

UPPER RESPIRATORY TRACT INFECTIONS

Kayla R. Stover, Pharm.D., FCCP, FIDSA, BCIDP, BCPS
Associate Professor of Pharmacy Practice
University of Mississippi School of Pharmacy
Jackson, Mississippi

LEARNING OBJECTIVES:

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Assess pharmacotherapies for upper respiratory tract infections.
2. Select the most appropriate pharmacotherapeutic plan and monitoring based on patient- and disease-specific information, antibiogram data, and best available evidence.
3. Recommend modifications of patient-specific treatment plans based on efficacy and adverse effects.
4. Identify recommended immunizations and potential adverse effects.

SELF-ASSESSMENT QUESTIONS

Answer key is provided at the end of this chapter.

1. ST is a 5-year-old female presenting to the emergency department with a 2-day history of fever (T_{\max} 38.5 °C), otalgia, and ear tugging. Upon evaluation it is determined that she has unilateral acute otitis media with possible effusions and opaque tympanic membrane. Currently, which of the following therapies is most appropriate to initiate for ST?
 - A. Amoxicillin 45 mg/kg/dose by mouth twice daily for 7 days
 - B. Ciprofloxacin 10 mg/kg/dose by mouth twice daily for 7 days
 - C. Amoxicillin/clavulanate 45 mg/kg/dose by mouth twice daily for 5 days
 - D. No antibiotic therapy should be initiated at this time.

2. A pediatrician is building an outpatient general pediatrics practice and would like to integrate an outpatient antimicrobial stewardship intervention in his clinic. His focus is improving appropriateness of use for patients presenting with signs and symptoms of an acute bacterial rhinosinusitis (ABRS). Which of the following recommendations would be preferred for management of ABRS in this patient population?
 - A. Reduce use of fluoroquinolones by listing doxycycline as the first-line agent for patients with confirmed ABRS.
 - B. Recommend clindamycin + third-generation cephalosporin therapy for patients with ABRS and confirmed hypersensitivity to penicillin to reduce fluoroquinolone use.
 - C. Reduce third-generation cephalosporin use by initiating amoxicillin monotherapy for patients with ABRS.
 - D. Utilize azithromycin + third-generation cephalosporin for treatment of ABRS in penicillin-allergic patients.

3. AC is a 35-year-old female with a history of heart transplantation 6 months ago, seasonal allergic rhinitis, and recurrent urinary tract infections. She is presenting to the clinic today with complaints of purulent nasal discharge and headaches that have been present for about 10 days. She states that initially she had some relief with over-the-counter medications, but about 72 hours later she began feeling worse and finally decided to come in for evaluation. At this time, which of the following would be the most appropriate next step in the management of this patient?
 - A. Obtain imaging to determine if she has acute bacterial rhinosinusitis.
 - B. Initiate therapy with amoxicillin/clavulanate 875 mg by mouth twice daily for 7 days.
 - C. Initiate therapy with levofloxacin 750 mg by mouth once daily for 7 days.
 - D. Instruct the patient to start intranasal corticosteroids to aid in management of her seasonal allergies in addition to her ABRS.

4. RH is a 56-year-old male with a history of diabetes mellitus type 1 and COPD requiring multiple hospitalizations for acute exacerbations (AE) of his COPD. He presents to the outpatient setting for a routine annual physical exam. Which of the following vaccines should be offered to him at this time to aid in reducing AE COPD episodes?
- A. Annual influenza vaccine
 - B. PCV-13
 - C. PPSV-23
 - D. PCV-7
5. Which of the following pathogens is most often implicated in ABRS in adult patients?
- A. *Staphylococcus aureus*
 - B. *Haemophilus influenzae*
 - C. *Streptococcus pneumoniae*
 - D. *Pseudomonas aeruginosa*

UPPER RESPIRATORY TRACT INFECTIONS: PEDIATRIC OTITIS MEDIA

SEGMENT 1

Patient Case #1:

Pediatric Acute Otitis Media

AK is a 5-year-old female with no known drug allergies presenting to the urgent care setting today with right ear tugging, otorrhea, rhinorrhea, scratchy throat, and a dry cough. She has been difficult to console for the last 48 hours, and dad reports she “feels warm to the touch.”

Past medical history

- Hydrocephalus, ventricular-peritoneal shunt placed (2015)
- Hospitalized for respiratory syncytial virus (2018)
- Mild persistent asthma (diagnosed 6 months ago)

Social history

- Lives with mother who smokes 3 packs per day, father who works at a petroleum refinery, and two younger siblings 18 months and 6 months old, respectively
- Attends pre-kindergarten at the local school

Medication history

Drug Name	Dose/Route	Frequency
Albuterol 90 mcg HFA MDI	2 puffs oral inhalation	Every 6 hours as needed for wheezing and/or shortness of breath
Ranitidine 25 mg/mL solution	5 mg/kg/dose by mouth	Twice daily
Fluticasone propionate HFA MDI 88 mcg/actuation	1 puff oral inhalation	Twice daily

Immunization history

Vaccine	Doses (last received)
Hepatitis B virus	3 doses (2015)
Rotavirus	2 doses (2015)
Diphtheria, tetanus, pertussis (DTaP)	4 doses (2016)
<i>Haemophilus influenzae</i> b (Hib)	1 dose (2017)
13-valent pneumococcal conjugate vaccine (PCV-13)	2 doses (2017)
Measles, mumps, rubella (MMR)	1 dose (2017)
Varicella	1 dose (2017)
Hepatitis A virus	2 doses (2017)

Question 1: Which of the following characteristics is most likely to be a risk factor in AK for AOM?

- A. Chronic use of inhaled fluticasone
- B. Father’s job at a refinery
- C. History of asthma
- D. Hospitalization for RSV in 2018

I. Overview¹⁻⁵

- A. Most common presenting illness in pediatrics (~31.7 million outpatient visits for upper respiratory conditions in pediatric patients)
- B. Antimicrobials prescribed in >70% of associated annual outpatient visits for children in the U.S.
- C. Primary complication of other URI (viral predominantly) in pediatric patients
 - 1. Acute otitis media (AOM): 20-50% of all viral URIs (e.g., sinusitis) progress into AOM
 - 2. Acute bacterial rhinosinusitis (ABRS): less common in pediatric patients but similar pathogen etiology
- D. Viral infections put pediatric patients at increased risk of bacterial infection because the initial viral infection leads to inflammation and decreases in the ability to control overgrowth of bacteria that subsequently result in an infection
- E. Early development of AOM increases risk of future recurrence

II. Why are children at risk for URI?

- A. Microbiome diversity: children have higher nasal carriage of viral and bacterial pathogens than adults (including increased *S. pneumoniae*) that is inversely proportional to age
- B. Social and environmental factors
 - 1. Factors associated with increased risk irrespective of age
 - a. Smoke exposure
 - b. Exposure to dust and other particulate matter
 - c. Day care attendance
 - d. Siblings or co-inhabitants <5 years of age (of greatest importance if <18 months secondary to incomplete vaccination history)
 - 2. Factors associated with decreased risk of development
 - a. Exclusively breast-fed for at least 6 months (protective effect throughout childhood)
- C. Comorbid disease states
 - 1. Asthma or reactive airway disease
 - 2. Allergic rhinitis

Figure 1: Pediatric URI: Viral v. Bacterial Etiology

Viral Etiology (~60%)	Bacterial Etiology
Rhinovirus	<i>Streptococcus pneumoniae</i>
Adenovirus	<i>Haemophilus influenzae</i>
Respiratory syncytial virus	<i>Moraxella catarrhalis</i>
Influenza	
Human metapneumovirus	

III. Clinical presentation and diagnostic criteria of acute otitis media

- A. Symptoms vary based on age and developmental milestones
- B. Predominant non-specific patient findings
 - 1. +/- Otorrhea
 - 2. Irritability
 - 3. Discomfort
 - 4. Rhinorrhea
 - 5. Ear tugging: can be a significant finding in infants and children <2 years old, as these patients do not have the ability to drain inner ear fluid as efficiently as older patients, including adults, secondary to the angular differences that don't occur developmentally until closer to adolescence (≥10-12 years of age)
 - 6. Otalgia
- C. Definitive acute otitis media specific patient findings⁴
 - 1. Bulging tympanic membrane
 - a. Demonstrated in a small study to aid in differentiation between viral and bacterial etiology
 - b. A bacterial pathogen was isolated in 75% of patients for whom a culture was obtained
 - c. Fever in the presence of a bulging tympanic membrane was associated with isolation of *Streptococcus pneumoniae*
- D. Diagnostic considerations for acute otitis media
 - 1. Stepwise approach to determining diagnosis of AOM is vital for appropriate selection of treatment options
 - 2. Younger patients must meet fever criterion as well as have bulging tympanic membrane for diagnosis
 - 3. Unilateral versus bilateral involvement should be assessed across age groups to guide options

Table 1: Severity of Illness Staging for AOM

Severity of illness staging for AOM	
Severe	AOM with the presence of moderate to severe otalgia or fever equal to or higher than 39°C
Non-severe	AOM with the presence of mild otalgia and a temperature below 39°C
Uncomplicated	AOM without otorrhea

Table 2: Determining Severity of AOM

Pertinent distinguishing features to determine severity	Involvement	Age
T _{max} >39 °C	Unilateral	6 months to 2 years
Presence of otalgia >48 hr	Bilateral	>2 years

Patient Case #1, continued:

Physical Exam Findings:

Vital signs

- T_{max}: 40 °C
- Vital signs (RR, BP HR): normal for age

Laboratory tests

- Throat swab negative for *Streptococcus pyogenes*
- COVID-19 PCR negative

Pertinent positives

- Bilateral bulging of the tympanic membranes
- Otorrhea

Question 2: Which of the following options would be preferred for the management of AK's AOM?

