PROTOCOL FOR ADULT PATIENTS WITH PNEUMONIA REQUIRING HOSPITAL ADMISSION AT UF HEALTH FLAGLER HOSPITAL

Development of standardized protocols reduces practice variations and facilitates the care of hospitalized patients and are usually associated with better outcomes.

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary to meet individual patient needs. This protocol is not intended to replace the practitioner's judgment; it is intended to provide guidance to the physician for the group of patients described in the protocol.

OBJECTIVES:

- Optimize the outcome of hospitalized patients with PNA
    - Identify the varied pneumonia presentations to facilitate early and accurate diagnosis
    - Apply appropriate antibiotic stewardship principles in the management of PNA ensuring optimal antimicrobial selection, dosage, and duration to minimize resistance and adverse effects
- Prevent early PNA readmissions

All patients presenting to the ED or hospitalized patients at UF Health Flagler Hospital with suspected or confirmed diagnosis of pneumonia will be eligible to be included in this protocol.

MONITORING:
On initial presentation to the ED or admitted patients with suspected or confirmed PNA the following tests will be requested if not done:

- CBC with differential, CMP, PCT, sputum Gram stain and culture, Quad PCR viral respiratory panel, and CXR
- The following tests will be conditional:
    - CT chest for patients with high suspicion of PNA and negative CXR, or to identify suspected complications (such as necrotizing PNA, abscess, parapneumonic effusions, or empyema), or to assess alternate or concurrent diagnosis
    - Blood cultures if present risk factor for Pseudomonas, MDR pathogens or MRSA or severe PNA
    - Legionella spp antigen (PCR when available, urinary antigen test as an alternative) if occupational or epidemiologic risk factors are present
    - Film array PCR respiratory viral panel only in case-by-case analysis in patients with negative Quad PCR viral respiratory panel
    - PNA panel PCR testing for severe PNA or immunocompromised patients

For all patients with suspected or diagnosed PNA admitted to the hospital, the PNA will be classified based on site of acquisition and severity, and if applicable, by etiology.

- Patients with moderate PNA will be admitted to the general floor unless there is a non-PNA related reason for ICU admission
    - No further PNA monitoring will be required other than the stated above

    - Pulmonary and/or ID consult will be at the discretion of the ED and or admitting physician
- Patients with severe PNA will require a critical care service consult and ICU admission
    - ID consult will be at the discretion of the intensivist team
    - Further monitoring if not done will include blood cultures and sputum or BAL PNA panel. Additional testing on case-by-case analysis will include:
        - Tuberculosis, fungal pathogens, and nocardia testing for patients with cavitary PNA
        - Opportunistic pathogens such as Pneumocystis jirovecii, fungal pathogens, parasites, and less common viral pathogens such as cytomegalovirus for immunocompromised patients
        - Galactomannan or β-D-glucan for patients with suspected invasive pulmonary aspergillosis (IPA) or invasive candidiasis:
            - Patients with CT chest findings consistent with IPA or invasive candidiasis associated with either:
                - Immunosuppression particularly with neutropenia, or
                - Underlying conditions such as prolonged steroid therapy, COPD, cirrhosis, malnutrition, parenteral nutrition, severe influenza or COVID-19 infection, even in the absence of severe immunosuppression

All patients admitted with suspected or diagnosed PNA will have:

- Aspiration precautions including elevating the head of the bed 30 to 45 degrees unless contraindicated and ensuring good oral hygiene
- Encourage patient mobility with ambulation
- Nasal screen for MRSA followed by nasal decolonization with mupirocin ointment applied to each nostril twice daily and chlorhexidine gluconate wipes applied to skin after daily bath for 5 days

ANTIBIOTIC THERAPY

- In all patients with appropriate working diagnosis of PNA, antibiotics should be started within four hours of presentation for patients with mild to moderate PNA and within one hour for those with severe PNA who are critically ill
    - For patients with severe PNA or who are critically ill antibiotics will be administered IV at the start of therapy
- The selection of an empiric antibiotic regimen will be based on the severity of illness, site of care, most likely pathogens, the likelihood of infection with multidrug-resistant (MDR) pathogens or Pseudomonas, or MRSA, and patient drug allergy or intolerance

Risk factors for Pseudomonas or MDR pathogens

- Strong - patients with these risk factors generally require treatment with an empiric regimen that includes coverage for these organisms
    - Known colonization or past infection with these organisms
    - Detection of gram-negative rods on a good-quality sputum Gram stain
    - Hospitalization with receipt of IV antibiotics in the prior 3 months
- Other risk factors that should raise suspicion

