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Inside this issue: Pneumonia

Articles selected and commented on by: Professor Ki-Suck Jung, M.D., Ph.D. (the head of the APSR Respiratory Infections, non-tuberculous, Assembly), Sunghoon Park, M.D., Ph.D., Ji Young Park, M.D., and Hwan Il Kim, M.D., Dept of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Korea

To advertise, subscribe a colleague or to unsubscribe please contact : Secretariat, Asian Pacific Society of Respirology, 2F, UK's Bldg. 2-29-3 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan. Email: apsrinfo@theapsr.org

Ceftazidime-Avibactam Versus Meropenem in Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia (REPROVE): A Randomised, Double-Blind, Phase 3 Non-Inferiority Trial

Authors: Torres A, et al.

Reference: Lancet Infect Dis. 2018; 18:285-295

URL: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30747-8/fulltext

Nosocomial pneumonia is one of the most common hospital-acquired infections and is associated with high mortality and health-care expenditure. Nearly 50% of the antibiotics prescribed in intensive-care units are to treat ventilator-associated pneumonia. Moreover, carbapenem resistance, mainly among gram-negative pathogens, is an ongoing public health problem of global dimensions. This study (REPROVE: multinational, phase 3, double-blind, non-inferiority trial) showed ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia. Novel non-β-lactam β-lactamase inhibitor avibactam extends the in-vitro activity of ceftazidime to include gram-negative organisms producing Ambler class A (eg, ESBL and *Klebsiella pneumoniae* carbapenemase), class C (AmpC), and some class D β-lactamases. In the previous randomized controlled trials (RCTs), ceftazidime-avibactam had shown similar efficacy with carbapenem in patients complicated intra-abdominal or urinary tract infections. The current study enrolled adults with nosocomial pneumonia from 136 centers in 23 countries and assigned (1:1) to ceftazidime-avibactam or meropenem for 7-14 days. Seven-hundred and twenty six patients were included in the clinically modified intention-to-treat population. The primary endpoint was the clinical cure at the test-of-cure visit (21–25 days after randomization); 68.8% of patients in the ceftazidime-avibactam group were clinically cured, compared with 73.0% in the meropenem group (difference –4.2% [95% CI –10.8 to 2.5]). The authors noted that ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia. The recently published meta-analysis (including 7 RCTs) evaluating ceftazidime-

avibactam versus comparator (mostly carbapenems) for the treatment of any infection also showed no significant difference in clinical response (J Antimicrob Chemother 2018; 73:2021-2029). Hence, based on these data, ceftazidime-avibactam combination seems to be a potential treatment option as a carbapenem-sparing strategy for nosocomial pneumonia. However, caution is needed before introducing ceftazidime-avibactam as 1st-line antibiotics. Current study results showed numerical trends in favor of meropenem despite meropenem being given by rapid (30 min) rather than extended (2–4 h) infusion, whereas ceftazidime-avibactam was given by 2 h extended infusion. Serious adverse events occurred in 19% of patients in the ceftazidime -avibactam group versus 13% in the meropenem group.

Global Initiative for Methicillin-Resistant Staphylococcus aureus Pneumonia (GLIMP): an International, Observational Cohort Study

Authors: Aliberti S, et al.
Reference: Lancet Infect Dis. 2016; 16:1364-1376
URL: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30267-5/fulltext

During the past decade, several reports described the emergence of community-acquired pneumonia (CAP) caused by *Staphylococcus aureus* and, specifically, methicillin-resistant *S. aureus* (MRSA) as a cause of severe pneumonia that leads to critical illness and death. Several studies also reported an increase in the prevalence of MRSA in patients with CAP. The incidence of *S. aureus* CAP has been reported in about 1-3% (based on the culture) from the previous CAP etiologic studies. The proportion of MRSA is about 50% in *S. aureus* isolates (N Engl J Med 2015; 373:415–427). However, the true prevalence and associated risk factors for MRSA infection had not been fully elucidated. This Global Initiative for MRSA Pneumonia (GLIMP) study was the first international, multicenter study to explore the prevalence of MRSA CAP (3,702 patients

