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### **Pulmonary & Critical Care Insider: Issue 1**

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# **PULMONARY & CRITICAL CARE INSIDER**

**Issue 1**

**COMPILED AND REVIEWED BY  
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# A LARGE-SCALE MULTICENTER RETROSPECTIVE STUDY ON NEPHROTOXICITY ASSOCIATED WITH EMPIRIC BROAD-SPECTRUM ANTIBIOTICS IN CRITICALLY ILL PATIENTS, CHEST 2023

VC = vancomycin and cefepime; VM = vancomycin and meropenem; VPT = vancomycin and piperacillin-tazobactam

## Aim of Study:

Comparison of two commonly prescribed regimens of empiric antibiotics. Does a difference exist in the association between commonly prescribed empiric antibiotics on ICU (Intensive Care Unit) admission (VC, VM, & VPT) and acute kidney injury?

## Clinical Features- Inclusion/Exclusion – Methods:

Large multicenter retrospective cohort study using patient data/records for 3,089,748 unique ICU stays between 2010 and 2015 across 335 distinct hospital units.

Inclusion Criteria	Exclusion Criteria
ED (Emergency Department) to ICU Admission	Admission to ICU < 1 hour
VPT, VM or VC exclusively one of the combinations	Patient with missing data
	Hemodialysis before Abx administration
	No antibiotics or more than one combination of antibiotics

**Methods:** Baseline serum creatinine (SCr) was estimated using the lowest SCr value recorded within the window of ICU admission. The primary outcome was development of acute kidney injury (AKI) in the first week after antibiotic exposure, or more explicitly (12 h, 7 days) from recorded time of admission to the ICU.

**Results:** Greater risk of AKI exists when using VPT compared with VC or VM, especially in patients with normal kidney function on admission requiring antibiotic treatment for longer than 48 hours (about 2 days). In addition, patients receiving VPT showed greater odds of initiating dialysis and dialysis, or in-hospital mortality compared with those receiving VC or VM.

**Notes & Limitations:** Approximately 60% of patients excluded for missing data and 17% excluded for using multiple beta lactams reducing generalizability of study findings.

**Clinical Interpretation:** When prescribing empiric antibiotic regimens to critically ill patients, clinicians should consider VM or VC over VPT to reduce the risk of nephrotoxicity and adverse clinical outcomes. Trying to de-escalate antibiotics as soon as possible within 48 hours (about 2 days) if clinically indicated could mitigate the risk of VPT induced nephrotoxicity. VPT is associated with a higher risk of acute kidney injury than both VC and VM in patients in the ICU, especially for patients with normal initial kidney function requiring longer durations of therapy.

# DOES VANCOMYCIN PIPERACILLIN-TAZOBACTAM CAUSE PSEUDO-AKI, TRUE NEPHROTOXICITY, OR BOTH?

**Connected Commentary for *A Large-Scale Multicenter Retrospective Study on Nephrotoxicity Associated with Empiric Broad-Spectrum Antibiotics in Critically Ill Patients, CHEST 2023***

*Commentary Summary:* The combination of vancomycin and piperacillin-tazobactam (VPT) is a common antimicrobial therapy in most ICUs (Intensive Care Unit), even though there is a recent concern for increased risk of acute kidney injury (AKI) with this regimen. This risk has been repeatedly found in small prospective and large retrospective cohort studies, but not in randomized clinical trials. There are many limitations, unknown factors, and biases in retrospective studies, and thus it is questioned if VPT might cause pseudo-nephrotoxicity (Transient reduction in creatinine clearance).

Also, there is some evidence supporting the hypothesis that VPT increases true nephrotoxicity. In this study a significant number of patients progressed to AKI stage 2 or 3 and even needed Renal replacement with OR of 1.56. There is suggestion that more data concerning antibiotic indications (early empiric administration vs definitive treatment) and potential group differences at baseline would be useful in future studies to further explore the mechanistic and pathophysiologic aspects to enhance our understanding of this intriguing nephrotoxicity. In the absence of definitive evidence from randomized clinical trials, it is prudent to consider VPT-associated AKI as potentially true AKI, pseudo-AKI, or even a combination of both, and to tailor management accordingly.

