ASP Handbook: Community-Acquired Pneumonia (CAP)

Commentary

Why the change in risk stratification to outpatient, inpatient nonsevere, and inpatient severe CAP?
The previous version of our ASP Handbook chapter used an empiric treatment schema of low to high severity CAP structured around CRB-65 scores. While a similar schema is used by the UK NICE 2019 CAP guidelines, revised ATS/IDSA 2019 guidelines (Metlay 2019) and Bugs & Drugs both use the classification of outpatient, inpatient nonsevere, and inpatient severe CAP. We now use a similar schema to other North American organizations to maintain consistency. The risk stratification categories also simplify treatment decisions for our end users.

One notable difference is that we have selected a CRB-65 score of 2 or greater to correspond to severe CAP. A CRB-65 score of 2 has a predicted 30 day mortality of 12% (Lim 2003). A PSI score of IV is considered severe pneumonia, which correlates to a 30 day mortality of 9% (Fine 1997). While a set of criteria for severe CAP are provided in the ATS/IDSA 2019 guidelines, these are better at predicting need for ICU care than overall mortality. CRB-65 is easy to calculate and sufficient for guiding initial empiric therapy.

Is 3 days sufficient to treat CAP?
Multiple meta-analyses of randomized controlled trials that have shown short course therapy for hospitalized CAP (7 days or less) to be equivalent to longer courses of therapy (Tansarli 2018; Furlan 2019). Furthermore, a randomized controlled trial validated the use of clinical stability criteria to stop antibiotics for hospitalized CAP (mean PSI class III) at day 5, showing equivalent clinical outcomes (Uranga 2016). This led to our previous ASP Handbook recommendation of 5 days therapy for mild-moderate CAP, with an upper limit of 7 days in otherwise uncomplicated disease.

Criticisms of the trial by Uranga and colleagues included its open-label nature and lack of placebo control. A more recent randomized controlled trial of hospitalized CAP (mean PSI class III) with improved methodology has since been published (Dinh 2021). This trial design had more standardization including beta-lactam monotherapy for all patients for the first 3 days, followed by randomization if they met clinical stability criteria to 5 more days of oral beta-lactam (8 days total antibiotics) versus 5 more days of oral placebo (3 days total antibiotics). This trial demonstrated non-inferiority of 3 days of therapy; 15 and 30 day outcomes were similar between groups. An older but smaller randomized, placebo-controlled trial in hospitalized CAP (median PSI class II) similarly showed non-inferiority of 3 days treatment compared to 8 days (el Moussaoui 2006).

Based on the literature, 3 days of antibiotic therapy is sufficient in hospitalized CAP for those who meet clinical stability criteria. In patients who fail to meet clinical stability criteria at day 3, daily assessment for clinical stability and antibiotic discontinuation should be performed. Those who fail to meet clinical stability by day 5 should be evaluated for potential complications of pneumonia as well as alternative etiologies for their respiratory or infectious syndrome.

Duration of therapy has not been as well studied in patients with CAP admitted to critical care units. While clinical stability criteria have not been validated in the critically ill CAP population, the underlying rationale is still applicable. The existing evidence does not suggest benefit in more than 7 days of therapy. Seven days is also the recommended duration of therapy for MRSA and *Pseudomonas* HAP/VAP in the IDSA/ATS 2016 guidelines (Kalil 2016).

Therefore, we recommended a minimum 3 days therapy for hospitalized CAP of any severity based on validated clinical stability criteria. In the absence of complications, treatment for CAP should not extend beyond 7 days.

Why is routine atypical coverage not recommended in nonsevere CAP?
The role of atypical coverage has remained controversial in nonsevere CAP. The ATS/IDSA 2019 guidelines continue to recommended atypical coverage in outpatient CAP with comorbidities and all inpatient CAP. The UK NICE 2019

guidelines do not recommend atypical coverage in mild severity CAP, and addition of atypical coverage in moderate severity CAP only when atypical pathogens are suspected.

There is little evidence to support the practice of adding atypical coverage to a beta-lactam for outpatient CAP.

