ADDENDUM 3

Discussion and Review of the Evidence

Contents

1 Etiology

The etiology of CAP varies by age, with viral etiologies predominating in infants and toddlers and bacterial etiologies predominating in children and adolescents. In numerous studies, the most commonly identified bacterial etiologies include *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* with nontypeable *Haemophilus influenzae*, group A *Streptococcus*, *Chlamydophila pneumoniae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* identified much less frequently.[1-5,19-21] A significant limitation to all of the studies, however, is that they only discover the causative pathogens for which they are testing, likely resulting in under-detection of some organisms. Additionally, no two studies utilize the same testing methods, even for the same organism; their definitions of pneumonia are occasionally different; and not all study participants in any given study undergo testing for every organism under investigation.

1.1 Streptococcus pneumoniae

Even after the introduction of pneumococcal vaccines in the last ten years, *S. pneumoniae* continues to be an important pathogen in childhood CAP.[18,19] In addition to lobar pneumonia, pneumococcus can cause complicated disease such as effusion, empyema, and necrotizing pneumonia.[1] Rarely, *S. pneumoniae* can cause hemolytic uremic syndrome (HUS) in severe or complicated disease.[22-25]

The seven-valent pneumococcal vaccine, introduced in 2000, was effective in decreasing the incidence of clinical and radiographically confirmed pneumonia in children less than age 2.[26] Because of changes in the most common serotypes after introduction of the seven-valent vaccine, the 13-valent pneumococcal vaccine was introduced in 2010 and seems to have yielded similarly impressive results.[27-28] The serotypes most commonly associated with HUS are included in the 13-valent vaccine.[22-23]

Likely because the 13-valent vaccine is reducing highly drug-resistant forms of pneumococcus, DCMC's most recent antibiogram demonstrates that all locally isolated strains of pneumococcus are sensitive to penicillin (MICs ≤ 2 mg/L). Locally, there are continued high levels of resistance to azithromycin.

1.2 Mycoplasma pneumoniae

M. pneumoniae is a common etiology of CAP in children, with some studies detecting it in patients even as young as age 2 to 3 years.[4,5,19,29] Recent systematic reviews, however, have shown that the clinical diagnosis of *M. pneumoniae* is difficult in all ages, with very few exam or CXR findings being sensitive or specific for *Mycoplasma* infection.[30] Diagnostic testing is problematic as well since it is not available in a clinically relevant time frame and is confounded by a high prevalence of asymptomatic carriage.[31-32] Despite these known difficulties with accurate diagnosis, a recent European study suggests that *M. pneumoniae* infection should be considered in patients who are not responding to initial antibiotic therapy.[18] Recently, multiple systematic reviews have failed to uncover any evidence regarding efficacy of *Mycoplasma* treatment.[33-34]

1.3 Haemophilus influenzae

The IDSA's 2011 pediatric CAP guidelines describe *H. influenzae* as an infrequent pathogen in pediatric CAP.[1] Widespread use of the *H. influenzae* type b (Hib) vaccine since the 1980's has decreased the incidence of Hib, but studies continue to demonstrate nontypeable *H. influenzae* as a causative organism in CAP[2-3] and studies investigating invasive *H. influenzae* disease have described pneumonia as the primary source of infection.[23,35-36] In a recent European study evaluating the etiology of CAP in patients not responding to treatment, *H. influenzae* was the most common etiology identified by BAL specimen, but this study was limited by the lack of a control group.[18] Infrequent use of specific testing for *H. influenzae* (e.g. serum titers, PCR, etc) may result in under-identification of this pathogen in many studies.[4]

1.4 Streptococcus pyogenes

Group A *Streptococcus* is an uncommon, though increasingly recognized, cause of pediatric CAP.[1,19,37] It is associated with more severe and rapid clinical presentations, toxin-mediated disease, empyemas, and necrotizing pneumonia.[1,37-39] One study comparing GAS pneumonia to those caused by *S. pneumoniae* found that GAS disease is more likely to cause effusion, prolonged fever, and longer hospital stays.[39]

