pulmonary inflammation and our findings would be consistent with impaired epithelial TGF β activation in the lungs of these mice. Further studies are required to determine the origin of the cells activating TGF β in these lungs.

S124 MACROPHAGE DELETION OF VHL RESULTS IN ALTERNATIVE ACTIVATION AND ENHANCED LUNG FIBROSIS INDEPENDENT OF HIF-1

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Background Hypoxia-inducible factor (HIF-1) is a master regulator of the cellular hypoxic response and has been implicated in the pathogenesis of inflammatory and fibrotic disease including IPF.

Aims To study the role of hypoxia and HIF-1 activation in macrophages in the i.t. bleomycin-induced lung fibrosis model.

Methods The i.t. bleomycin model was used to study the effect of HIF-1 manipulation in mice. The primary end-point was lung collagen content at day 24 post i.t. bleomycin instillation. The HIF-1 α inducer dimethyloxallyl glycine (DMOG) was administered i.p. on days 14, 17 and 21. The role of myeloid-HIF-1 activity in lung fibrosis was determined using mice in which either HIF-1 α or vHL (the dominant negative-regulator of HIF-1 α) was selectively knocked out of lysosome M expressing cells (LysM-Cre-Hif-1 and Cre-LysM-vHL). Lung tissue hypoxia was determined using Hypoxyprobe-1TM administered on day 24. Alternative activation status of HIF-1 null and vHL null macrophages was studied in bone-marrow derived cells from LysM-Cre-Hif-1 and Cre-LysM-vHL mice.

Results Pharmacological induction of HIF-1 in the late period of the bleomycin model with i.p. dimethyloxallyl glycine (DMOG) resulted in significantly enhanced lung collagen (mean $\pm$ s.e.m μ g/lung) on day 24 compared to controls (193 $\pm$ 15 vs 152 $\pm$ 8, p <0.05, n >7 per gp). Hypoxyprobe-1 staining in the bleomycin-injured lung revealed hypoxic alveolar macrophages even in areas of lung distant to patches of severe fibrosis, implying a role for hypoxic/HIF-1 expressing alveolar macrophages in lung fibrosis. However, lung collagen content was identical in myeloid-cell Hif-1 null mice and wild-type litter-mate controls (276 $\pm$ 23 vs 277 $\pm$ 22, n =8 per gp). In contrast, myeloid-cell vHL-null mice exhibited significantly enhanced lung collagen deposition versus controls (373 $\pm$ 36 vs 282 $\pm$ 54, p <0.05, n >9 per gp). Isolated vHL-null macrophages exhibited enhanced expression of the alternative activation markers YM-1, mannose receptor, arginase-1 and FIZZ-1.

Conclusions vHL deletion in macrophages enhances alternative activation and promotes lung fibrosis independent of HIF-1.

S125 LY6CHI CIRCULATING MONOCYTES DIRECTLY ALTERNATIVELY ACTIVATED, PRO-FIBROTIC, LUNG MACROPHAGE REGULATION OF PULMONARY FIBROSIS

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Introduction and objectives Idiopathic pulmonary fibrosis (IPF) remains one of the few respiratory conditions for which there are no effective therapies. The role of monocytes and macrophages in IPF

has been disputed as anti-inflammatory therapies produce questionable benefit. Corticosteroids, however, actually induce an alternatively activated, pro-fibrotic, macrophage phenotype. We sought to determine whether monocytes and macrophages play a role in disease pathogenesis in an attempt to explain why current hypotheses and anti-inflammatory therapies have produced limited clinical benefit despite years of research.

Methods Using multiple in vivo depletion strategies, backed up by an adoptive transfer technique, we extensively investigated the role of monocytes and macrophages during lung fibrogenesis. We performed studies on samples from patients with IPF in an attempt to determine the translational importance of our findings.