- A. Watchful waiting with follow-up in 72 hours
- B. Initiate amoxicillin 45 mg/kg/day orally in two divided doses x 5 days.
- C. Initiate ceftriaxone 50 mg/kg/dose IM daily for 3 doses.
- D. Initiate amoxicillin/clavulanate 90 mg/kg/day orally in two divided doses x 7 days.

IV. Acute otitis media management strategies²⁻⁴

A. Watchful waiting

1. McCormick, et al.⁴
 - a. 233 patients randomly assigned to watch and wait versus antibiotic therapy
 - b. 60% of patients completed the study without antibiotics and still did well
 - c. Provides greater benefit for age <2 yr at initial presentation than for older children: subgroup of 6 months to 2 years demonstrated greater benefit in resolution of pain, fever, and improvement to baseline as compared to older children when patients had unilateral AOM with mild symptoms only
 - d. 30-day recurrence rates were similar between groups (irrespective of age group); antibiotic use in this age group did not necessarily prevent recurrence
2. Consider watchful waiting for:
 - a. 6 months to 2 years old with unilateral AOM and mild symptoms
 - b. ≥2 years old with bilateral or unilateral AOM and mild symptoms

B. Initiation of antibiotic therapy – general considerations

1. Greater benefit for patients younger than 2 years at initial presentation; lower NNT with most benefit demonstrated in patients presenting as “severe”
2. Lower NNT for bilateral presentation with otorrhea
3. Antibiotic therapy indications:
 - a. Pain for **>48 hours** (categorizes symptoms as “severe”)
 - b. **Otorrhea** regardless of age

- c. **Severe symptoms** (can appear toxic [i.e. dehydration, hypotension, increased pallor, need for IV fluids] at younger age because AOM impacts nutritional status)
 - d. 6 months to 2 years old with **bilateral AOM**
- C. Complications of inappropriate management
 - 1. Meningitis
 - 2. Recurrence
 - 3. Hearing deficits
 - 4. Intracranial involvement
- D. Surgical intervention may be warranted
 - 1. Implantation of tympanostomy tubes
 - 2. Must have previously received appropriate first-line therapy for appropriate duration based on age

V. Antimicrobial considerations: initial episode of AOM²

- A. Drug of choice is high-dose amoxicillin (80-90 mg/kg/day in divided doses)
 - 1. Vital to ensure dosing is appropriate; therefore, amoxicillin was not chosen for our patient because it was 45 mg/kg/day, which would not be enough to overcome the alteration of penicillin-binding proteins associated with resistance to *S. pneumoniae*
 - 2. Addition of a beta-lactamase inhibitor in the initial episode can be considered if there is a high prevalence of beta-lactamase positive *H. influenzae* or if concerns for *Moraxella catarrhalis*, given most produce a beta-lactamase. This option may be beneficial in patient populations that have a low immunization rate within the community
 - a. When utilizing amoxicillin/clavulanate in pediatric patients, the concentrated formulation (Augmentin ES) of amoxicillin/clavulanate (containing 42.9 mg of clavulanic acid) should be used in order to decrease the incidence of side effects (diarrhea)

Question 3: Despite appropriate first-line therapy with amoxicillin/clavulanate, AK presents with presumed therapeutic failure after 72 hours. Which therapeutic agent would be the most appropriate as a subsequent choice?

- A. Amoxicillin/clavulanate 90 mg/kg/day orally in two divided doses x 10 days
- B. Ceftriaxone 50 mg/kg/dose IM daily for 3 doses
- C. Clindamycin 15 mg/kg/day orally in three divided doses plus cefpodoxime 10 mg/kg/day orally in two divided doses x 10 days
- D. Levofloxacin 10 mg/kg/dose orally daily x 5 days

VI. Alternative antimicrobial considerations^{2,6}

- A. Cephalosporins recommended for the following conditions:

1. Can be considered as alternative first-line therapy although discouraged unless hypersensitivity to penicillin
2. Treatment failure 48-72 hr after receipt of amoxicillin/clavulanate (patient must have received adequate dosing of amoxicillin to be considered a treatment failure)
 - a. Ceftriaxone: 50 mg/kg/dose IM daily x 1 (if initial infection) or x 3 doses (if recurrent infection)
3. Guideline endorsed agents and recommended dosing
 - a. Cefpodoxime: 10 mg/kg/day by mouth in 2 divided doses
 - b. Cefuroxime: 25 mg/kg/day by mouth in 2 divided doses
 - c. Cefdinir: 14 mg/kg/day by mouth in 2 divided doses
4. Special considerations⁷
 - a. Impaired ability to reach pharmacodynamic endpoint (time above MIC; T>MIC) of the organisms in the middle and inner ear
 - b. Studies show higher dosages needed to achieve reliable concentrations at the primary site of infection – would probably need to use a larger dose than what is recommended in the guidelines

VII. Alternative antibiotic considerations for AOM – penicillin allergy? ^{8,9,10}

- A. Penicillin allergy
 1. ~50% infants and children younger than 5 years of age will develop a rash while on aminopenicillin therapy
 - a. Typically, causal relationship with concomitant viral process
 - b. Rash does not define an IgE-mediated hypersensitivity reaction, so we should still consider using first-line therapy (amoxicillin)
 2. Should use aminopenicillins as first-line therapy unless IgE-mediated hypersensitivity reaction
 - a. Incidence of cross-reactivity between aminopenicillin and cephalosporins is 0-15 % (at a max) – probably closer to 0-5% for true IgE-mediated hypersensitivity reactions
 - b. Role for penicillin allergy evaluation
 - 1) Vyles, et al.¹⁰ evaluated pediatric patients (3-18 years) with documented low-risk penicillin allergy
 - a) 3-step evaluation performed to determine penicillin allergy (percutaneous → intracutaneous → oral challenge testing)
 - b) 100% of patients were found to have negative penicillin allergy testing result
 - c. De-sensitization for IgE-mediated reactions
 3. Agent of choice for confirmed penicillin allergy
 - a. Third-generation cephalosporin

VIII. Penicillin-resistant *Streptococcus pneumoniae* (PRSP)²

- A. Clindamycin + third-generation cephalosporin (not recommended as monotherapy!)
 - 1. Clindamycin is preferred in geographic areas where PRSP more common (Midwest and Northeast)
 - 2. Clindamycin efficacy may be limited as it will not cover multiple serotype mechanisms of resistance – but does seem to be better than using a third-generation cephalosporin alone
- B. Very important to use local antibiogram to determine:
 - 1. Cephalosporin with greatest activity (if variability exists)
 - 2. Will combination therapy with clindamycin + cephalosporin be sufficient for pathogens of interest
- C. Guidelines do not address other combinations or alternatives
 - 1. Desire to limit use of fluoroquinolones for chronic suppurative otitis media (mainly due to the shift in what the predominant organism may be and risk of exposure in younger population as it relates to *S. pneumoniae* susceptibilities within the community)
 - 2. Exposure to FQ early in childhood selects for colonization/nasal carriage of resistant strains of *Streptococcus pneumoniae*

IX. Recommended duration of antibiotic therapy for AOM ^{2,11,12}

Table 3: Recommended Duration of Antibiotic Therapy According to Age and Severity

Age/Presentation	6-23 months	2-5 years with mild to moderate presentation	≥6 years with mild to moderate presentation	Any age, but with severe disease
Duration	10 days	7 days	5-7 days	10 days, can consider shorter courses as per mild to moderate group

- A. Reduced duration of antimicrobial treatment (5 days versus 10 days) in patients younger than 23 months is associated with less-favorable outcomes
 - 1. Increased treatment failures witnessed in 5-day treatment group
 - 2. No decrease in nasopharyngeal colonization
 - 3. Persistence of severe symptoms (fever, otorrhea, etc.)
- B. No difference between 5 and 7 days for patients 6 years or older

Question 4: Which of the following is associated with reductions in the incidence of AOM infections and complications?

