357. Pulmonary infections and sepsis

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Late-breaking abstract: Effects of oleanolic acid on pulmonary morphofunctional and biochemical variables in experimental sepsis

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Sepsis present high morbidity and mortality despite recent advances in therapeutic strategies. Recently, natural products derived from plant extracts and their synthetic derivatives are being increasingly used to treat a wide range of diseases due to their anti-inflammatory property. Thus, oleanolic acid (OA), a triterpenoid compound, modulates the production and activity of pro-inflammatory cytokines and enzymatic antioxidant defense. We tested the hypothesis that OA may curtail the inflammatory process, improving lung morphology and function in experimental sepsis. 36 BALB/c mice were assigned to 2 groups: a) Sepsis was induced by cecal ligation and puncture (CLP) surgery, and b) *Sham* operated group was used as control. One hour after surgery, *Sham* and CLP groups were further randomized into subgroups receiving saline (SAL *ip*) and OA (10 mg/kg *ip*). After 24 h, static lung elastance (Est,L), lung histology, levels of interleukin (IL)-6 and IL-8 in the bronchoalveolar lavage fluid and the degree of cell apoptosis in lung and kidney were analyzed. Est,L (55%) and alveolar collapse (75%) were higher in CLP-SAL group compared to *Sham*-SAL ($p < 0.05$). Furthermore, CLP-SAL group showed interstitial edema, neutrophil infiltration, and higher degree of apoptosis in lung and kidney compared to *Sham*-SAL. OA reduced Est,L (35%) and alveolar collapse (70%), as well as minimized neutrophil infiltration and the degree of apoptosis in lung and kidney compared to CLP-SAL group. OA did not decrease the levels of IL-6, and IL-8. In conclusion, OA improved lung morpho-function, as well as acted on distal organs in the present model of sepsis.

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Inflammatory biomarkers in predicting ICU admission of severe community-acquired pneumonia (CAP)

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Introduction: Increased inflammation is related with severity and outcome in CAP, but the role of inflammatory biomarkers in deciding ICU admission is unknown. We assessed the relationship between inflammatory response, prediction for ICU admission, delayed ICU admission, and outcome in patients with CAP.

Methods: We prospectively assessed 627 ward and 58 ICU patients (36 direct and 22 delayed ICU admission), determined serum levels of C-reactive protein (CRP), Procalcitonin, TNF-alpha, IL-1, IL-6, IL-8 and IL-10 at admission, and assessed the prediction for ICU admission of biomarkers and the IDSA/ATS guidelines criteria for severe CAP.

Results: Procalcitonin (p=0.001), CRP (p=0.005), TNF-alpha (p=0.042) and IL-6 (p=0.003) levels were higher in ICU patients, but the IDSA/ATS guidelines minor criteria predicted better ICU admission (OR 12.0, 95% CI 5.1-28.2, $p<0.001$). No patient with ≥ 3 minor criteria and Procalcitonin levels < 0.35 ng/mL needed ICU admission, compared with 14 (23%) with levels above this optimal cutoff (p=0.032). In initially-ward patients, Procalcitonin (p=0.012) and CRP (p=0.039) predicted subsequent ICU transfer, adjusted for age, co-morbidities and PSI risk class. Despite initially in wards, 14 (64%) patients with delayed ICU admission had criteria for severe CAP at admission, compared with 73 (12%) ward patients ($p<0.001$).

Conclusion: Although the IDSA/ATS guidelines minor criteria identified patients needing ICU admission better than biomarkers, low levels of Procalcitonin discarded ICU admission in those with minor criteria. Correctly applying these guidelines would reduce delayed ICU admission.

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Reduction of the systemic inflammatory response in patients with CAP treated with corticosteroids improves clinical outcome and reduces mortality and ICU admittance

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Corticosteroids can improve clinical outcome in patients with pneumonia. However, little is known about the effects of corticosteroids on systemic cytokine levels in these patients or which patients benefit most from corticosteroid therapy.

Hospitalized, non-immunocompromised patients with CAP were randomly assigned to a 4-day course of dexamethasone (5 mg once a day) or placebo. Serum levels of IL-1Ra, IL-6, IL-8, IL-10, IL-17, TNF-α, INF-γ, MIP and MCP were measured at various time-points during hospital stay.

We enrolled 304 patients. The median levels of IL-6, MCP, TNF-a, IL-8, and IL1ra, all were significantly lower ($p < 0.01$) on day 2 in the dexamethasone treated patients compared to the placebo treated patients. In patients with an atypical bacterium, IL-1ra ($p<0.01$), IL-6 ($p<0.01$), IL-10 (p=0.06) and MCP (p=0.03) decreased faster in the dexamethasone group compared to placebo; in pneumococcal pneumonia only MCP (p=0.07) and TNF-a (p=0.05) decreased faster.

When IL6, IL-8 and MCP, being the most prominent proinflammatory cytokines were combined, patients who had all three cytokines above a predefined cut-off point benefited most from dexamethasone therapy. In the dexamethasone group only 2 patients (8,3%) died, while in the placebo group 8 patients (47%) died ($p: <0.01$).

