

## S10 ARE WE OVERLOOKING PERSISTENT SMALL AIRWAYS DYSFUNCTION IN COMMUNITY-MANAGED ASTHMA?

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**Background** It is unknown if small airways dysfunction persists in asthmatics receiving standard community treatment. Impulse oscillometry (IOS) is a sensitive measure of small airways function. We wished to assess the degree of small airways dysfunction in a cross-section of community-managed asthmatics.

**Methods** We analysed primary care referral data from persistent asthmatics (n=378) receiving standard community therapy, screened using spirometry and IOS. We compared patients by British Thoracic Society asthma treatment step (2–4).

**Results** Step 2 were not different from step 3 patients receiving long-acting beta-agonist (LABA). Step 4 patients differed from step 2 by: higher inhaled corticosteroid (ICS) dose ( $p<0.0001$ ); lower forced expiratory volume in 1s (FEV<sub>1</sub>,  $p=0.02$ ) and forced mid-expiratory flow (FEF<sub>25–75</sub>,  $p=0.001$ ); higher frequency of resonance (Fres,  $p=0.02$ ) and peripheral airway resistance (R5–R20,  $p=0.006$ ); while for steps 3 vs. 4, there were differences in Fres ( $p<0.05$ ) and R5–R20 ( $p=0.006$ ). There were high proportions of abnormality for R5–R20 ( $>0.03\text{kPa/L/s}$ ) at steps 2, 3 & 4 respectively: 64.6%, 63.5% and 69.9%. Step 2 patients receiving extra-fine particle ICS demonstrated lower total airway resistance at 5Hz (R5) versus patients receiving standard ICS (124.1% vs. 138.3%,  $p<0.05$ ), with no difference in FEV<sub>1</sub> (Table 1). At step 4, R5 remained elevated at 141.3% despite concomitant LABA, with only 2.4% using extra-fine ICS.

**Conclusion** There is persistent small airways dysfunction despite treatment at steps 2–4 of current asthma guidelines. Extra-fine ICS may reduce airway resistance at step 2. Prospective studies with extra-fine ICS±LABA at steps 2–4 are required to discern whether improving small airways function might result in long-term improved control.

Abstract S10 Table 1

Variable	Extra-fine ICS (n=67)	Standard ICS (n=125)	p-value
ICS dose ( $\mu\text{g/day}$ )	279 (249, 309)	406 (364, 447)	<b>&lt;0.0001</b>
FEV <sub>1</sub> (% predicted)	88.9 (84.8, 92.9)	90.3 (87.5, 93.1)	0.56
FEF <sub>25–75</sub> (% predicted)	63.7 (57.5, 69.8)	67.1 (62.7, 71.5)	0.38
R5* (% predicted)	124.1 (113.5, 135.8)	138.3 (130.0, 147.0)	<b>&lt;0.05</b>
R20* (% predicted)	126.0 (117.0, 135.8)	136.7 (130.0, 143.9)	0.07
R5–R20* (kPa/L/s)	0.069 (0.05, 0.088)	0.088 (0.071, 0.105)	0.18
F <sub>res</sub> * (kPa/L/s)	13.9 (12.6, 15.2)	14.6 (13.6, 15.7)	0.36
FeNO* (ppb)	31.4 (24.9, 39.5)	25.3 (21.9, 29.2)	0.11

**Comparisons of extra-fine particle solution formulation of inhaled corticosteroid (ICS) vs. standard particle size (suspension CFC/HFA, or dry powder formulation) ICS outcomes at step 2.** Data presented as arithmetic means (95% CI) unless stated. \*Geometric mean (95% CI). Means comparison performed using Student's T-test for independent samples (two-tailed), significance  $p<0.05$ . ICS dose=nominal inhaled corticosteroid dose. FEV<sub>1</sub>=forced expiratory volume in 1s. FEF<sub>25–75</sub>=forced expiratory flow between 25–75% of vital capacity. R5=total airway resistance at 5Hz. R20=central airway resistance at 20Hz. F<sub>res</sub>=frequency of resonance. R5–R20=peripheral airways resistance between 5Hz and 20Hz. FeNO=fractional exhaled nitric oxide.

## S11 EXPRESSION OF TENASCIN-C REGULATES AIRWAY SMOOTH MUSCLE DERIVED MATRIX METALLOPROTEINASE-1 IN ASTHMA

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**Background** Collagenases are differentially regulated in conditions of lung remodelling. Literature documents the capacity of extracellular matrix (ECM) proteins to induce collagenase expression. The current study aims to characterise ECM regulation of the collagenase matrix metalloproteinase-1 (MMP-1) in human airway smooth muscle (ASM) cells, and the applicability of this mechanism to remodelling.

