationally. Susceptibility data in Oregon come from our participation in the Center for Disease Control's (CDC) Emerging Infections Program, which conducts surveillance for invasive cases<sup>i</sup> of SP and group A streptococcus (GAS) in the Portland tricounty metropolitan area.<sup>ii</sup> Decreases in rates of invasive disease following introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in children in 2000 were attenuated somewhat by increases in non-vaccine type serotypes; overall rates of invasive SP infection, however, have still remained below baseline a decade after introduction.<sup>6</sup> The 13-valent vaccine (PCV13), which received FDA approval in 2010, has already had an impact on rates of invasive SP in young children targeted by the vaccine as well as in older age groups, likely due to a herd immunity effect.<sup>7</sup>

The impact of PCV7 on the prevalence of penicillin-resistant SP (PRSP) has been significant: national estimates from the CDC's Emerging Infections Program of the prevalence of penicillin-resistant SP (PRSP) reached 27% in 1999, and by 2011 had fallen to 11%.<sup>iii</sup> In the Portland tricounty metropolitan area, which has participated in the Emerging Infections Program since 1995, the prevalence of PRSP traditionally has been lower than the national estimates, likely due to lower use of antibiotics by Oregon clinicians. In 2011, only 5% of invasive isolates of pneumococcus were resistant to penicillin (Table 1), and only 3% were fully resistant (MIC > 8).

Similarly, isolates from invasive GAS in the Portland metropolitan area (and the rest of the country for that matter) are still universally sensitive to penicillin, and only low rates of resistance to cephalosporins and clindamycin have been identified locally (Table 1). In general, acute bacterial respiratory infections other than CAP (namely sinusitis, otitis media and pharyngitis) can be safely treated with a narrow-spectrum drug, amoxicillin (or penicillin for documented GAS pharyngitis), except where allergies come into play or concern about beta-lactamase-producing *Haemophilus influenzae* (HI) warrants use of amoxicillin-clavulanate.

Availability of these data should prove useful to Oregon clinicians: guidelines published by the Infectious Diseases Society of America (IDSA) for sinusitis suggest local resistance data for invasive cases of SP be used to guide therapy; specifically, standard doses of amoxicillin or amoxicillin-clavulanate should be adequate to treat SP in settings where the prevalence of resistance to penicillin is less than 10%, as they are in Oregon.<sup>iii</sup> IDSA also prefers

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i. Invasive disease is defined as an isolate from a normally sterile site; the majority of isolates come from bloodstream infections.

ii. As well as other organisms: group B streptococcus, *Haemophilus influenzae*, *N. meningitidis*, *B pertussis* and *Legionella* species. See the Oregon ABCs website for more information: <http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/EmergingInfections/Pages/ActiveBacterialCoreSurveillance.aspx>

iii. See CDC's Active Bacterial Core Surveillance Reports: <http://www.cdc.gov/abcs/reports-findings/surv-reports.html>.

amoxicillin-clavulanate over amoxicillin as a first-line agent for sinusitis due to observed increases in the prevalence of non-typeable HI following widespread use of pneumococcal conjugate vaccine, citing data from observational studies reviewing cultures from middle ear fluid in children.<sup>8-10</sup>

Other guidelines take different stances on the optimal approach to providing coverage for infections due to PRSP and beta-lactamase-producing HI. Authors of the American Academy of Pediatrics (AAP) guidelines for AOM prefer use of high-dose amoxicillin over regular dose in order to provide better coverage for PRSP, and suggest that amoxicillin be the first choice of antibiotic over amoxicillin-clavulanate based on its safety, acceptable taste and narrow spectrum.<sup>5</sup> The AAP AOM guidelines cite many of the same prevalence studies used to support the IDSA sinusitis guidelines, perhaps leading clinicians to question which approach to use, since the same pathogens (SP, HI, and *Moraxella catarrhalis*) are responsible for both clinical syndromes. An important caveat to the

prevalence studies cited by both groups is that most studied middle ear fluid from children with persistent or recurrent AOM, many of whom had likely been treated with antibiotics in the preceding month (and thus more likely to due to either PRSP or beta-lactamase-producing HI).

Whether clinicians use amoxicillin or amoxicillin-clavulanate, the low prevalence of PRSP in Oregon suggests that regular dose is likely adequate to treat cases of sinusitis or AOM due to SP; AWARE guidelines recommend high dose for patients at risk for PRSP, such as those with antibiotic use in the last 3 months, recent hospitalization, age less than 2 years or over 65 years, exposure to a child attending daycare, or presence of an immunocompromising condition (Table 2). Adherence to these criteria would result in automatic use of high-dose amoxicillin for all children < 2, the group with the highest risk of complications of AOM (and would be in keeping with AAP guidelines).

**Table 1. Resistance to selected antibiotics, invasive cases of *S. pneumoniae* and Group A streptococcus, Portland tricounty metropolitan area, 2010–2011.**

Antibiotic	<i>S. pneumoniae</i> (n=350)			Group A Streptococcus (n=108)		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Vancomycin	100	-	-	100	-	-
Ceftriaxone	98	2	-	Not tested	-	-
Amoxicillin	96	-	4	100	-	-
Cefotaxime	97	3	-	100	-	-
Cefuroxime	94	-	6	Not tested	-	-
Clindamycin	92	1	7	96	-	4
Penicillin	95	2	3	100	-	-
Tetracycline	93	1	7	85	-	15
Erythromycin	88	-	12	91	1	8
Trimethoprim-sulfamethoxazole	84	5	9	Not tested	-	-

The decision to use amoxicillin-clavulanate (either regular dose or high dose) should be based on whether risk factors for HI are present. Any patient who has received amoxicillin recently and meets criteria for treatment for AOM or sinusitis is a candidate for amoxicillin-clavulanate, as is a child with AOM concurrent with conjunctivitis (which is commonly associated with HI). Clinicians also may consider using amoxicillin-clavulanate for patients with more severe symptoms, or for those at risk for complications, such as bilateral otitis media.

Lastly, many of the guidelines make a solid case that macrolides are not appropriate first-line therapy for treatment of SP, which is the most common bacterial etiology for CAP, sinusitis and AOM.<sup>1-3</sup> Although rates of PRSP have fallen nationally and locally, SP is more often resistant to macrolides than other commonly used classes of antibiotics (Table 1). Empiric use of macrolides generally should be restricted to treatment of CAP in age groups most at risk for infection with one of the atypical pneumonias, or for lab-confirmed cases of *Bordetella pertussis* (or in patients with contact with a known case of pertussis).

**Table 2. Initial antibiotic choice for acute otitis media and bacterial rhinosinusitis.**

	Low risk for beta-lactamase producing HI (No risk factors )	High risk for beta-lactamase producing HI (Recent amoxicillin use, AOM associated with conjunctivitis, consider for bilateral OM, severe disease)
Low risk for PRSP (Based on local prevalence data showing risk for PRSP < 10%)	Regular-dose amoxicillin	Regular-dose amoxicillin + clavulanate
High risk for PRSP (Antibiotic use in the last 3 months, recent hospitalization, age less than 2 years or over 65 years, exposure to a child attending daycare, or presence of an immune-compromising condition)	High-dose amoxicillin	High-dose amoxicillin + clavulanate

## ACUTE OTITIS MEDIA (AOM)

### Diagnosis

Although the rate of diagnosis of AOM has declined since the mid-nineties, AOM remains the most common reason for children to receive antibiotics.<sup>11</sup> While clinical trials published in the last few years suggest cases of AOM meeting stringent criteria warrant antibiotic therapy,<sup>12,13</sup> continued emphasis and education about criteria for treatment with antibiotics could potentially result in lower antibiotic prescribing rates for this common condition in children.

Published jointly by the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) in 2004, a previous clinical practice guideline on management of AOM used a three-part definition for AOM: 1) acute onset of symptoms; 2) presence of middle ear effusion (MEE); and 3) signs of acute middle ear inflammation.<sup>14</sup> This definition has been criticized for lack of precision, since it would not exclude non-infectious cases of otitis media with effusion (OME), and the use of the phrase “uncertain diagnosis” may have permitted diagnoses of AOM without clear visualization of the tympanic membrane (TM).

Although studies attempting to identify symptoms (or clusters of symptoms) predictive of AOM have failed to identify any that could be used with much accuracy, studies evaluating otoscopic findings have found that the combination of a cloudy, bulging TM with impaired mobility was the best predictor of AOM.<sup>15-17</sup> Impaired mobility had the best sensitivity and specificity (identifying 95% of cases and ruling out 85%), followed by cloudiness, with 74% sensitivity and 97% specificity. Although a bulging TM identified only 51% of cases, a bulging TM was highly associated with the presence of a bacterial pathogen.<sup>18</sup>

The definitions developed for the 2013 guidelines have attempted to incorporate these findings in order

to identify children with highest risk for bacterial infection that would benefit from antibiotics.

Clinicians should diagnose AOM in children who present with: 1) moderate to severe bulging of the TM or new onset of otorrhea not due to otitis externa; or 2) mild bulging of the TM and recent (< 48 hours) onset of ear pain or intense erythema of the TM. In either case, clinicians should not diagnose AOM in the absence of MEE, as evidenced by lack of mobility of the TM with insufflation or the presence of an air-fluid interface behind the TM.