1.5 Staphylococcus aureus

S. aureus is an infrequent [4,19,40] but potentially devastating cause of CAP. It is associated with recent viral infections, especially influenza [37,41-42], and commonly causes parapneumonic empyemas, cavitary lesions, pneumatoceles, pulmonary abscesses, and necrotizing pneumonias. [43-44]

1.6 Viruses

Viral infections, including RSV and influenza, are common etiologies of CAP, especially in young children. [1,4,8,20] A secondary bacterial pneumonia is unlikely in a viral illness but should be considered if a patient experiences clinical worsening, persistent fever, or a biphasic illness (initial improvement followed by recurrence of fever and deterioration). When a secondary bacterial pneumonia does occur in the presence of influenza infection, patients appear to be at increased risk of disease caused by *S. aureus* and group A *Streptococcus* in addition to *S. pneumoniae*. [1,37,41-42]

1.7 Underimmunized patients

Despite the IDSA's 2011 recommendations that under-immunized children hospitalized with CAP receive broader-spectrum antibiotic therapy than appropriately immunized children, no studies were found that evaluate how the etiology of CAP differs between vaccinated and unvaccinated children. There is evidence, however, that the introduction of the 7-valent and 13-valent pneumococcal vaccines does protect unvaccinated populations from invasive disease caused by these vaccine serotypes [28,45] and that pneumococcal serotypes causing nasopharyngeal colonization is altered even in unvaccinated individuals after introduction of the 13-valent pneumococcal vaccination in their community. [46-47] Additionally, the serotypes discovered in adults with invasive pneumococcal disease are associated with the vaccination status of that patient's child contacts.[48]

2 Diagnostic Evaluation

2.1 History

Patients with community-acquired pneumonia commonly present with symptoms of fever, cough, tachypnea, and respiratory distress. Some patients may complain of shortness of breath, chest pain, vomiting, or abdominal pain. Occasionally, they will also experience systemic symptoms such as headache and malaise. One study demonstrated that a history of chest pain and a longer duration of fever are both correlated with the finding radiographic pneumonia in the emergency department.[49]

As part of routine history-taking for suspected CAP, providers should also assess the patient's vaccination and immunologic status and inquire about risk factors for fungal disease, tuberculosis, and aspiration pneumonia. Aspiration pneumonia may be suspected in the setting of neurologic impairment, swallowing dysfunction, or recent sedation.

2.2 Physical Exam

A thorough physical exam is important to the diagnosis and evaluation of community acquired pneumonia. Particular attention should be paid to the pulmonary exam, which may reveal tachypnea, respiratory distress (accessory muscle use, nasal flaring, head bobbing, or grunting), inspiratory crackles, rhonchi, or decreased breath sounds overlying areas of consolidation. While many physical manifestations of respiratory disease are nonspecific, the presence of focal crackles has been shown to correlate well with radiographic pneumonia. [49]

Because no single physical exam finding, including cyanosis, reliably predicts hypoxemia, pulse oximetry should be used to estimate the arterial oxygen saturation in patient's suspected of having CAP. [6-7] By pulse oximetry, hypoxemia is generally defined as an oxygen saturation < 90-92% on room air. [1,49] The presence of hypoxemia by pulse oximetry been shown to predict radiographic pneumonia in the emergency department[49] and correlates with disease severity[1,7]; therefore, it has utility in the diagnostic evaluation and in determining the need for hospitalization. Changes in pulse oximetry have been reported to lag arterial oxygen saturations. Because of this, pulse oximetry is not recommended as substitution for cardiorespiratory monitoring in critically ill children. [7]

2.3 Laboratory Testing

Despite commonly held beliefs, serum white blood cell count and acute phase reactants are not reliable at distinguishing between viral and bacterial etiologies of pneumonia. [1] In patients with severe or complicated disease, acute phase reactants do have utility as objective markers of response to therapy. Although there are limitations in the use of the serum white blood cell count in determining etiology, the complete blood count can be useful in evaluating for complications of severe disease, such as HUS. [1] Although rarely clinically relevant, serum electrolytes may be indicated in severely ill patients to evaluate for the presence of acute kidney injury or electrolytes disturbances such as hyponatremia.[50]

