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Editorial Comment



EDITORIAL COMMENT

# AIN't got no easy answers: recent advances and ongoing controversies around acute interstitial nephritis

Joshua Storrar[1], Alexander Woywodt [1] and Cheralathan Arunachalam[1]

[1]Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK

Correspondence to: Alexander Woywodt; E-mail: Alex.Woywodt@lthtr.nhs.uk

## ABSTRACT

Acute interstitial nephritis (AIN) is a common cause of acute kidney injury that was first described in 1898. It is most commonly caused by drugs and infections, although other aetiologies are implicated. Here we review two papers published in this issue of *Clinical Kidney Journal* and provide an update on current advances and controversies relating to AIN. Nussbaum and Perazella describe the diagnostic tools (namely urinary and serum biomarkers) available for AIN and highlight that there is no single test that can accurately predict the diagnosis. As such, renal biopsy remains the gold standard. Wendt *et al.* present findings from a 20-year retrospective study of biopsy-proven AIN. They found that a high degree of inflammation was associated with a greater chance of renal recovery, in contrast to the presence of cortical scars, which were associated with a worse outcome. There was also a significant number who required renal replacement therapy. They advocate the use of a scoring system for AIN to help direct management. We also discuss new drugs associated with AIN (in particular new anticancer drugs) and unusual forms including granulomatous AIN. Finally, we discuss the opportunities for future research and how this may impact clinical practice.

**Keywords:** acute interstitial nephritis, acute kidney injury, laboratory markers, renal biopsy

## INTRODUCTION

Acute interstitial nephritis (AIN) was first appreciated as a significant cause of acute kidney injury (AKI) in the 1960s [1], although the disease had been described long before by Baldwin *et al.* after antibiotic use [2]. Some 50 years later, two articles in this issue of *Clinical Kidney Journal (CKJ)* highlight interesting aspects of AIN. Nussbaum and Perazella provide a well-written clinical update of AIN and aim to dispel some myths around the condition that are often deeply ingrained in renal 'folklore' [3]. Their article is a great opportunity to reflect on clinical features, urinary and laboratory findings and diagnostic pitfalls. Also in this issue, Wendt *et al.* [4] provide interesting single-centre data on prognostic factors obtained from renal biopsies in AIN. Their article is an opportunity to review the role of renal biopsy, appreciate the discussion around steroid treatment and consider prognostic indicators in renal biopsies. Concurrent to Baldwin *et al.*'s 1968 paper, American blues singer Nina Simone (1933–2003) published her single 'Ain't got no/I got life', which contrasts conflict in the singer's life with positive achievements. In this editorial, we aim to put both studies into perspective, highlight recent advances and reflect on current controversies around AIN.

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## AIN't got no perfect tools: clinical features, tests and time-honoured myths

Ian Councilman first described infection-associated AIN in 1898 in children with diphtheria and scarlet fever [2]. With increased antimicrobial use, drugs rather than infections have now become the predominant cause for AIN. Antibiotics, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) continue to top the list [1, 5–9]. In this issue of *CKJ*, Nussbaum and Perazella [3] provide a timely reminder of the difficulties clinicians face in diagnosing AIN and also address some time-honoured myths regarding clinical and laboratory features of the disease. One of the main strengths of this article is that the authors systematically evaluate the known urinary and serum biomarkers that may be associated with AIN and report on the findings from the literature that support or refute their use in clinical practice. They emphasize that AIN can occur days to months after exposure to the offending drug and also the fact that a rash and other systemic symptoms are often absent.

Furthermore, they note that urinalysis does not help that much in decision making, with as many as 20% of patients with AIN having bland urinary sediment. Even peripheral eosinophilia, the most time-honoured laboratory clue to AIN, may only be present in a quarter of patients. Nussbaum and Perazella also make the point that the degree of proteinuria can be misleading, for example, if there is pre-existing glomerular damage or use of drugs that may result in both AIN and glomerular lesions, such as NSAIDs or the new immune checkpoint inhibitors. Recent interest in urinary markers of transplant rejection [10] and in urinary proteomics, in general, may lead to interesting new urinary markers of AIN and improved methodology. Zhao *et al.* [11] described soluble C5b-9 as a promising urinary marker, whereas a study by Moledina *et al.* [12] looked at urinary testing of the T-cell-derived cytokines tumour necrosis factor α and interleukin 9 to aid pre-biopsy diagnosis of AIN. These results are interesting and thought-provoking but require confirmation.