### Treatment

Since the 2004 guidelines were published, there has been significant research on initial management of AOM, including randomized controlled trials of antibiotic therapy versus no therapy or delayed therapy (trial of observation) that use stringent criteria for defining cases of AOM.<sup>12,13,19-21</sup> In general, these studies provide support for the safety of strategies utilizing observation or delayed prescription for young children. A systematic review concluded that antibiotics produced a small reduction in the number of children with persistent ear pain 2–7 days after diagnosis, with an overall number needed to treat (NNT) of 8, and that the majority of cases resolved spontaneously without complications.<sup>22</sup> Antibiotics provided the most benefit in children younger than 2 years of age with bilateral AOM and in children with otorrhea.

Accordingly, treatment should be reserved for children with severe signs and symptoms (i.e., severe otalgia for at least 48 hours or temperature of 39° C or higher). Secondly, children under 24 months of age, even those without severe signs and symptoms, but with *bilateral* otitis media warrant antibiotic therapy. Lastly, for the following two situations in which the benefit of antibiotics is less certain, the clinician may either prescribe antibiotics or offer observation with close follow-up, based on joint decision making with the parent or caregiver: 1)

unilateral AOM in children 6–23 months with only mild symptoms; or 2) children  $\geq$  24 months with mild symptoms (either unilateral or bilateral).

Several studies have found that only a third of children initially managed with the observation option required a rescue antibiotic, suggesting that antibiotic use could potentially be reduced by 65% in eligible children.<sup>20,23,24</sup> If used, initial observation of AOM should be part of a larger strategy that includes analgesics, parent information, and provision of a rescue antibiotic. Education of parents should include an explanation of the self-limited nature of most episodes of AOM, especially in children over 2 years of age, but should also point out the need for pain medication in the first 48–72 hours (regardless of whether antibiotics are prescribed). The decision not to prescribe antibiotics should be a joint decision between clinician and parent or caretaker, and should include a plan to provide an antibiotic if symptoms do not improve in 48–72 hours, either through use of a “safety net” or “wait and see” prescription or arrangement for phone contact in 2–3 days.

Recommendations for the first-line treatment of AOM (namely, amoxicillin) have not changed since 2004, despite the changing epidemiology of pneumococcal disease attributable to the use of conjugate vaccine. Some studies of pathogens recovered from middle ear fluid in the post-licensure period have documented a higher prevalence of HI in the period immediately following vaccine licensure, although these studies often included only patients

with persistent or recurrent AOM (and thus had likely had exposure to amoxicillin prior to undergoing tympanocentesis). More recent studies conducted 6–8 years post-vaccine licensure have found an increase in serotypes of SP not covered by vaccine, with the proportion of cases due to SP either equivalent or higher than HI.<sup>8-10,25</sup> Investigators have been unable to predict the responsible pathogen based on severity of symptoms or other clinical/otoscopic findings, although AOM associated with conjunctivitis often is caused by nontypeable HI.<sup>26-28</sup>

Justification for the continued recommendation of amoxicillin as a first-line agent (except when the patient has recently received amoxicillin) is based on its safety, low cost, acceptable taste, and narrow spectrum. Although the 2013 AAP guidelines recommend high-dose amoxicillin because it is more likely to be effective against resistant strains of pneumococcus, **use of the regular dose (45 mg/kg/day) is likely to be effective in Oregon, where the prevalence of PRSP is lower than in the rest of the country.** Similar to our recommendations for sinusitis, high-dose amoxicillin is recommended in children with risk factors for PRSP: those who have been on antibiotics in the last 3 months, recent hospitalization, age less than 2 years, exposure to a child attending daycare, or presence of an immunocompromising condition. For children who simultaneously present with conjunctivitis or whose symptoms do not improve in 48–72 hours, an antibiotic that provides additional beta-lactamase coverage should be chosen. High-

**Table 3. Initial management of children with AOM, by age and clinical characteristics.**

Characteristics	Patient Age	
	6-23 months	> 24 months
Otorrhea with AOM	Antibiotic therapy	Antibiotic therapy
Severe* symptoms (either bilateral or unilateral AOM)	Antibiotic therapy	Antibiotic therapy
Bilateral AOM (no otorrhea)	Antibiotic therapy	Antibiotic therapy or observation
Unilateral AOM (no otorrhea)	Antibiotic therapy or observation	Antibiotic therapy or observation

\* Persistent otalgia > 48 hours, temperature > 39°, or if follow-up is uncertain.

dose amoxicillin-clavulanate provides coverage for both PRSP and beta-lactamase producers. Cephalosporins are another alternative (cefixime, cefdinir or cefpodoxime) that can provide coverage for beta-lactamase producing organisms, although they are often inadequate against PRSP. Macrolides have limited efficacy against both HI and SP; clindamycin lacks efficacy against HI but is a reasonable choice for SP.

For most children allergic to penicillin, the cephalosporins listed above may be given safely. Data from the 1960s and 1970s showed that the rate of

cross-sensitivity to cephalosporins among penicillin-allergic children was 10%; while this is true of first-generation cephalosporins, the chemical structure of the second- and third-generation drugs is sufficiently different that cross-reactivity is extremely rare (approximately 0.1% in children who do not have a history of hives or anaphylaxis with penicillin).<sup>29</sup>

Lastly, the optimal duration of therapy is uncertain, although several studies suggest that 10 days is needed in children under 2 years, while a 5–7 day treatment course is likely adequate in children over 2 years of age.<sup>30,31</sup>



# SINUSITIS

## Diagnosis

Acute rhinosinusitis is defined as inflammation of the nasal and paranasal sinus mucosa for up to 4 weeks duration. There are many causes of rhinosinusitis, both infectious and non-infectious. It is an extremely common condition; in 2009, 13% of adults were diagnosed with rhinosinusitis in the previous 12 months.<sup>32</sup> Most episodes are related to viral infections, which are experienced by the average toddler six times a year.<sup>33</sup> However, acute bacterial rhinosinusitis (ABRS) comprises only a small fraction of cases. Most cases of acute sinusitis diagnosed in ambulatory care offices are caused by uncomplicated viral upper respiratory tract infections. Studies evaluating adults and children with upper respiratory tract symptoms have estimated that only 0.5%–5% of viral upper respiratory tract infections are complicated by bacterial sinusitis.<sup>34-36</sup>

Differentiating viral and bacterial sinusitis can be difficult. The gold standard for diagnosis of bacterial sinusitis is culture of sinus puncture aspirate. Due to the invasive nature of the procedure, it is seldom performed. Thus, clinicians have to rely on clinical signs and symptoms to make the diagnosis despite poor predictive value when compared to sinus aspirate culture.<sup>37</sup> Consensus guidelines have been published recently recommending that at least 1 of 3 of the following criteria be met to reach a diagnosis of ABRS:

- Onset with *persistent* signs or symptoms of acute rhinosinusitis, lasting for  $\geq 10$  days without clinical improvement;
- Onset with *severe* symptoms or signs of high fever ( $\geq 39^{\circ}\text{C}$ ) AND purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of the illness;

- Onset with *worsening* symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral upper respiratory infection that lasted 5–6 days and was initially improving (“double-sickening”).<sup>38,39</sup>

Currently, there are no validated studies that directly address the predictive value of specific signs and symptoms to diagnose ABRS when compared to sinus culture. Wald, et al., were able, however, to show that in pediatric patients who presented with either persistent symptoms or severe disease, a causative bacterial pathogen was isolated in 77% by sinus puncture.<sup>40</sup>

There have been multiple studies published that looked at the diagnostic utility of radiographic studies for ABRS. Unfortunately, these have all been disappointing. Although a normal radiograph has a strong negative predictive value, sinus radiographs, CTs, and MRIs often are abnormal in healthy children as well as children and adults with viral or bacterial URIs, rendering these non-specific tools unhelpful, costly, and with associated risks.<sup>41-47</sup>

Presence of a mucopurulent discharge, color of discharge, or sinus congestion or pressure have historically been used as criteria to make the diagnosis of ABRS. Unfortunately, these symptoms can be present with non-infectious, viral and bacterial causes of rhinosinusitis, and therefore are too non-specific to be of diagnostic value. It is a fallacy to equate the presence of purulent nasal discharge as helpful in distinguishing bacterial from viral rhinosinusitis.

## Treatment of adult patients

Successful treatment of ABRS rests largely on making a correct diagnosis, as antibiotics will not successfully treat a viral infection. Once a diagnosis of ABRS is made, it is recommended that empiric antibiotics

be prescribed promptly with a goal of shortening duration of illness, provide earlier symptomatic relief, and prevent recurrence or complications. This recommendation is a change from a previously held practice of “watchful waiting,” where antibiotics were held until patients failed non-antibiotic symptomatic management as many patients were thought to improve spontaneously with placebo.<sup>48</sup> This change in strategy comes as new evidence has shown that with more stringent diagnostic criteria excluding viral rhinosinusitis, a clearer antibiotic effect for ABRS can be seen. Wald, et al., were able to show that 64% of children with ABRS treated with amoxicillin-clavulanate showed improvement, compared to 32% of those treated with placebo, giving a number needed to treat (NNT) of only 3.<sup>49</sup> In contrast, a recent meta-analysis conducted by the Cochrane Collaborative reviewing the benefit of antibiotics for ABRS in adults showed a weaker benefit with a NNT of 18. This difference in the effectiveness of antibiotics likely can be attributed to much less stringent case definitions resulting in more non-bacterial sinusitis cases being enrolled.<sup>50</sup>

Although IDSA guidelines for the management of ABRS suggest use of amoxicillin-clavulanate rather than amoxicillin alone as first-line empiric antibiotic therapy for ABRS in adults, the recommendation was graded as weak, supported by low quality evidence.<sup>3</sup> Although data from some studies have found a higher prevalence of beta-lactamase HI in the post-pneumococcal conjugate vaccine era, little data exist for sinusitis; much of the literature comes from studies of otitis media, in which isolates were largely drawn from cases of recurrent or persistent disease, and thus more likely to be biased by previous antibiotic treatment.<sup>8,51,52</sup> Thus, AWARE recommends use of amoxicillin alone at the normal dose (1 g po bid).