Unless a patient is not responding to therapy as expected, diagnostic testing aimed at identifying an etiology such as serum titers or PCR is usually not available in a clinically relevant time frame and is generally not indicated. Viral testing during the appropriate season, e.g. rapid respiratory syncytial virus (RSV) or influenza testing, may be indicated if the results would impact clinical management, such as decisions regarding antimicrobial therapy, further testing, or the need for imaging. The risk of serious bacterial infection is low in laboratory confirmed viral infection, and a positive influenza test has been proven to decrease the need for ancillary tests, including blood evaluation, CXR, urine cultures and CSF evaluation as well as decrease length of stay in the ED, reduce admission to the hospital and decrease use of antibiotics. [51-55]

Sputum cultures or tracheal aspirates may be helpful in guiding antimicrobial therapy for more severely ill patients; however, these specimens are difficult to obtain in children and susceptible to contamination by colonizing organisms and are therefore not as reliable as bronchial alveolar lavage (BAL) specimens, which are seldom indicated.

Blood cultures are rarely useful in the care of simple CAP, but may be helpful in narrowing antibiotic therapy in patients not responding to appropriate therapy or in those with severe or complicated disease. The likelihood of a true positive blood culture in children with CAP is <3%. [1,13,56-59] Frequent false positives occur due to skin contaminants and can lead to unnecessary prolonged hospitalization and excessive resource utilization and treatment. [57,59-61]

Although the greatest risk exists in foreign-born patients or in those with international travel, clinicians should perform protein-purified derivative (PPD) and serum quantiferon gold assay on patients when tuberculosis is a strong consideration.

2.4 Imaging

A chest x-ray (CXR) will usually confirm the diagnosis of pneumonia; however, CXR cannot reliably distinguish among the various etiologies. [62] Since there is significant intra-observer variation in the diagnosis of pneumonia on radiograph [62-64] and there exists evidence that CXRs may not affect the clinical outcome in outpatients who meet the clinical diagnosis of pneumonia[65-66], CXR is not required to confirm the diagnosis in patients well enough to be managed on an outpatient basis. These recommendations must be weighed against evidence that presence of an alveolar infiltrate or effusion (in contrast to an interstitial infiltrate) results in high concordance between interpreters as well as a suggestion of bacterial pneumonia cause. [67-69] Furthermore, the negative predictive value of a CXR for pneumonia is high. [70-71] Diagnosis of pneumonia by clinical assessment without radiograph may lead to overtreatment and increase in antibiotic resistance[15] and clinical factors alone do not reliably predict pneumonia. [69,72-74]

CXR should be obtained in those with more severe disease, including those requiring hospitalization, deteriorating on therapy, or not responding to initial management within 48-72 hours. In these instances, imaging is useful to document the presence, size, and character of parenchymal infiltrates and to identify complications of pneumonia that may lead to interventions beyond antibiotic and supportive medical therapy. [1] Response to therapy is generally not gauged by changes in CXR findings, but rather by improvement in laboratory markers (if indicated), fever, tachypnea, respiratory distress, or oxygen saturations.

Repeat CXR should be obtained 4-6 weeks after the diagnosis of CAP in patients with recurrent pneumonia involving the same lobe and in patients with lobar collapse on initial CXR if there is suspicion of foreign body aspiration, chest mass or anatomic anomaly. [1]

In general, chest ultrasound or computerized tomography (CT) is reserved for patients with complicated disease, including evaluation of the size and character of pleural effusions. Clinicians should refer to the *Complicated Pneumonia Guidelines* for further instruction on the indications for use of these modalities.

3 Management

Antibiotic therapy is not required when a viral etiology is suspected or confirmed.

3.1 Empiric Antibiotic Selection

Empiric antibiotic therapy should target the most common pathogens, with emphasis placed on *S. pneumoniae* since it is the most frequently isolated bacterial pathogen in most studies, and when untreated, may lead to serious sequelae. [(1)]

Amoxicillin/Ampicillin is the preferred first-line treatment for *S. pneumoniae* because it has a narrow-spectrum of activity in addition to improved tolerability and advantageous pharmacokinetics when compared to intravenous/oral penicillin and oral cephalosporins. National *S. pneumoniae* resistance rates to penicillin are decreasing and DCMCCT *S. pneumoniae* resistance rates to penicillin are minimal such that all patients regardless of immunization status are recommended to receive amoxicillin/ampicillin as first line therapy.