It is likely that clinicians overlook some cases of mild AIN and ascribe deterioration of kidney function to other factors, such as hypovolaemia or natural progression of chronic kidney disease (CKD). The emerging evidence that links PPI use with CKD adds further to these concerns [13, 14]. This is further compounded by the increasing trend for polypharmacy in an ageing population [15], which makes identification of the offending drug even more challenging. We would also suggest that knowledge of AIN in a primary care setting is much less established than, for example, the risk of hyperkalaemia with blockage of the renin–angiotensin–aldosterone system. Perhaps the renal community could do more to educate primary care providers about AIN and also take on polypharmacy as a public health (and renal) problem.

## AIN't got no scoring system: renal biopsy and prognostic factors

Given the pitfalls in clinical diagnosis, Nussbaum and Perazella emphasize the role of renal biopsy to establish the diagnosis, depict the severity and chronicity of the inflammatory lesions and help with prognosis. Also in this issue of *CKJ*, Wendt *et al.* [4] report single-centre biopsy data on AIN with a focus on prognosis for renal recovery. They emphasize a significant number of patients requiring temporary or permanent renal replacement therapy and suggest that nephrologists should regard AIN as a renal emergency akin to crescentic glomerulonephritis. This contrasts with a previous case series involving 133 patients that found only 12% of steroid-treated drug-induced AIN showed no recovery of renal function at 6 months post-biopsy [16] and another case series of 60 patients in which only 3.3% were dialysis dependent at 12 months [17]. Such differences may represent different attitudes to renal biopsy, structural differences in the provision of renal care or other factors.

Another interesting finding in their study [4] relates to a trend for worse outcomes with AIN associated with PPI, which the authors suggest may be due to lack of awareness. It is also interesting that angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers were the predominant offending medications in their cohort [4], which is at odds with other studies that identified antibiotics, NSAIDs and PPIs as common offenders [6, 9]. Again different attitudes towards biopsy, different provision of renal care and differences in prescribing patterns may be responsible.

In the study of Wendt *et al.*, patients achieving complete or partial recovery had a better baseline creatinine when compared with those achieving no recovery. Patients who had acute inflammatory infiltrates and without cortical scars were more likely to recover renal function. They also noted a lower probability of recovery with steroid treatment. Most of the evidence for benefit with steroid treatment is from retrospective observations, with some showing benefits [6, 8, 18] with treatment and the others suggesting no benefit [5, 17]. Early withdrawal of the offending drug remains an important step in treatment, but whether early steroid treatment prevents irreversible fibrosis is yet to be established. In their seminal study of 1068 patients, Schwarz *et al.* [19] noted that > 1-month intake of the suspected drug, few or no symptoms at presentation, extensive interstitial inflammation and tubular atrophy all indicated poor recovery. These findings underscore the importance of performing a biopsy whenever possible.

One of the strengths of the paper by Wendt *et al.* is that it attempts to provide prognostic information for patients with AIN, something that has been difficult to ascertain to date. Determining which patients are likely to recover renal function compared with those patients who will end up requiring long-term renal replacement therapy remains elusive. They offer some clues as to how we may overcome this problem. However, we should also take into consideration the limitations of their work as a single-centre retrospective study that identified only 39 full data sets over a 20–year period. Clearly, a larger sample size would provide more robust evidence, but this will remain a challenge to deliver in a single-centre setting. A registry of AIN with clinical and biopsy data and outcomes could provide more answers in this regard. It might also help to find out whether the renal prognosis differs for various causative drugs.

Wendt *et al.* also suggest a potential role in the development of a histopathological scoring system to help predict the likelihood of renal recovery in patients with AIN. They have scored those biopsies with active inflammation as 'highly active' and those with no acute inflammation but only chronic lesions as 'no activity'. Their point is well made given that histopathological scores are now in widespread use in other renal disorders such as immunoglobulin A (IgA) nephropathy [20], where the decisions around immunosuppression and prognosis are equally difficult. Ramachandran *et al.* [21] worked on a scoring system for AIN using the severity of interstitial oedema, the degree of interstitial infiltrate and tubular damage and reported that patients with neutrophil infiltration showed a good response to steroid treatment. It is worth noting that scoring of

interstitial disease has been attempted in glomerular disorders since tubulointerstitial disease is a risk factor for disease progression independent of the severity of the glomerular disease. Hsieh *et al.* [22] described a scoring system for interstitial inflammation in lupus nephritis using CD45 staining. In IgA nephropathy, Rankin *et al.* [23] demonstrated a unique method of scoring tubulointerstitial inflammation in the non-atrophic cortex. They demonstrated that >10% active inflammation in the tubulointerstitium of the viable cortex is independently associated with renal outcome. We agree with Wendt *et al.* and suggest that there is indeed a need for a scoring system for AIN. Based on the available evidence, such a scoring system would have to include information on the extent and cell phenotype of the interstitial infiltrate, oedema, chronic changes and fibrosis and perhaps also on concomitant glomerular damage.