The literature around atypical coverage for hospitalized CAP is more varied:

- A Cochrane meta-analysis of randomized controlled trials of hospitalized CAP found no mortality benefit to regimens with atypical coverage compared to regimens without atypical coverage (Eliakim-Raz 2012). Atypical coverage improved clinical success in the subset of patients with confirmed *Legionella*.
- Numerous observational studies of hospitalized CAP have found an association between atypical coverage and improved mortality (Lee 2016; Nie 2014).
- A randomized controlled trial of beta-lactam (n=291) versus beta-lactam + macrolide (n=289) was inconclusive though trended towards improved day 7 clinical stability in the beta-lactam + macrolide group (Garin 2014). There was a nonsignificant trend towards benefit with combination therapy in patients with more severe disease (PSI IV or CURB-65 2-5). This corresponds to a predicted 30 day mortality of 9%.
- A larger cluster randomized controlled trial of beta-lactam (n=656) vs beta-lactam + macrolide (n=739) vs fluoroquinolone (n=888) found noninferiority of the beta-lactam monotherapy strategy in 90 day mortality (Postma 2015). However, nearly a third of patients in the beta-lactam monotherapy group ended up receiving atypical coverage during their hospitalization. Early clinical response was not assessed, though median length of stay was similar amongst all three groups.
- A meta-analysis of observational and randomized trials found a benefit from beta-lactam + macrolide in the subgroup with severe CAP only, defined as PSI ≥IV or CURB-65≥2 or CRB-65≥2 corresponding to a predicted 30 day mortality of 9% or higher (Horita 2016).

The available literature remains inconclusive and contradictory. The preponderance of observational data suggest benefit of atypical coverage, though the effect of this is most evident in studies focusing on severe CAP (predicted mortality of 9% or higher). The two randomized controlled trials to date have been inconclusive, though also suggestive of a potential benefit to atypical coverage in a similar severe CAP population.

Therefore, we recommend atypical coverage in severe inpatient CAP (CRB-65 ≥2). Routine atypical coverage is not recommended in nonsevere inpatient CAP nor in most cases of outpatient CAP. Suspected or confirmed atypical pneumonia, particularly *Legionella*, warrants atypical coverage regardless of severity.

Why the change to amoxicillin/amoxicillin-clavulanate TID?
There is limited literature supporting the clinical equivalence of amoxicillin-clavulanate 875 mg PO BID and 500 mg PO TID (Calver 1997). Multiple pharmacologic studies have shown lower cumulative daily doses of amoxicillin given more frequently are preferred (de Velde 2016; Kiffer 2011). This is consistent with our understanding of beta-lactams where the primary pharmacologic target of efficacy is the amount of time the free (non-protein bound) drug is sustained above the organism's MIC. Therefore, we recommend TID amoxicillin/amoxicillin-clavulanate, while allowing BID dosing as an alternative.

Why amoxicillin 500 mg PO TID instead of 1000 mg PO TID as recommended in Bugs and Drugs?
We recommended amoxicillin 500 mg PO TID as the standard dosing for mild severity CAP. Based on both local and international distributions of amoxicillin susceptibility in *S. pneumoniae*, we expect amoxicillin 500 mg PO TID to be effective against 90-95% of *S. pneumoniae* isolates (EUCAST; Kiffer 2011; Lifelabs 2020). The incremental benefit of higher dose amoxicillin 1000 mg PO TID is minimal (<5% improvement).

Rather, we recommend a risk-based strategy. While most patients can be prescribed amoxicillin 500 mg PO TID, those with risk factors for penicillin non-susceptible *S. pneumoniae* should be prescribed amoxicillin 1000 mg PO TID. This will better limit the risk of dose-related adverse events to those patients most likely to benefit from higher dosing.

Is doxycycline effective in outpatient CAP?

Doxycycline is a recommended by Bugs & Drugs for outpatient CAP in those with penicillin or amoxicillin allergies. It is also a recommended option in the ATS/IDSA 2019 guidelines and UK NICE 2019 CAP guidelines. FH does not routinely test *S. pneumoniae* isolates against doxycycline but rather tetracycline. *S. pneumoniae* susceptibility to tetracycline in FH is 75%. However, susceptibility testing for tetracycline and doxycycline in *S. pneumoniae* has some practical challenges. Our antibiograms likely underestimate the true susceptibility of *S. pneumoniae* to doxycycline. Furthermore, outpatients with CAP typically have a low risk for poor outcomes. While beta-lactams like amoxicillin and cefuroxime are strongly preferred, doxycycline remains a viable option when such agents are contraindicated for outpatient CAP.

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