The amoxicillin/ampicillin dosing regimen required for effective therapy is directly related to the susceptibility of *S. pneumoniae* strains. Amoxicillin dosed as 80-90 mg/kg/day divided into 2 equal doses (twice daily dosing) will provide effective treatment for fully susceptible *S. pneumoniae* strains (penicillin MICs ≤ 2 ug/mL). When *S. pneumoniae* strains have elevated penicillin MICs ≥ 2 ug/mL, the 80-90 mg/kg/day may need to be divided into 3 equal doses (three times daily) to achieve higher clinical and microbiologic cure, 90% with three times daily versus 65% with twice daily dosing. [(75)]

Ampicillin dosed as 200 mg/kg/day divided into 4 equal doses (every 6 hour dosing) will provide effective treatment for fully susceptible *S. pneumoniae* strains (penicillin MICs ≤ 2 ug/mL). The typical maximum daily dose is 8 grams/day however maximum daily doses may range between 4 – 12 grams. Adult literature has shown that a maximum daily dose of 4 grams achieves adequate concentrations for effective treatment of fully susceptible *S. pneumoniae* strains (penicillin MICs ≤ 2 ug/mL). Since pharmacokinetic and pharmacodynamic parameters are similar between adult and children, the maximum dose of ampicillin may be limited to 1 gram every 6 hours for fully susceptible *S. pneumoniae* strains (penicillin MICs ≤ 2 ug/mL). [(76-77)] When *S. pneumoniae* strains have elevated penicillin MICs ≥ 2 ug/mL dosing up to 400 mg/kg/day divided into 4 equal doses (every 6 hour dosing) may be necessary, maximum daily dose 12 grams. [(78-79)]

The 2011 PIDS and IDSA Clinical Practice Guidelines for the management of CAP in infants and children recommend inpatients receive alternative first line therapy with ceftriaxone/cefotaxime if a patient is not fully immunized for *H. influenzae* type b and *S. pneumoniae*. However, no evidence was located to support this recommendation and local *S. pneumoniae* resistance rates to penicillin are low such that it is recommended all patients receive amoxicillin/ampicillin as first line therapy.

DCMCCT resistance demonstrates all *S. pneumoniae* strains have MICs ≤ 2 ug/mL such that the recommended amoxicillin dose is 80-90 mg/kg/day divided BID and ampicillin 200 mg/kg/day divided every 6 hours, maximum dose 1.75 gram/dose. Alterative dosing regimens as described above may be considered when *S. pneumoniae* strains with elevated penicillin MICs are suspected or once a penicillin MIC ≤ 2 ug/mL is confirmed.

Azithromycin should not be used alone as empiric therapy for CAP due to unacceptably high national and local resistance rates against *S. pneumoniae*, the most likely pathogen. National resistance rate for *S. pneumoniae* isolates is 56-63% and DCMCCT resistance rate for *S. pneumoniae* isolates is 51%.

3.2 Empiric Therapy for Patients with IgE-mediated Penicillin Allergies

For patients with an IgE-mediated penicillin allergy or a history of serious penicillin reaction, an alternative agent should be selected that has the greatest activity for *S. pneumoniae*, the most likely pathogen. Alternative agents include intravenous ceftriaxone, oral second or third generation cephalosporins (i.e. cefuroxime, cefpodoxime, cefdinir), or clindamycin. For these patients, based on national and local resistance data for *S. pneumoniae*, ceftriaxone (intravenous) and clindamycin (oral/intravenous) are considered the best available options. Clindamycin is the preferred oral agent over second or third generation cephalosporins because national and local resistance rates are lower for *S. pneumoniae* strains. Additionally no oral cephalosporin at doses studied in children provides activity at the site of infection that equals high-dose amoxicillin.