# DUPILUMAB FOR COPD WITH TYPE 2 INFLAMMATION INDICATED BY EOSINOPHIL COUNTS, NEJM 2023

**Aim of Study:** Investigate the efficacy and safety of dupilumab in patients with COPD who had evidence of type 2 inflammation despite the receipt of standard inhaled triple therapy that consisted of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting  $\beta$ 2 - agonist (LABA).

**Clinical Features, Inclusion/Exclusion, Methods:** The BOREAS trial was a phase 3, multicenter, international, double-blind, randomized, placebo-controlled trial conducted at 275 sites in 24 countries. Patients who had a 4-week screening period were randomly assigned in a 1:1 ratio to receive subcutaneous dupilumab as add-on therapy at a dose of 300 mg or matching placebo once every 2 weeks for 52 weeks (about 12 months). Enrollment of current smokers was capped at 30%. After the 52-week trial period, patients entered a 12-week follow-up safety period during which they were no longer receiving dupilumab or placebo.

**Inclusion:** 40-80 years of age, Evidence of type 2 inflammation, BMI (Body Mass Index)  $>16\text{kg/m}^2$ , Current or Former Smokers, Moderate to Severe COPD, MRC Dyspnea Scale grade of greater than 2, Patient Reported history of Chronic Bronchitis, Documented history of high exacerbation risk, background triple therapy (ICS+LAMA+LABA) for 3 months prior.

**Exclusion:** COPD dx less than 12 months, Current or History of Asthma, Evidence of Cardiac Failure, Significant pulmonary disease outside of COPD, Treatment with oxygen of more than 12 hours per day, Hypercapnia requiring bi-level ventilation, respiratory tract infection or exacerbation as defined in inclusion criteria within 4 weeks prior to or during screening period, active tuberculosis, history of systemic hypersensitivity to any biologic therapy, history of or planned lung volume reduction surgery, patients who participated in the acute phase of a pulmonary rehab program, previous use of dupilumab, patients less than 80% compliant with controller therapy during screening, received or planned to receive live, attenuated vaccinations during study, Receiving macrolide therapy, and diagnosis of  $\alpha$ -1 anti-trypsin deficiency.

**Results:** 939 patients underwent randomization: 468 to the dupilumab group and 471 to the placebo group. Dupilumab was also associated with significantly greater improvements in lung function and health-related quality of life and significantly less severe respiratory symptoms than those seen with placebo, and these differences were observed within 2 to 4 weeks after the initiation of dupilumab or placebo and were sustained throughout the 52-week trial period.

**Notes & Limitations:** The most common adverse events were nasopharyngitis, upper respiratory tract infection, and headache. Serious adverse events were reported in 13.6% of the patients in the dupilumab group and in 15.5% of those in the placebo group. Randomization was not stratified according to smoking status.

**Clinical Interpretation:** Treatment with dupilumab resulted in a lower annualized rate of exacerbations, better lung function and quality of life, and less severe symptoms than placebo in adults with COPD who had type 2 inflammation as indicated by elevated blood eosinophil counts.

# BIOLOGICS FOR COPD — FINALLY HERE

**Connected Commentary for Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts, NEJM 2023**

*Commentary Summary:* This was an important trial for the future of COPD treatment, but a few concerning study elements should be noted.

Dupilumab is a fully human monoclonal antibody that blocks the effects of both interleukin-13 and interleukin-4 by binding to a component of the interleukin-4 receptor  $\alpha$  shared by both cytokines, whereas previous trials targeted the interleukin-5 pathway with mepolizumab or benralizumab. The broader inhibition of type 2 inflammation that was achieved with dupilumab than with mepolizumab or benralizumab, along with a greater effect on airway mucus and airway smooth muscle, may account for the clearer evidence of efficacy that was seen with dupilumab.

This study had a carefully selected subgroup of patients with COPD — those with a blood eosinophil count of at least 300 per microliter. Therefore, the results cannot be generalized automatically to all patients with COPD. Further studies are needed to evaluate whether these clinical effects are also seen in patients with lower levels of circulating eosinophils.