among 222 hospitals in 54 countries, with 405 patients in Asia). In this study, the overall prevalence of MRSA was 3% (95/3193) among community-dwelling patients presenting with pneumonia and who needed admission (versus 93 methicillin-sensitive *S. aureus*). Three risk factors were independently associated with MRSA pneumonia: previous MRSA infection or colonization (odds ratio 6.21, CI 3.25-11.85), recurrent skin infections (2.87, 1.10–7.45), and severe pneumonia disease (2.39, 1.55–3.68). The authors also noted that there were important differences in MRSA prevalence between different continents and among countries within the same continent (highest in Oceania and lowest in Europe). However, because the etiologic tests were not uniform in each study hospitals, it could not be concluded that specific site has a higher MRSA incidence than other sites. Besides, 29% of patients with MRSA pneumonia were diagnosed with blood culture, for which we cannot rule out the possibility of contamination. The authors suggests that the global prevalence of MRSA as an etiology in hospitalized patients with CAP was lower than has been previously estimated. However, we need to pay attention to the three specific risk factors identified in the current study. In the future, further epidemiological studies will be needed in Asian countries.

The Clinical Utility of Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

Authors: Parente DM, et al.
Reference: Clin Infect Dis 2018; 67:1-7
URL: https://academic.oup.com/cid/article/67/1/1/4798927

Despite a relatively low prevalence, methicillin-resistant *Staphylococcus aureus* (MRSA) remains an important pathogen in considering empirical antibiotic therapy for patients hospitalized with pneumonia. Although current guidelines for the treatment of pneumonia recommend MRSA

coverage in at-risk patients (ex. antibiotics exposure within 3 months), there is no guidance on de-escalation before the availability of respiratory culture results. However, currently, there has been growing evidence for the usefulness of nasal MRSA screening by PCR as a surrogate marker for MRSA respiratory tract infections. The absence of MRSA colonization has reported to be a negative predictor of MRSA pneumonia. Hence, the authors of this meta-analysis evaluated the diagnostic value of MRSA nasal screening in MRSA pneumonia. Data were extracted from 22 studies (retrospective studies, n = 19), comprising 5,163 patients. The pooled sensitivity and specificity of the test for all MRSA pneumonia types were 70.9% and 90.3%, respectively. With a 10% prevalence of potential MRSA pneumonia, the calculated positive predictive value (PPV) was 44.8%, and the negative predictive value (NPV) was 96.5%. These results indicate that a positive test result is not diagnostic of MRSA pneumonia, but a negative result can effectively rule it out. However, interestingly, the test showed a low sensitivity (40.3%) in ventilator-associated pneumonia, indicating a low utility in ruling out MRSA ventilator-associated pneumonia. Based on these data, MRSA nasal screening is a valuable tool to guide antibiotic de-escalation, especially for avoiding unnecessary vancomycin use. The authors suggested that future CAP guidelines should incorporate MRSA nasal screening for the antimicrobial stewardship program, as well as diagnostic purpose. However, additional research into the impact of the use of MRSA nasal screening on patients' outcomes will be needed.

Prognostic and Pathogenic Role of Angiopoietin-1 and -2 in Pneumonia

Authors: Gutbier B, et al.
Reference: Am J Respir Crit Care Med. 2018;198:220-231.
URL: https://www.atsjournals.org/doi/full/10.1164/rccm.201708-1733OC

Endothelial disruption and pulmonary hyperpermeability are hallmarks of pneumonia-induced acute lung injury. This is well documented in case of acute respiratory distress syndrome