Providers should consider a trial of amoxicillin/ampicillin under observation if patients report "non-serious" or non IgE-mediated reaction to penicillin. Despite 5-10% of the general population reporting a penicillin allergy; recent studies have shown that up to 95% of these patients are not truly allergic. Additionally, the alternative agents are broad spectrum agents whose unnecessary use increase the risk of development of resistance amongst normal bacterial flora and put patients at increased risk of development of *C. difficile* infections. Finally, no alternative agent is going to provide as optimal of coverage of S. pneumoniae as high-dose amoxicillin/ampicillin such that providers should carefully investigate penicillin allergies before deciding to select an alternative agent. [3]

3.3 Empiric Use of Cephalosporins + Clindamycin

A national surveillance study of *S. pneumoniae* isolated from pediatric respiratory isolates of patients experiencing serious or recurrent/persistent infections showed the following alternative agents had the greatest activity for *S. pneumoniae* (ranked most to least active): ceftriaxone (89-95% susceptible), clindamycin (85% susceptible), cefuroxime (69% susceptible), cefdinir (59% susceptible).[83] DCMCCT resistance data for S. pneumoniae isolates showed the following alternative agents had the greatest activity for *S. pneumoniae* (ranked most to least active): ceftriaxone (100% susceptible), clindamycin (90% susceptible), cefuroxime (76% susceptible), cefdinir (unknown). Cefpodoxime was not included in the national surveillance study or local resistance data, however it is the preferred third generation cephalosporin over cefdinir due to its superior in-vitro activity against *S. pneumoniae* and pharmacokinetic/pharmacodynamic profile. In comparative trials in the treatment of pediatric CAP patients (ages 3 months – 11.5 years), cefpodoxime has shown similar clinical cure rates and improvement as cefuroxime and amoxicillin-clavulanate.[84] The safety and efficacy of cefdinir has only been studied in pediatric CAP patients (ages > 12 years) in comparison to cefaclor. [85] In order to achieve adequate serum drug concentrations for adequate bactericidal killing at the site of action, both cefpodoxime and cefdinir should have the total recommended daily dose divided twice daily which maximizes the time serum drug concentrations spend above the MIC during a dosing interval. [1,80-82]

3.4 Inpatient and Outpatient Treatment Failures

Patients in the inpatient and outpatient settings who fail to show improvement or worsen within 48-72 hours may require broadening of antibiotic therapy to target less likely pathogens such as penicillin-resistant *S. pneumoniae*, *H. influenzae*, *S. aureus*, or atypical organisms.

In the outpatient setting, amoxicillin-clavulanate with or without azithromycin is the preferred first line treatment for patients failing to show improvement or worsening on high dose amoxicillin because it provides the most optimal coverage for other pathogens such as non-typeable *H. influenzae*, B-lactamase positive, methicillin sensitive *S. aureus* (MSSA) and because the incidence of penicillin-resistant *S. pneumonaie* is low the addition of azithromycin would have the benefit of providing coverage for atypical organisms such as *Mycoplasma*.

A national surveillance study of non-typeable *H. influenzae* isolated from pediatric respiratory isolates of patients experiencing serious or recurrent/persistent infections showed the following alternative agents had the greatest activity for non-typeable *H. influenzae*, B-lactamase positive (ranked most to least active): ceftriaxone (100% susceptible), high-dose amoxicillin/clavulanate (100% susceptible), cefuroxime (90-100% susceptible), cefdinir (80-100% susceptible). [83]

Published reviews on in-vitro activity and DCMCCT resistance data for MSSA isolates indicate amoxicillin-clavulanate provides to best coverage for MSSA. One hundred percent of MSSA isolates at DCMCCT are susceptible to amoxicillin-clavulanate.

In the inpatient setting, ceftriaxone with or without azithromycin is the preferred first-line treatment for patients failing to show improvement or worsening on high-dose amoxicillin/ampicillin/amoxicillin-clavulanate because it provides coverage for other pathogens such as penicillin-resistant *S. pneumoniae*, non-typeable *H. influenzae*, B-lactamase positive, methicillin-sensitive *S. aureus,* and atypical organisms. If concern for penicillin-resistant *S. pneumoniae* is low, ampicillin-sulbactam is an acceptable alternative. The addition of azithromycin would have benefit of providing coverage for atypical organisms.