Beneficial effects were observed when dupilumab treatment was added to inhaled triple therapy, but inhaled triple therapy itself is known to reduce exacerbations of COPD and alleviate symptoms in many patients with COPD, regardless of the level of circulating eosinophils. Dupilumab by itself cannot be used as a mono therapy. We do not know whether there was a differential effect among various inhaled triple-therapy combinations.

The average patient in this trial was 65, and the recently released Global Initiative for Chronic Obstructive Lung Disease (GOLD) report clearly emphasizes the need to study COPD in young patients, and hopefully this clinical trial encourages future study on younger patients with COPD.

# SIMPLE ASPIRATION VERSUS DRAINAGE FOR COMPLETE PNEUMOTHORAX A RANDOMIZED NONINFERIORITY TRIAL.

## AM J RESPIR CRIT CARE MED, 2023

**Aim of Study:** To determine whether first-line simple aspiration is noninferior to first-line chest tube drainage for lung expansion in patients with complete primary spontaneous pneumothorax. Clinical Features, Inclusion/Exclusion, Methods: A prospective, open-label, randomized noninferiority trial. Adults aged 18–50 years with complete primary spontaneous pneumothorax received simple aspiration (n = 200) or chest tube drainage (n = 202) as first-line treatment.

**Inclusion:** Aged 18–50 years, symptomatic (chest pain and/or dyspnea) for less than 48 hours (about 2 days) and experiencing their first episode of primary and complete pneumothorax identified on a chest radiograph ventrally or laterally.

**Exclusion:** tension pneumothorax, traumatic and recurrent pneumothorax, and primary pneumothorax associated with pleural effusion or secondary pneumothorax with underlying lung disease. Pregnant or lactating women; patients not available for follow-up; and those with major incapacitation.

**Procedural Method:** Each participant received an intravenous general analgesic (1 g of paracetamol) 15 minutes before insertion, and a local anesthetic (200 mg of lidocaine in 1% solution) was injected at the insertion site.

The aspiration device was inserted into the second intercostal space on the midclavicular line, whereas the draining tube was inserted there or into the fourth or fifth intercostal space of the midaxillary line according to the physician's preference and clinical requirements.

Drainage was achieved using Joly (Vygon) or Monod (Landanger) trocars and a 16-French or 20-French large chest tube, depending on the physician's preference. The evacuation systems used were single-use sterile devices designed for this indication.

### Results:

The primary outcome was pulmonary expansion notable as absence of residual pneumothorax or persistence of an apical residual pneumothorax smaller than 2 cm (about 0.79 in), 24 hours after the procedure, based on chest radiography. Failure was therefore defined as lack of persistent lung expansion. Aspiration was considered to have failed after a second attempt and any chest tube drainage that may have been deemed necessary.

Primary outcomes	Aspiration group	Chest tube Drainage Group
Treatment Failure %	29%	18%
Recurrence %	20%	27%

# SIMPLE ASPIRATION VERSUS DRAINAGE FOR COMPLETE PNEUMOTHORAX A RANDOMIZED NONINFERIORITY TRIAL.

## AM J RESPIR CRIT CARE MED, 2023

Secondary outcomes	Aspiration group	Chest tube drainage group
Treatment failure 7 days	16%	15%
Recurrent pneumothorax in 1 year	20%	27%
Pain	Better tolerated	Worse
Anxiety/Dyspnea	No difference	No difference
Minor adverse events		
Pain limiting breathing	16%	34%
Device kink	2%	11%
Major adverse events		
Hemothorax, organ perforation, local abscess, re-expansion edema	0%	0-1%
Persistent air leak	1%	3%
Hospital LOS	5.8%	7.6%

**Notes & Limitations:** Inclusion/Exclusion and Failure definitions as well as methods of non-inferiority statistical validity debatable.