Conclusion: Proinflammatory cytokines and chemokines decreased more rapidly in dexamethasone treated patients compared to placebo treated patients. This effect was most evident in patients with an atypical bacterium. In patients with highest cytokine response, dexamethasone showed a reduction in mortality and ICU admittance.

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Impact of bronchoalveolar lavage (BAL) multiplex PCR with DNA macrocip based diagnosis on outcomes of severe pneumonia in ICU

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Objective: To evaluate BAL multiplex PCR with DNA macrochip (Syndrome Evaluation System (SES), Xcyton Diagnostics Pvt. Ltd., India) in etiological diagnosis of severe pneumonia and its impact on outcomes.

Method: Bronchoscopic BAL in 25 (27 episodes) adult patients with severe pneumonia was tested by conventional culture methods (CC) and SES. Empirical antibiotics were modified based on the results. Index infection, ICU, hospital and 30 day outcomes were compared with matched controls.

Results: BAL was obtained from 25 (27 episodes) study patients [mean±SD age 61.3±18.3 yrs] and 27 control patients [age 60.9±18.3 yrs]. There was no significant difference in the age (p=0.94), APACHE IV score (74.6±27.3 vs. 76.6±29; p=0.8) and predicted mortality (29±22.3 vs. 26.9±21.2; p=0.72), ICU length of stay (LOS) (p=0.49) and hospital LOS (p=0.73) between the groups. Mechanical ventilation was required for 26 episodes in study and 25 in controls.

In the study arm all BAL were positive by SES, 9 were sterile by CC and 18 were positive by both methods. SES missed 4 organisms picked up by CC. In controls 7/27 BAL were sterile by CC.

In the study arm there was significantly less time to antibiotic modification ($p<0.001$) based on SES (31.18±8.44 hrs) as compared to CC (including Gram stain and colony morphology) (52.81±17.71 hrs). Observed 30 days mortality was 15/25 (study) and 13/27 (control). Index infection cure rates (p=1) and ICU (p=0.27), hospital (p=0.49) and 30 day (p=0.57) mortality were not significantly different in the two groups.

Conclusions: Multiplex PCR (SES) helps in early modification of empirical therapy but shows no impact on severe pneumonia outcome.

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Hyaluronan infusion improves survival in endotoxemic rats

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Background: It has been proposed that Hyaluronan (HA) acts as a vehicle for cytokines due to the strong negative charge on its surface. We hypothsized that HA would function like a cytokine scavenger, reducing inflammatory signaling cascade leading to improved survival in endotoxemia.

Methods: Endotoxin (Salmonella, 10 mg/kg) or an equal amount of 0.9% NaCl (NS) was injected into the jugular vein of rats. HA (1600 kDa, 0.35%) or NS was given 0.5 ml/h for 3 h. HA or NS infusion was started at three different time points; 30 min before, 1 hour after, and 4 hour after endotoxin injection. Rats were divided into control and HA groups at three different time point.

Results: The survival rate (%) of rats treated with HA was higher (90%) than in controls' (60%) treated with NS infusion 30 min before LPS injection; HA was higher (90%) than in controls' (50%) when HA or NS infused 1 h after LPS; HA was higher (60%) than in controls' (20%), when HA or NS infused 4

h after LPS. Bronchoalveolar lavage (BAL) of the animals surviving HA or NS infusion 4 h after LPS showed that total cell count and neutrophils were significantly ($p < 0.01$) reduced in the HA treated groups compared to controls (total cell count, 9.2×10^4/ml vs. 61×10^4/ml; neutrophils, 21×10^4/ml vs. 0.2×10^4/ml, respectively). Serum cytokines of the animals surviving HA or NS infusion 4 h after LPS showed that TNF-alpha and MIP-2 were significantly ($p < 0.01$) lower in the HA treated groups compared to controls (70.7 vs. 120.3 pg/ml; 1506 vs. 3459 pg/ml, respectively).
Conclusion: Continuous infusion of hyaluronan, 1600 kDa, reduced BAL cell count and serum cytokines, and improved survival in the endotoxemic rats.

