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Timing of renal replacement therapy in acute kidney injury

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Timing of renal replacement therapy in acute kidney injury: case closed?

Acute kidney injury is a common syndrome defined by an acute deterioration in renal function, and affects a wide variety of patients. It encompasses a heterogeneous group of underlying causes and thereby variable pathophysiological processes.¹ In high-income countries, acute kidney injury is frequently associated with multiple organ failure, as well as sepsis, use of nephrotoxic drugs, and major surgery. In low-income and middle-income countries (LMICs), however, it is more likely to be associated with a single disease.² Among community-dwelling patients in LMICs, acute kidney injury is often associated with environmental factors such as endemic infections or contaminated water, whereas in inpatients, the aetiology resembles that among patients in high-income countries.² Although the exact worldwide incidence and prevalence of acute kidney injury are uncertain because of variability in reporting systems (eg, the Risk, Injury, Failure, Loss, and End-stage renal disease criteria, the Acute Kidney Injury Network criteria, or the Kidney Disease: Improving Global Outcomes [KDIGO] criteria), absence of baseline serum creatinine concentration data, or non-availability of data (especially in LMICs), acute kidney injury is estimated to occur in 10–15% of all hospitalised patients, increasing to 50% in those admitted to intensive care units.^{3–5}

Acute kidney injury is associated with increased morbidity, mortality, and costs of care, not only as a consequence of impaired renal function but

also because of remote tissue injury caused by the generalised inflammatory response induced by the syndrome. Hospital mortality rates vary from 10% to 20%, and correlate strongly with the severity of renal dysfunction.^{6–8} In addition, acute kidney injury is associated with development of chronic kidney disease and negatively influences long-term outcomes and survival for up to 10 years after the primary insult.^{8,9} It is imperative that, where possible, acute kidney injury is prevented, the diagnosis is made swiftly and correctly, and the treatment is initiated at an early stage. If the syndrome proceeds, renal replacement therapy (RRT), in the form of continuous venovenous haemofiltration, haemodialysis, or haemofiltration, might be indicated to correct life-threatening complications such as fluid, acid-base, and electrolyte imbalances. In everyday practice, the decision to start RRT is frequently more arbitrary, as physicians consider the overall clinical context of the patient. The optimal timing of RRT initiation in the absence of these complications is therefore a subject of ongoing debate and is not known.^{10,11}

In *The Lancet*, Stéphane Gaudry and colleagues¹² report the results of an individual patient data meta-analysis addressing this important topic. Data from randomised clinical trials published between 2008 and 2019 were included if they compared delayed with early initiation of RRT in critically ill patients with acute kidney injury of KDIGO stage 2 or 3. The primary outcome was

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28-day all-cause mortality. From the ten eligible studies (2143 patients), individual patient data were obtained from the investigators of nine studies, and the final analysis was done with data from 1879 (88%) patients: 946 in the delayed RRT group (609 [64%] men, 337 [36%] women; mean age 64.3 years [SD 15.9]) and 933 in the early RRT group (591 [63%] men, 342 [37%] women; 63.5 years [15.4]). Mortality at day 28 after randomisation (the primary outcome) was not significantly different between the delayed RRT group (366 [44%] of 837 patients with available data) and the early RRT group (355 [43%] of 827; risk ratio 1.01 [95% CI 0.91–1.13]), and nor was the 60-day or 90-day mortality. Gaudry and colleagues concluded that the timing of RRT did not affect survival in critically ill patients with severe acute kidney injury who had no urgent indications for RRT. No significant interactions were found between baseline characteristics (including age and sex) and treatment effect.

This well designed study involved data from almost all relevant randomised clinical trials from the past decade, including a representative group of patients with various pathophysiological mechanisms underlying acute kidney injury. The authors should be congratulated for this achievement and the worldwide collaboration that facilitated this analysis.

One limitation of the study is that, as the authors indicated, the definitions of early and delayed initiation of RRT varied among the included studies. Additionally, the studies differed in the type and dosage of RRT administered. Nevertheless, minimal heterogeneity was found across the studies, and the use of individual patient data is a particular strength here.

