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Histological findings in acute interstitial nephritis – a role for scoring non-fibrotic inflammation.

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Objectives
Acute interstitial nephritis (AIN) is a histological diagnosis. However, the clinical significance of common histological findings is uncertain. The aim of this study was to categorise the main histological findings in a cohort of patients with AIN and evaluate the utility of histology in predicting clinical outcomes.

Methods
Adult renal biopsies yielding a diagnosis of AIN between 2000 and 2015 in our centre were re-examined and scored for inflammation, tubular atrophy and characteristics of inflammatory cell infiltrates. Patients were divided into tertiles based on: 1) i-score: the percentage of non-scarred cortex containing inflammation (i1=0-24%, i2=25-74%, i3=75-100%), and 2) ct score: percentage of cortex containing tubular atrophy (ct1=0-9%; ct2=10-24%, ct3=25-100%). Baseline characteristics and clinical outcomes were collected. The primary outcome was a composite of ≥50% reduction in serum creatinine (sCr) or an eGFR >60 ml/min/1.73m² 1 year post biopsy.

Results
From a total of 2817 biopsies, 147 (5%) were identified as diagnostic for AIN. 27 patients were excluded (pathology slides faded (n=7), insufficient clinical information (n=4), dual pathology (n=4) and died within 1 year of biopsy (n=12)). Of the remaining 120 patients, 73 (61%) were male, 75 (63%) had an identified drug cause and 97 (81%) received steroids. A total of 63 (53%) patients achieved the primary outcome.

On univariable logistic regression, i-3 was associated with a 16 times increased likelihood of achieving the primary outcome compared to i-1 (HR 16 (95% CI 5.2-50, p<0.001)). In contrast, ct-2 and ct-3 were associated with 70% and 90% reduced likelihood of achieving the primary outcome compared to ct-1 (HR 0.3 (95% CI 0.1-0.8), p=0.01 for ct-2; HR=0.10 (95%CI 0.0-0.3) p<0.001 for ct-3). There was no difference in primary outcome between patients who did and did not have an identified drug cause, nor was there a difference between patients with and without eosinophils, neutrophils or granulomas on biopsy.

When age, sex, baseline sCr and identified drug cause were accounted for, both i-score and ct-score had an independent predictive effect on the primary outcome on multivariable logistic regression. Patients with high ct-score and low i-score were least likely to achieve the primary outcome (Figure 1).

Of the 97 patients who received steroids, 56 (58%) achieved the primary outcome compared to 10 (43%) of the 23 patients who did not receive steroids. As ct-score increased, the proportion of patients receiving steroids who achieved the primary outcome reduced from 80% in ct=1, 58% in ct=2, and 39% in ct=3, while it increased with i-score from 28% in i=1, 50% in i=2 and 86% in i=3.

Conclusions
In patients with biopsy-proven AIN, of whom the majority received steroids, a lower percentage of cortical tubular atrophy and, paradoxically, a higher percentage of inflammation in non-fibrosed cortex was

associated with an increased likelihood of a positive clinical outcome. Larger studies to assess the effect of steroid therapy with regard to histological phenotype in AIN are warranted.