Results Depletion of lung macrophages during fibrogenesis reduced pulmonary fibrosis as measured by lung collagen (p =0.0079), fibrosis score (p =0.0051), and qPCR for surrogate markers of fibrosis *Col1* (p =0.0083) and *α -smooth muscle actin* (p =0.0349). There was an associated reduction in expression of markers of alternative macrophage activation, *Ym1* (p =0.0179), and *Arginase1*. This reduction was confirmed by immunohistochemistry (IHC) for Ym1 (p =0.0233). IHC on lung macrophages from patients with IPF demonstrated the novel finding of expression of the human alternative macrophage marker CD163. Depletion of Ly6C^{hi} circulating monocytes reduced pulmonary fibrosis (p =0.0052). Adoptive transfer of Ly6C^{hi} BMDMs during fibrogenesis exacerbated pulmonary fibrosis (p =0.0304). Furthermore, depletion of circulating Ly6C^{hi} monocytes lead to a subsequent reduction in the number of Ym1-positive alternatively activated lung macrophages (p =0.0310) with a concomitant reduction in the expression of *Ym1* and *Arginase1*.

Conclusions We have demonstrated that monocytes and macrophages do modulate pulmonary fibrosis and suggest that Ly6C^{hi} monocytes (possible fibrocyte precursors) are precursors of alternatively activated, pro-fibrotic, lung macrophages. These findings could link the 'inflammatory' and aberrant wound healing hypotheses and explain the lack of effectiveness of corticosteroids in treating IPF. By enhancing our understanding of the pathogenesis of this dreadful disease, our results may enable new therapeutic targets to be developed, facilitate targeted cell-based therapy, and bring hope to one of the longstanding enigmas of respiratory medicine.

Lung infection: a multi-faceted problem

S126 MEASURING QUALITY IN PNEUMONIA CARE. THE NORTH WEST ADVANCING QUALITY PROGRAMME 2008–2009

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As part of an initiative within the North West Strategic Health Authority to improve the quality of care, 'quality markers' (QMs) were measured in all adult admissions with pneumonia in all 24 Acute Trusts in the North West Region for 1 year (discharges from October 2008 to September 2009). Only adults who fulfilled a prescribed definition of 'pneumonia' were included. QMs were taken from a USA initiative and adapted for UK use. Patient identification was based on clinical coding. Data were recorded in each individual Trust and centrally collated.

Combined data from all trusts QMs were recorded with the following frequencies (no in parentheses is number of patients included): Oxygenation assessment within 24 h or prior to hospital arrival 96.9% (11 127), blood culture performed in the A & E prior to initial antibiotic received in hospital 58.5% (3323), smoking cessation advice/counselling given in 38.1% (2788), initial antibiotic consistent with local CAP guidelines 80.8% (6337) and initial antibiotic received within 6 h of hospital arrival 64.6% (7889). Over the four

quarters of the year there was no change in the frequency (%) of oxygenation assessment (96.0, 96.1, 97.6, 98.8), initial antibiotic selection (81.9, 77.9, 80.9, 83.7), or initial antibiotic within 6 h (67.1, 64.0, 63.6, 63.5) or blood cultures performed before antibiotics (58.8, 56.3, 57.9, 62.4) but a small rise in smoking cessation advice (36.4, 32.6, 40.3, 45.5). Overall score, whether composite or appropriate did not change.

Individual trusts Of the 22 Trusts with complete results, overall score over the year was <80% in one, 80–85% in two, 85–90% in three, 90–95% in 13 and >95% in three. Comparing last with first quarter scores only five individual Trusts showed a rise in score of >5%, three a fall of >5% and all others changed less than this amount. The biggest change was in the Trust that performed worst in the first quarter. Practical problems identified included accurate case identification and case note data recording. Despite this the Advancing Quality programme is a practical way of measuring QMs in pneumonia. Further work is required to generate improvements in patient care.

S127 IS HEALTHCARE ASSOCIATED PNEUMONIA A DISTINCT CLINICAL PHENOTYPE?

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Introduction US Guidelines define healthcare associated pneumonia (HCAP) as patients with regular contact with healthcare (eg, nursing home residents, patients with recent hospital admissions or regular outpatient clinics). It is argued that such patients are more likely to develop infection with resistant organisms and require broader spectrum antibiotics. UK guidelines do not distinguish between HCAP and community-acquired pneumonia (CAP). The aim of this study was to investigate whether HCAP is a distinct clinical phenotype.