(ARDS). Angiopoietin ligands (Ang-1 – Ang-4) and the Tie (Tie1 and Tie2) receptor tyrosine kinases form an endothelial signaling pathway that is necessary for embryonic cardiovascular and lymphatic development. In adults, this system regulates vascular homeostasis, and controls vessel permeability, inflammation, and angiogenic responses. Ang-1 has vasculo-protective effects, whereas Ang-2 is an antagonist for Tie2 and promotes endothelial permeability in synergy with inflammatory cytokines. Previous studies showed that Ang-2 levels in plasma correlated with poor prognosis and mortality in ARDS. The current study showed decreased serum Ang-1 and increased Ang-2 levels in pneumonia cohort, as compared to healthy controls, and that high Ang-2 levels were a poor prognostic factor among pneumonia patients. Besides, Ang-2 serum levels added the prognostic accuracy of CURB-65 for 28-day survival, need for intensive care unit admission, and length of hospital stay. *In vivo* mice experiments, ventilated and perfused lungs of mice with Ang-2-knockdown showed reduced vascular permeability. Ang-1 therapy reduced inflammation and permeability in murine pneumococcal pneumonia. The authors suggested that interventional reduction of the Ang-2/Ang-1 ratio may have a therapeutic potential for acute lung injury in pneumonia. However, prior to clinical trials, further studies are needed to make clear the time when the interventions are appropriate and which agent might show the best protective effects.

Blood Eosinophil Count and Risk of Pneumonia Hospitalisations in Individuals with COPD

Authors: Vedel-Krogh S, et al.
References: Eur Respir J. 2018 May 24;51. pii: 1800120.
URL: https://doi.org/10.1183/13993003.00120-2018

Previous studies revealed that blood eosinophil counts were associated with an increased risk of COPD exacerbations. This prospective study, using the Copenhagen Cohort, was quite rele-

vant in that individuals with COPD with high blood counts frequently use inhaled corticosteroid (ICS) and ICS treatment is known to be associated with an elevated risk of pneumonia. A total of 7,180 individuals with COPD, defined as a ratio of FEV/FVC <0.7 and less than lower limit of normal, were included in this study. Among individuals with severe lung impairment (FEV_1 <50% predicted), multivariable-adjusted incidence rate ratio was 2.17 (95% CI, 1.31–3.58) for pneumonia, and 2.65 (1.08 – 6.52) for all-cause mortality, comparing individuals with high blood eosinophil counts (≥ 0.34×10^9 cells/L) *versus* those with low blood eosinophil counts. However, the risk of pneumonia did not differ by blood eosinophil count among individuals with FEV_1 ≥ 50% predicted. Regarding the use of ICS, although the treatment increased the risk of pneumonia among all individuals with FEV_1 <50% predicted, it did not significantly increase the risk when stratified by blood eosinophil count. The authors also demonstrated similar results in individuals with clinical COPD. However, caution should be taken when interpreting the relationship between eosinophil counts and overall pneumonia risk. This study did not include patients with less serious pneumonia treated out of hospitals, and the diagnosis of pneumonia has been only confirmed in the national health record. However, the current study suggests that individuals with COPD and FEV_1 <50% predicted are associated with a higher risk of pneumonia, and that among those with high blood eosinophil counts and FEV_1 <50% predicted, the use of ICS may not significantly increase the risk of pneumonia further.

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Authors: Huang DT, et al.
Reference: N Engl J Med. 2018;379:236-249.
URL: https://www.nejm.org/doi/full/10.1056/NEJMoa1802670

Procalcitonin (PCT) is frequently used as a biomarker to determine antibiotic use in clinical practice. It is usually more elevated in bacterial infections than in viral infections. But, it is uncer-