- A. *Haemophilus influenzae* type B (Hib) vaccine
- B. Antibiotic prophylaxis in high-risk patients younger than 23 months
- C. 13-valent pneumococcal conjugate vaccine (PCV-13)
- D. Probiotics

X. Role of antibiotic prophylaxis in AOM²

- A. No clearly defined role; however, can be considered in the following scenarios:
 - 1. Recurrent infections
 - a. >6 episodes per year
 - b. Must have received first-line therapy and completed appropriate duration for age
- B. Randomized controlled trial demonstrated that NNT=5
- C. Risk/benefit must be weighed
- D. Guidelines advocate against antibiotic prophylaxis use because risks usually outweigh benefits

Patient Case #1, continued:

AK's immunization history:

Vaccine	Doses (last received)
Hepatitis B virus	3 doses (2015)
Rotavirus	2 doses (2015)
<i>Diphtheria, tetanus, pertussis</i> (DTaP)	4 doses (2016)
<i>Haemophilus influenzae</i> b (Hib)	1 dose (2017)
13-valent pneumococcal conjugate vaccine (PCV-13)	2 doses (2017)
Measles, mumps, rubella (MMR)	1 dose (2017)
Varicella	1 dose (2017)
Hepatitis A virus	2 doses (2017)

Question 5: Which of the following vaccines should be administered to decrease her risk for recurrent AOM?

- A. Inactivated influenza vaccine
- B. 23-valent pneumococcal polysaccharide vaccine (PPSV-23)
- C. 7-valent pneumococcal conjugate vaccine (PCV-7)
- D. Live attenuated influenza vaccine

XI. Impact of vaccination on AOM outcomes¹³

- A. PCV conjugate vaccine:
 - 1. Historical perspective: PCV-7 – introduced in 2000, conjugated to non-toxic diphtheria toxin analogue CRM 197
 - a. Enhanced and sustained antibody response – can still detect antibody years later
- B. PCV-13 – extension to cover more serotypes
 - 1. Noted shift in serotype associated with invasive disease caused by non-vaccine serotype 19A
 - 2. Bryant, et al. (2010)¹³
 - a. Head-to-head comparison of infants randomly assigned to either PCV-7 or PCV-13
 - b. Set targeted antibody concentration to each serotype desired prior to study and assessed achievement

- c. Both met set targeted antibody concentrations for the serotypes covered with greater serotype coverage in the PCV-13 group
- 3. Increase in nasopharyngeal carriage of non-vaccine serotypes with each iteration of conjugate vaccine
- 4. Decline in invasive disease persists despite selection for other serotypes that are not adequately covered by the vaccine
- 5. Geographically distributed phenomena
- 6. Key benefits
 - a. Significant decrease in overall URI complications in pediatric patients
 - b. Several double-blind, randomized controlled trials with different PCVs all demonstrate reductions in overall incidence of AOM by up to 34% depending on the study and vaccine serotypes covered
 - c. Significant reduction in penicillin resistance
 - d. **Current recommendation: All patients should receive PCV-13 and complete 4-dose series prior to 18 months of age**
- C. Influenza vaccine
 - 1. 2/3 of children with influenza develop AOM – this is a viral infection that puts patients at risk for developing AOM
 - 2. ~30-55% efficacy in preventing AOM in patients who receive annual influenza vaccine during respiratory infection season
 - 3. Greatest benefit during high-activity influenza seasons
 - 4. **Current recommendation: all patients ≥6 months of age should receive annual influenza vaccine**
 - a. 2 vaccines in first season for patients 6 months to 8 years old
- D. Vaccination schedules can be easily accessed at the following website:
 - <https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf>
 - 1. Please review these schedules in detail with a focus on the vaccines discussed that lead to decreases in invasive disease (e.g., meningococcus, pneumococcus, *Haemophilus*)
 - 2. Provides recommendations on receiving PCV-13 series before 18 months of age and influenza vaccine (1 versus 2 dose recommendations) and when they need to also receive PPSV-23 (indicated for high-risk groups)
 - 3. Catch-up vaccine schedules for children delayed in receiving vaccines or who have missed vaccines

XII. Vaccine considerations

- A. Autism spectrum disorder¹⁴⁻¹⁷

1. Concerns primarily associated with measles, mumps, and rubella and diphtheria-pertussis vaccines containing thimerosal
 2. Decades of debate related to association of childhood vaccines with autism
 3. Some overlap between age-based/developmental changes and presentation of autism
 4. Taylor, et al. (2014)¹⁴
 - a. Meta-analysis of association between vaccine receipt and development of autism
 - b. 5 cohort studies (~1,000,000 pts) + 5 case-controlled studies (>10,000 pts)
 - c. No association between vaccines containing thimerosal or mercury and autism, even when grouped by specific exposure (including consideration of all confounders)
 - d. Advocate for vaccines in this patient population
 5. Hviid, et al. (2019)¹⁷
 - a. Retrospective cohort (~685,000 children)
 - b. No association between MMR vaccine and autism diagnosis
 - 1) Adjusted hazard ratio 0.93 (0.85 to 1.02)
 - c. No increased risk in subgroups: sibling groups, those with risk factors, those who received other childhood vaccines
- B. Egg allergy and influenza vaccine
1. No longer contraindicated if allergic to egg or egg protein
 2. Pediatric patients should receive standard inactivated influenza vaccine
 3. Advisory Committee on Immunization Practices (ACIP) recommends administration by a “trained health care professional”
 4. Hypersensitivity reactions – only contraindication to use of any vaccine
- C. Reporting: FDA Vaccine Adverse Event Reporting System (VAERS) online

XIII. Clinical Pearls for Otitis Media

- A. Acute otitis media is one of the most common complications of viral URI in pediatric patients
- B. Appropriate management is dependent upon identification of patients at highest risk
 - a. Stratified by age, involvement, and symptoms for decision about use of antibiotic treatment versus watchful waiting
- C. Drug of choice is high-dose amoxicillin
 - a. Treatment failure may be secondary to pathogens other than *S. pneumoniae*
- D. Timely immunization is a beneficial preventive strategy to help decrease recurrence

UPPER RESPIRATORY TRACT INFECTIONS: ACUTE BACTERIAL SINUSITIS (ABRS)¹⁸⁻²³

SEGMENT 2

Patient Case #2:

Acute Bacterial Rhinosinusitis

DR is a 35-year-old male presenting to the primary care setting with complaints of facial pain, purulent nasal discharge, and a persistent headache that initially seemed to improve with ibuprofen, fluticasone propionate nasal spray, and use of his neti pot but then started to worsen in the last 2 weeks.

Past medical history:

- Exercise-induced asthma, well controlled
- Type 1 diabetes, well controlled (last A1c = 5.5)

Vital signs:

- BP 140/80 mm Hg
- RR 25 breaths/min
- HR 120 beats/min
- T_{max} 39°C

Medication list:

Name	Dose/Route	Frequency
Albuterol 90 mcg HFA MDI	2 puffs inhaled	30 minutes prior to activity and as needed for wheezing and shortness of breath
Metformin 500 mg tablet	1 tablet oral	Twice daily
Fluticasone propionate 50 mcg/spray	2 sprays in each nostril	Twice daily

I. Overview

A. Common complication of upper respiratory infections

1. Impacts ~30 million adults annually in the United States
2. 6-7% of children seeking care for respiratory symptoms meets strict criteria from the American Academy of Pediatrics guidelines
 - a. Differences in sinus development impact evaluation and treatment in children
 - b. Bacteria more commonly involved in progression from URI to sinusitis in children

B. Differentiated based on **duration** of symptoms (used to determine when to treat or not treat)

1. Acute: up to 4 weeks
2. Subacute: 4 weeks to 3 months
3. Chronic: >3 months

II. Factors associated with increased risk of ABRS

- A. Smoking or smoke exposure
- B. Asthma (level of control not significant)
- C. Allergic rhinitis
- D. Anatomic abnormalities
- E. Nasal polyps
- F. Trauma
- G. Diving, swimming
- H. Immune deficiency
- I. Cystic fibrosis
- J. Ciliary disorder
- K. Wegener's granulomatosis
- L. Viral upper respiratory infections can progress to sinusitis without concomitant bacterial infection, which opposes the pathophysiology associated with their pediatric counterparts