Ceftriaxone remain active against nearly all *S. pneumoniae*, including penicillin-resistant strains. See empiric antibiotic selection section for more information on ceftriaxone activity against *S. pneumoniae*. Additionally the national surveillance study of non-typeable *H. influenzae* isolated from pediatric respiratory isolates of patients experiencing serious or recurrent/persistent infections showed ceftriaxone activity as being 100%. Though not considered the cephalosporin-of-choice for MSSA, ceftriaxone has activity against it and resistance rates described in the literature have been low. [81-83]

3.5 Treatment of Suspected Atypical Pneumonia

Since mycoplasmas lack a cell wall and are inherently resistant to beta-lactams, suspected *Mycoplasma* pneumonia is most commonly treated with oral macrolides, such as azithromycin and clarithromycin. Doxycycline and floroquinolones are also effective but used less often because of concerns for side effects such as permanent dental discoloration in patients age 7 years and younger, and the risk of *Clostridium difficile* colitis, respectively (AAP Red Book 2015). Because of the lack of evidence regarding efficacy of treatment [33-34], difficulty in accurate clinical diagnosis [30], and significant growing concern for the development of macrolide-resistant Mycoplasma [86], British experts advocate for treatment of *Mycoplasma* only in limited situations such as severe infection or after a patient has failed treatment with a beta-lactam [13]. The 2011 IDSA CAP guidelines recommended treating with a macrolide in the outpatient setting if a patient's symptoms are "compatible with" atypical infection, whereas they recommend one should add a macrolide to a beta-lactam when atypical organisms are a "significant consideration" in the inpatient setting; however, the IDSA does not provide guidance on when clinicians should suspect atypical organisms and their evidence supporting the efficacy of macrolide treatment is not strong. Based on a review of the currently available evidence, the DCMC CAP Guidelines work group has concluded that, in most situations, macrolides should not be used as mono-therapy for CAP given the difficulty in accurate diagnosis, lack of evidence towards their efficacy, and the risks associated with not treating S. pneumoniae.

IgE-mediated reactions to macrolides are rare and most patients reporting an allergy experienced a mild reaction. Evidence suggests that majority of patients who react to one macrolide tolerated other macrolides suggesting little allergic cross-reactivity, however most patients will tolerate the initial macrolide if it is given again. If patients cannot tolerate azithromycin, clarithromycin or doxycycline may be considered. [87]

3.6 Inpatient and Outpatient Treatment Failures in Patients with an IgE-mediated Allergy to Penicillin

For patients with an IgE-mediated penicillin allergy experiencing a treatment failure an alternative agent should be selected with consideration for penicillin-resistant *S. pneumoniae*, non-typeable *H. influenzae*, B-lactamase positive, atypical organisms, and/or methicillin-sensitive *S. aureus*. Alternative agents include clindamycin, oral second or third generation cephalosporins (i.e. cefuroxime, cefpodoxime, and cefdinir), levofloxacin, and linezolid. When providers consider alternative agents for treatment of this subgroup of patients, they need to consider the spectrum of the initial empiric antibiotic and assess what likely pathogens are not being included. Antibiotic therapy may require expansion to include single or combination antibiotic(s) to ensure adequate treatment of not included pathogens.

See "Empiric use of Cephalosporins + Clindamycin" antibiotic selection section for discussion of activity of alternative agents for S. pneumoniae.

A national surveillance study of non-typeable *H. influenzae* isolated from pediatric respiratory isolates of patients experiencing serious or recurrent/persistent infections showed cefuroxime (90-100% susceptible) had greater activity over cefdinir (80-100% susceptible). [83,88] Though not included in this study, based on in-vitro activity cefpodoxime is the most active oral second/third generation cephalosporin against *H. influenzae* followed by cefuroxime and cefdinir. [81-82,89] Clindamycin provides no coverage for *H. influenzae* as the organism is intrinsically resistant to clindamycin; however, H. influenzae is usually susceptible to azithromycin. The addition of Azithromycin to Clindamycin or use of a second or third-generation cephalosporin over Clindamycin is required for the penicillin-allergic patient in whom there is concern for H. influenzae.