tain whether PCT-guided use of antibiotics is effective or applicable to patients with suspected lower respiratory infections. In this Procalcitonin Antibiotic Consensus Trial (ProACT), 1,656 patients who presented to the emergency department with a suspected lower respiratory infection were randomly assigned to PCT or usual-care group. PCT group also used an antibiotic-use guideline with graded recommendations based on four tiers of PCT levels. Initially, the authors hypothesized that with PCT-guided use of antibiotics, the antibiotic-day would be lower, and the incidence rate of adverse outcomes would not be higher, compared with usual-care group. However, in the results, although the PCT level-tier was associated with the decision to prescribe antibiotics in both groups, there were no statistically significant differences, between both groups, in the duration of antibiotics (4.2 and 4.3 days, respectively) or the proportion of adverse outcomes (11.7% and 13.1%) within 30 days. In the usual-care group, even when physicians did not know the PCT level, they prescribed antibiotics less frequently to patients in the lower PCT-level tiers than to the higher PCT-level tiers. Patients with low PCT levels also had fewer clinical symptoms or signs. Hence, it seemed that PCT assay results provided a modest amount of information to guide antibiotic decisions. One of the strengths of this study was that the target populations were those for whom there was uncertainty regarding the need of antibiotics, and this study was well powered to detect small differences between the two groups. However, in this study, the authors did not directly test whether physicians can safely withhold antibiotics based on a low PCT level, but rather tested the effect of a deployment strategy in clinical practice.

Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia

Authors: Self WH, et al.

Reference: Clin Infect Dis. 2017;65:183-90

URL: https://doi.org/10.1093/cid/cix317

Procalcitonin (PCT) is a serum biomarker that has shown promise in discriminating between viral and bacterial infections. This study was conducted as part of the EPIC (Etiology of Pneumonia In the Community) study, which was a prospective, multicenter, active surveillance study conducted in the United State. Hospitalized adult patients with community acquired pneumonia (CAP, n = 1,735) were enrolled, and pathogens were identified in 38% of patients, including 10% with typical bacteria, 4% with atypical bacteria, and 24% with virus. Median PCT level in patients with viral pathogens was 0.09 ng/mL (IQR, <0.05–0.54 ng/mL), which was the lowest among etiologic groups; 2.5 ng/mL (0.29–12.2 ng/mL) in typical bacteria; 0.20 ng/mL (< 0.05-0.87 ng/mL) in atypical bacteria; and 0.19 ng/mL (0.05–0.68 ng/mL) in mycobacteria/fungi. The value of area under the receiver operating characteristic curve was 0.73 (0.69– 0.77) for discrimination of bacterial pathogens from viral pathogens, and 0.79 (0.75 – 0.82) for discrimination of typical bacteria from the combined group of viruses and atypical bacteria. A PCT threshold of ≥0.1 ng/mL had a sensitivity of 80.9% and specificity of 51.6% for identifying bacterial pathogens; among patients with a PCT of <0.1 ng/mL, only 3% of patients had typical bacteria and 3% had atypical bacteria detected. Although, interestingly, PCT levels for patients with atypical bacteria were more similar to those with viruses than typical bacteria, the levels were high in patients with *Legionella* pneumonia, more similar to that of typical bacterial pneumonia than *Mycoplasma* or *Chlamydophila* pneumonia. However, the results should be confirmed with further research. To date, this is the largest study evaluating the association of PCT levels with etiologic pathogens, and comprehensive pathogen testing was used including cultures, serolo-

gy, urinary antigen tests, and molecular detections. Based on the results, high PCT levels were associated with increased probability of bacterial pathogens, particularly typical bacteria.

Prolonged Versus Short-Term Intravenous Infusion of Antipseudomonal β-lactams for Patients with Sepsis: A Systematic Review and Meta-Analysis of Randomised Trials

Authors: Vardakas KZ, et al.
Reference: Lancet Infect Dis 2018;18:108-20
URL: https://www.sciencedirect.com/science/article/pii/S1473309917306151?via%3Dihub

