Ageing is associated with increased episodes of sepsis and poorer outcomes. Statins are associated with improved outcomes during infection. We aimed to characterise the impact of age and acute severe infection on key neutrophil functions, assess whether physiologically relevant doses of simvastatin altered neutrophil functions and if benefits were seen, when during a septic episode statins could be utilised.

**Methods** Neutrophils from healthy volunteers and patients with lower respiratory tract infections (LRTI), pneumonia and sepsis were assessed for migratory accuracy, phagocytosis and neutrophil extracellular trap production before and after in-vitro treatment with simvastatin. Healthy elderly volunteers received 80mg simvastatin or placebo in a cross over double-blind randomised controlled trial and neutrophil functions were assessed. Data presented is for migration.

**Results** Neutrophils from healthy subjects (n = 70, aged 21–94) demonstrated preserved neutrophil movement (R² = -0.48, p < 0.0001) towards chemotactants (data shown for IL-8). Neutrophil chemotaxis decreased after 60yrs (comparing <35 to >65yrs; mean difference (MD)1.25μm/min, p = 0.02).

There was a progressive decrease in neutrophil chemotaxis in old patients with a LRTI, pneumonia and severe sepsis (MD compared to healthy control; LRTI (n = 10), 0.7μm/min, p = 0.04; pneumonia (n = 5), MD1.1μm/min, p = 0.02; sepsis (n = 22) MD1.6μm/min, p = 0.01) with “septic neutrophils” unable to mount targeted chemotaxis. Improvements to baseline were seen following recovery.

**In-vitro** treatment of neutrophils from healthy older people with simvastatin (1μM) restored “old” neutrophil chemotaxis to that of “young” cells. Simvastatin also restored neutrophil migration from old patients with LRTI and pneumonia to baseline but not in patients with sepsis.

Two weeks of oral simvastatin 80mg once daily therapy in healthy old volunteers (Age>65,n = 20) increased the accuracy of neutrophil migration (MD1.68μm/min, p = 0.02) replicating benchwork.

**Conclusions** “Elderly” neutrophil function is compromised in health, and deteriorates during infective episodes, in accordance with the severity of the insult. Migratory accuracy can be improved with simvastatin therapy however neutrophil function in sepsis patients cannot be modulated during short term in-vitro therapy. Our data suggest statin therapy might be a preventative or an early adjuvant intervention rather than a treatment in established sepsis. We are testing whether simvastatin 80mg for seven days modifies neutrophil responses in elderly patients with pneumonia and sepsis (SNOOPI Trial).
S97 Alveolar epithelial DNA damage, inflammation and altered autophagy following exposure to silver nanoparticles is exacerbated by viral ligands in vitro
MZ Zambianchi, TD Tetley and AJ Thorley

Thorax 2013 68: A52
doi: 10.1136/thoraxjnl-2013-204457.104