Published reviews on in-vitro activity indicate cefdinir is the most active against MSSA followed by cefuroxime and cefpodoxime. [81-82] There is no DCMCCT resistance data for oral second/third generation cephalosporins for MSSA isolates; clindamycin susceptibility for MSSA isolates is 82%.

Providers should consider a trial of amoxicillin-clavulanate under observation if patients report "non-serious" or non-IgE-mediated reaction types to penicillin because no alternative agent is going to provide as optimal of coverage of *S. pneumoniae* and less common pathogens such as *H. influenzae* and MSSA as amoxicillin-clavulanate.

3.7 Considerations for Levofloxacin, Linezolid, and Vancomycin

Use of levofloxacin, linezolid, and vancomycin should be limited due to the high adverse effect profile associated with each agent and to prevent the growth of resistance to such broad spectrum agents.

Levofloxacin, linezolid, and vancomycin provide activity against > 95% *S. pneumoniae* strains nationally and ≥ 99% *S. pneumoniae* strains at DCMCCT. Levofloxacin has activity against non-typeable *H. influenzae*, B-lactamase positive, and atypical organisms; however, its coverage of MSSA is not as optimal as linezolid or vancomycin and it provides no coverage for methicillin-resistant *S. aureus* (MRSA). Vancomycin and linezolid provide coverage of 100% MSSA and MRSA strains at DCMCCT, but they provide no coverage against non-typeable *H. influenzae*, B-lactamase positive, or atypical organisms.

Levofloxacin is associated with a variety adverse effect such as CNS events (seizures, headaches, dizziness, and sleep disorders), peripheral neuropathy, and photosensitivity with skin rash, hypo-/hyperglycemia, prolongation of QT interval, hepatic dysfunction, and skeletomuscular complaints. Additionally, the fluoroquinolone drug class has been associated with increased risk for the development of C. difficile infections. Many providers feel hesitant to use levofloxacin in the pediatric population due to concerns about risk of tendon rupture and tendinitis; however, a recent study determined the risks of cartilage injury appear to be uncommon or clinically undetectable/reversible during a 5 year follow-up period. [90-91]

Linezolid is associated with a variety of adverse effects such as reversible platelet and neutrophil suppression and peripheral nerve injury (peripheral/optic); however, these typically do not occur until the end of the second week of therapy (> 14 days of therapy). Linezolid can increase the risk of serotonin syndrome in patients taking other serotonin reuptake inhibitors, as well as any other drugs that increase serotonin concentration in the central nervous system. Linezolid may be preferred over vancomycin when treating patients with pre-existing renal dysfunction or in the outpatient setting. [92]

3.8 Antibiotic Selection for Oral Step-down Therapy

Inpatients may transition from intravenous to oral antibiotic therapy after showing improvement in clinical signs (i.e. fever, oxygen saturation, and respiratory rate) and upon meeting criteria for outpatient management (i.e. oxygen saturations ≥ 90% on room air for ≥ 8 hours, ability to tolerate oral antibiotics, mild-normal work of breathing, and close follow-up).

Patients receiving intravenous ampicillin should be transitioned to oral high dose amoxicillin. [1] Patients receiving intravenous ceftriaxone may also be transitioned to oral high dose amoxicillin if adequate cultures are either not obtained or are obtained after antimicrobial treatment has begun and do not document a pathogen as long as the patient was without an effusion, empyema, or complicated clinical course. [1]

It is recommended patients be transitioned from intravenous ceftriaxone to oral high dose amoxicillin-clavulanate if an effusion or empyema was present or if the clinical course was complicated due to likelihood of infection with pathogens other than *S. pneumoniae* (i.e. *H. influenzae*, MSSA). [1]