For adults from areas with high rates of penicillin-resistant *Streptococcus pneumoniae* (PRSP), those

with severe infection, antibiotic use within the past 3 months, daycare exposure, advanced age, immunocompromise, recent hospitalization, high-dose amoxicillin (2g po bid) is recommended.<sup>53-55</sup> The frequency of PRSP varies geographically, and treatment with high-dose amoxicillin or amoxicillin-clavulanate is generally not recommended in areas where the rate of PRSP is < 10% (only 5% of invasive isolates had MICs > 2 in the period 2010–2011 in the Portland metropolitan area, which is the cutoff requiring treatment with a high dose of amoxicillin).\*

In cases of treatment failure, high-dose amoxicillin-clavulanate is recommended. Alternative options, such as doxycycline, can be considered for second-line therapy for those intolerant to beta-lactams. Macrolides, cephalosporins, or trimethoprim/sulfamethoxazole (TMP/SMX) are not recommended for empiric monotherapy due to high rates of resistance to SP.<sup>56,57</sup> Routine empiric coverage of *S. aureus* is not recommended due to low prevalence of this organism as a pathogen in ABRS.<sup>39</sup>

IDSA guidelines recommend that adults with uncomplicated ABRS be treated for 5–7 days.<sup>39</sup> Adjunctive therapies, such as saline irrigation of the nasal sinuses and intranasal corticosteroid spray, have been shown to improve symptoms and can be considered in addition to antibiotics.

### **Treatment of pediatric patients**

As with adults, antibiotic treatment should be reserved for patients seen with the criteria outlined above to minimize the number of children with viral URIs who receive antibiotics. In children, the most common pathogens responsible for bacterial sinusitis are SP, HI, and *Moraxella catarrhalis*, the same pathogens that cause AOM.

The antibiotic recommendations for sinusitis thus mirror the treatment recommendations for AOM.

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\* Annual *Streptococcus pneumoniae* surveillance reports are published by the Oregon Public Health Division's Emerging Infections Program and can be accessed at: <http://public.health.oregon.gov/DiseasesConditions/DISEASESAZ/Pages/disease.aspx?DID=24>

Amoxicillin is the preferred first-line agent. If the child has any risk factors for PRSP (age < 2 years, daycare attendance, recent hospitalization, antibiotic use within the last 3 months, presence of an immunocompromising condition), use of high-dose amoxicillin (90 mg/kg/day) should cover most strains of PRSP (MICs of  $\geq 2\mu\text{g/mL}$ ). In cases of treatment failure or if the patient has received amoxicillin in the past 3 months, switching to amoxicillin-clavulanate (high-dose) adds coverage for infections due to beta-lactamase-producing HI or *M. catarrhalis* (or ceftriaxone if the patient is unable to tolerate oral medications). Antibiotics previously used as alternatives are no longer recommended for empiric therapy due to high levels of resistance; these include macrolides, due to high rates of resistance to SP, and TMP/SMX, due to resistance to both SP and HI.<sup>56,57</sup>

In patients with a questionable history of penicillin allergy, skin testing can guide decisions about therapy. For children who have only mild allergies to penicillin (no history of hives or anaphylaxis) a third-generation oral cephalosporin (cefixime, cefdinir or cefpodoxime) can be used.

For children with a history of hives or anaphylaxis associated with penicillin, levofloxacin (the respiratory fluoroquinolone that has been most studied in pediatric patients) may be used. Although not approved by the FDA for use in this age group, the AAP has concluded that use of a fluoroquinolone maybe justified in situations where alternatives are limited.<sup>58</sup> Doxycycline has activity against most respiratory pathogens and provides an additional option in children over the age of 8 years.<sup>59,60</sup>

**Although the prevalence of penicillin-resistant *Streptococcus pneumoniae* in Oregon is low, if other risk factors for penicillin resistance (age <2 years or > 65 years, antibiotic use within the past 3 months, daycare exposure, immunocompromise, or recent hospitalization) are present, high-dose amoxicillin is the preferred therapy.**

The optimal duration of treatment for bacterial sinusitis has not been established. Recently published IDSA guidelines suggest a treatment course of 10–14 days, but admit that the evidence base for this recommendation is weak.<sup>39</sup> A treatment course of 7–10 days is commonly used and will avoid prolonged courses of antibiotics, thereby minimizing the risk of developing resistant strains of bacteria.

There is some evidence that saline irrigation and intranasal corticosteroids (the latter primarily in patients with a history of allergic rhinitis) may be of some benefit in patients with ABRS. Saline irrigants should be prepared from sterile or bottled water in light of reports of primary amebic encephalitis from contaminated tap water used for saline nasal irrigation.<sup>61</sup> For the vast majority of children likely to have a viral etiology for their symptoms, the mainstays of treatment are supportive, and may include ibuprofen or acetaminophen, nasal irrigation, and over-the-counter decongestants in children over the age of 2 years.

## COUGH ILLNESS/BRONCHITIS

### Diagnosis of adult patients

Bronchitis is a self-limited inflammation of the bronchial respiratory mucosa, resulting in a cough lasting longer than 5 days, often accompanied by bronchospasm and sometimes associated with sputum production. Although this respiratory condition generally is caused by a virus, a diagnosis of bronchitis often results in a prescription for antibiotics. In recent studies, antibiotics were prescribed in more than 75% of patients diagnosed with bronchitis, approximately 60% of which were broad-spectrum.<sup>62-64</sup>

The vast majority of cases of acute bronchitis have a non-bacterial cause.<sup>65,66</sup> Reviews of studies in both pediatric and adult patients have implicated respiratory viruses, particularly influenza, parainfluenza, rhinovirus, and respiratory syncytial virus, as the etiology of most cases of cough illness. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* each account for only 1%–5% of cases in adults and children. *B. pertussis* should be considered in patients with paroxysmal cough or any cough lasting > 2 weeks.<sup>67</sup> There is no convincing evidence to support the concept of acute bacterial bronchitis caused by bacterial pathogens that cause pneumonia in adults.

Lack of efficacy of antibiotics in patients with cough illness is well-documented. Three recent meta-analyses reviewed the published literature on acute bronchitis in adults and found no impact of antibiotic treatment on duration of illness, limitation of activity, or loss of work.<sup>65,68,69</sup> Several studies have similarly found no benefit in children. Additionally, several reviews in children and adults have examined the role of antibiotic treatment for prevention of bacterial complications of viral respiratory illnesses and found that antibiotics did not prevent or decrease the severity of bacterial complications.<sup>70</sup>

Evaluation of the patient with acute cough illness should focus on ruling out pneumonia, which usually

indicates a need for antibiotics. Fever is unusual in patients with acute bronchitis, who have few systemic symptoms. The absence of abnormalities in vital signs and chest examination usually reduces the likelihood of pneumonia to the point where further diagnostic testing is not necessary.<sup>66</sup> Although the presence of purulent sputum, reported in 50% of patients with bronchitis, is often used as a clinical criterion for initiating antibiotics, purulence occurs when inflammatory cells or sloughed mucosal epithelial cells are present, and it can result from either viral or bacterial infection.<sup>71</sup>

### Treatment of adult patients

For patients with acute bronchitis of suspected viral etiology, use of the term “viral chest cold” rather than bronchitis may help reduce patient expectations for receipt of antibiotics.

Cough in patients with acute bronchitis usually lasts 10 to 20 days. Wheezing also may occur. In the absence of signs and symptoms of pneumonia, antibiotics generally are not warranted for cough illnesses of < 3 weeks duration. For patients with cough persisting for more than 3 weeks, chest radiography is recommended in the absence of other known causes. The most common causes of prolonged cough are postnasal drip, asthma/reactive airway disease, gastroesophageal reflux disease (GERD) and post-infectious cough. Angiotensin-converting-enzyme (ACE) inhibitor drug cough, chronic bronchitis, bronchiectasis, and malignancy are less commonly seen.<sup>65,66</sup> Therapy should be directed at specific underlying causes.