## AIN't got no histology: the patient who cannot be biopsied and empirical steroid treatment

Drug-induced AKI appears to be on the rise, particularly in elderly patients. Renal biopsy has been shown to be safe in this group [24], although Hogan *et al.* [25] noted increased bleeding risks with larger needle size, older patients with high serum creatinine and higher systolic BP. However, in the real world, for some elderly patients, especially those with multiple comorbidities, a renal biopsy will be contraindicated or at the very least associated with substantial risk. Examples include patients with a solitary kidney, those with clotting disorders or on therapeutic anticoagulation or the patient with longs-tanding CKD. The latter is particularly relevant when an ultrasound shows significant signs of chronicity. Some patients simply decline biopsy. It is therefore worth discussing what to do when biopsy is contraindicated, associated with high risk or otherwise undesirable.

While pointing out renal biopsy is the gold standard, Wendt *et al.* [4] also acknowledge that a biopsy may not be possible for all patients or even necessary; for example, if there is only mild AKI and full recovery after stopping potentially offending medication. They also suggest empirical steroid therapy if a biopsy cannot be performed and if there is no contraindication to such therapy and suspicion of AIN is high. Of note, previous standard practice has been to rapidly taper steroids over 4–6 weeks, while Wendt *et al.* [4] suggest a 2-week high-dose course only and advise against the use of intravenous methylprednisolone, which is still widely used and recommended. Robust evidence on this topic is currently lacking and a trial comparing different steroid regimens for AIN could provide answers in this regard. This problem is further compounded by the fact that among patients who cannot be biopsied, many are not ideal candidates for empirical steroid treatment either. Good examples are patients with suspected AIN due to recent antibiotic use for severe infection, poorly controlled diabetes or those with recent high-dose treatment with PPIs for acute gastrointestinal bleeding.

For now, the correct approach to the patient who cannot be biopsied remains unclear, particularly when empirical steroid treatment appears unattractive. Many clinicians will advocate a cautious strategy and stop or replace potentially offending medication first, followed by watchful waiting. However, in adopting such an approach, one needs to be mindful of the fact that delay between identification of AIN and initiation of steroids correlates with non-recovery [6]. Watchful waiting may thus appear intuitively the safer option, but on closer inspection may not be. One should not lose sight of the fact that in severe AKI with no signs of recovery after stopping potentially offending medications, very few patients will have an absolute contraindication for a biopsy. Renal biopsy may require additional precautions, a more experienced operator or perhaps help from an interventional radiologist. In our experience, kidney function will often improve without intervention, but we acknowledge that others may be more aggressive in their approach and suggest early use of steroids if there is a high degree of clinical suspicion. We emphasize a careful individualistic approach taking into consideration each patient and the risks versus benefits. Involving the patient in decision making may also be possible and clinicians should be open about explaining the risks of each approach. Ultimately, only further studies comparing early steroid treatment with a more cautious approach with cessation of potentially offending drugs will provide an answer to this question.