In the subgroup analysis, no difference in outcome was found between patients with and without pre-existing chronic kidney disease. However, more data are needed to clarify the potential differences in the effects of RRT timing between different patient subgroups. The STARRT-AKI trial of more than 3000 patients, the results of which are yet to be published, should provide sufficient power for subgroup analyses, including comparisons among patients with and without sepsis, and should also provide useful information on long-term quality of life in this population.¹³

Although Gaudry and colleagues did not find differences in complication rates between groups, it is possible that complications related to the early start of RRT might

have been under-reported. These results contrast with those of a previous Cochrane meta-analysis, in which more complications were found in the early RRT group.¹⁴ Additionally, Gaudry and colleagues reported that 42% of patients in the delayed group never received RRT, which could have the advantage of allowing scarce resources to be saved. Unfortunately, this meta-analysis showed no significant increase in RRT-free days in the delayed group compared with the early group, although the authors note that this lack of difference might have been due to a methodological issue.

Overall, this meta-analysis shows that early initiation of RRT is not associated with improved outcome, and seems to support a delayed initiation strategy in critically ill patients, on the basis that a delay might avoid the need for any RRT in these patients.

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The key role of palliative care in response to the COVID-19 tsunami of suffering

Coronavirus disease 2019 (COVID-19) has brought a tsunami of suffering that is devastating even well resourced countries. The disease has wreaked havoc on health systems and generated immense losses for families, communities, and economies, in addition to the growing death toll. Patients, caregivers, health-care providers, and health systems can benefit from the extensive knowledge of the palliative care community and by taking heed of long-standing admonitions to improve access to essential medicines, particularly opioids for the relief of breathlessness and pain.¹⁻³

For low-income and middle-income countries (LMICs), the COVID-19 pandemic is likely to be even more severe than in high-income countries. There will probably be a high burden of COVID-19 in settings where there are weak health-care systems, lack of access to clean water and disinfectants, poor outbreak preparedness, severe shortages in personal protective equipment (PPE) and medical technology, challenges in enforcing physical distancing regulations, and reliance on informal employment. In such settings, it is expected that patients with severe COVID-19 who are unable to access the limited supply of intensive care resources or hospital beds will suffer and die at home, where they would be cared for by family members without PPE and access to relevant information, training, or palliative care resources. These caregivers will probably become infected and spread the disease. Additionally, if resources are reallocated to respond to COVID-19, patients with other life-limiting conditions could find themselves pushed out of their health-care settings with reduced access to opioid medication.

During the COVID-19 pandemic, access to essential palliative care at end-of-life, including bereavement support, will be limited in the face of high demands in all countries. There will be increased isolation and suffering for palliative care patients and those who are bereaved.^{4,5} Strict physical distancing regulations to

slow disease transmission mean that patients who die from COVID-19 will usually be without loved ones by their side, who in turn will be unable to say goodbye or undertake traditional grieving rituals.^{4,6} Providers of palliative care, including private hospices, will require additional human and financial resources.

Basic palliative care training to all medical and nursing students has been the recommendation of the palliative

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Panel: Strategies to extend palliative care during and after the COVID-19 pandemic

Immediate responsiveness to adapt to pandemic parameters

Optimise cooperation and coordination

- Initiate formal and informal pathways for collective action and exchange by governments, bilateral and multilateral organisations, civil society, and the private sector based on the principle of solidarity.

Preserve continuity of care

- Ensure the availability and rational use of personal protective equipment and encourage self-care among palliative care health-care professionals and all caregivers.
- Ensure an adequate and balanced supply of opioid medication to all patients for relief of breathlessness and pain by instituting the simplified procedures of the International Narcotics Control Board.
- Conduct rapid training for all medical personnel to address additional palliative care needs of COVID-19 patients.
- Engage technology partners to equip community health workers with telehealth capabilities to virtually conduct home-based palliative care activities.
- Enable families to virtually visit and partake in health decisions with loved ones, especially at the end of life to address the almost universal fear of dying alone.

Enhance social support

- Enlist informal networks of community-based and faith-based organisations to mobilise and train a citizen volunteer workforce that is ready and able to teleconnect with patients in need of basic social support, delivering on palliative care's cornerstone feature—compassionate care.

Assess emerging needs

- Link with contact tracing activities and testing sites to collect data from the general public to better understand the social dimension of pandemic suffering.

Long-term preparedness strategies that embed palliative care into the core of medicine

- Expand all medical, nursing, social work, and community health worker curricula, as well as training of clergy, to include core palliative care competencies.
- Establish standard and resource-stratified palliative care guidelines and protocols for different stages of a pandemic and based on rapidly evolving situations and scenarios.