III. Clinical features of acute bacterial rhinosinusitis (ABRS)

- A. Purulent nasal discharge
 - 1. Increased association with bacterial versus viral etiology
 - 2. When present, more often associated with positive findings of ABRS on imaging studies
 - a. Of note, despite this association, imaging is not routinely indicated in the management of ABRS and should be reserved for patients at high risk for complications of ABRS
 - 1) Orbital or intracranial involvement (e.g., meningitis or orbital cellulitis)
 - 2) Immunocompromised patients
- B. Some groups¹⁸ also include:
 - 1. Unilateral disease with or without unilateral pain
 - 2. Fever above 38° C
 - 3. Increased laboratory markers (e.g., CRP and procalcitonin)
- C. Temporal relationship
 - 1. Viral etiology associated with quick resolution
 - 2. Bacterial etiology associated with "double sickening" where patients initially get better but then decline
- D. Pediatrics: the American Academy of Pediatrics has more specific diagnostic criteria
 - 1. Persistent illness: nasal discharge, daytime cough, or both lasting >10 days

2. Worsening cough: worsening or new onset of discharge, cough, or fever after initial improvement
3. Severe onset: temperature $\geq 39^{\circ}\text{C}$ (102.2°F) or purulent nasal discharge for 3 consecutive days

IV. ABRS management¹⁹⁻²¹

- A. Clinical practice guidelines
 1. Infectious Diseases Society of America (IDSA) – 2012
 2. European position statement – 2012
 3. Canadian practice guidelines – 2011
 4. American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) guideline – 2015
 5. Pediatrics: American Academy of Pediatrics – 2013
- B. These guidelines differ in management strategies
 1. Approach to self-care (watchful waiting versus when to treat)
 2. Initial therapy
 3. Role of adjunctive agents (and how these agents rank compared to each other)
 4. Definition of treatment failure

V. ABRS management: the case for watchful waiting^{4,19-21,24}

- A. Different opinions based on guideline
 1. Not endorsed in the IDSA guidelines: Need for improved diagnostic considerations to rule out patients who may be suffering from a viral etiology
 2. AAO-HNS prefers watchful waiting strategy as first-line management strategy regardless of severity upon presentation
- B. What does the literature tell us?
 1. Randomized controlled trials do not demonstrate a significant difference in the median duration of pain or illness (possible confounder in these trials is that these patients were diagnosed too soon and haven't had symptoms for 7-10 days)
 2. Higher rate of clinical improvement at 1-2 weeks compared with placebo
 3. Cochrane review
 - a. Meta-analysis of 8 trials assessing antibiotic therapy for ABRS and characteristics associated with cure or failure
 - b. Antibiotics shortened the time to cure
 - c. NNT=18 patients for cure at day 7 or 14
 4. Burgstaller, et al. (2016)²⁴

- a. Systematic review of 6 trials to determine impact of antibiotic therapy on ABRS course/progression
 - b. Restricted inclusion criteria to patients with symptoms >7 days to ensure appropriate diagnosis based on minimum duration of symptoms for classification as ABRS
 - c. Demonstrated no benefit from antibiotic therapy over placebo in rate of clinical improvement after day 10
 - d. Supports watchful waiting
- C. Risks of treatment
- 1. Allergic reactions
 - 2. Emergence of drug-resistant bacteria
 - 3. Adverse effects of antibiotic therapy
 - a. Cochrane review
 - 1) NNH=8-12 patients (need to treat more patients to see a benefit but don't need to treat as many patients to see harm)
 - 2) Adverse events associated with treatment (gastrointestinal in ~27% of patients)
- D. Pediatrics: similar to AOM, the AAP endorses watchful waiting for 3 days as an option in children with persistent illness
- 1. Not recommended in those with severe illness or worsening course

Patient Case #2, continued:

Question 6: Based on DR's presenting symptoms, which of the following oral agents would be most appropriate for treating his ABRS?

- A. Amoxicillin/clavulanate 2 g by mouth twice daily for 7 days
- B. Amoxicillin/clavulanate 500 mg (amoxicillin component) by mouth three times daily for 10 days
- C. Doxycycline 100 mg by mouth twice daily for 7 days
- D. Cefdinir 300 mg by mouth twice daily for 10 days

VI. ABRS management: symptom evaluation^{23,24}

- A. Purulent nasal discharge is major feature!
- B. Fever for 72-96 hours is typically associated with acute sinusitis
- C. Presence and duration of fever are important in considering an accurate diagnosis of acute sinusitis

Table 4: Major and Minor Symptoms Associated with ABRS

Major Symptoms	Minor Symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal drainage	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (subacute or chronic sinusitis)
Fever (acute sinusitis)	Fatigue

VII. ABRS pathogen considerations¹⁹

- A. Predominant pathogen: *Streptococcus pneumoniae* ~40%
- B. *Haemophilus influenzae* ~35%
 - 1. Increased prevalence of beta-lactamase producing strains (reason for amoxicillin/clavulanate recommendation)
- C. *Moraxella catarrhalis* ~15%
 - 1. Majority of isolates produce a beta-lactamase enzyme
- D. *Staphylococcus aureus* ~10%
 - 1. Routine coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) is **NOT** recommended
- E. *Streptococcus pyogenes* <5%

VIII. ABRS antimicrobial considerations^{19,21,23}

- A. Amoxicillin/clavulanate – drug of choice for ABRS
 - 1. Initial empirical therapy: standard dosing (500 mg orally three times daily OR 875 mg orally twice daily)
 - 2. High-dose therapy (2 g orally twice daily) reserved for high-risk patients meeting the following criteria:
 - a. Patients with severe presentation (fever >39° C, systemic toxicity)
 - b. Patients in areas with high endemic rates of invasive *Streptococcus pneumoniae* not susceptible to penicillin
 - c. Patients at high risk for infection with multidrug-resistant (MDR) pathogens (refer to same criteria as in diagnosis tables within the IDSA clinical practice guideline)
- B. Rationale for use of amoxicillin-clavulanate as first-line therapy
 - 1. Increased amoxicillin resistance demonstrated for *Haemophilus influenzae*
 - 2. No increased resistance observed with amoxicillin/clavulanate
 - 3. Resistance varies geographically
 - a. Example: 10% difference between southwestern and southeastern regions in the U.S.

4. Consider *Moraxella catarrhalis* coverage
 - a. Increased amoxicillin/clavulanate resistance since guideline release
 5. Initiation of amoxicillin/clavulanate as first-line therapy was a weak recommendation based on Scandinavian study but is still guideline-endorsed
 - a. Guideline recommends using amoxicillin/clavulanate as first-line therapy is based on one Scandinavian study (retrospective cohort) and is therefore considered a weak, low evidence-based recommendation
- C. Doxycycline
1. Retains high activity against all primary pathogens worldwide
 2. Favorable PK/PD profile
 - a. Studies comparing doxycycline versus levofloxacin for treatment of community-acquired pneumonia demonstrated that it is an acceptable alternative for therapy
 - 1) Similar efficacy
 - 2) Lower costs
 - 3) Lower side-effect profile
- D. Fluoroquinolones
1. No superiority demonstrated in 8 RCTs in adults with ABRS
 - a. Delafloxacin not yet studied for this indication
 2. No significant difference in outcomes when compared with amoxicillin/clavulanate or cefuroxime
 3. Adverse effects occurred more frequently in FQ group
 4. 2016 FDA black box warnings
 - a. “Reserve use of ciprofloxacin for treatment of acute bacterial sinusitis...for patients who have no alternative treatment options because of the risk of disabling and potentially serious adverse reactions (e.g., tendinitis and tendon rupture, peripheral neuropathy, CNS effects).”
<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm513183.htm>
 5. Utilize this as an opportunity for a targeted antimicrobial stewardship initiative
- E. Cephalosporins
1. All are inferior in efficacy to penicillin-based therapy
 2. Not all cephalosporins are created equal
 - a. Cefpodoxime demonstrates the best susceptibility and PK/PD profile
 - 1) Specifically for *H. influenzae* and *M. catarrhalis*
 - 2) Best in class for managing ABRS
 - b. Cefadroxil has no activity against isolates with intermediate susceptibility to penicillin
 3. Recommended third-generation cephalosporins: cefixime or cefpodoxime

4. Third-generation cephalosporin in combination with clindamycin is the guideline-based recommendation that applies primarily to pediatric patients and not adults
- F. Alternative antibiotic class considerations
1. Trimethoprim/sulfamethoxazole is **NOT recommended** for treatment secondary to high rates of resistance with *H. influenzae* and lack of adequate activity against *S. pneumoniae*
 2. Macrolide therapy is **NOT recommended** secondary to lack of reliable coverage against *S. pneumoniae*
- G. Pediatrics
1. First-line therapy: amoxicillin with or without clavulanate
 2. Alternatives:
 - a. Limited data on second-line or alternative therapies
 - b. If the patient worsens in 72 hours, the AAP recommends:
 - 1) Clindamycin and cefixime
 - 2) Linezolid and cefixime
 - 3) Levofloxacin
- H. Recommendations for patients with penicillin allergy
1. First-line alternative for penicillin allergy is doxycycline
 2. Second-line alternative is either levofloxacin or moxifloxacin
 - a. Use should be limited per the recent FDA warnings and not utilized as first-line, alternative therapy

Question 7: DR has been taking amoxicillin as prescribed and developed a maculopapular rash and irritation on his lower trunk. Which of the following strategies should be used as first-line therapy to treat his ABRS at this time?