    - Recent hospitalization or stay in a long-term care facility
    - Recent antibiotic use of any kind
    - Frequent COPD exacerbations requiring glucocorticoid and/or antibiotic use
    - Structural lung diseases (e.g., bronchiectasis, cystic fibrosis)
    - Presence of multiple medical comorbidities (e.g., chronic heart, lung, kidney, liver disease, diabetes mellitus, alcoholism)
    - Immunosuppression

Risk factors for MRSA

- Strong - patients with these risk factors generally require treatment with an empiric regimen that includes MRSA coverage
    - Known MRSA colonization
    - Prior MRSA infection
    - Detection of gram-positive cocci in clusters on a good-quality sputum Gram stain
- Other risk factors that should raise suspicion
    - Recent hospitalization particularly with receipt of intravenous antibiotics within the prior three months
    - Recent influenza-like illness
    - Necrotizing or cavitary pneumonia
    - Empyema
    - Immunosuppression
    - Risk factors for MRSA colonization
        - End-stage kidney disease
        - Crowded living conditions (e.g., incarceration)
        - Injection drug use
        - Contact sports participation
        - Men who have sex with men

Antibiotics recommended doses

- Amoxicillin-clavulanate orally 875 mg every 12 hours
- Ampicillin-sulbactam 3 g IV every 6 hours
- Azithromycin 500 mg orally or IV daily
- Doxycycline 100 mg orally or IV every 12 hours
- Cefdinir 300 mg orally every 12 hours
- Ceftriaxone 1 to 2 g IV daily
- Cefepime 2 g IV every 8 hours
- Levofloxacin 750 mg IV or orally daily
- Ciprofloxacin 400 mg IV every 8 hours or 750 mg orally every 12 hours
- Moxifloxacin 400 mg orally daily
- Piperacillin-tazobactam 4.5 g every 6 hours
    - For critically ill patients extended-4h IV continuous infusion after the initial loading dose is preferred)
- Vancomycin loading dose of at least 20 mg/Kg IV with interval adjustments based on AUC/MIC (preferred), and renal function. Dose per pharmacy protocol
- Linezolid 600 mg IV every 12 hours

- Aztreonam 2 g IV every 8 hours
- Meropenem 1 g IV every 8 hours
    - For critically ill patients extended-3h IV continuous infusion after the initial loading dose is preferred)
- Ertapenem 1 gr IV daily (does not cover Pseudomonas)
- Metronidazole 500 mg IV or orally every 8 hours
- Tobramycin
    - Systemic: 7 mg/Kg/dose IV daily extended infusion protocol (dose per pharmacy protocol)
    - Inhaled: 300 mg by nebulization every 12 hours x7 days
- Amikacin
    - Systemic 15-20 mg/Kg/dose IV daily extended infusion protocol (dose per pharmacy protocol)
    - Inhaled 400 mg every 12 hours or 20 mg/Kg IBW by nebulization daily x7 days
- Inhaled colistin: three nebulizations of 5 million IU can be administered/24 h

Initial antibiotics for patients admitted with CAP

Without risk factors for Pseudomonas or MDR pathogens

- Intravenous combination with an antipneumococcal beta-lactam plus a macrolide (preferred) or doxycycline if prolonged QTc
    - Ceftriaxone, or
    - Ampicillin-sulbactam

  AND
    - Azithromycin, or
    - Doxycycline
- Alternative regimen
    - Monotherapy regimen with levofloxacin or moxifloxacin

With risk factors for Pseudomonas or MDR pathogens

- Intravenous therapy with an antipseudomonal/antipneumococcal beta-lactam
    - Piperacillin-tazobactam, or
    - Cefepime, or
    - Meropenem if prior history of ESBL
- On individual analysis a fluoroquinolone (levofloxacin or ciprofloxacin IV) can be added for patients with increased mortality risk (septic shock or need for mechanical ventilatory support on admission)

With risk factors for MRSA add:

- Vancomycin, or
- Linezolid

Initial antibiotics for patients with nvHAP or VAP

- Piperacillin-tazobactam, or
- Cefepime, or

- Meropenem if:
    - Prior history of ESBL, or
    - Consider for patients with VAP and risk factors for increased mortality
        - Septic shock at the time of VAP
        - ARDS preceding VAP
        - ≥5 days of hospitalization prior to the occurrence of VAP
        - Acute renal replacement therapy prior to VAP onset

    AND
- Vancomycin or linezolid

- On individual analysis a fluoroquinolone (levofloxacin or ciprofloxacin IV) or an aminoglycoside can be added for patients with increased mortality risk as stated above

Initial antibiotics for patients with special conditions

Aspiration pneumonia

- Routine coverage for anaerobe pathogens is not needed but indicated in those at risk:
    - Poor dental health
    - Necrotizing pneumonia
    - Lung abscess or empyema

