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Acute kidney injury changes with the seasons

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Many diseases and numerous physiological processes display significant variation throughout the seasons of the year. In temperate climates, it is well recognized that sepsis [1, 2], pneumonia [3], heart failure [4, 5], acute myocardial infarction [6] and sudden cardiac death [7] are all more common in winter, alongside seasonal surges in influenza and viral respiratory infections. There are a multitude of other phenomena associated with winter, such as higher haemoglobin A1c levels in patients with diabetes [8], Anti–neutrophil cytoplasmic antibody-associated vasculitis is diagnosed more frequently [9] and exacerbations of inflammatory bowel disease are seen more often [10]. Examples of seasonal physiological changes include those seen in vitamin D, cortisol, fibrinogen and factor VII levels, and colder temperatures have been shown to result in increased sympathetic activity, higher vascular tone and elevations in blood pressure [11–13]. Within these broad trends there are further more subtle patterns. For example, despite a higher incidence of sepsis in winter, *Escherichia coli* bloodstream infection is more common in summer months, as are hypoglycaemic episodes in type 1 diabetes and new diagnoses of Crohn's disease [8, 10, 14]. With such a broad range of conditions displaying seasonal variation, it is surprising that there have been so few reports pertaining to acute kidney injury (AKI). It is certainly possible to make a coherent hypothesis that seasonal changes in AKI epidemiology occur due to the well-recognized winter increases of many of the conditions that precipitate AKI. In parallel, there has been growing interest in the effect of warmer temperatures and heat stress as causative factors for AKI [15].

In this issue of *Nephrology Dialysis Transplantation*, Iwagami *et al.* [16] report the epidemiology of AKI across the different seasons of the year in Japan, a country with temperate climate and seasonal patterns of temperature and rainfall. Using a large administrative database covering 38 community hospitals, the incidence and outcomes of AKI were retrospectively determined for each month of the year from a cohort of >550 000 patients. AKI, which occurred in 14.6% of admissions (81 279 AKI episodes), was suitably defined using the serum creatinine component of the Kidney Disease: Improving Global Outcomes criteria. Pre-specified analyses compared hospital versus community-acquired AKI, as well as examining the effects of age and primary diagnosis categories. Results showed a clear increase in the crude incidence and mortality of AKI in winter, with levels peaking in January. Both absolute numbers of AKI and the percentage of admissions with AKI rose. The severity of AKI and of overall illness (defined by the number of organ failures) were both higher in winter, and a higher rate of renal replacement therapy for AKI was observed. There were also a number of other interesting findings. The seasonal pattern of AKI was predominantly seen in community-acquired AKI (AKI present on the first day of admission), with a progressive attenuation of effect with increasing time between admission date and onset of AKI. The effect of season was also more pronounced in admissions that had either a respiratory or cardiovascular primary diagnosis and was more marked in the elderly. From this, the authors quite reasonably speculate that the well-recognized seasonal changes of cardiorespiratory disease in the general population, particularly in more vulnerable groups such as the elderly, could explain the majority of the changes in seasonal AKI rates and outcomes. This held true particularly for AKI-associated mortality, as the seasonal effect disappeared in fully adjusted models that accounted for other significant factors including primary diagnosis and presence of sepsis. This was in contrast to the seasonal pattern of AKI incidence that persisted even after adjustment for co-factors, albeit with attenuation of effect size. This suggests the existence of additional factors that contribute to an increase in rates of AKI in winter; these may reflect methodological factors (e.g. a lack of granularity of patient-level data in an administrative database resulting in unmeasured confounders) or possibly alternative environmental factors. As a counter to the latter, a recent study found only a small, non-significant association between a decrease in daily mean temperature and AKI-related hospitalization during the cold season [15].

The results from the current study are consistent with the only other published data looking at AKI seasonality in temperate climates [17]. Phillips *et al.* [17] used the national AKI database in Wales to study trends over a single calendar year, with comparisons made between 3-month quarters; 48 457 AKI

episodes were included that had been identified using a standardized, validated detection algorithm. Similar patterns were observed with the highest levels of AKI and mortality in the period January–March. This study included AKI episodes in patients in primary care (some of whom were not admitted to hospital) who also demonstrated the same trends. In contrast to the study by Iwagami *et al.* [16], seasonal changes were seen in hospital-acquired AKI, although the definition of hospital-acquired AKI differed between the two studies. The authors reached the same conclusions that seasonal changes in the underlying diseases that precipitate AKI were the most likely explanation for their observations.