Patients with exacerbations of chronic obstructive pulmonary disease (defined by a change in sputum volume or quality, with or without systemic symptoms) may benefit from short courses of antibiotics, although only patients with severe exacerbations are likely to benefit.<sup>72,73</sup> Appropriate empiric therapies include amoxicillin, trimethoprim/sulfamethoxazole or doxycycline. These patients also have been shown to benefit

from a short course of oral corticosteroids.<sup>74</sup> Azithromycin, clarithromycin or doxycycline is recommended for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*.<sup>75</sup>

### Diagnosis in children

Cough is a common presenting complaint in pediatric patients, and approximately one in 10 children in the United States uses a cough and cold medication in a given week.<sup>76</sup> Although recent review articles from the fields of pediatric allergy, otolaryngology and pulmonology report different estimates of the relative frequencies of various etiologies of cough in pediatric patients, they all suggest that infectious etiologies are the most common sources of cough, with acute viral upper respiratory infection accounting for the majority.<sup>77-79</sup> Other infectious syndromes to consider are bronchiolitis, croup, and pneumonia; in terms of specific etiologies, pertussis, mycoplasma, and *Chlamydophila pneumoniae* can all cause prolonged episodes of cough. Postnasal drip (also termed upper airway cough syndrome) causes irritation or inflammation of upper airway receptors and commonly follows acute viral respiratory tract infections, but also can be associated with sinusitis and allergic rhinitis.<sup>80</sup>

In addition to the infectious etiologies for cough mentioned above, considering etiologies by age group may be helpful.<sup>78</sup> In infants under 1 year of age, consideration should be given to congenital and neonatal infections as well as congenital malformations, such as tracheoesophageal fistula, vascular rings or airway malformations. Cystic fibrosis may present with cough and failure to thrive, while GERD often is accompanied by feeding difficulties. The sudden onset of cough in a preschool-aged child could signal an inhaled foreign body, while a persistent cough could herald the onset of asthma, and cystic fibrosis still figures in the differential diagnosis at this age. Asthma also can present for the first time in school-aged children and adolescents, as does habit or psychogenic cough, which is a diagnosis

of exclusion. Clinicians should always inquire about smoke exposure, either passive in younger children or active in older children who have adopted bad habits.

### Treatment in children

In general, most children with cough for less than 3–4 weeks duration are likely to have an infectious etiology, which is most likely viral and does not require specific treatment (although an inhaled foreign body should always be considered in children under 5 years of age). Although most symptoms of acute viral upper respiratory infections resolve in 7 days, cough and runny nose can last up to 20 days;<sup>81</sup> providing parents with information on the expected length of time for resolution of acute viral infections may reduce the anxiety and the need for medication for the child. For children diagnosed with pertussis, *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*, azithromycin or doxycycline (the latter in children over the age of 8 years) are recommended. Authors from all three disciplines (allergy, otolaryngology and pulmonology) agree that patients with a history of cough for greater than 4 weeks warrant evaluation; in addition to a thorough history and physical, chest radiology and spirometry (in children > 3–6 years of age) are suggested. As with adults, therapy should be directed at underlying causes.

Authors of these recent guidelines and reviews all tend to agree that over-the-counter medications are commonly overused, with large potential for adverse events. Over-the-counter cough and cold medications are no longer recommended for children under the age of 2, and most have little benefit in older children. In particular, the AAP recommends against codeine- and dextromethorphan-containing cough medications in children due to their unproven efficacy in children.<sup>82</sup> Currently recommended home remedies include honey before bedtime, saline nasal washes, and topical vapor rubs.<sup>83</sup>

## PHARYNGITIS

### Diagnosis

A wide range of infectious agents, most commonly viruses, causes pharyngitis. Group A beta-hemolytic streptococcus (GABHS, or *Streptococcus pyogenes*) accounts for 5%–15% of pharyngitis cases.<sup>84</sup> Rationale for treatment of GABHS traditionally has included prevention of rheumatic fever, prevention of suppurative complications, relief of symptoms, and reduction in transmission of infection to household and other close contacts.

Although use of penicillin has demonstrated reductions in the sequelae of rheumatic fever, the relative benefit of antibiotics is low given the rareness of this complication.<sup>85</sup> Rheumatic fever is now so rare in the U.S. that 3,000–4,000 patients with GABHS would need to be treated to prevent a single case of acute rheumatic fever (ARF).<sup>86</sup> Recent studies reviewing the presentation of peritonsillar abscess suggest that as many as 50% of patients diagnosed with this complication present without prior consultation for sore throat, and may not be prevented by antibiotics.<sup>87,88</sup> Antibiotic therapy for pharyngitis has never been shown to prevent acute glomerulonephritis. Lastly, streptococcal infection due to groups C and G has not been linked to acute rheumatic fever or glomerulonephritis, nor is there any evidence that antibiotic treatment impacts clinical improvement.

Relief of suffering often is a concern of both patients and clinicians. Antibiotic therapy instituted within

**In a study of children and adults with sore throat, 68% of children with a Centor score of 3 or 4 had a positive throat culture, compared to 31% of adults. Empiric treatment of GAS based on symptoms alone should be discouraged.**

2–3 days of symptom onset hastens symptomatic improvement in patients with GABHS by only 1–2 days.<sup>85</sup> Antibiotics have no effect on the clinical course of patients with negative cultures.

Given the low prevalence of GABHS in cases of pharyngitis, it is important to reduce use of antibiotics for cases of pharyngitis unlikely to be due to GABHS. A combination of the Centor criteria (tonsillar exudates, tender anterior cervical lymphadenopathy, absence of cough, history of fever) and rapid antigen testing can be used to predict the presence of GABHS with reasonable accuracy.<sup>89</sup> Positive and negative predictive values will vary depending on the prevalence of GABHS in the population studied, but several studies have found that the presence of 3–4 of these criteria has a poor positive predictive value (in other words, a low chance that the patient actually has GABHS).<sup>86</sup> In one validation study that reviewed a series of 787 children and adults with sore throat who underwent rapid testing and throat culture, 68% of children with a score of 3 or 4 had a positive throat culture, compared to 31% of adults.<sup>90</sup> In comparing combinations of strategies for testing and treatment, total antibiotic prescriptions were lowest with rapid testing only (at the expense of missed infections) and highest for empirical treatment, largely due to a high rate of unnecessary prescriptions in adults.

A reasonable strategy that maximizes the probability of identifying cases of GABHS, but avoiding unnecessary treatment is to defer testing and treatment in persons who meet only 1 criterion, test patients who meet 2–4 criteria with a rapid antigen test, and limit antibiotic therapy to patients with positive test results.<sup>4</sup> Diagnostic studies for GABHS are not indicated for children < 3 years old because acute rheumatic fever is rare in infants and toddlers and the incidence of streptococcal pharyngitis and the classic presentation of streptococcal pharyngitis are uncommon in this age group.<sup>4</sup>

For children and adolescents, a negative rapid antigen test should be confirmed with a throat culture

result, unless the clinician has ascertained in his or her own practice that the rapid antigen test used is comparable to a throat culture. Since the risk of ARF is much lower in adults than children, diagnosis of this infection in adults can be ruled out by a negative rapid antigen test. Use of a sensitive rapid antigen test without culture confirmation has not been associated with an increase in suppurative and nonsuppurative complications of GABHS.

### Treatment

The management of GABHS pharyngitis is straightforward. The goal is to use as narrow spectrum an agent as possible. Since GABHS is still universally susceptible to penicillin, either penicillin or amoxicillin remain the first choice for children and adults.<sup>4</sup> Although not FDA-approved, standard-formulation amoxicillin given once daily has efficacy in children similar to that of twice-daily amoxicillin or penicillin;<sup>91,92</sup> an oral, time-released formulation of amoxicillin recently was approved by

the Food and Drug Administration for once-daily therapy of GABHS pharyngitis in those 12 years of age and older.

Although macrolides historically have been recommended for patients with allergies to penicillin, their use has been discouraged in recent years due to the emergence of low levels of erythromycin-resistant GABHS in the U.S.<sup>93</sup> Narrow-spectrum cephalosporins are recommended for use in patients with mild penicillin allergies and clindamycin for those with severe allergies (i.e., hives or anaphylaxis), since the prevalence of macrolide-resistant GABHS tends to be more common than resistance to clindamycin in the U.S. If a macrolide or azalide is used, preference should be given to azithromycin over erythromycin due to the lower incidence of gastrointestinal side effects.

**Table 4. Centor Criteria for evaluating risk of GAS in cases of pharyngitis**

Signs and symptoms predictive of GAS pharyngitis
Tonsillar exudate
Tender anterior cervical lymph nodes
Absence of cough
Presence of fever



## COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Pneumonia is the eighth most common cause of death in the U.S.<sup>94</sup> An estimated 915,900 cases of community-acquired pneumonia occur annually among seniors in the United States, and approximately 1 of every 20 persons aged  $\geq 85$  years will have a new episode of community-acquired pneumonia each year.<sup>95</sup> At the other end of the spectrum of age, 3–4 cases of pneumonia per 100 children under 5 years of age occur annually in the U.S.<sup>96</sup>

A number of pathogens can cause pneumonia, although a few organisms are responsible for most cases.<sup>97</sup> SP is the most common agent across all patient settings; other common bacterial etiologies are non-typeable HI and *Moraxella catarrhalis*. The incidence of atypical agents rises after the age of 5 years, with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* the most commonly identified. Use of polymerase chain reaction (PCR) testing methods has increased the number of viral agents identified in cases of pneumonia, particularly among preschool-aged children.<sup>98,99</sup>

The Infectious Diseases Society of America (IDSA) has published separate guidelines for the management of community-acquired pneumonia, one focusing on adults and one with guidance for infants and children over 3 months of age.<sup>1,2</sup> The approach to diagnosis (including the need for chest radiography and whether to pursue diagnostic testing for specific agents), site of care, and empiric treatment regimens vary by age and are covered separately below.