Optimization of β-lactams plasma concentration is considered important for the improvement of clinical effectiveness, and it depends on the proportion of time when free plasma concentration of antibiotics is higher than the pathogen's minimum inhibitory concentration (%fT>MIC) in patients with normal renal function. This systemic review and meta-analysis (22 randomized controlled trials [RCTs]) showed that prolonged infusion of antipseudomonal β-lactams was associated with lower all-cause mortality than short-term infusion (0.70, 95% CI 0.56–0.87) in patients with sepsis. Although clinical cure rate was not higher with prolonged infusion, fewer RCTs provided clinical cure than mortality and clinical cure is rather a subjective outcome. Among β-lactams class, prolonged infusion of carbapenems and penicillin with β-lactamase inhibitors was associated with lower mortality rate than short-term infusion, but prolonged infusion of cephalosporins did not, as previously reported. This could be attributed to the small number of patients and studies or the more heterogeneous populations. In subgroup analyses, patients with severe infections (APACHE II ≥ 20) seemed to benefit more from prolonged infusion. Although the authors did not do analyses regarding microbiological data, contrary to susceptible pathogens, non-fermenting or multi-drug resistant gram-negative bacteria usually have higher MICs. Hence, prolonged infusion may be more beneficial for those cases. However, the majori-

ty of RCTs in the study enrolled only patients with normal renal function, so the results cannot be extrapolated to patients with variable degrees of renal function. However, despite several limitations, prolonged infusion seems theoretically convincing and clinically relevant in circumstances where treatment options are limited due to antibiotic resistance.

Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults with Acute Lower Respiratory Tract Infection: A Randomized Clinical Trial

Author: Hay AD, et al.
Reference: JAMA 2017;318:721-730.
URL: https://jamanetwork.com/journals/jama/fullarticle/2649201

Traditionally, many physicians have used systemic or topical corticosteroids for symptom relief, as monotherapy or adjunctive to antibiotics, in the treatment of acute upper respiratory infections such as acute sinusitis, severe sore throat, and acute croup. If it is used appropriately, we may be able to reduce the use of antibiotics. However, evidences supporting their use so far are still inconclusive. In this OSAC (Oral Steroids for Acute Cough) trial, the authors restricted the eligible patients (n = 398) to those without asthma or chronic respiratory disease. Only patients with an acute cough (< 28 days) and at least one other lower respiratory tract (LRT) symptom within 24 h were included and randomized to 40 mg prednisolone or placebo for 5 days; they delayed antibiotic prescriptions as possible as they could. As primary outcome, the duration of moderately bad or worse cough (5 days [3-8 days] vs. 5 days [3-10]), or mean symptom severity score between day 2 and day 4 was not different between prednisolone and placebo groups. Besides, no between-group differences were observed for duration or severity of other LRT symptoms, antibiotics use, and adverse events. Previously, there were several studies where the effect of inhaled corticosteroid was investigated and mixed results

were found. However, the OSAC trial was the first multicenter, randomized placebo controlled study investigating oral corticosteroid for acute LRT infection. Although objective parameters were not used, this trial has several strengths: with a large number of participants, they were fully masked and the rate of missing data was very low. Interestingly, a recent study by Hayward et al. (JAMA 2017;317:1535-1543), dexamthasone (10mg) had a better symptom control at 48 h, not at 24 h in adult patients on acute sore throat. Corticosteroids may offer some therapeutic benefits in those with severe acute upper airway symptoms such as severe sore throat and croup or those with severe community-acquired pneumonia. However, based on the OSAC trial, it is very unlikely that oral corticosteroid reduces symptom severity and duration in patients with acute LRT infection and without asthma or chronic respiratory disease.

Initial Inflammatory Profile in Community-Acquired Pneumonia Depends on Time since Onset of Symptoms

Author: Mendez R, et al.
Reference: Am Respir J Crit Care Med 2018 Mar 6. doi: 10.1164
URL: https://www.atsjournals.org/doi/pdf/10.1164/rccm.201709-1908OC

Procalcitonin (PCT) and C-reactive protein (CRP) are well-known biomarkers that have been frequently used in decision process for the diagnosis and severity assessment in patients with infections, including community-acquired pneumonia (CAP). Especially, PCT is known to have an important role in deciding the duration of antibiotic treatment in pneumonia or sepsis. However, in clinical practice, physicians frequently encounter patients with disproportionate levels of these biomarkers, despite their severity of illness. It could be because of different time of presentation, immunological status or sites of infections, among different patients. Hence, in this aspect, this article by Mendez et al. is very relevant. They noted that in early presenter