- A. Discontinue amoxicillin, conduct penicillin skin testing, and start ciprofloxacin 500 mg by mouth twice daily.
- B. Continue amoxicillin therapy with no changes.
- C. Switch to doxycycline 100 mg by mouth twice daily.
- D. Switch to clindamycin 300 mg by mouth three times daily plus cefpodoxime 200 mg by mouth twice daily.

IX. ABRS management: risk factors for resistance^{6,7,24,25}

- A. Determine if patient has risk factors for resistance
1. Age: <2 or >65 years
 2. Antibiotic exposure within the last month
 3. Hospitalization within the last 5 days
 4. Comorbidities
 - a. Smoking

- b. Diabetes
 - c. Chronic cardiac disease
 - d. Chronic hepatic or renal disease
- 5. Immunocompromised host (actively receiving chemotherapy, chronic corticosteroid use, etc.)

X. Duration of antimicrobial therapy

- A. Falagas, et al. (2009)²⁵
 - 1. Systematic review of 12 trials
 - 2. Demonstrated no significant difference in rates of clinical success or AEs between groups
 - a. Group 1 received 3-7 days of therapy with amoxicillin-clavulanate
 - b. Group 2 received 6-10 days of therapy with amoxicillin-clavulanate
 - 3. Sensitivity analysis compared 5 vs. 10 days of therapy
 - a. Fewer AEs (21%; 95% CI: 2 to 37) with shorter treatment duration
 - b. No significant difference in clinical success
- B. Summary recommendation: 5-7 days in adults, 10-14 days in pediatrics

XI. Adjunctive therapy^{19,20}

- A. Topical intranasal corticosteroids
 - 1. Provide small but significant benefit in time to improvement in symptoms (pain and nasal congestion)
 - 2. Optimal benefit in patients with history of allergic rhinitis
- B. Nasal irrigation with saline
 - 1. Although inconsistent data to support, use of hypertonic or physiologic saline have been demonstrated in a Cochrane review to decrease associated antibiotic use for ABRS when utilized
 - 2. May be a good interim strategy for management before initiation of antibiotics in low-risk patients with mild symptoms
- C. Use of systemic corticosteroids is **discouraged**

XII. Antimicrobial treatment failure^{19-20,23-24}

- 1. Definitions IDSA 2012
 - a. Symptoms that don't abate after 3-5 days of therapy OR worsening after 48-72 hours of therapy
- 2. AAO-HNS guidelines
 - a. No decrease in symptoms with treatment after 7 days have elapsed since diagnosis OR any worsening in symptoms

XIII. Antimicrobial treatment failure considerations²⁴

- A. Did the patient receive a first-line antimicrobial agent?
- B. Is the patient at risk for resistance? (Comorbidities?)
- C. Is there a non-infectious etiology?
- D. Have structural abnormalities been ruled out?

Table 5: Diagnostic Considerations for Complicated Presentations of ABRS after Treatment Failure

Culture	Imaging
<ul style="list-style-type: none">Endoscopy guidedJust say NO to nasopharyngeal swabs!	<ul style="list-style-type: none">Only in suppurative complicationsCT with contrast preferred over MRI

XIV. Know when to refer to ENT or other specialist

- A. Severe infection, orbital edema, severe headache, visual disturbances
- B. Presence of immunosuppression
- C. Not responding to antimicrobial therapy and all other causes ruled out
- D. Presence of complex comorbidities
- E. Fungal sinusitis
- F. Presence of anatomic defects requiring surgical intervention
- G. >3-4 episodes per year (chronic sinusitis)

Table 6: Summary of Key ABRS Guideline Recommendations

	ABRS Clinical Criteria	Initial Treatment Strategy	Antibiotic of Choice	PCN-Allergy Alternative
ISA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis	>10 days without improvement or “double sickening”	Antibiotic therapy for any patient with presumed bacterial sinusitis	Amoxicillin/clavulanate	Doxycycline OR FQ
AAO-HNS Clinical Practice Guideline for Adult Sinusitis		Watchful waiting or antibiotics	Amoxicillin with or without clavulanate	
Canadian Clinical Practice Guideline for Acute and Chronic Rhinosinusitis	>7 days without improving or biphasic illness	Watchful waiting for mild symptoms; antibiotics for severe symptoms	Amoxicillin	Macrolide OR TMP/SMX
European Position Statement on Rhinosinusitis	>10 days or biphasic illness + T _{max} >38°C		No recommended antibiotics specified	
American Academy of Pediatrics	>10 days of symptoms; worsening after initial improvement; T _{max} >39°C x 3 days	Antibiotic therapy; observation is an option in patients without severe or worsening course	Amoxicillin with or without clavulanate	Cefdinir, cefuroxime, or cefpodoxime with or without allergy assessment

Question 8: DR returns to clinic 4 months later with persistent nasal symptoms despite completion of antibiotic therapy and resolution of his acute infection. An endoscopy-guided culture is performed, and CT imaging reveals inflammation in the paranasal sinuses. Which of the following treatment options is most appropriate at this time?

- A. Repeat doxycycline therapy for 14 days for antibacterial and anti-inflammatory effects.
- B. Provide supportive care with intranasal corticosteroid therapy.
- C. Start moxifloxacin 400 mg by mouth twice daily to provide coverage for anaerobes and resistant gram-negative bacilli.
- D. Start systemic corticosteroid pulse therapy in conjunction with nasal saline rinses.

XV. Chronic sinusitis^{26,27}

- A. Huge opportunity for antimicrobial stewardship
 - 1. Accounts for high rate of unnecessary antibiotic prescriptions in the outpatient setting
- B. Recognition based on strict diagnostic criteria for ABRS is important
- C. Duration of symptoms is key
 - 1. At least 12 weeks

Table 7: Chronic Sinusitis Symptoms

At Least 2 of These Symptoms		Any 1 of These Signs of Inflammation
<ul style="list-style-type: none"> ○ Mucopurulent drainage ○ Nasal obstruction (congestion) ○ Decreased sense of smell ○ Facial pain, pressure, or fullness 	+	<ul style="list-style-type: none"> ○ Purulent mucus or edema in the middle meatus or anterior ethmoid sinus ○ Polyps in the nasal cavity or middle meatus ○ Radiographic imaging shows sinus inflammation
*** Acute exacerbations can occur: sudden worsening of symptoms after return to baseline		

- D. Chronic sinusitis considerations
 - 1. Characterized by an inflammation of the upper airways; similar to the pathophysiology associated with asthma
 - 2. Role of viruses and bacteria is not clear
 - 3. Bacterial etiology very different from ABRS
 - a. Primary pathogens are mixed and can include *Staphylococcus aureus*, Enterobacteriaceae, and *Pseudomonas aeruginosa* in addition to anaerobes
 - b. Influenced by previous antibiotic exposures
 - c. Gram-negative etiology can be present

XVI. Chronic sinusitis management^{26,27}

- A. Topical antibiotics
 - 1. Unfavorable PK/PD profile in the absence of sinus surgery

- 2. No benefit compared with nasal saline irrigations
 - a. This includes nasal irrigation with aminoglycosides – AVOID
- B. Systemic antibiotics
 - 1. Several studies demonstrate no benefit overall
- C. 2015 AAO-HNS guideline
 - 1. Recommends saline irrigation +/- intranasal corticosteroids
 - 2. Avoid antibiotic therapy

XVII. What about acute exacerbations?

- A. May require short courses of antibiotics
 - 1. Target typical ABRS pathogens (versus targeting the Gram-negative pathogens that are more common with chronic)
 - 2. Use culture data (if available) to guide therapy
- B. No evidence-based treatment recommendations available as data are lacking
- C. Doxycycline may be beneficial in patients with nasal polyps
- D. Debates about long-term macrolide therapy
 - a. Historically have said this should be avoided
 - b. Newer study indicates that azithromycin might be appropriate in select groups (refractory chronic disease post-surgery and steroid irrigations)²⁸

XVIII. Clinical pearls for ABRS

- A. Differentiating viral from bacterial ABRS is essential
 - 1. Symptoms may serve as a guide
- B. Strict criteria for type and duration of symptoms are vital to ensure that only patients who need antibiotics are treated
 - 1. Algorithm available from IDSA
- C. Antimicrobial agent of choice is amoxicillin/clavulanate
- D. Adjunctive therapies of choice are nasal irrigations (WITHOUT antibiotics) +/- intranasal corticosteroids

UPPER RESPIRATORY TRACT INFECTIONS: ACUTE EXACERBATION OF COPD

SEGMENT 3

Patient Case #3

KS is a 66-year-old female with chronic obstructive pulmonary disease (COPD) presenting with cough, increased sputum production (purulent), and dyspnea. She reports that her symptoms have worsened over the last few days after her return from visiting her grandchildren in Maine. She also reports worsening fatigue in addition to her respiratory symptoms and having trouble walking from her front door to her car.