### Diagnosis and treatment of adult patients

The use of objective admission criteria can accurately identify patients at low risk for mortality and decrease the number of patients hospitalized with CAP.<sup>100</sup> Since the costs of inpatient management of CAP are 20-fold higher than outpatient treatment, identifying the patient most

likely to benefit from hospitalization is one of the single most important decisions made by clinicians in managing CAP.<sup>101</sup> The following guidelines are only applicable to patients in the outpatient setting, not human immunodeficiency virus (HIV) infected or immunocompromised, who are over the age of 18 years.

The most recent British Thoracic Society scoring system for determining risk of mortality has the acronym CURB-65.<sup>102</sup> It gives 1 point for each of the following: confusion, blood urea nitrogen (BUN  $> 7$ ), respiratory rate  $>30$ , low blood pressure (systolic  $< 90$  or diastolic  $< 60$ ), and age  $\geq 65$ . Patients with a score of 0–1 have less than approximately 2% mortality and likely are safe to be treated as an outpatient. Patients with 2 or more points have greater than 9% mortality and should be admitted to the hospital for treatment. Patients with scores of 3 or more may benefit from intensive care treatment. Any scoring system is intended to be an aid to clinical judgment and should not override the clinical judgment of an experienced practitioner.

**Table 5. CURB-65: Risk of mortality and site of care.**

Total score	Mortality %	Suggested site of care
0	0.7	Outpatient
1	2.1	Outpatient
2	9.2	Inpatient
3	14.5	Inpatient/ICU
4 or 5	40	ICU

**Table 6. Assign 1 point for each factor that is present.**

	Clinical factor
<b>C</b>	Confusion
<b>U</b>	Urea
<b>R</b>	Respiratory rate $>30$ breaths per minute
<b>B</b>	Blood pressure (systolic $<90$ or diastolic $<60$ )
<b>65</b>	Age $>65$ years

Although IDSA guidelines for adults make it very clear that all episodes of pneumonia need to be confirmed by chest radiography (CXR), the

guidelines do not provide specific objective criteria for the decision to obtain a chest radiograph, and the decision to obtain a CXR remains a clinical decision. No single criterion, such as presence of cough or tachypnea, is clinically useful in predicting the presence of pneumonia, particularly in the elderly.<sup>103,104</sup> Decision rules based on combinations of these findings are also imperfect. Although presence of several signs and symptoms increases the probability that a patient has pneumonia, specificity is low (meaning that many patients predicted to have pneumonia are actually false positives), which would result in overuse of antibiotics if these rules were applied without obtaining radiologic confirmation.<sup>105</sup>

**The use of objective admission criteria can accurately identify patients at low risk for mortality and decrease the number of patients hospitalized with CAP, lowering cost and the risk of complications.**

The CXR, in addition to confirming the diagnosis, may shed light on the etiology and prognosis of the patient as well as identify alternative diagnoses, such as congestive heart failure or pulmonary malignancy. CXR does not detect all infiltrates; a heightened level of scrutiny may be required for elderly or immunocompromised patients.

Although patients treated as outpatients require no diagnostic testing beyond CXR, patients admitted to the hospital require the following workup: complete blood cell count and differential, routine chemistries, measurement of oxygen saturation (oximetry or arterial blood gas) and pneumococcal urinary antigen. Consideration should be given to obtaining 2 pre-treatment blood cultures, *Legionella* urinary antigen, and sputum gram stain and culture. All patients admitted to the intensive care unit (ICU) should get all of the above with the addition of a

*Legionella* urinary antigen. For selected patients, especially those aged 15–24 years, HIV testing should be considered, and patients with specific risk factors should be tested for tuberculosis.

Treatment should be pathogen-specific if the etiology is known or strongly suspected, with an emphasis on choosing the agent that is most cost-effective, least toxic and with the narrowest spectrum possible. Recommendations for empirical treatment are based on severity of illness, pathogen probabilities, resistance patterns of *S. pneumoniae* (the most common and most lethal agent), and comorbid conditions.

For patients treated as outpatients, previously healthy adults should receive an advanced macrolide (azithromycin or clarithromycin) or doxycycline unless they have been on antibiotics recently. Patients who have received antibiotics in the past 3 months or who have comorbidities (chronic obstructive pulmonary disease [COPD], diabetes, congestive heart failure, malignancy, end-stage renal disease, alcoholism, liver disease or asplenia) are at higher risk for PRSP.<sup>53,106</sup> These patients should receive a macrolide plus a beta-lactam (high-dose amoxicillin, high-dose amoxicillin-clavulanate, cefdinir, cefpodoxime, cefprozil or cefuroxime) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin). The recommendations for inpatients are an advanced macrolide plus a beta-lactam (in this case, cefotaxime, ceftriaxone, ampicillin or ampicillin-sulbactam), again with a respiratory fluoroquinolone alone as a second choice. Anti-pseudomonal and/or anti-methicillin resistant *Staphylococcus aureus* therapy should be used for severely ill patients with recent health care exposure.<sup>107</sup>

### **Diagnosis and treatment of children**

AWARE guidelines for management of children with CAP are largely based on recently published recommendations that provide guidance in the care of otherwise healthy infants, children

and adolescents;<sup>2</sup> management of neonates and young infants through the first 3 months of life, immunocompromised children, children receiving home mechanical ventilation, and children with chronic conditions, such as cystic fibrosis, are beyond the scope of these guidelines.

Unlike published recommendations for adults, decisions about site of care should be largely based on clinical assessment of severity of illness, since no validated scoring systems exist that predict which children with pneumonia should be hospitalized. Children who have moderate to severe CAP as defined by respiratory distress (presence of tachypnea, retractions, grunting, nasal flaring, apnea, altered mental status) should be hospitalized for management; a pulse oximetry measurement <90% on room air generally is considered the threshold for hypoxemia suggesting the need for hospitalization.<sup>108</sup> Historically, infants under 3 months have been treated in the inpatient setting, and admission of infants aged 3–6 months with suspected CAP is also prudent.<sup>109</sup>

Pulse oximetry should be performed in all children with pneumonia and suspected hypoxemia, while blood cultures and chest X-rays are not necessary for nontoxic, fully immunized children with CAP managed in the outpatient setting;<sup>110-115</sup> both are recommended, however, for children who are sufficiently ill to warrant inpatient management and have a higher likelihood of a bacterial etiology (based on the presence of hypoxia or other signs and symptoms of respiratory distress). Sputum samples for culture and Gram stain should also be obtained in hospitalized children who can produce sputum, although urinary antigen detection tests for pneumococcus are not recommended due to the high likelihood of false positives.<sup>116</sup> Sensitive and specific tests for the rapid diagnosis of influenza virus, respiratory syncytial virus (RSV) and other respiratory viruses (if available) should be used in

**Preschool children not requiring inpatient admission typically do not require antibiotic therapy, since viral pathogens cause the majority of cases of CAP in this age group.**

the evaluation of children with CAP. A positive test for a viral pathogen may decrease the need for both additional diagnostic studies and antibiotic use.<sup>117-120</sup>

Recommendations for antimicrobial therapy for CAP vary by age group and site of care. Preschool children treated as outpatients do not routinely require antimicrobial therapy for CAP, because viral pathogens are responsible for the majority of cases in this age group,<sup>99,121,122</sup> amoxicillin should be used as first-line therapy for previously healthy, immunized preschool and school-aged children and adolescents.<sup>123</sup> Given that the prevalence of penicillin resistance among invasive isolates of pneumococcus is low in the Portland metropolitan area (5% in 2011), use of a standard dose of amoxicillin 3 times a day is likely to be successful; alternatively, use of a high dose (90 mg/kg/day) divided into 2 daily doses is likely to achieve satisfactory levels of amoxicillin in infected lung tissue and may improve patient compliance.<sup>124,125</sup> To achieve sufficient amoxicillin levels to successfully treat a relatively resistant infection (MICs > 2 µg/mL), a high total daily dose of 90 mg/kg/day divided into 3 doses should lead to microbiologic and clinical cure.<sup>126</sup>

Oral cephalosporins do not provide activity at the site of infection that equals high-dose amoxicillin, and currently available macrolides are not recommended as empiric therapy when pneumococcal CAP is suspected, due to high levels of resistance to macrolides.

Atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, should be considered in the differential of school-aged children and adolescents with compatible clinical findings: a slowly progressing course, characterized by malaise, sore throat, low-grade fever, and cough developing over 3–5 days. In the latter scenario, azithromycin (or doxycycline in children over age 8) would be preferred.<sup>127</sup> Influenza antiviral therapy should be administered as soon as possible to children with lab-confirmed influenza who are under the age of 5 years or with underlying conditions putting them at risk for sequelae of influenza.<sup>128</sup>

With respect to inpatient management, ampicillin or penicillin G should be given to fully immunized infants or school-aged children with CAP (given the low level of PRSP in Oregon). Empiric therapy with a third-generation cephalosporin (ceftriaxone or cefotaxime) is preferred for children who are not fully immunized or for infants and children

with life-threatening infections, including those with empyema.<sup>129</sup>

A few clinical scenarios dictate the need for double coverage. Empiric therapy with a macrolide, in addition to a beta-lactam, should be prescribed in a hospitalized child with clinical symptoms compatible with an atypical bacteria; laboratory testing for *M. pneumoniae* should be performed if results can be made available quickly enough to impact care. If clinical or laboratory characteristics are consistent with infection due to *S. aureus*, vancomycin or clindamycin should be provided in addition to beta-lactam therapy.

Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for mild cases treated as an outpatient. Longer durations of therapy may be required for certain pathogens, such as community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA).



## PREVENTION OF RESPIRATORY INFECTIONS

### Vaccination

Infants should be vaccinated against *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and pertussis; infants over 6 months of age, as well as children and adolescents, should receive an annual influenza vaccination.<sup>130</sup> High-risk infants (including prematurity, chronic lung disease or congenital heart disease) should be provided immune prophylaxis with respiratory syncytial virus (RSV)-specific monoclonal antibody to decrease the risk of severe pneumonia and hospitalization caused by RSV.<sup>131</sup>

In adults, the CDC's Advisory Committee on Immunization Practices (ACIP) recommends a one-time dose of Tdap and an annual influenza vaccination for all adults.<sup>132,133</sup> Persons at high risk for complications of influenza (and for whom additional efforts should be made to ensure annual vaccination) include those with underlying conditions such as cardiovascular or chronic lung disease, metabolic and immune-compromising conditions, pregnant women, and those aged > 65 years.<sup>133</sup> Health care workers are urged to receive influenza based on their higher risk of exposure to influenza and higher likelihood of spreading infection to vulnerable patients.

Another group considered a priority for influenza vaccination includes parents, siblings, grandparents, child care providers and health care workers who care for infants < 6 months of age, including pregnant women. Similarly, adolescents and adults who anticipate having close contact with infants < 12 months of age should receive 1 dose of Tdap; the ACIP recently recommended that pregnant women (after 20 weeks gestation) receive a dose of Tdap with each pregnancy, regardless of the patient's prior history of receiving Tdap.<sup>134</sup>

Use of pneumococcal vaccine in adults was limited to 23-valent polysaccharide vaccine (PPSV23, recommended for all adults > 65 years and those at high risk for pneumococcal disease) until 2012, when the ACIP published guidelines for use of PCV13 in persons over 19 years of age with immunocompromising conditions, functional or anatomic asplenia, CSF leaks or cochlear implants.<sup>135</sup> Given that PPSV23 contains 12 of the serotypes included in PCV13, plus 11 additional serotypes, PPSV23 is still recommended for adults who have also received PCV13.

### Behavioral changes

Use of tobacco is associated with increased risk of pneumococcal disease, as is legionella infection. Smoking cessation should be a goal for persons hospitalized with CAP who smoke, and persons who will not quit should be vaccinated for both SP and influenza.<sup>136</sup>

In children, passive smoking is a risk factor for invasive *Streptococcus pneumoniae*, and eliminating exposure to passive smoke has been postulated to reduce the incidence of AOM in infancy.<sup>5,137</sup> The consistent finding of a lower incidence of AOM and recurrent AOM with increased breastfeeding supports the AAP recommendation to encourage exclusive breastfeeding for the first 6 months of life, and breastfeeding has also been associated with a reduced risk of hospitalization from lower respiratory tract infection.<sup>138</sup>

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## Practice Guidance for Judicious Use of Antibiotics

In the well-appearing patient, antibiotics are not the answer.

### Acute Otitis Media (AOM)

Diagnosis requires middle ear effusion (MEE) plus:

1. Moderate to severe bulging of the tympanic membrane (TM); *or*
2. New onset of otorrhea not due to otitis externa; *or*
3. Mild bulging of the TM and recent (< 48 hours) onset of ear pain or intense erythema of the TM

#### Criteria for Treatment with Antibiotics

Antibiotic therapy is indicated for patients with:

1. Severe\* signs and symptoms of any age; *or*
2. Children < 2 yrs with milder symptoms but *bilateral* disease

Consider antibiotics or offer observation in the following situations, in consultation with parent/caretaker:

1. Children 6–23 months with mild symptoms and unilateral AOM;
2. Children > 2 years with mild symptoms, either unilateral or bilateral

All patients with AOM, whether treated with antibiotics or not, need an assessment for pain.

Oral medications are preferred due to longer duration of action.

\* Severe symptoms defined as severe otalgia for at least 48 hrs. or temperature > 39°C.

#### Management

Amoxicillin (45 mg/kg/day po bid)

Use high-dose amoxicillin (90 mg/kg/day) if risk factor for penicillin-resistant pneumococcus present (local rates of resistance > 10%, age < 2 years, daycare exposure, recent hospitalization, immunocompromise or antibiotic use in past 3 months.)

For patients with conjunctivitis or who fail to improve after 48–72 hours, use antibiotic that provides coverage for beta-lactamase-producing organism, such as amoxicillin-clavulanate, cefixime, cefpodoxime, cefdinir or ceftriaxone.\*

Duration: 10 days if < 2 years, 5–7 days if older.

Mild penicillin allergy (no hives or anaphylaxis): cefixime, cefdinir or cefpodoxime.

If history of hives or anaphylaxis with penicillin or unresponsive to above regimens: clindamycin, consider levofloxacin, consider ENT consultation and tympanocentesis.

\* If used for persistent infection, may need 3 daily doses of ceftriaxone.

These guidelines were produced in collaboration with the Infectious Diseases Society of Oregon.

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# Practice Guidance for Judicious Use of Antibiotics

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## Pharyngitis in Children and Adults

### Signs and symptoms:

1. Tonsillar exudate
2. Tender anterior cervical lymph nodes
3. Absence of cough
4. Fever

2–4 CRITERIA PRESENT

< 2 CRITERIA PRESENT

OBTAIN RAPID STREPTOCOCCAL ANTIGEN TEST

DO NOT TEST

POSITIVE

NEGATIVE

### Group A Streptococcal Pharyngitis Management

Adults: single-dose benzathine penicillin 1.2 million units IM or penicillin V 500 mg po bid x 10 days.

Children < 12 years: single-dose benzathine penicillin 25,000 units/kg IM (max. dose 1.2 million units) or amoxicillin or penicillin V 50 mg/kg/day po divided bid or tid x 10 days.

Mild penicillin allergy: (no hives or anaphylaxis): cephalexin or cefadroxil.

Severe allergy: clindamycin

*Children with streptococcal pharyngitis should not return to school or child care during the first 24 hours after beginning antimicrobial therapy. Follow-up throat culture is not recommended.*

### Viral Pharyngitis Management

90% of pharyngitis is viral in origin.

Antibiotics benefit only the 10% of cases caused by Group A beta-hemolytic streptococcus.

Symptomatic treatments:

- Avoid cigarette smoke
- Gargle with dilute salt water
- Acetaminophen or ibuprofen as needed for fever or pain
- Throat lozenges (age-appropriate)
- Hydration—drink plenty of liquids
- Adequate rest

For children, a negative rapid antigen test should be confirmed with a throat culture. Due to the lower incidence of strep infection and acute rheumatic fever in adults, a negative rapid test alone is sufficient to rule out Group A strep infection in adults.\*

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\* According to Clinical Laboratory Improvement Amendments (CLIA) guidelines, throat culture should be performed if required by the manufacturer.

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## Practice Guidance for Judicious Use of Antibiotics

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### Acute Sinusitis / Rhinosinusitis – Adults

#### Sinus congestion/pressure, nasal discharge

UPPER RESPIRATORY INFECTION WITH MILD TO MODERATE DISCHARGE LASTING < 10 DAYS

OR

SEVERE SYMPTOMS LASTING < 3 DAYS

PERSISTENT SYMPTOMS FOR > 10 DAYS WITHOUT IMPROVEMENT

OR

SEVERE SYMPTOMS AND PURULENT NASAL DISCHARGE OR FACIAL PAIN FOR >3 DAYS AT BEGINNING OF ILLNESS

OR

WORSENING OF SYMPTOMS (NEW FEVER, HEADACHE, NASAL DISCHARGE) AFTER HAVING INITIALLY IMPROVED AFTER 5 DAYS OF A TYPICAL UPPER RESPIRATORY INFECTION

Purulent nasal secretions or sputum do not predict bacterial infection.

The majority of case of acute rhinosinusitis seen as outpatients are caused by uncomplicated viral upper respiratory infection.

Treatment of viral infections with antibiotics does nothing to prevent complications or improve symptoms.

#### Management

Nasal corticosteroid spray (particularly in patients with allergic rhinitis)

Sinus irrigation

Acetaminophen or ibuprofen as needed

Supportive care

#### Management

Amoxicillin 1g po bid x 5–7 days (macrolides are not recommended due to high rates of resistance).

Use high dose amoxicillin (2g po bid) if risk factor for penicillin-resistant pneumococcus (PCN resistance  $\geq$  10%, severe infection, day care exposure, advanced age, immunocompromise, recent hospitalization or antibiotic use in past 3 months)

Treatment failure: High dose amoxicillin-clavulanate

If PCN allergic: Doxycycline

Consider Adjunctive Therapy:

- Nasal corticosteroid spray
- Sinus irrigation

If still no improvement after 72 hours, consider imaging or ENT consultation.

