BTS/BLF/BALR Early Career Investigators Symposium

T1 FLUTICASONE PROPIONATE ALTERS THE RESIDENT AIRWAY MICROBIOTA AND IMPAIRS ANTI-VIRAL AND ANTI-BACTERIAL IMMUNE RESPONSES IN THE AIRWAYS

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Background Inhaled corticosteroids are the cornerstone of therapy in asthma and COPD but cause only modest reduction in exacerbations and are associated with increased pneumonia frequency. This has raised concern about potential detrimental effects on host-defence against respiratory pathogens. The aim of this study was to evaluate the effects of fluticasone propionate on airway anti-viral and anti-bacterial host-defence.

Methods C57BL/6 mice were intranasally treated with fluticasone propionate (1 mg/kg) or vehicle control. 16S Quantitative PCR was used to evaluate total bacterial loads and pyrosequencing was used to evaluate microbiota community composition in lung tissue. Using mouse models of infection with rhinovirus 1B and *S. pneumoniae* D39, effects of fluticasone administration on anti-viral and anti-bacterial immune responses, airway inflammation and pathogen control were evaluated.

Results Mice treated with fluticasone had increased lung bacterial loads compared to vehicle-treated controls at 8 h post administration ($p < 0.05$). Evaluation of community composition revealed that fluticasone treatment was associated with significant increases in *Stenotrophomonas* genera ($p < 0.05$). In a mouse model of *S. pneumoniae* infection, fluticasone administration suppressed anti-bacterial responses including expression of cytokines IL-6 and TNF-α (4 h post-infection; $p < 0.001$) and airway neutrophil recruitment (8 h post-infection; $p < 0.001$) and was also associated with increased lung bacterial loads measured by quantitative culture (8 h post-infection; $p < 0.001$). In a mouse model of rhinovirus infection, fluticasone suppressed innate anti-viral responses including BAL protein levels of interferon-β and -λ2/3 (day 1 post-infection; $p < 0.001$). Virus clearance was impaired by fluticasone with increased viral RNA copies observed in lung tissue (day 1&2 post-infection; $p < 0.001$). The late expression of rhinovirus-induced airway mucins MUC5AC and MUC5B BAL proteins was increased by fluticasone ($p < 0.01$ and $p < 0.05$ respectively at day 7). Administration of recombinant interferon-β in combination with fluticasone and rhinovirus led to upregulation of interferon-stimulated genes and improved virus clearance, thereby demonstrating that adverse effects of fluticasone on RV clearance are causally related to interferon suppression. Recombinant IFN-β did not alter the increased mucins observed with fluticasone treatment.

Conclusion Fluticasone alters the airway microbiota and impairs airway anti-viral and anti-bacterial host-defence in mice. Human studies are required to confirm the relevance of these effects in the context of inflammatory airway diseases.

T2 VITAMIN D SUPPLEMENTATION REDUCES PERIOPERATIVE SYSTEMIC AND ALVEOLAR INFLAMMATION IN PATIENTS UNDERGOING OESOPHAGECTOMY: RESULTS OF THE VINDALOO TRIAL

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Vitamin D deficiency is associated with increased risk of ARDS post-oesophagectomy. We recruited patients to a double-blind, randomised controlled trial of high dose Vitamin D supplementation 3–14 days pre-oesophagectomy.

79 patients were randomised to receive placebo or 300,000 IU oral Vitamin D liquid 3–14 days prior to oesophagectomy. Blood samples were collected pre-dose, post-dose (pre-op) and post-op and analysed for 25-OH and 1,25-dOH Vitamin D, inflammatory cells and cytokines. Broncho-alveolar lavage fluid was collected at the end of the operation. PICCO biomarkers of alveolar capillary damage (EVLWI and PVPI) were measured pre- and post-op.

Pre-operative supplementation with Vitamin D was well tolerated with no SUSARs and significantly increased circulating 25-OH and 1,25-OH Vitamin D ($p < 0.0001$). This was associated with reduced systemic inflammation (IL-6 ($p = 0.02$) and IL-8 ($p = 0.002$)) and an increase in circulatory Treg ($p = 0.027$).

Changes in PICCO biomarkers were lower in supplemented patients suggesting lower perioperative alveolar oedema (EVLWI $p = 0.05$, PVPI $p = 0.04$). This did not result in a significant difference in oxygenation at 24 h.

Post-op, systemic and alveolar alarmin (IL-1B, IL-6, IL-8) response was similar in treated and untreated patients but the systemic release of IL-1ra ($p = 0.046$), sTNFR-1 ($p = 0.05$) and s-TNFR-2 ($p = 0.02$) were elevated in treated patients. There was also evidence of decreased alveolar macrophage efferocytosis in patients with Vitamin D deficiency ($p = 0.003$).

Clinical diagnoses of ARDS were significantly lower in this cohort than in previous cohorts, but the study was not powered to detect that outcome. Mortality post-operative was not significantly different at 30 or 90 days but there is a significant difference after 300 days of follow-up (placebo 33% mortality, Vitamin D 8% mortality $p = 0.033$).

In conclusion, vitamin D supplementation was a safe, well tolerated pre-operative intervention that reduced systemic inflammation and biomarkers of alveolar oedema. With evidence of enhanced anti-inflammatory mechanism that may have influenced longer term post-operative survival, Vitamin D deficiency should be identified and treated in patients at risk of ARDS.

T3 MITOCHONDRIAL TRANSFER IS AN IMPORTANT MECHANISM BY WHICH MESENCHYMAL STROMAL CELLS (MSC) FACILITATE MACROPHAGE PHAGOCYTOSIS IN THE *IN VITRO* AND *IN VIVO* MODELS OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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