Past medical history

- Congestive heart failure (CHF) diagnosed in 2016
- Type 1 hypersensitivity to sulfa-containing compounds
- Recent hospitalization for COPD exacerbation 2 months ago (the third time this year)

Social history

- 25 pack-year smoking history, currently in a smoking cessation program
- Works as an environmental toxicologist
- Lives at home with husband and 2 dogs

Medications

Medication	Dose	Frequency
Vilanterol/fluticasone	100 mcg/25 mcg per inhalation	Once daily
Tiotropium dry powder inhaler	18 mcg per capsule for inhalation	Once daily
Spironolactone	25 mg oral tablet	Once daily
Lisinopril	40 mg oral tablet	Once daily
Moxifloxacin	400 mg oral tablet	5 days per week (currently in week 6 of pulse)

Pertinent Findings

- Spirometry
 - FEV₁ 1.56 L (predicted 3.07 L)
 - FVC 2.28 L
 - FEV₁/FVC = 68%
- RR 35 breaths/min (increased respiratory rate)
- Expiratory wheezing on auscultation
- SpO₂ = 89%
- T_{max} = 39.5 °C
- COVID-19 PCR negative

Diagnosed with acute exacerbation of COPD (AECOPD).

I. Acute exacerbations of COPD²⁹⁻³²

- A. Any acute worsening of respiratory symptoms that require additional therapy
 - 1. Classified as mild, moderate, or severe based on therapy needs

2. Because of typical multiple comorbidities, the GOLD COPD guidelines suggest a broad differential diagnosis to rule out: pneumonia, pneumothorax, pleural effusion, pulmonary embolism, pulmonary edema (cardiac), cardiac arrhythmias (specifically atrial fibrillation/flutter)
- B. Usually precipitated by a viral or bacterial infection
- C. Risk factors for exacerbations
 1. Past exacerbations
 - a. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study³²
 - 1) Multicenter, observational cohort study of 2138 patients stratified by GOLD staging and number of exacerbations
 - 2) Demonstrated that history of COPD exacerbations is the single best predictor of future exacerbations regardless of severity of COPD
 2. Asthma/COPD overlap
 3. Allergic phenotypes
 4. High degree of inflammation
 5. Chronic bronchitis

Patient Case #3 (cont'd)

Question 9: Which of the following therapies would be best to initiate in KS at this time for AECOPD?

- A. Amoxicillin/clavulanate 875 mg by mouth for 5 days
- B. Moxifloxacin 400 mg by mouth for 10 days every 21 days
- C. Doxycycline 100 mg by mouth for 14 days
- D. Azithromycin 250 mg by mouth daily

II. Pathogens in AECOPD^{30,31}

- A. Viral etiology predominates
 1. Rhinovirus
 - a. Typically, severe presentation
 - 1) Often requires hospitalization
 - b. Winter months (peaked)
 - 1) Some geographic variation in peak timing
 - c. Longer duration of symptoms
 2. Influenza
 3. Eosinophilia is associated with increased viral infection risk
 - a. May respond well to steroid therapy and no antibiotics needed
- B. Associated bacteria

1. *Haemophilus influenzae*
 - a. Biofilm formation in the lung
 - b. Impacts intracellular signaling in the lung – leads to increased inflammation, which then leads to the exacerbation
2. *Streptococcus pneumoniae*
3. *Pseudomonas aeruginosa*
 - a. Patients with bronchiectasis at higher risk for resistant Gram-negative organisms

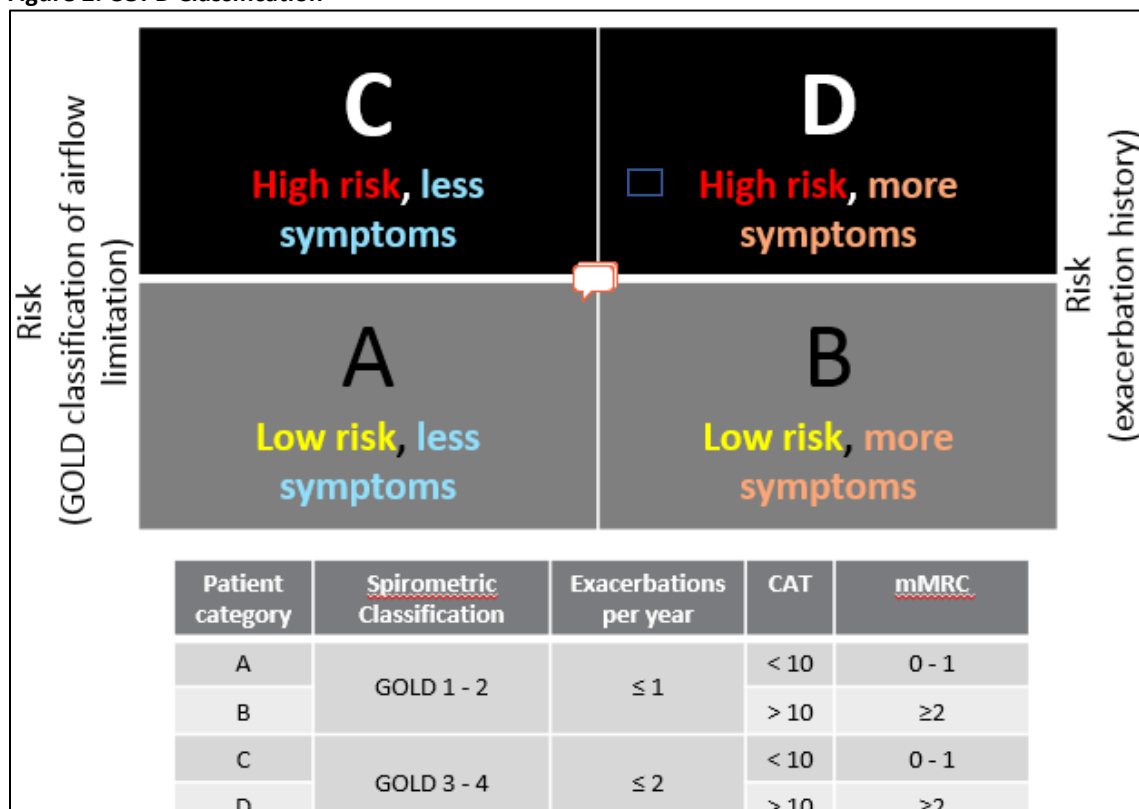
III. Antimicrobial management for AECOPD²⁹

- A. In addition to respiratory symptoms, patients should have evidence of bacterial infection prior to initiation of antibiotic (e.g. increased sputum production [volume and purulence], increase in dyspnea)
 1. There may also be a role for biomarkers (e.g. CRP, procalcitonin), but these have not been widely advocated
- B. Short course antibiotic therapy (5-7 days) is beneficial, especially in moderately to severely ill patients
 1. Improvement in acute symptoms of:
 - a. Sputum volume
 - b. Purulence and color
 - c. Shortness of breath
 2. Consider starting therapy when changed from baseline in these factors exist coupled with fever and/or leukocytosis
 3. Reduce:
 - a. Short-term mortality in 77%
 - b. Treatment failure in 53%
 - c. Sputum purulence in 44%

IV. Global Initiative for Chronic Obstructive Lung Disease (GOLD)^{29,30,33}

- A. Global strategy for the diagnosis and prevention of chronic obstructive pulmonary disease
 1. Scientific committee established in 2011 to review research on COPD management and create consensus recommendations
 2. Provide staging criteria to classify COPD
 3. Assess symptoms and determine exacerbation risk to aid in management
 4. Also consider exacerbations/year

Figure 2: COPD Classification



V. Antimicrobial therapy initiation considerations²⁹

A. Antibiotic initiation should consider the following:

1. Increase in dyspnea
2. Increase in sputum volume
3. Increase in sputum purulence
4. Require mechanical ventilation (invasive or non-invasive)
5. Antimicrobial choice based on local resistance patterns

Table 8: Antimicrobial Management for AECOPD

Agents of Choice for Patients with Low Risk for <i>Pseudomonas</i>	Agents of Choice for Patients with High Risk for <i>Pseudomonas</i> (Recent Antimicrobial Therapy, Recent Hospitalization, Bronchiectasis)
Amoxicillin/clavulanate	Perform Cultures
Tetracycline	
Macrolide	
Duration of therapy: 5-7 days	

Patient Case #3 (cont'd)

Question 10: Which of the following adjunctive agents may improve KS's treatment outcome from her AECOPD at this time?