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## Practice Guidance for Judicious Use of Antibiotics

In the well-appearing patient, antibiotics are not the answer.

### Acute Sinusitis / Rhinosinusitis – Children

#### Sinus congestion/pressure, nasal discharge

UPPER RESPIRATORY INFECTION WITH MILD TO MODERATE DISCHARGE LASTING < 10 DAYS

OR

SEVERE SYMPTOMS LASTING < 3 DAYS

PERSISTENT SYMPTOMS FOR >10 DAYS WITHOUT IMPROVEMENT

OR

SEVERE SYMPTOMS AND PURULENT NASAL DISCHARGE OR FACIAL PAIN FOR >3 DAYS AT BEGINNING OF ILLNESS

OR

WORSENING OF SYMPTOMS (NEW FEVER, HEADACHE, NASAL DISCHARGE) AFTER HAVING INITIALLY IMPROVED AFTER 5 DAYS OF A TYPICAL UPPER RESPIRATORY INFECTION

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Nasal corticosteroid spray (particularly in patients with allergic rhinitis)

Sinus irrigation

Acetaminophen or ibuprofen as needed

Supportive care

#### Management

Amoxicillin (45 mg/kg/day bid x 7–10 days)

Use high dose amoxicillin (90 mg/kg/day bid) if risk factor for penicillin-resistant pneumococcus present (local rates of PCN resistance > 10%, age < 2 years, day care exposure, immunocompromise, recent hospitalization or antibiotic use in past 3 months)

Treatment failure: High dose amoxicillin-clavulanate

Mild penicillin allergy (no hives or anaphylaxis): cefixime, cefpodoxime or cefdinir

If history of hives or anaphylaxis with penicillin: levofloxacin or doxycycline (if age > 8 years)

If still no improvement after 72 hours, consider imaging or ENT consultation

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## Practice Guidance for Judicious Use of Antibiotics

In the well-appearing patient, antibiotics are not the answer.

### Cough Illness / Bronchitis\* — Adults

Cough without evidence of pneumonia

#### ACUTE / < 3 WEEKS COUGH

Evaluation should focus on ruling out serious illness; normal vital signs and chest exam effectively rule out pneumonia. Cough illness/bronchitis is caused by viral pathogens in > 90% of cases.

Antibiotics are not effective in treating cough illness/bronchitis in patients without chronic lung disease.

Antibiotic treatment does not prevent bacterial complications such as pneumonia.

The presence of sputum and its characteristics are not helpful in distinguishing bacterial from viral infections.

#### Management

Do not use antibiotics for cough less than 21 days in a well-appearing adult without clinical evidence of pneumonia.

Therapeutic measures include: avoid cigarette smoke, consider bronchodilators, drink plenty of liquids, steam (e.g., from shower or bath) to loosen secretions, acetaminophen or ibuprofen as needed for fever or pain and adequate rest for symptom relief.

These guidelines were produced in collaboration with the Infectious Diseases Society of Oregon.

Oregon Alliance Working for Antibiotic Resistance Education  
Oregon Health Authority/Public Health Division  
Acute and Communicable Disease Prevention  
800 NE Oregon, Ste. 772, Portland OR 97232  
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[www.healthoregon.org/antibiotics](http://www.healthoregon.org/antibiotics)  
[oregon.aware@state.or.us](mailto:oregon.aware@state.or.us)

#### CHRONIC / > 3 WEEKS COUGH

Adults with prolonged cough or recurrent episodes can be evaluated for:

- Post-nasal drip syndrome
- Asthma or reactive airway disease
- Gastroesophageal reflux disease (GERD)
- Post-infectious cough
- Smoking or second-hand smoke exposure
- ACE-inhibitor drug cough
- Chronic bronchitis
- Bronchiectasis
- Malignancy

Other infectious agents rarely causing prolonged cough include *B. pertussis*, *M. pneumoniae* or *C. pneumoniae*.

#### Management

Obtain CXR.

Treat COPD exacerbation (fever, leukocytosis and purulent sputum) with amoxicillin, TMP/SMX or doxycycline, and a short course (7–10 days) of oral corticosteroids.

Treat confirmed *B. pertussis*, *M. pneumoniae* or *C. pneumoniae* with azithromycin or clarithromycin.

For other etiologies, direct therapy to the specific underlying cause.

\* The term bronchitis triggers an expectation for antibiotics and should be avoided or carefully explained. Other terms, such as “chest cold,” may be preferable.

Updated: August 2013

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In the well-appearing patient, antibiotics are not the answer.

### Cough Illness / Bronchitis\* — Children

Cough without evidence of pneumonia

#### ACUTE / < 4 WEEKS COUGH

Most cough illness in children is caused by viral pathogens.

Antibiotic treatment does not prevent bacterial complications such as pneumonia.

Rhinovirus often triggers a cough that lasts up to 3 weeks.

The presence of sputum and its characteristics are not helpful in distinguishing bacterial from viral infections.

#### Management

Do not use antibiotics for cough less than 4 weeks in a well-appearing child without clinical evidence of pneumonia.

Therapeutic measures include: avoid cigarette smoke, drink plenty of liquids, nasal saline washes, topical vapor rubs, acetaminophen or ibuprofen as needed for fever or pain, and adequate rest.

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#### CHRONIC / > 4 WEEKS COUGH

Consider pertussis in children with paroxysmal cough, inspiratory whoop, or history of exposure.

Obtain CXR and spirometry (> 3–6 years).

Non-infectious causes that need to be ruled out:

- Post-nasal drip
- Allergies
- Habit cough
- Sinusitis
- Cystic fibrosis
- Foreign body aspiration
- Reactive airway disease
- Second-hand smoke exposure
- Gastroesophageal reflux disease (GERD)
- Congenital malformation

#### Management

Treat confirmed *B. pertussis* with a macrolide (azithromycin or clarithromycin).

Treat *M. pneumoniae* or *C. pneumoniae* with a macrolide (azithromycin or clarithromycin), or, if > 8 years of age, doxycycline.

For other etiologies, direct therapy to the specific underlying cause.

\* The term bronchitis triggers an expectation for antibiotics and should be avoided or carefully explained. Other terms, such as “chest cold,” may be preferable.

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### Community-Acquired Pneumonia – Children

#### CLINICAL CONSIDERATIONS

Unlike for adults, decisions about site of care should be based on clinical assessment of severity of illness.

Factors favoring hospitalization:

- Presence of respiratory distress (tachypnea, retractions, grunting, nasal flaring, apnea, altered mental status)
- Pulse oximetry measurement < 90%
- Age < 6 months

CXR and blood culture:

- Should be obtained from children treated as inpatients.
- Not necessary for nontoxic-appearing children who are fully vaccinated against SP and HI treated as outpatients.

Consider testing for viral agents (influenza, RSV) based on clinical symptoms and season.

#### MANAGEMENT OF OUTPATIENTS

Children < 5 years:

- Do not routinely require antibiotics, since the majority of cases of CAP in this age group are of viral etiology.
- Amoxicillin or amoxicillin-clavulanate (45 mg/kg/day bid) for presumed bacterial pneumonia.
- Use high dose amoxicillin or amoxicillin-clavulanate (90 mg/kg/day bid) if risk factor for penicillin-resistant pneumococcus present (local rates of pneumococcus PCN resistance  $\geq$  10%, age < 2 years, day care exposure, immunocompromise, recent hospitalization, or antibiotic use in past 3 months.)

Children > 5 years:

- For presumed atypical pneumonia add coverage with azithromycin (10 mg/kg on day 1, followed by 5 mg/kg once a day on days 2–5) or clarithromycin (15 mg/kg/day bid) or doxycycline for children > 8 years of age unless etiology known.

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### Community-Acquired Pneumonia (CAP) – Adults

#### Treatment of adults not HIV-infected or immunocompromised

##### CLINICAL CONSIDERATIONS

CAP should be suspected in patients with newly-acquired lower respiratory tract symptoms (cough, sputum production, or dyspnea) especially if accompanied by fever, altered breath sounds, and rales. A CXR is required to make the diagnosis.

The initial site of care is the single most important decision made by clinicians during an episode of CAP. This decision involves 3 steps: 1) assessment of any preexisting conditions that compromise the safety of home care; 2) calculation of the CURB-65 (see page 35); and 3) clinical judgement.

A significant number of treatment failures have been documented for *Streptococcus pneumoniae* resistant to macrolides.

Fluoroquinolones should be used for outpatients only when the patient has failed first-line therapy, has known allergy to first-line agents, or where highly resistant pneumococcus (penicillin MIC > 4 mcg/ml) is prevalent.

##### MANAGEMENT

Previously healthy, no recent (within 3 months) antibiotic therapy: 1) azithromycin, clarithromycin or doxycycline.

Antibiotics within past 3 months or comorbidities (COPD, diabetes, renal or congestive heart failure, malignancy): 1) azithromycin or clarithromycin, **plus** high dose amoxicillin, amoxicillin-clavulanate, cefdinir, cefpodoxime, cefprozil, or cefuroxime; 2) a respiratory fluoroquinolone alone.

Inpatients: 1) advanced macrolide plus a beta-lactam (cefotaxime, ceftriaxone, ampicillin, or ampicillin-sulbactam); 2) respiratory fluoroquinolone.