It is recommended patients receiving intravenous ceftriaxone with suspected penicillin-resistant *S. pneumoniae* (MICs ≥ 4 ug/mL) be transitioned to oral levofloxacin, however the likelihood of this occurrence is low as the presence of resistance amongst *S. pneumoniae* has decreased due to PCV7 and PCV13.[1]

Patients receiving intravenous ceftriaxone due to an IgE-mediated allergy should be transitioned to an alternative agents such as clindamycin, oral second or third generation cephalosporins (i.e. cefuroxime, cefpodoxime, cefdinir), or levofloxacin. Providers should select an alternative that has the greatest activity for the suspected pathogen (i.e. penicillin-resistant *S. pneumoniae*, non-typeable *H. influenzae*, B-lactamase positive, and/or methicillin-sensitive *S. aureus*.) See above for discussion regarding spectrum of activity of alternative agents.

Clindamycin, azithromycin, and levofloxacin are available in both intravenous and oral dosage forms and demonstrate excellent bioavailability such that patients may be transitioned from intravenous to oral therapy after signs of clinical improvement (i.e. fever, oxygen saturation, and respiratory rate).

Patients in whom a pathogen is documented should have intravenous antibiotics transitioned to the narrowest spectrum oral antibiotic based on susceptibilities to limit selection of antibiotic resistance.

3.9 Antibiotic Selection for Suspected MRSA or Life-threatening Presentations

Patients with life-threatening presentations (i.e. rapid deterioration, septic shock) suspected MRSA and those meeting PICU criteria should receive combination therapy with ceftriaxone and vancomycin with clindamycin. Due to declining MRSA susceptibilities to clindamycin, vancomycin is preferred in life-threatening presentations. DCMCCT local resistance data indicate 87% MRSA isolates susceptible to clindamycin versus 100% MRSA isolates susceptible to vancomycin. Clindamycin may be considered for coverage of MRSA in non-life-threatening presentations and in those presentations consistent with toxin-mediated disease. [1]

3.9.1 Influenza Antiviral Therapy

It is recommend antiviral therapy with oseltamivir be considered in patients with documented influenza virus infection or those experiencing clinical worsening and presentation consistent with influenza virus infection. Providers should weigh the benefits and risks in patients with mild disease and undocumented influenza virus infection because in oseltamivir treatment studies in children no benefit in clinical outcomes such as clinical course or severity of illness has been demonstrated, whereas adverse effects such as headaches, vomiting, and nausea were reported. [1,93]

3.10 Duration of Therapy

A duration of therapy of 7 to 10 days is recommended based on studies demonstrating both short and longer courses of therapy are effective. The shortest effective duration of therapy should be selected to minimize exposure of both pathogens and normal flora to antibiotics limiting the selection of antibiotic resistance. Shorter courses, 7 days of therapy, should be considered in patients with non-severe disease and/or those in the outpatient setting. Pathogens such as MRSA or complicated courses may require a longer duration of therapy. [1,94]

3.11 Probiotics

The use of probiotics containing Lactobacillus rhamnosus and Saccharomyces boulardii have demonstrated a decrease in the incidence of antibiotic-associated diarrhea when provided in doses ranging from 5.5-20 billion colony-forming units/day. A single capsule of Culturelle® [OTC] contains 10 billion colony-forming units of Lactobacillus rhamnosus GG. A single capsule or powder packet of Florastor® [OTC] contains 5 billion colony-forming units of Saccharomyces boulardii. Use of probiotics in immunocompromised patients is recommended with caution due to risk of infection from live bacteria or yeast.

3.12 Oxygen use, pulse oximetry, and intravenous hydration

Supplemental oxygen therapy should be administered to patients with oxygen saturations persistently < 90% [1], but there is no evidence regarding its use for the treatment of respiratory distress in patients with normal oxygen saturations.

Patients with hypoxemia or respiratory distress should be monitored on continuous pulse oximetry until oxygen saturations are ≥ 90% on room air and they are otherwise showing signs of improvement.

3.12.1 If maintenance IV hydration is required because of vomiting, dehydration or poor oral intake, isotonic fluids are preferred to hypotonic fluids in older infants and children so as to decrease the risk of hyponatremia, which is not uncommon in pediatric respiratory infections. [50]