**Methods** ASM cells were derived from patients with and without asthma and cultured with ECM proteins for 24 hours. MMP-1 gene expression was quantitated by Real-time PCR, with secreted protein and activity levels assessed by ELISA, Western Blotting and fluorometric activity assay. Pathways mediating MMP-1 induction were mapped using a phosphoprotein array, specific inhibitors and blocking antibodies. Tenascin-C and MMP-1 expression were studied in endobronchial biopsies from patients with and without asthma by immunohistochemistry.

**Results** Tenascin-C increased MMP-1 mRNA, protein and activity in a dose and time dependent manner. Tenascin-C phosphorylated MAPK intermediates ERK and P38, and inhibitors to these intermediates attenuated MMP-1 induction. Blocking antibodies showed this response was mediated by the  $\beta 1$  and  $\beta 3$  integrins. Control tissue showed minimal tenascin-C and MMP-1 expression, but strong co-localising Tenascin-C and MMP-1 expression in the subepithelial layer and to a lesser extent in ASM bundles. ASM cells from patients with asthma had elevated basal levels of MMP-1, which was further increased by Tenascin-C stimulation.

**Discussion** Tenascin-C upregulates expression and activity of MMP-1 via the  $\beta 1$  and  $\beta 3$  integrin subunits and MAPK signalling in ASM cells. These proteins were increased in lung remodelling diseases, with overlapping localisation. The functional consequences of this observation needs to be evaluated in vivo, however, this could potentially yield a new target for therapeutic in airway remodelling.

## Pleural disease

### S12 EXPERIENCE WITH INTRAPLEURAL TISSUE PLASMINOGEN ACTIVATOR AND DNASE IN THE TREATMENT OF PLEURAL INFECTION

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**Introduction** Intrapleural infection remains a significant cause of morbidity and mortality. In many patients medical management with chest tube drainage and antibiotics fails and surgical intervention is required. The MIST2 trial reported improved resolution following intrapleural treatment with combined tissue plasminogen activator and DNase (tPA/DNase).

**Aims** To study the outcomes in patients with pleural infection treated with tPA/DNase over a one year period in a 1,109 bed city centre hospital.

**Methods** A prospective audit was undertaken of all patients with pleural infection treated with intrapleural tPA/DNase. The decision to initiate therapy was at the discretion of the treating team. The main outcomes were changes in chest drain output and CXR opacification, complications, and surgical intervention. The area of pleural opacity was calculated using the method described by the MIST2 group.

**Results** Ten patients were treated over a one year period, all of whom had clinical features of infection and yielded frank pus or pleural fluid with a pH below 7.2.

Treatment with tPA/DNase was not initiated as a first line therapy in any patient. All were initially managed with chest tube drainage and antibiotics and the decision to initiate tPA/DNase was due to subsequent poor or absent drain output combined with evidence of persistent pleural fluid.

Changes in pleural fluid output and pleural opacification on CXR following treatment are shown in Table 1.

In one patient treatment was discontinued after 1 dose due to a non-functioning drain and in one patient treatment was discontinued after the fifth dose due to heavy blood staining of the pleural fluid. There were no other treatment related complications. Only one patient required cardiothoracic intervention and all patients were discharged home.

**Conclusions** In keeping with the MIST2 trial, these data suggest that intrapleural tPA/DNase can safely be used to treat pleural infection. In this selected group of patients that failed to respond to conventional medical management tPA/DNase treatment led to further fluid drainage with an associated reduction in pleural opacification and a low requirement for cardiothoracic intervention.

Abstract S12 Table 1

	Pre tPA/DNase	Post tPA/DNase
Fluid output, ml - mean (range)	940 (20...1980)	3130 (435...8070)
Change in % CXR opacification - mean (range)	-	-24 (-8...-39)

### S13 THE BACTERIOLOGY AND EPIDEMIOLOGY OF PLEURAL INFECTION – A REVIEW OF THE LITERATURE AND ITS RELEVANCE TO CLINICAL PRACTISE

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**Introduction** Pleural infection is described in the medical literature as far back as Hippocrates, yet even now the best management strategy remains uncertain. A rising case incidence places an increasingly significant burden on healthcare systems worldwide, with 65,000 patients per annum diagnosed with pleural infection in the UK and USA alone. It is increasingly accepted that pleural infection is a separate phenomenon to parenchymal lung infection, with its own epidemiology and bacteriology. This review sought to identify the data on pleural infection in adults published since 2000, to create a detailed up-to-date record on its bacteriology that might inform future research and guidelines.