**Clinical Interpretation:** In this study, the results of simple aspiration as a first-line treatment of primary spontaneous pneumothorax argue in favor of noninferiority to the standard chest tube draining treatment, based on observation 24 hours and 7 days after the procedure. However, there was higher treatment failure in the simple aspiration group than in the chest tube drainage group, but with a lower rate of recurrence at 1 year and less overall pain.

Additionally, this study challenges the conclusions of a Cochrane Library systematic review that compared of the clinical efficacy and safety of simple aspiration versus intercostal tube drainage for the management of primary spontaneous pneumothorax; indicating that chest tube drainage had a better immediate success rate than simple aspiration, as well as simple aspiration having lower LOS (length of stay) and lower adverse events.

However, in this study, chest tube drainage showed a better immediate success rate, first-line simple aspiration was better tolerated and safer as an operating procedure. It is reasonable to consider simple aspiration in the right clinical setting as opposed to chest tube insertion for PSP provided patients can be closely monitored for subsequent need for chest tube placement.



# PRIMARY SPONTANEOUS PNEUMOTHORAX. TREAT THE PATIENT, NOT THE X-RAY.

**Connected Commentary for *Simple Aspiration versus Drainage for Complete Pneumothorax A Randomized Noninferiority Trial*. *Am J Respir Crit Care Med*, 2023**

*Commentary Summary:* The study results serve to confront clinicians to examine their priorities for PSP management. More invasive drainages provide better CXR improvement, reassuring clinicians, but at the expense of patient comfort and procedural risks. The EXPRED trial should be interpreted together with the published PSP randomized trial, which investigated the noninferiority of conservative management of pneumothorax (i.e., no drainage at all) against conventional chest-tube drainage. The trial reported successful management of 85% of patients without drainage, again suggesting that the air leak had stopped or was minimal by the time the patients were presented. Radiographic lung re-expansion was, as expected, slower with conservative management, but there were no significant intergroup differences by 8 weeks (about 2 months).

It is hypothesized that conservative management (i.e., no drainage) allows the lung to remain deflated and brings the edges of any defect to the closest proximity, enhancing healing. Patients conservatively treated in the PSP trial enjoyed better patient relevant outcomes, including significant reductions in hospital stay, days off work, need for chest tubes or eventual surgical treatment, and the associated pain and complications.

Accumulating data now suggest that most patients presenting with PSP, irrespective of size, can be managed conservatively provided that the safety criteria (i.e., normal vital signs, stable pneumothorax on interval CXRs, and walking freely around the emergency department) are met. Chest-tube drainage should be reserved for those with an ongoing air leak or cases of failed conservative management.

## REFERENCED STUDIES & COMMENTARY

Chen, A. Y., Deng, C. Y., Calvachi-Prieto, P., de la Hoz, M. Á. A., Khazi-Syed, A., Chen, C., ... & Dagan, A. (2023). A large-scale multicenter retrospective study on nephrotoxicity associated with empiric broad-spectrum antibiotics in critically ill patients. *Chest*, 164(2), 355-368.

Côté, J. M., Desjardins, M., & Murray, P. T. (2023). Does Vancomycin-Piperacillin-Tazobactam Cause Pseudo-AKI, True Nephrotoxicity, or Both?. *Chest*, 164(2), 273-274.

Bhatt, S. P., Rabe, K. F., Hanania, N. A., Vogelmeier, C. F., Cole, J., Bafadhel, M., ... & Abdulai, R. M. (2023). Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *New England Journal of Medicine*.

Agusti, A. (2023). Biologics for COPD—Finally Here. *J Med*, 389, 205-14.

Marx, T., Joly, L. M., Parmentier, A. L., Pretalli, J. B., Puyraveau, M., Meurice, J. C., ... & Desmettre, T. (2023). Simple Aspiration versus Drainage for Complete Pneumothorax: A Randomized Noninferiority Trial. *American Journal of Respiratory and Critical Care Medicine*, 207(11), 1475-1485.

Lee, Y. G. (2023). Primary Spontaneous Pneumothorax: Treat the Patient, Not the X-Ray. *American Journal of Respiratory and Critical Care Medicine*, 207(11), 1416-1417.