Confirmed penicillin or cephalosporin allergy

- Severe (IgE-mediated reactions, e.g., urticaria, angioedema, anaphylaxis), severe delayed reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
    - Without risk factors for Pseudomonas or MDR pathogens
        - levofloxacin or ciprofloxacin oral or IV
    - With risk factors for Pseudomonas or MDR pathogens
        - Meropenem AND levofloxacin or ciprofloxacin oral or IV
- Mild (non-IgE-mediated reactions, e.g., maculopapular rash)
    - A third or fourth-generation cephalosporin can safely be given with the doses stated above
    - Carbapenems have broader coverage but are also reasonable and safe alternatives for most patients

Prior documented resistance to carbapenems

- Will follow yearly IDSA guidelines and consult ID if not following the patient https://www.idsociety.org/practice-guideline/amr-guidance/

Presence of MDR pathogens that are only sensitive to colistin and/or aminoglycosides

- Will initiate inhaled antibiotic therapy in addition to the systemic therapy and consult ID if not following the patient

Influenza treatment

For all patients who test positive for the influenza virus and are admitted to the hospital will use:

- Oseltamivir 75 mg orally q12h for 5 days

Use of adjunctive glucocorticoids

For immunocompetent patients with severe PNA in the ICU will use systemic glucocorticoids if any of the following conditions is present:

- Need for invasive or non-invasive mechanical ventilation or HFNC
- Severe hypoxemia: PaO2:FiO_2 ratio <300 requiring FiO_2 ≥50%

Will avoid the use of glucocorticoids, unless indicated for other reasons such as septic shock, acute exacerbations of COPD, or COVID-19, in patients with:

- Influenza, fungi infections, tuberculosis, herpes, or acute viral hepatitis

In immunocompromised patients with severe PNA will weigh the risks and benefits on an individual basis.

Glucocorticoids regimen

- Hydrocortisone IV continuous infusion 200 mg/d or 50 mg IV q6h during the first 4 days
    - If clinical improvement on the fourth day
        - Taper hydrocortisone for a total treatment of 8 days
    - If no clinical improvement on the fourth day
        - Continue IV hydrocortisone infusion for 7 days and then initiate taper for a total treatment of 14 days
- Or other glucocorticoids at a dose equivalent to hydrocortisone of 200 mg/d

In all cases, glucocorticoids will be discontinued at the time of discharge from the ICU.

SUBSEQUENT MANAGEMENT

Duration of antibiotics

Will be determined based on clinical improvement, microbiologic diagnosis, serial procalcitonin levels, underlying comorbidities, and the presence of complications.

Clinical response to therapy with appropriate antibiotics is usually seen within 48 to 72 hours and most patients become clinically stable within 3 to 4 days of starting antibiotic treatment

- For most patients with good clinical response antibiotics will be used for 5 to 7 days total
- For patients with severe PNA or underlying chronic comorbidities will consider extending the duration to 10 days
- The duration of therapy may need to be extended beyond 10 days in certain patients despite clinical stability
    - Complications such as necrotizing PNA, parapneumonic effusions, empyema, or lung abscess
        - For lung abscess, until CT chest evidence of decreasing size or abscess resolution
    - MRSA PNA with bacteremia
    - Metastatic complications of bacteremia
    - Immunocompromised patients
- Before stopping therapy, the patient should be:
    - Afebrile for 48 to 72 hours (unless fever is attributed to noninfectious source), and
    - No need for supplemental oxygen unless required for preexisting disease, and

    - Have no more than one clinical instability factor defined as:
        - HR >100 beats/minute
        - RR >24 breaths/minute, and
        - SBP ≤90 mmHg).
- Procalcitonin levels will be monitored only with the intention to discontinue the antibiotics in patients who are clinically stable and have been receiving antibiotics regardless of the duration
    - Levels of less than 0.5 µg/L or levels that decrease by greater than or equal to 80% from peak levels may guide antibiotic discontinuation once patients stabilize
- Radiographic response typically lags behind the clinical response
    - Infiltrates usually resolves within 4 to 6 weeks in younger population and 6 to 8 weeks in the elderly population
- Antimicrobial stewardship programs can help to shorten the duration of antibiotics and narrow the spectrum of antibiotics

Lack of response to antibiotics

Failure to respond to antibiotic treatment within 72 hours will be considered a non-responder and will prompt reconsideration of the diagnosis and empiric treatment regimen as well as an assessment for complications.