## AIN't seen one like this before: new drugs, unusual histological patterns and infectious causes

Causes of AIN are a favourite topic during teaching and ward rounds and most trainees will soon recall the 'usual suspects' (Table 1). More recently, several new substances have entered this field, particularly in our evolving subspecialty of 'onco-nephrology' [26]. Of note, these drugs are too new to feature in Wendt *et al.*'s article [4] or in recent other large series. Improved pharmacovigilance would be another advantage with national or international registries of AIN. Immune checkpoint inhibitors can cause AIN [27] (Figure 1) as part of the spectrum of newly recognized immune-related adverse events associated with these medications, sometimes with unusual features [28]. Izzedine *et al.* [29] described 12 patients with AKI following exposure to pembrolizumab and found AIN in 4. Mamlouk *et al.* [30], in a similar series, emphasized concomitant glomerular pathology. It is also interesting to note that AIN may occur as late as 56 weeks after initial exposure to these drugs [30]—a nice reminder that timing can be very variable with AIN [3]. It has been suggested that oncologists sometimes rush into stopping immune checkpoint inhibitors and start steroid treatment without exploring alternative causes of AKI [28]. An algorithm for such patients has been suggested [28], mainly to allow patients to continue potentially crucial treatment but also to avoid unnecessary steroid exposure in patients who do not actually have AIN. In our experience, interaction with nephrologists often occurs late in these patients and some of them are approaching de-escalation of treatment or palliative care. As a result, discussing biopsy and treatment is often difficult and requires time, pragmatism and realistic expectations on all sides. Other new substances used in cancer chemotherapy can also cause AIN, again with unusual presentations and histological patterns. Pemetrexed is a new antifolate drug used in lung cancer and mesothelioma. Zattera *et al.* [31] reported two cases and reviewed the literature: among 13 reported patients, 4 required dialysis, and the pattern reported in renal biopsies included significant oedema and chronic damage [31]. Several caveats apply whenever AIN is described in patients with cancer undergoing such new treatments. First, there may be significant underreporting in particular for cases without a renal biopsy. Second, as with immune checkpoint inhibitors, in our experience most if not all of these patients will be on other medications that are capable of causing AIN, most notably PPIs and allopurinol, as well as recurrent courses of antibiotics as a consequence of immunosuppression. Causality is therefore very difficult to ascertain.

**Table 1. Unmet research needs in AIN**

| Research Need | Description |
|---|---|
| Is there a urinary biomarker that can accurately predict AIN in the absence of a renal biopsy? | An accurate urinary biomarker would be highly useful in the clinical setting, particularly when biopsy is impossible or risky. It might also help detect more cases of AIN. There is early experience with novel urinary biomarkers [10], but further work is needed to determine whether such biomarkers can be used in the clinical setting. |
| Is there a role for a scoring system for AIN? | Wendt *et al.* [4] argue that histological findings, such as acuity or chronicity of the inflammation and the presence of cortical scars, carry prognostic information. Scoring systems are well established in other renal conditions, for example, in IgA nephropathy. Developing a scoring system for AIN would require collaboration between nephrologists and pathologists, followed by studies to assess methodology and utility in clinical practice. |
| What is the role for corticosteroids in the treatment of AIN? | Previous studies may be confounded by the fact that patients who are given steroids could have a more aggressive form of AIN that is less amenable to therapy. A multicentre prospective randomized double-blind controlled trial would help to answer this question. |
| What is the optimum steroid regimen for AIN? | A randomized trial comparing different doses and durations of steroid treatment would help answer this question. |
| How can multicentre data be generated? | Most of the evidence in relation to AIN comes from case reports and series, usually from a single centre. National or international registries of new AIN cases (to include likely cause, biopsy findings, therapy received and renal outcomes) would allow for much larger-scale research to help address some of the questions that remain. This approach would also help with pharmacovigilance: identifying new drugs causing AIN. |

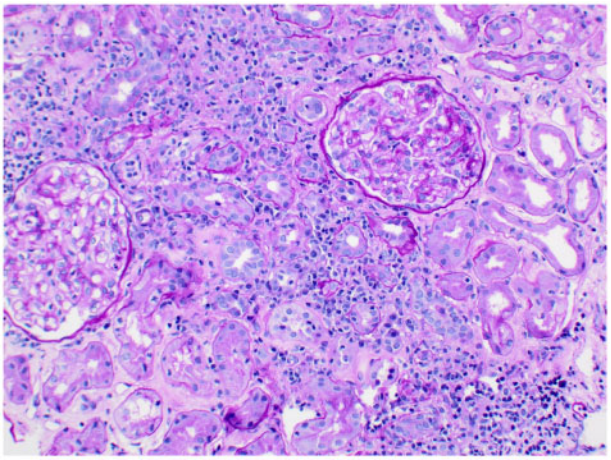

**FIGURE 1:** AIN associated with pembrolizumab in a 72-year-old patient with squamous cell lung cancer. Renal biopsy, ×250 magnification, haematoxylin and eosin stain. With permission from Dr Beena Nair, Consultant Pathologist, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK.

Recent years have also improved our knowledge of a number of some unusual forms of AIN. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a hypersensitivity reaction most commonly caused by allopurinol and anti-epileptic drugs that results in a severe erythematous skin eruption and can lead to end-organ involvement including AIN [32]. It is generally managed with withdrawal of the causative drug and steroids if required, and usually has a good prognosis. IgG4 disease is a systemic condition characterized by multiorgan infiltrates rich in IgG4 plasma cells, including the kidney [33]. Serological tests include elevated IgG, IgG4 and IgE, as well as low complement. Our knowledge of IgG4 disease is still evolving, but it is usually managed with steroids initially and may require long-term steroid-sparing agents.