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Multi organ failure in severe sepsis patients followed at intensive care unit: Risk factors
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Aim: We aimed to detect risk factors for mortality and multi organ failure (MOF) for patients with severe sepsis and MOF in intensive care unit (ICU).
Material-method: Retrospective data collection and prognostic cohort study. Between January 2009-March2010 patients with severe sepsis who stayed more than 24 hours in 22 bed ICU were retrieved. Demographics, ICU severity scores (initial APACHE II, 1st and 3rd day SOFA score), use of mechanical ventilation (noninvasive, invasive), sepsis agent, application of sepsis protocol, ICU length of stay (LOS), mortality were recorded. Logistic regression analysis was done for risk factors and mortality risk factors in patients with and without MOF.
Results: 347 patients (232 males) with severe sepsis were involved. Fortythree (12.4%) developed MOF and overall mortality rate was 14.9% (n=52). Presence of resistant pathogen, shock, total parenteral nutrition (TPN) and high APACHE II score were found to be risk factors for MOF ($p<0.015$ Odds ratio (OR) 3.47 confidence interval (CI): 1.27-9.47, $p<0.000$, OR:30.8 CI:11.41-83-49, $p<0.028$, OR:3.08, CI:1.13-8.39, $p<0.003$, OR:1.10, CI:1.04-1.18, respectively). Risk factors for overall mortality were presence of nosocomial infection, high 3rd day SOFA score, presence of shock, sedation and TPN ($p<0.005$, OR:3.39, CI:1.45-7.93; $p<0.000$, OR:1.51, CI:1.27-1.81; $p<0.014$, OR:3.24, CI:1.27-8.25; $p<0.003$, OR:3.64. CI:1.54-8.58; $p<0.000$, OR 3.38, CI:1.51-7.57, respectively).
Conclusion: In severe sepsis patients who need ICU follow up, in addition to known sepsis protocols, rational use of antibiotics and application of hospital acquired infection control programmes will further reduce MOF and mortality.

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Prediction of clinical severity and outcome of ventilator-associated pneumonia in a tertiary hospital using the VAP PIRO scoring system
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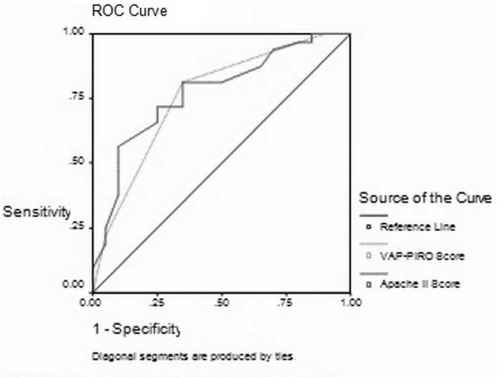
Background: Management and decision-making in ventilator-associated pneumonia (VAP) was commonly guided by diagnostic tools, until a recent study validated a severity assessment tool for prognostication.
Objective: To determine if VAP PIRO Scoring System can predict mortality risk compared to APACHE II.
Methods: A prospective, observational study was performed including 52 patients with VAP in a tertiary hospital. The ability of the VAP PIRO score to discriminate mortality was assessed by ROC curve analysis and was compared to APACHE II.
Results: Six hundred eighty six patients received mechanical ventilation during the study period and fifty two (7.58%) developed VAP. Mortality for VAP was significantly associated with the VAP PIRO score ($p<0.01$), APACHE II ($p<0.01$), and appropriateness of empiric antibiotics ($p=0.027$). The VAP PIRO score showed good discrimination for mortality (AUC 0.759) and was comparable to APACHE II (z statistic=0.0504; $p=0.96$).



APACHE II score: AUC 0.773; 95% CI, 0.643 to 0.904
VAP PIRO score: AUC 0.759; 95% CI, 0.620 to 0.897
Figure 1. Comparison of ROC curves for predicting mortality.

In the Cox Regression Analysis, the high/very high risk group of VAP patients was associated with a higher risk of death (OR, 8.048; 95% CI, 2.243- 28.875).
Conclusion: This study showed that the VAP PIRO scoring system is a good practical clinical tool that could substitute the complex and costly APACHE II in predicting severity and outcome of illness.

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De-escalation therapy in ventilator acquired pneumonia (VAP)
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Objective: To evaluate the new strategy (De-Escalation therapy) for patients with VAP.
Methods: We studied patients who were admitted to the ICU in a tertiary university Hospital. The study ran for 2009 full year, with a total 602 patients admission, 337 of them required mechanical ventilation, according to the daily assessment by CPIS below 6, 235 patients developed VAP (69,73%), Bacterial evaluation was achieved for 78 patients with BAL during guided Fibroscopy. We divided ours patients randomly into two groups:
Group A: 32 of the patients were treated in the traditional manner using Broad spectrum antibiotics for two weeks.
Group B: 46 of the patients were treated according to the new strategy (De-Escalation of Antibiotics) for eight days. All patients were followed up and assessed clinically and by CPIS (Clinical Pulmonary Infection Score), at starting therapy and the days (three, eight, and fourteen)
Results: The proportions of patients with late and early VAP in Group A were 56.25%, 43,75% and Group B were 54.34%, 45.65%. The mortality rate was significantly higher in late and early VAP in both groups. In Group B the CPIS and clinical improvement was noticed and statistically significant in day eight, comparing to Group A (39.13%, 28.12% respectively). We studied the type of bacteria and its resistance to antibiotics, the proportion of Gram-negative almost consists two thirds in both groups with no difference in distribution of germ. The mortality rate in Group A and Group B was (65.62%, 56.52% Respectively) the difference was statistically significant.
Conclusion: The (De-Escalation of antibiotics) was possible and safe with diminution of mortality, the amounts of antibiotics used and a shorter stay in the ICU.