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### The Use of CURB-65 for Determining Site of Care in Adults

The most recent British Thoracic Society scoring system for determining risk of mortality has the acronym CURB-65. It gives one point for each of the following: confusion, urea (BUN > 7), respiratory rate > 30, low blood pressure (systolic < 90 or diastolic < 60), and age ≥ 65. Patients with a score of 0-1 have less than approximately 2% mortality and are likely safe to be treated as an outpatient. Patients with two or more points have greater than 9% mortality and should be admitted to the hospital for treatment. Patients with scores of 3 or more may benefit from intensive care treatment. Any scoring system is intended to be an aid to clinical judgment and should not override the clinical judgment of an experienced practitioner.

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#### CURB-65: RISK OF MORTALITY AND SITE OF CARE

Total score	Mortality %	Suggested site of care
0	0.7	Outpatient
1	2.1	Outpatient
2	9.2	Inpatient
3	14.5	Inpatient/ICU
4 or 5	40	ICU

Assign one point for each factor that is present:

	Clinical Factor
C	Confusion
U	Urea
R	Respiratory rate > 30 breaths per minute
B	Blood Pressure (systolic < 90 or diastolic < 60)
S	Age > 65 years

Updated: August 2013

# OREGON ALLIANCE WORKING FOR ANTIBIOTIC RESISTANCE EDUCATION (AWARE)

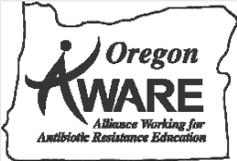
**Mission:** Oregon AWARE encourages the appropriate use of antibiotics and aims to reduce the problem of antibiotic-resistant bacteria in Oregon.

The coalition's goals are to:

- Raise public awareness about the importance of using antibiotics wisely.
- Encourage Oregon's physicians, physician assistants and nurse practitioners to appropriately prescribe antibiotics.
- Enlist the aid of community-based organizations to reduce the unnecessary use of antibiotics and promote self-care for viral illnesses.

## Community partners:

Abbott Laboratories	Oregon Health Authority, Acute and Communicable
Agate Healthcare	Disease Prevention Program
American College of Physicians	Oregon Health Management Services
CareOregon	Oregon Medical Association
Cascade Comprehensive Care	Oregon Nurses Association
Cigna Healthcare	Oregon Pediatric Society
Complementary Healthcare Plans	Oregon Parent Teacher Association
Conference of Local Health Officials	Oregon Rural Practice-based
Department of Medical Assistance Programs/ Oregon Health Plan	Research Network
Doctors of the Oregon Coast South	Oregon School Nurses Association
Douglas County Independent Practice Association	Oregon Society of Physician Assistants
FamilyCare	Oregon State Pharmacists Association
GlaxoSmithKline	Oregon State University College of Pharmacy
Health Net Health Plan of Oregon	PacificCare of Oregon/UnitedHealthcare
Health Net Pharmaceutical Services	PacificSource Medicare
Infectious Diseases Society of Oregon	Pacific University
Kaiser Permanente Northwest	-School of Pharmacy
Linfield-Good Samaritan School of Nursing	-School of Physician Assistant Studies
MedImpact HealthCare Systems, Inc.	Providence Health Plan
Moda Health	Reckitt-Benckiser
Multnomah County Health Department	Regence BlueCross BlueShield of Oregon
Nature Cures Clinic	Safeway
Nurse Practitioners of Oregon	Samaritan Health Services
Oregon Academy of Family Physicians	Trillium Medicaid
Oregon Association of Naturopathic Physicians	Tuality Health Alliance
Oregon Board of Pharmacy	WVP Health Authority
Oregon Coalition of Health Care Purchasers	
Oregon Department of Education	
Oregon Health & Science University	
-Infectious Diseases	
-Nursing	
- Otolaryngology/Head & Neck Surgery	
-Pediatric Infectious Diseases	
-Physician Assistant Education	



# Safe Use of Antibiotics EDUCATIONAL MATERIALS ORDER FORM

*Oregon Alliance Working for Antibiotic Resistance Education*

<b>Item</b>	<b>Indicate desired amount</b>
*Due to a limited amount of materials, orders are based on availability	

<b>Brochures for Parents</b> (packets of 50)	<input type="checkbox"/> Antibiotics Are Not Always the Answer (English) <input type="checkbox"/> ¡Los Antibióticos No Sirve Para Todo! (For Parents)
<b>Brochures for the General Population</b> (packets of 50)	<input type="checkbox"/> Warning: Unnecessary Antibiotics Can Be Harmful <input type="checkbox"/> Cold or Flu, Antibiotics Aren't for You <input type="checkbox"/> ¿Catarró o Gripe? ¡Los Antibióticos No Son para Usted! (Spanish)
<b>Brochure for 55 and older</b> How does antibiotic resistance affect your health? (packets of 50)	<input type="checkbox"/> English <input type="checkbox"/> Chinese <input type="checkbox"/> Spanish <input type="checkbox"/> Vietnamese
<b>Question &amp; Answer Sheet</b> (packets of 50)	<input type="checkbox"/> Q & A Sheet: Fluid in the Middle Ear/Runny Nose (For Parents)
<b>Poster</b>	<input type="checkbox"/> A Parent's Care is Sometimes the Best Medicine
<b>Children's Activity Kit</b> Grades K-3 (packets of 50)	<input type="checkbox"/> English <input type="checkbox"/> Spanish
<b>Germ Activity Kit</b> Grades 4-6 (packets of 50)	<input type="checkbox"/> English
<b>Drug Adherence Prescription Pad</b> (pad of 50 sheets)	<input type="checkbox"/> Adherence Rx Pad (For Pharmacists)
<b>Viral "Prescription" Pad</b> (pad of 20 sheets)	<input type="checkbox"/> Viral Rx Pad
<b>Child Care Advice Letter</b> (pad of 50 sheets)	<input type="checkbox"/> English <input type="checkbox"/> Spanish



**SHIP TO:** (please print or type clearly)

**Name** \_\_\_\_\_

**Street Address (no P.O. boxes)** \_\_\_\_\_

**City** \_\_\_\_\_ **State** \_\_\_\_\_ **Zip** \_\_\_\_\_

**Phone** \_\_\_\_\_ **Fax** \_\_\_\_\_ **E-mail** \_\_\_\_\_

**MAIL REQUEST**

Mail form to:  
**Oregon AWARE**  
**800 NE Oregon, Suite 772**  
**Portland, OR 97232**

- or -

**FAX REQUEST**

Fax Number:  
**971-673-1100**

- or -

**GO ONLINE**

Visit:  
[www.healthoregon.org/antibiotics](http://www.healthoregon.org/antibiotics)  
 Go to AWARE Publications and use the Online request form.

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# HELP SPREAD THE WORD ABOUT APPROPRIATE ANTIBIOTIC USE!

## Brochures for Parents

### *¡Los Antibióticos No Sirve Para Todo!*

Clarifies the role of antibiotics in treating upper respiratory infections and suggests some home-care options for common viral illnesses.



### *Antibiotics Are Not Always the Answer*

Encourages the appropriate use of antibiotics and answers parents' questions about common childhood upper respiratory infections.



## Brochures for the General Population

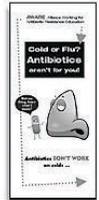


### **Warning: Unnecessary Antibiotics Can Be Harmful**

Explains how taking unnecessary antibiotics leads to resistant bacteria. Lists which types of illnesses respond to antibiotic treatment.

### *Cold or Flu? Antibiotics Aren't for You -and- ¡Los Antibióticos No Sirve Para Todo!*

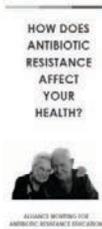
Outlines the steps of effective hand washing and gives advice on proper compliance when taking antibiotic prescriptions. Available in English and Spanish.



## Brochure for Ages 55 and Older

### *How Does Antibiotic Resistance Affect Your Health?*

The elderly population is more at risk for suffering from adverse effects when using antibiotics. Encourages the appropriate use of antibiotics, hand washing and taking medications as prescribed.



## Question & Answer Sheet



A fact sheet that answers questions about the treatment of ear infections and runny noses.

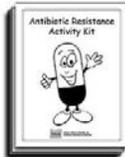
## Poster



Explains that antibiotics don't cure everything. Sometimes a parent's care is the best medicine.

## Children's Activity Kit

An 8-page booklet of coloring sheets and games that teaches children and their parents about antibiotic resistance. Suitable for grades K-3. Available in English and Spanish.



## Adherence Rx Pad



50 pre-formatted sheets promote adherence to antibiotic therapy by citing ways that consumers can use antibiotics correctly.

## Viral Rx Pad

20 pre-formatted sheets "prescribe" home treatments to relieve the symptoms of viral upper respiratory infections.

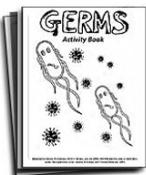


## Childcare Advice Letter Pad



50 pre-formatted letters to childcare providers explain that your pediatric patient's viral upper respiratory infection does not require antibiotics. Available in English and Spanish.

## Germs: Viruses & Bacteria Activity Kit



An 18-page booklet of coloring sheets and games that teaches children and their parents about antibiotic resistance. Suitable for grades 4-6.

All materials are written at a seventh grade reading level. They may be viewed and downloaded in PDF format at <http://www.healthoregon.org/antibiotics>.

For bulk orders, use the form on the other side.









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