Another unusual form of AIN is its granulomatous variant (GIN). In a 2015 editorial for *CKJ*, GIN was described as 'a chameleon in a globalised world' [34]. It has become clear that from a worldwide perspective, infectious diseases are a leading cause of GIN, most notably tuberculosis and human immunodeficiency virus. A whole variety of other pathogens, such as *Cryptococcus*, also need to be considered in GIN. Interestingly, GIN also occurs in renal transplantation [35]. The topic of AIN in transplants is beyond the scope of this editorial; however, contrary to another widely held myth, AIN does occur in transplanted kidneys [3] and is often linked to trimethoprim–sulphamethoxazole and NSAIDs [36]. The differential diagnosis between AIN and acute rejection remains difficult and multiple infectious aetiologies, such as polyoma [37], need to be considered. Polyomavirus infection [37] is also a good example of a clinical scenario where viral infection, AIN and rejection may coexist. Often the immunosuppression is reduced when viraemia is diagnosed and by the time of biopsy, it can be difficult to differentiate between infection and rejection, as both may be present. The same is true for adenovirus infection [38, 39]. Taken together, these reports should be seen as a cautionary note to clinicians when considering steroid bolus treatment following a preliminary transplant biopsy report of a tubulointerstitial infiltrate.

## CONCLUSION

Nina Simone's hit, which was released on her album 'Nuff said' in the same year of Baldwin *et al.*'s seminal article, is all about appreciating what one has, as opposed to bemoaning what one does not. As for AIN, we have a much better understanding of the condition and our biopsy sessions are also considerably less stressful than those undertaken by our forefathers in the 1960s. However, in the real world of inpatient nephrology, significant problems remain: some patients cannot have a biopsy and some of those patients also tend to be less than ideal candidates for empirical steroid treatment. The two articles on AIN in this issue of *CKJ* provide useful guidance for clinicians and interesting findings from biopsy data but, as with all good research, more questions remain. We have taken the opportunity to take stock, reflect and highlight research needs (see Table 1). As in Nina Simone's song, appreciating the complexity but also celebrating what we have learned seems a very reasonable way forward.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES


1. Baldwin DS, Levine BB, McCluskey RT *et al*. Renal failure and interstitial nephritis due to penicillin and methicillin. *N Engl J Med* 1968; 279: 1245–1252
2. Councilman WT. Acute interstitial nephritis. *J Boston Soc Med Sci* 1898; 2: 189–192
3. Nussbaum E, Perazella MA. Diagnosing acute interstitial nephritis: considerations for clinicians. *Clin Kidney J* 2019. doi: 10.1093/ckj/sfz080
4. Wendt R, Schliecker J, Beige J. Inflammatory leukocyte infiltrates are associated with recovery in biopsy proven Acute Interstitial Nephritis. A 20 year registry-based case-series. *Clin Kidney J* 2019. doi: 10.1093/ckj/sfz097
5. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. *Nephrol Dial Transplant* 2004; 19: 8–11
6. Gonzalez E, Gutierrez E, Galeano C *et al*. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int* 2008; 73: 940–946
7. Praga M, Sevillano A, Auñón P *et al*. Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. *Nephrol Dial Transplant* 2015; 30: 1472–1479
8. Prendecki M, Tanna A, Salama AD *et al*. Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids. *Clin Kidney J* 2017; 10: 233–239
9. Valluri A, Hetherington L, McQuarrie E *et al*. Acute tubulointerstitial nephritis in Scotland. *QJM* 2015; 108: 527–532
10. Lim JH, Lee CH, Kim KY *et al*. Novel urinary exosomal biomarkers of acute T cell-mediated rejection in kidney transplant recipients: a cross-sectional study. *PLoS One* 2018; 13: e0204204
11. Zhao WT, Huang JW, Sun PP *et al*. Diagnostic roles of urinary kidney injury molecule 1 and soluble C5b-9 in acute tubulointerstitial nephritis. *Am J Physiol Renal Physiol* 2019; 317: F584–F592
12. Moledina DG, Wilson FP, Pober JS *et al*. Urine TNF-$\alpha$ and IL-9 for clinical diagnosis of acute interstitial nephritis. *JCI Insight* 2019; 4: e127456
13. Xie Y, Bowe B, Li T *et al*. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2016; 27: 3153–3163
14. Lazarus B, Chen Y, Wilson FP *et al*. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016; 176: 238–246
15. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and deprescribing. *Am Fam Phys* 2019; 100: 32–38
16. Muriithi AK, Leung N, Valeri AM *et al*. Biopsy-proven acute interstitial nephritis, 1993–2011: a case series. *Am J Kidney Dis* 2014; 64: 558–566
17. Clarkson MR. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. *Nephrol Dial Transplant* 2004; 19: 2778–2783
18. Muriithi AK, Leung N, Valeri AM *et al*. Clinical characteristics, causes and outcomes of acute interstitial nephritis in the elderly. *Kidney Int* 2015; 87: 458–464
19. Schwarz A, Krause PH, Kunzendorf U *et al*. The outcome of acute interstitial nephritis: risk factors for the transition from acute to chronic interstitial nephritis. *Clin Nephrol* 2000; 54: 179–190
20. Coppo R, D'Arrigo G, Tripepi G *et al*. Is there long-term value of pathology scoring in immunoglobulin A nephropathy? A validation study of the Oxford Classification for IgA Nephropathy (VALIGA) update. *Nephrol Dial Transplant* 2018. https://doi.org/10.1093/ndt/gfy302
21. Ramachandran R, Kumar K, Nada R *et al*. Drug-induced acute interstitial nephritis: a clinicopathological study and comparative trial of steroid regimens. *Indian J Nephrol* 2015; 25: 281–286
22. Hsieh C, Chang A, Brandt D *et al*. Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. *Arthritis Care Res (Hoboken)* 2011; 63: 865–874
23. Rankin AJ, Kipgen D, Geddes CC *et al*. Assessment of active tubulointerstitial nephritis in non-scarred renal cortex improves prediction of renal outcomes in patients with IgA nephropathy. *Clin Kidney J* 2019; 12: 348–354
24. Tugcu M, Kasapoglu U, Sahin G *et al*. Evaluation of kidney biopsies in elderly patients. *Int Urol Nephrol* 2019; 51: 869–874
25. Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol* 2016; 11: 354–362
26. Cosmai L, Porta C, Gallieni M *et al*. Onco-nephrology: a decalogue. *Nephrol Dial Transplant* 2016; 31: 515–519
27. Manohar S, Albright RC Jr. Interstitial nephritis in immune checkpoint inhibitor therapy. *Kidney Int* 2019; 96: 252
28. Perazella MA, Sprangers B. AKI in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol* 2019; 14: 1077–1079
29. Izzedine H, Mateus C, Boutros C *et al*. Renal effects of immune checkpoint inhibitors. *Nephrol Dial Transplant* 2017; 32: 936–942
30. Mamlouk O, Selamet U, Machado S *et al*. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *J Immunother Cancer* 2019; 7: 2
31. Zattera T, Londrino F, Trezzi M *et al*. Pemetrexed-induced acute kidney failure following irreversible renal damage: two case reports and literature review. *J Nephropathol* 2016; 6: 43–48
32. Esposito AJ, Murphy RC, Toukatly MN *et al*. Acute kidney injury in allopurinol-induced DRESS syndrome: a case report of concurrent tubulointerstitial nephritis and kidney-limited necrotizing vasculitis. *Clin Nephrol* 2017; 87: 316–319
33. Pradhan D, Pattnaik N, Silowash R *et al*. IgG4-related kidney disease – a review. *Pathol Res Pract* 2015; 211: 707–711
34. Aleckovic-Halilovic M, Nel D, Woywodt A. Granulomatous interstitial nephritis: a chameleon in a globalized world. *Clin Kidney J* 2015; 8: 511
35. Farris AB, Ellis CL, Rogers TE *et al*. Renal allograft granulomatous interstitial nephritis: observations of an uncommon injury pattern in 22 transplant recipients. *Clin Kidney J* 2017; 10: 240–248
36. Woywodt A, Schwarz A, Mengel M *et al*. Nephrotoxicity of selective COX-2 inhibitors. *J Rheumatol* 2001; 28: 2133–2135
37. Zhang Y, Ahmed H, Haririan A *et al*. Granulomatous inflammation in BK polyomavirus-associated nephropathy. *Transpl Infect Dis* 2018; 20: e12939
38. Veer M, Abdulmassih R, Como J *et al*. Adenoviral nephritis in a renal transplant recipient: case report and literature review. *Transpl Infect Dis* 2017; 19: e12716
39. Storsley L, Gibson IW. Adenovirus interstitial nephritis and rejection in an allograft. *J Am Soc Nephrol* 2011; 22: 1423–1427