- A. Methylprednisolone 80 mg IV every 12 hours for 3 days
- B. Azithromycin 250 mg IV every day for 5 days
- C. Prednisone 40 mg orally twice daily for 5 days
- D. Magnesium sulfate 2 g IV as a single dose

VI. Role of Corticosteroids in AECOPD^{34,35}

- A. Infection + inflammation = exacerbation – need to target both factors
 - 1. Corticosteroids improve outcomes
 - a. VA study
 - 1) Patients receiving corticosteroids had lower rates of treatment failure at 30 and 90 days (death, need for mechanical ventilation, readmission, intensification of therapy)
 - 2) Reduced hospital length of stay
 - 3) Improved rate of recovery
 - 2. Oral = IV (no benefit in one form over the other)
 - a. 20-40 mg given by mouth or IV of prednisone equivalent
 - 3. REDUCE trial
 - a. Short course is not inferior to longer treatment course
 - b. Recommend 5 days of therapy
 - 1) No more than 7 days total without a taper

VII. Corticosteroid controversy

- A. Clear benefit
- B. Some concerns about increased risk of pneumonia
 - 1. Concern that steroids may decrease immune function thereby increasing risk of infection; however, this has not been demonstrated in AECOPD patients
 - 2. Ongoing studies in progress
 - 3. Benefit currently outweighs risk for AECOPD

VIII. AECOPD prevention strategies

- A. Antimicrobial prophylaxis
 - 1. Azithromycin: 250 mg orally three times per week for up to 1 year
 - 2. Moxifloxacin pulse: 400 mg orally daily for 8 weeks

- a. Azithromycin therapy preferred over moxifloxacin therapy
- b. Azithromycin reduced rates of exacerbation, but was also associated with increased risk of bacterial resistance, prolonged QTc interval, and impaired hearing
- c. Moxifloxacin was not associated with a beneficial effect on overall exacerbation rate
- d. Need to balance risks from antimicrobial exposure with risk for future exacerbations from shifts in lung microbiome

IX. PPSV-23 and COPD

- A. Polyvalent pneumococcal vaccines reduce risk of pneumonia in patients with COPD
 - 1. Risk reduced for community acquired pneumonia at 6 and 36 months after immunization
 - 2. Non-significant trends toward reduction in future exacerbations and all-cause mortality
 - 3. Past exacerbation history increases future risk
- B. PPSV-23 is recommended for all patients with COPD according to the ACIP
- C. Pneumococcal conjugate vaccine (PCV-13) may be given in immunocompetent patients aged 65 years and older if deemed a candidate by shared clinical decision-making

Patient Case #3 (cont'd)

Question 11: Upon review of her medical record, you see that she has not yet received any pneumococcal vaccination. Which of the following would be a contraindication to immunization with the 13-valent pneumococcal conjugate vaccine (PCV-13)?

- A. Anaphylaxis to the diphtheria tetanus vaccine
- B. Recent upper respiratory infection with accompanying fever
- C. Anaphylaxis to the hepatitis B vaccine
- D. Anaphylaxis to latex and latex-containing products

X. Adult immunization schedule

- A. Centers for Disease Control and Prevention. Recommended immunization schedule for adults aged 19 years or older, United States, 2021. Available at <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html>.
- B. Contraindications and precautions for vaccines recommended for adults age 19 years or older
 - 1. The Advisory Committee on Immunization Practices (ACIP) recommendations and package inserts for vaccines provide information on contraindications and precautions related to vaccines. Contraindications are conditions that increase chances of a serious adverse reaction in vaccine recipients and the vaccine should not be administered when a contraindication is present. Precautions should be reviewed for potential risks and benefits for vaccine recipients.

Table 9: General Vaccination Contraindications and Precautions*

Contraindications and precautions for vaccines routinely recommended for adults		
Vaccine(s)	Contraindications	Precautions
All vaccines routinely recommended for adults	<ul style="list-style-type: none"> Severe reaction, e.g., anaphylaxis, after a previous dose or to a vaccine component 	<ul style="list-style-type: none"> Moderate or severe acute illness with or without fever

* Adapted from: CDC. Table 6. Contraindications and precautions to commonly used vaccines. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. MMWR 2011;60(No.RR-2):40-1 and from: Hamborsky J, Kroger A, Wolfe S, eds. Appendix A. Epidemiology and prevention of vaccine preventable diseases. 13th ed. Washington, DC: Public Health Foundation, 2015. Available at www.cdc.gov/vaccines/pubs/pinkbook/index.html.

Table 10: Vaccine-Specific Contraindications and Precautions*

Additional contraindications and precautions for vaccines routinely recommended for adults		
Vaccine(s)	Additional Contraindications	Additional Precautions
IIV ³		<ul style="list-style-type: none"> History of Guillain-Barré syndrome within 6 weeks after previous influenza vaccination Egg allergy other than hives, e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis; or required epinephrine or another emergency medical intervention (IV may be administered in an inpatient or outpatient medical setting and under the supervision of a healthcare provider who is able to recognize and manage severe allergic conditions)
RIV ¹		<ul style="list-style-type: none"> History of Guillain-Barré syndrome within 6 weeks after previous influenza vaccination
Tdap, Td	<ul style="list-style-type: none"> For pertussis-containing vaccines: encephalopathy, e.g., coma, decreased level of consciousness, or prolonged seizures, not attributable to another identifiable cause within 7 days of administration of a previous dose of a vaccine containing tetanus or diphtheria toxoid or acellular pertussis 	<ul style="list-style-type: none"> Guillain-Barré syndrome within 6 weeks after previous dose of tetanus or diphtheria toxoid-containing vaccine. Defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine For pertussis-containing vaccine, progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy (until a treatment regimen has been established and the condition has stabilized)
MMR ²	<ul style="list-style-type: none"> Severe immunodeficiency, e.g., hematologic and solid tumors, chemotherapy, congenital immunodeficiency or long-term immunosuppressive therapy,³ human immunodeficiency virus (HIV) infection with severe immunocompromise Pregnancy 	
VAR ²	<ul style="list-style-type: none"> Severe immunodeficiency, e.g., hematologic and solid tumors, chemotherapy, congenital immunodeficiency or long-term immunosuppressive therapy³, HIV infection with severe immunocompromise 	<ul style="list-style-type: none"> Recent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product)⁴ Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination)

	<ul style="list-style-type: none"> • Pregnancy 	
ZVL²	<ul style="list-style-type: none"> • Severe immunodeficiency, e.g., hematologic and solid tumors, chemotherapy, congenital immunodeficiency or long-term immunosuppressive therapy³, HIV infection with severe immunocompromise • Pregnancy 	<ul style="list-style-type: none"> • Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination)
HPV vaccine		<ul style="list-style-type: none"> • Pregnancy
PCV-13	<ul style="list-style-type: none"> • Severe allergic reaction to any vaccine containing diphtheria toxoid 	

1. For additional information on use of influenza vaccines among persons with egg allergy, see CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2016-17 influenza season. *MMWR*. 2016;65(RR-5):1-54. Available at www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm.
2. MMR may be administered together with VAR or ZVL on the same day. If not administered on the same day, separate live vaccines by at least 28 days.
3. Immunosuppressive steroid dose is considered to be daily receipt of 20 mg or more of prednisone or equivalent for 2 or more weeks. Vaccination should be deferred for at least 1 month after discontinuation of immunosuppressive steroid therapy. Providers should consult ACIP recommendations for complete information on the use of specific live vaccines among persons on immune-suppressing medications or with immune suppression because of other reasons.
4. Vaccines should be deferred for the appropriate interval if replacement immune globulin products are being administered. See: Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.
5. Measles vaccination may temporarily suppress tuberculin reactivity. Measles-containing vaccine may be administered on the same day as tuberculin skin testing or testing should be postponed for at least 4 weeks after vaccination.

* Adapted from: CDC. Table 6. Contraindications and precautions to commonly used vaccines. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No.RR-2):40-1 and from: Hamborsky J, Kroger A, Wolfe S, eds. Appendix A. Epidemiology and prevention of vaccine preventable diseases. 13th ed. Washington, DC: Public Health Foundation, 2015. Available at www.cdc.gov/vaccines/pubs/pinkbook/index.html.

XI. Pertinent clinical pearls for AECOPD

- A. Acute exacerbations of COPD are marked by inflammation and incited by pathogens
- B. Prompt treatment with short courses of antibiotic therapy improve outcomes
- C. Agent selection based on patient risk factors
- D. Vaccination improved outcomes in COPD
- E. Less exacerbations also provide cardiac benefit
- F. Corticosteroid benefits during AECOPD outweigh risks

ANSWER KEY TO CASE QUESTIONS

1. Answer: C

Comorbidities, including asthma or allergic rhinitis, are risk factors for AOM. Although exposure to dust or other particulate matter is a risk factor, the father's position at the refinery is more likely to directly impact him than AK (answer B is incorrect). Use of inhaled fluticasone and historical hospitalizations are not characterized as specific risk factors for AOM (answers A and D are incorrect).