Methods We studied consecutive patients aged 18+ presenting to an emergency department with CAP according to current UK definitions (NHS Lothian 2006–2009). Exclusion criteria included hospital acquired pneumonia, immunosuppressed patients, and patients not actively treated (palliative). Cases were reviewed by two investigators and HCAP patients were defined according to 2005 ATS/IDSA guidelines. Survival was analysed by Kaplan–Meier analysis and logistic regression.

Results This study analysed 1111 consecutive patients. Of these, 224 (20.2%) met the criteria for HCAP (39.3% hospitalised within 3 months, 37.5% nursing home residents, 10.7% recent outpatient appointments, 12.5% 'other'). 96.4% of HCAP patients received standard 'CAP' antibiotic therapy without coverage of *Pseudomonas aeruginosa* or MRSA. Demographic comparison of HCAP and CAP patients showed HCAP patients were significantly older (median age 76 vs 64, $p<0.0001$) and more likely to have co-morbidities, for example, congestive cardiac failure (30% vs 17%, $p<0.0001$), COPD (33.5% vs 20.8%, $p<0.0001$). HCAP patients had higher markers of severity and worse outcomes on univariate analysis. Mean admission CURB65 score was greater (2.32 vs 1.78, $p<0.0001$), median length of stay was longer (7 vs 5 days, $p=0.01$) and 30-day mortality was double that of CAP patients (16.5% vs 8.2%, $p=0.0004$). Kaplan–Meier analysis showed higher mortality for HCAP patients (Log rank test χ^2 13.24 df=1, $p=0.0003$) as shown in Abstract S127 Figure 1. On multivariate analysis, however, after adjustment for age, co-morbidities and initial pneumonia severity, HCAP was not independently associated with increased 30-day mortality AOR 1.13 (0.69–1.84, $p=0.6$).

Abstract S127 Figure 1

Conclusions Healthcare associated pneumonia is common, with around 20% of CAP patients meeting the definition. Although HCAP patients are older and have more co-morbidities, HCAP is not independently associated with 30-day mortality.

S128 ANALYSIS OF VOLATILE BIOMARKERS WITHIN EXHALED BREATH FOR THE DIAGNOSIS OF PNEUMONIA

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Introduction Whilst pneumonia is a common condition affecting both medical and surgical patients there is currently no definitive diagnostic test. One novel approach may be through the non-invasive analysis of volatile metabolites within exhaled breath, released either by pathogens or host cells. The objective of this study was to delineate the metabolic phenotype of the exhaled breath of patients with community acquired (CAP) and post-operative pneumonia.

Methods Breath samples were collected from patients with a confirmed diagnosis of CAP ($n=26$). Targeted analysis of six prominent breath metabolites was performed by selected ion flow tube-mass spectrometry. Metabolites found to be significantly different in the breath of CAP patients were subsequently investigated in patients undergoing both major abdominal and thoracoabdominal surgery ($n=40$). Receiver operating characteristic (ROC) analysis of putative pneumonia biomarkers was performed in an independent cohort of patients with suspected CAP ($n=21$). A diagnosis of pneumonia was established through fulfilment of pre-defined radiological, microbiological, haematological and clinical criteria.

Results Compared to healthy controls, CAP patients had significantly lower breath levels of hydrogen cyanide (6 vs 14ppb, $p=0.001$) and isoprene (72 vs 111ppb, $p=0.014$). Patients who developed postoperative pneumonia ($n=8$) had significantly lower levels of hydrogen cyanide within their breath compared to both those patients who had an uncomplicated recovery (4 vs 13ppb, $p=0.008$) and healthy controls. Whilst patients who underwent thoracoabdominal compared to abdominal surgery had higher breath levels of isoprene at both 96 (114 vs 176ppb, $p=0.02$) and 168 h (119 vs 176ppb, $p=0.02$) following surgery, this did not correlate with the onset of pneumonia. ROC analysis of hydrogen cyanide and isoprene are displayed in Abstract S128 Figure 1. In both medical and surgical patients there was no significant change in the levels of other examined breath metabolites: acetone, ethanol, propanol and acetic acid.