In parallel, associations between heat stress in tropical climates and the risk of AKI are increasingly reported [18–28]. A number of publications, focusing not only on sugarcane workers in Central America (so-called Meso-American nephropathy), but also incorporating Sri Lanka, areas of India, Thailand and Cameroon, have linked excessive elevations in chronic kidney disease (CKD) rates in young agricultural workers with exposure to environmental and occupational heat stress [18–28]. The proposed mechanism is that recurrent episodes of AKI due to hypovolaemia lead to CKD, which is supported by biochemical evidence of work-related AKI episodes detected at the end of shifts and elevations in kidney injury biomarkers [23, 28]. The risk of CKD also varies depending on job type (being greatest in those with prolonged exposure to high temperatures and most demanding physical work) and is lower in those using electrolyte rehydration solutions and in workers from cooler, more mountainous areas [22, 23, 29]. Although it appears the most likely explanation, it should be noted that a causal relationship between heat stress, dehydration, AKI and progressive CKD has not yet been definitively proven [30].

High environmental temperatures may also be relevant in countries further away from the equator. Recent studies from Ontario, Canada and Seoul, Korea have reported increases in the risk of AKI-associated hospitalization during hotter, summer periods [15, 31]. Both studies retrospectively analysed administrative databases and defined AKI using *International Classification of Diseases* diagnosis codes; both regions are similar in their humid continental climates, with four distinct seasons characterized by warm, humid summers (with temperatures that can exceed 30°C) and cold winters. The Canadian study focused on the elderly and reported a change in AKI rates during heat periods, defined as temperatures that were >95th centile of daily maximum temperature that persisted for ≥3 days [31]. During such heat periods, the odds of hospitalization with AKI were increased, but with borderline statistical significance [odds ratio 1.11 (95% confidence interval 1.00–1.23); $P = 0.05$]. Results did not differ between the 66–79 and ≥79 years age groups. The Korean study included all ages and reported an exponential increase in the risk of AKI once temperatures exceeded a break point of 28.8°C, with a striking 23% increase in AKI-associated admissions for each 1°C increase in mean temperature above this. The effect was particularly marked in male patients with hypertension.

So, how best to collate these observations? First, it should be stated that the effect of season on AKI incidence and outcomes is understudied, so recent publications, including the study by Iwagami *et al.* [16], are to be commended. Even though the current evidence base is small, there is a clear signal that season does impact the epidemiology of AKI, with effects seen both in winter months and during hot spells during summer. It is also clear that seasonal effects will therefore vary between regions depending on the local climate type. The most important immediate effect of these data are to inform the design and analysis plans of future AKI research, as seasonal change may be a potential source of variation in epidemiological and interventional studies that will need to be accounted for. This also has relevance to quality improvement work, particularly when using a time series 'before-and-after' design that would necessitate a balanced representation of season in baseline and post-interventional data collection periods.

Following this, however, a large knowledge gap exists. While seasonal trends in AKI incidence and outcomes may exist, it does not necessarily follow that such trends are preventable. Indeed, across all disease areas, other than seasonal vaccination (which is not entirely free of debate regarding its effectiveness [32, 33]), there are few successful interventions that have targeted seasonal variation. It is certainly possible to speculate about potential interventions for AKI, including better planning of health care resources in winter time; specific strategies to target variation in standards of care at times of high demand; community-based, wintertime AKI prevention in patients with chronic cardiorespiratory disease; increasing the uptake of influenza and pneumococcal vaccines or alternative strategies to increase their effectiveness; or public health initiatives to reduce dehydration during periods of extreme heat. Preventing or treating dehydration more effectively, which intuitively may seem more viable that other potential interventions, could also apply to occupational heat stress (e.g. Meso-American nephropathy or military training) or to recreational heat stress (e.g. endurance sports such as marathon running) [34, 35]. However, current knowledge of AKI seasonality arises solely from retrospective analyses of large databases, which come with the inherent methodological weaknesses of this approach. These include an inability to determine causality in associations and potential risks from unmeasured confounders. Before we get to the point at which potential interventions can be tested, there is a strong need for additional studies that will better inform the aetiology and mechanisms of AKI at different times of the year and how patterns may differ between regions with distinct climate types. Only then can we make an assessment as to the biological plausibility of potential interventions and make informed decisions as to whether any should be taken forward into clinical studies or evaluation within service improvement projects.

In conclusion, there is still much that we need to understand about seasonal trends in the epidemiology of AKI, although recent studies, including that by Iwagami *et al.* [16], have shone a much needed light on this area. At present, results are sufficient to say that seasonality should be given greater consideration in the design of future AKI research and quality improvement studies. However, there are several steps that will need to be taken before we can ascertain if feasible areas for intervention

will materialize, and it is likely that we will see the passage of a number of seasons before we arrive at that point.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Iwagami *et al*. Seasonality of acute kidney injury incidence and mortality among hospitalized patients. *Nephrol Dial Transplant* 2018; 33: 1354–1362)

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