(symptom duration < 3 days), the levels of PCT, interleukin-6, interlukin-8 were higher whereas CRP levels were lower. For non-early presenter (symptom duration ≥ 3 days), CRP levels were higher but the levels of PCT, interleukin-6 and interleukin-8 were lower. These results are in keeping with the results from a previous animal study, where a rapid increase in proinflammatory cytokines was observed early after a challenge with bacterium (Reyes et al. PLoS One 2016;11:e0166092). Besides, the peak levels of CRP was delayed by 48 h with regard to interleukin 6, which is a main inducer of CRP (Volanakis et al., Mol Immunol 2001;38:187-97). Mendez et al. tested their hypothesis in the derivation cohort and confirmed it in the validation cohort. This article highlights that we might underestimate the inflammatory process and, consequently, make an error in classifying disease severity if we rely on the biomarkers without consideration of the time of symptom onset. In particular, in patients for whom symptom duration is < 3 days (even in sepsis), the use of CRP could underestimated inflammatory response because it is still in an increasing phase. Therefore, taken together, the duration of symptom should be taken into account in clinical assessment of CAP.

Serotype-Specific Effectiveness of 23-Valent Pneumococcal Polysaccharide Vaccine against Pneumococcal Pneumonia in Adults Aged 65 Years or Older: A Multicentre, Prospective, Test-Negative Design Study

Author: Suzuki M, et al
Reference: Lancet Infectious 2917;17:313-321
URL: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30049-X/fulltext

The burden of pneumococcal diseases is increasing in many countries with aging population. Hence, to control the diseases, immunizations with pneumococcal vaccine (23-valent pneumococcal polysaccharide vaccine [PPV23] or 13-valent pneumococcal conjugate vaccine [PCV13]) is recommended for high-risk groups or elderly people. Although PPV23 is known to reduce the risk of invasive pneumococcal diseases (IPD), its protective effect against pneumonia is uncer-

tain. This article first demonstrated the serotype-specific effect of PPV23 against pneumococcal pneumonia in Japan. Hence, it is not only interesting but also very relevant to Asia-Pacific counties. The authors reported that the vaccine (PPV23) effectiveness was 33.5% for PPV23 serotype pneumonia and 40.1% for PCV13 serotype pneumonia; 27.4% for all pneumococcal pneumonia and 2.0% for non-vaccine type pneumonia. In a recent randomized multicenter trial (CAPITA), the efficacy of PCV13 on the vaccine type community-acquired pneumonia (CAP) was 45.0%, with no significant effect on non-vaccine type CAP. Hence, when comparing the results between two studies, it seems that the effect of PPV23 is not inferior to PCV13 against PCV13 serotypes (40.1% vs. 45.0%). Interestingly, although not statistically significant, the vaccine effectiveness was high in patients with lobar pneumonia and low in people aged ≥ 75 years. The high effectiveness of PPV23 in patients with lobar pneumonia is in keeping with its well-known effectiveness on IPD (i.e., severe disease). For patients aged ≥ 75 years, a new and more immunogenic vaccine may be needed. Although the effectiveness of PPV23 is weak and short-lived, this article suggests that the effectiveness of PPV23 might be higher in specific groups, and that variable effectiveness in different group of older people should be further investigated.

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Articles selected and commented on by Professor Ki-Suck Jung, M.D., Ph.D. (the head of the APSR Respiratory Infections, non-tuberculous, Assembly), Sunghoon Park, M.D., Ph.D., Ji Young Park, M.D., and Hwan Il Kim, M.D., Dept of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Korea

Editor in chief: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China
Compiled by Dr Christel Norman, Respirology Editorial Office, Perth, Australia

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