- Pulmonary and or ID consultations will be requested if not done
- Complete new physical examination, laboratory evaluation, imaging studies, and microbiologic workup will be necessary to define the etiology of non-resolving PNA looking for potential causes of non-resolving PNA such as:
    - Delayed clinical response particularly in those with multiple comorbidities, severe pneumonia, bacteremia, and infection with certain pathogens (eg, *S. pneumoniae*)
        - Treatment response may be slow
        - Eight or ten days of treatment may be needed before clinical improvement is evident
    - Loculated infection
    - Bronchial obstruction
    - Pathogens that cause subacute/chronic CAP
        - Mycobacterium tuberculosis, nontuberculous mycobacteria, or less common bacteria (e.g., Nocardia spp., Actinomyces) can cause subacute or chronic PNA
    - Incorrect initial diagnosis

- Initiation of workup for non-resolving PNA will not be automatically associated with a change in initial empiric antibiotic therapy

Antibiotic de-escalation

- Once a pathogen is established, will narrow the antibiotic therapy accordingly to target the specific pathogen.
- Will discontinue empiric treatment started based on the presence of risk factors for *Pseudomonas aeruginosa,* or MDR pathogens in patients who are clinically improving who do not have an identified pathogen from culture from a high-quality sputum or bronchoalveolar lavage specimen within 48 to 72 hours.

- Will discontinue empiric MRSA treatment for patients with negative nasal screening results or negative result in PNA panel and negative culture

IV to oral transition

- Patients will be switched from IV to oral therapy when they are:
    - Clinically improving and hemodynamically stable
    - Able to take oral medications and have a normally functioning gastrointestinal tract
- In patients who are treated with the combination of an IV beta-lactam and a macrolide
    - Will replace the IV beta-lactam with high-dose amoxicillin-clavulanic to complete the course of therapy
        - If the patient have already received 1.5 g of azithromycin and do not have legionella PNA will use amoxicillin-clavulanic alone, if not
        - Amoxicillin-clavulanic plus azithromycin or doxycycline
    - An alternative for patients without risk factors for drug resistant streptococcus pneumonia (DRSP) is to give a macrolide or doxycycline alone to complete the course of therapy.
- Patients who are treated initially with an IV respiratory fluoroquinolone or macrolide will be switched to the oral formulation of the same agent

Prevention

- Smoking cessation when applicable
- Yearly influenza vaccination for the general population
- COVID-19 vaccination
    - A 2023-24 mRNA vaccine regardless of previous vaccination
        - A single dose given at least 2 months after the most recent prior dose of COVID-19 vaccine for all non-immune-compromised patients
        - For patients with moderate to severe immune compromise, 3 or 4 vaccine doses are recommended
- Pneumococcal vaccination for at-risk populations
    - Either pneumococcal conjugate vaccine (PCV21) alone or PCV15 coupled with pneumococcal polysaccharide vaccine (PPSV23) one year later
    - PCV21 for patients who have never received any PCV or whose previous vaccination history is unknown
        - All patients ≥65 years old
        - Others with specific risk factors
            - Chronic heart, lung, and liver disease
            - Immunocompromising conditions including impaired splenic function
        - If PCV20 or PCV21 are used, a dose of PPSV23 is not indicated
        - If PCV15 is used, a dose of PPSV23 is needed one year later
    - For patients who already had vaccinations with prior PCV13 or PPSV23
        - Those who received only PCV13 can be followed by PPSV23 vaccination a year later
        - If the prior vaccine was only with PPSV23, then after a year, either PCV21 alone or PCV15 followed a year later with another PPSV23 can be given
- RSV vaccination for at-risk populations
    - All patients ≥75 years old

    - Ages 60-74 with specific risk factors as stated above and patients living in nursing homes
    - Currently is not an annual vaccine
    - Recommended in late summer and early fall
- Will consider on a case-by-case analysis using a single dose of ceftriaxone 2 gr IV within the 12 h following intubation in patients with severe brain injury expected to require mechanical ventilation for at least 48 hours
    - Severe acute brain injury is defined as ≤12 GCS after trauma, stroke, or subarachnoid hemorrhage.
- Will consider on a case-by-case analysis inhaled antibiotic therapy for critically ill patients undergoing invasive mechanical ventilation for at least 72 hours attempting to prevent VAP
    - Amikacin at a dose of 20 mg/Kg/IBW daily by nebulization, or
    - Tobramycin 300 mg by nebulization q12h

Discharge planning

Discharge will be appropriate when the patient is:

- Clinically stable from the PNA
- Can take oral medication
    - In a case-by case situation patients can be discharge on IV antibiotics under ID direction
- Has no other active medical problems
- Has a safe environment for continued care

Patients who have been discharged from the hospital with PNA should have:

- A follow-up visit usually within one week scheduled by the provider in coordination with the UF Health Flagler hospital administration and a later visit scheduled by the provider
- Patient-centered discharge instructions including:
    - Medications – antibiotics regimen reconciliation
    - Encourage to keep head elevation out of the bed 30 to 45 degrees and good oral hygiene to prevent aspiration
    - Encourage patient mobility with ambulation
    - Collection of SDOH data and demographic information before discharge to better understand which patients are at higher risk for readmission

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