**Methods** We searched the MEDLINE and EMBASE databases alongside the Cochrane Central Register of Controlled Trials using PubMed and OVID for studies relating to pleural infection in adults published since 2000. Studies were shortlisted for inclusion if they contained a record of confirmed microbiological diagnosis and methodology (using standard culture or nucleic acid amplification techniques); paediatric studies and tuberculous pleural infection were excluded. Studies were double-scored by clinicians with expertise in diagnosis and management of pleural infection to determine suitability and weighting.

**Results** Our initial search strategy identified 6126 references; of these, 2572 abstracts were relevant to respiratory practise and subsequently 136 papers were shortlisted for assessment of suitability for inclusion. Streptococcal species, notably the *anginosus* (*milleri*) group and *pneumoniae* are the most commonly identified pathogens in pleural infection as a whole. However, there is substantial variation in bacteriology according to where the infection is acquired – both “locally” (community vs. nosocomial) and “globally” (geographical location). The likelihood that many pleural infections are polymicrobial in nature, with the pathogenicity of different organisms being uncertain, is also raised.

**Conclusions** Pleural infection differs significantly in its bacteriology from parenchymal lung infection and according to where it is acquired. This has important implications for antibiotic choice and predicting morbidity and mortality. A high number of cases are undiagnosed using conventional culture and the role of techniques such

as nucleic acid amplification is promising but requires further clarification. Research is necessary to further define these bacteriological characteristics of pleural infection and inform future guidelines.

### S14 THE BEST WAY TO SECURE A 12-FRENCH INTERCOSTAL CHEST DRAIN TO THE CHEST WALL

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**Introduction and Objectives** Dislodgement of intercostal chest drains (ICDs) is common, affecting up to 21% of ICDs.<sup>1</sup> Why ICDs dislodge is not well understood. The optimum technique for securing ICDs has never been the subject of a randomised trial.

Current BTS guidelines recommend ‘0’ or ‘1’ sutures and caution against excessive adhesive dressings. Adhesive dressings are nevertheless widely used, sometimes instead of sutures. This study aims to identify the best technique for securing ICDs.

**Methods** A chest wall model was developed using 7mm medium-density fibreboard with one hole for a 12-French ICD and four smaller holes for sutures. Appropriately qualified doctors secured ICDs to the model with their usual sutures and technique. Some doctors who used small sutures repeated the experiment using larger sutures. The force required to remove the ICD from the model was measured with a Newton metre. A maximum force of 100N was applied, as ICDs snapped at forces over 110N. The force needed to detach ICDs fixed to the experimenter’s chest using adhesive dressings was also measured.

**Results** Using ‘1’ sutures, ICDs remained attached even at 100N ‘0’ sutures snapped at 86N ‘2/0’ sutures were most commonly used, but snapped at 57N ‘3/0’ and ‘4/0’ sutures were the least effective; the drain slipped at 25N and 20N respectively.

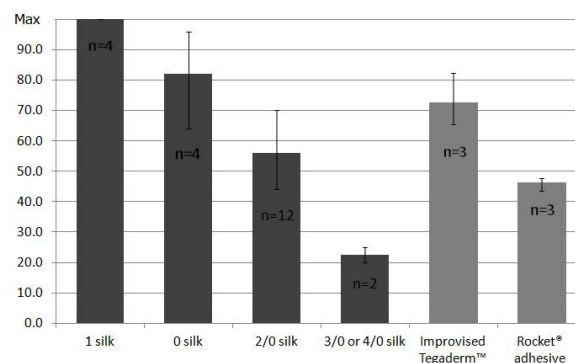
Individual doctors using the same technique with larger sutures (‘1’ or ‘0’ instead of ‘2/0’) attached ICDs more securely (92N vs 57N,  $p=0.03$ ) though the number of sutures, technique and doctor’s experience had no effect. ICDs detached painlessly from Rocket® dressings at 47N. An improvised tegaderm® dressing was more secure but detached painfully from the skin at 73N ( $p=0.03$ ). The force required didn’t diminish over 48 hours.

**Conclusions** ‘1’ sutures may be the best way to secure an ICD however the force required to pull sutures from the skin is unknown and knots may loosen over time. Using larger sutures improved ICD fixation. Adhesive dressings secure ICDs with similar strength to sutures and may represent an important alternative or adjunct, particularly in patients with fragile skin.

#### Reference

1. Davies HE et al. Respiriology (2008)13:603–607.

Force (in newtons with range) required to detach intercostal chest drains secured by sutures or adhesive dressings



Abstract S14 Figure 1