2. Answer: D

Treatment with antibiotics is recommended in this patient based on her age, presenting signs ($T_{\text{max}} > 39^{\circ}\text{C}$, bilateral bulging tympanic membranes), and symptoms. Amoxicillin 45 mg/kg/day is not the optimal dose for treatment of OM and based on her age (5 years old) the recommended duration of treatment would be a minimum of 7 days as patients 2-5 years of age demonstrate improved outcomes in resolution of symptoms when 7 days of therapy is used. A shorter course of therapy can only be considered in patients at least 6 years of age or older. Ceftriaxone IM is not recommended for initial therapy in patients who are able to take medications orally and should be reserved for patients who fail to respond after 48-72 hours of amoxicillin/clavulanate therapy, rendering Answer C incorrect.

3. Answer: B

Ceftriaxone at a dose of 50 mg/kg/dose IM daily given for 3 doses can be considered as an alternative first-line therapy in the event of treatment failure occurring 48-72 hours after receipt of amoxicillin/clavulanate. If initial therapy with amoxicillin/clavulanate failed, re-treating (even with an extended course of 10 days) would not be appropriate (answer A is incorrect). Clindamycin plus a third-generation cephalosporin is recommended in the event of a penicillin allergy, but not necessarily as alternative therapy after treatment failure (answer C is incorrect). Fluoroquinolones are not recommended, as exposure in childhood should be limited (answer D is incorrect).

4. Answer: C

PCV-13 has been demonstrated to lead to a decline in the incidence of invasive disease in patients, including a reduction of up to 34% in AOM for patients who have received the vaccine. The use of antibiotic prophylaxis or probiotic administration has not been shown to reduce the incidence of AOM infections and complications. Hib vaccination does aid in reduction of invasive infections secondary to *Haemophilus influenzae* and may impact resistance patterns; however, it does not decrease AOM infections.

5. Answer: A

Vaccination with the inactivated influenza vaccine has demonstrated a 30-50% reduction in recurrent AOM. Although vaccination with the live attenuated influenza vaccine has been reinstituted this year by the ACIP as part of the influenza recommendations, this patient is not a candidate for that vaccine because of her past medical history of asthma. PPSV-23 is indicated only in high-risk patients (including patients with asthma treated with high dose oral steroids), but this patient does not meet that criterion. PCV-7 is no longer recommended.

6. Answer: A

DR is high risk based on his comorbid conditions (DM) and severe presentation (T_{\max} 39° C) and, therefore, high-dose amoxicillin/clavulanate should be utilized for management of his ABRS. The 500-mg, thrice-daily dose should only be used in patients not at high risk. Furthermore, the severe presentation raises concern for resistance, which could be overcome with higher dosing based on the primary mechanisms expected with *Streptococcus pneumoniae* as well as *Haemophilus influenzae*.

7. Answer: C

In the setting of a penicillin allergy, the first-line alternative for management of ABRS is doxycycline. It would be inappropriate to continue the amoxicillin in the presence of a newly developed rash, and cefpodoxime plus clindamycin regimen is recommended for pediatric patients and not adults. The other answer selections are not the best choice because the question specifically asks for the best first-line alternative agent. In this setting, while fluoroquinolones can be used, they are considered second-line alternatives. Moreover, the recent FDA labeling and black box warnings warn against use of these agents for respiratory conditions, making answer selection A an inferior treatment option.

8. Answer B

Since it is 4 months after initial treatment in which his acute infection resolved with appropriate therapy, he is now considered to have chronic sinusitis. The use of antibiotics is not associated with improved outcomes (answers A and C) but intranasal corticosteroids can be a useful agent to aid in managing chronic sinusitis. Pulse dosing of steroids has not been demonstrated to have an impact on symptoms in the setting of chronic sinusitis.

9. Answer: A

Our predominant pathogens to cover in this scenario are *Haemophilus influenzae* and *Streptococcus pneumoniae*, given the exacerbation history KS presents with; therefore, amoxicillin/clavulanate is the preferred first-line therapy per the GOLD guidelines. While there may be a role for moxifloxacin or azithromycin for pulse therapy to prevent exacerbations in the setting of an active exacerbation, in the setting of an active exacerbation macrolide-based therapy is not recommended. Moxifloxacin as a fluoroquinolone would not be advocated for treatment of her AECOPD at this time either given the FDA-labeled warnings against use for respiratory infections as well as her previous inadequately dosed pulse therapy that may pose resistance risk to her. Therapy with amoxicillin/clavulanate provides the most targeted, appropriate option for managing KS at this time when considering the predominant pathogens of interest, *S. pneumoniae* and *H. influenzae*. Doxycycline therapy could be considered at this time as an alternative agent; however, it should be reserved for patients with a penicillin allergy that is documented and confirmed.

10. Answer C

Based on the VA study findings, the GOLD guidelines recommend corticosteroids as they provide a benefit in AECOPD by reducing the failure rates secondary to an exacerbation. Prednisone 40 mg BID for 5 days is the appropriate dose and duration. Methylprednisolone for 3 days is inappropriate duration and, since PO has similar

efficacy, it would not be the preferred route. Azithromycin is not beneficial for this patient in the acute setting, and magnesium sulfate has not demonstrated any benefit in improving outcomes in patients with AECOPD.

11. Answer: A

The only contraindication for receiving the PCV-13 vaccine is anaphylaxis to the diphtheria tetanoid toxin. Recent infection and allergies to hepatitis B vaccine and latex are not contraindications to receiving the PCV-13 vaccine.

ANSWER KEY TO SELF-ASSESSMENT QUESTIONS (from front of the chapter)

1. Answer: D

Answer D offers the most appropriate therapy to initiate in ST based on her age (>2 years old but <7 years old), presence of fever that is <39° C, and the presence of unilateral acute otitis media without a bulging tympanic membrane. Key characteristics indicating need for treatment with antimicrobials would be age less than 5, presence of bilateral disease, fever of ≥39° C, and/or severe appearance. Amoxicillin is the first-line treatment of choice, but the recommended dose would be 90 mg/kg. Fluoroquinolones are not indicated for acute otitis media as first-line nor alternative therapy for acute otitis media. Finally, amoxicillin/clavulanate, though utilized as first-line therapy in the clinical setting, is not a guideline-endorsed first-line agent for an initial episode of acute otitis media. It could be considered if she had presented with a recurrent infection; however, such is not the case as the question is currently written.

2. Answer: B

The key finding in this question is that the patient population is pediatrics and in contrast to adult patients, the guidelines endorse utilizing combination therapy with clindamycin plus a third-generation cephalosporin when treating ABRS in this subset of the population. Additionally, although fluoroquinolone reduction is an ideal goal for an antimicrobial stewardship intervention in the outpatient setting, doxycycline is not indicated for use in patients <7 years of age secondary to concerns for tooth discoloration and bone demineralization based on older studies and clinical experience with its parent compound tetracycline. Answers C and D are inaccurate because, even for pediatric patients, amoxicillin monotherapy is not indicated for ABRS secondary to concerns for beta-lactamase-producing strains of *Haemophilus influenzae*, and macrolides are not indicated for this upper respiratory indication.

3. Answer: A

Answer A is most appropriate. Although she meets criteria for ABRS by virtue of duration of illness and presence of nasal discharge that is purulent, she is an immune compromised host for which imaging would be indicated. Additionally, if ABRS is confirmed in the absence of another etiology of her presentation, she would require high-dose amoxicillin/clavulanate therapy which would render answer selection B inappropriate. Fluoroquinolone-based therapy is not indicated in the guidelines for this indication making answer selection C incorrect. Although intranasal corticosteroids are indicated for both seasonal allergies and as an adjunctive or alternative treatment option for ABRS, it would be inappropriate to intervene in this manner only for a high-risk patient.

4. Answer: C

Immunization with pneumococcal polysaccharide vaccine has been shown to have a protective benefit in reducing AECOPD in patients with multiple exacerbations. This answer selection is most appropriate because, while influenza vaccine is important as well, clinicians are specifically focused on reducing exacerbations requiring hospitalization for which the data are stronger for the role of PPSV to achieve that endpoint. The CDC specifically recommends PPSV-23 in patients with chronic lung disease, even at ages ranging from 19-64 years. While PCV-13 was also previously recommended, the CDC now recommends administration of PCV-13 only after age 65 in patients who qualify based on shared clinical decision-making. PCV-7 would no longer be recommended over PCV-13.

5. Answer: C

ABRS is characterized by a varied set of pathogens as compared to other URIs; however, the predominant pathogen remains *Streptococcus pneumoniae*. The other listed agents can be implicated at lower incidences as well. Therefore, the key is identification of which is MOST likely to be the pathogen etiology.

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