



Acute Kidney Injury in the Elderly: A Review.

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Abstract: The world's population is aging with proportionately larger increase at the upper extremes of age. Elderly patients not only exhibit age related renal changes and dysfunction, they also suffer from multiple comorbidities. Age related morphological changes in the kidney, functional alterations and accompanying comorbidities make elderly more vulnerable to AKI. Early diagnosis of AKI in these patients is vital as is its prevention. Awareness of the possibility of development of AKI, identifying patients at risk and its prompt recognition are keys to management of this condition. Although dialytic therapies are available and feasible in this group of patients, such supportive therapeutic modalities should not be lightly undertaken as quality of life, life expectancy and acceptable outcomes need to be carefully considered before embarking on such therapies.

Introduction: The number of human beings that inhabit this planet is rising steadily. More interestingly, the average age of this rising population is increasing due to reduced death in young and the longevity at the upper end of the age spectrum. In the UK, the proportion of those over 65



years of age has increases from 15% in 1984 to 16% in 2009, an increase of 1.7 million people¹. During the same 25 years, the largest increase has been in the 'oldest old', those 85 and above, from 660,000 in 1984 to 1.4 million in 2009. It is projected that in next 25 years, this number is expected to be 2.5 times of that in 2009 and the UK population seems to be aging faster than many other countries². In India, there has been a problem in the past in that many of her inhabitants did not know their exact dates of birth and therefore their age³. With people not living long and a high birth rate have kept India's population relatively young³ and, with a majority not being aware of their correct age, age related population comparisons have been difficult. Given these limitations, there still is evidence that there has been a steady increase in longevity (although the average varies from state to state)³ and a steady rise in over 60s population from 5.1% in 1971, to about 7% in 2001 and a projected increase to 9% of the population in 2016⁴. Thus, worldwide life expectancy is increasing exponentially and in most developed countries a sizeable portion of the population can be expected to live beyond the age of 80 years. It is suggested that the overall world population growth rate is 1.1% per year, increasing to 2.6% for the age group above 60 years and reaching 3.9% for those aged 80 years or above⁵. While these may be welcome developments in terms of improved health; an aging population gives rise to its own health problems. Thus elderly suffer from increased comorbidities, degenerative diseases as well as age related physiological decline in organ function and reserve. It, therefore, should not be surprising that in the elderly, renal function may become abnormal due to aging process itself, associated comorbidities and/or therapy for associated diseases.

The term 'elderly', not politically correct in many countries (in the UK, it has been generally replaced by the term "senior citizen"), refers to persons of advanced years in medical literature. The exact age at which a person becomes elderly is a matter of convenience rather than a physiological landmark and in Europe, the age of 65 years was arbitrarily decided upon as a 'pensionable' age by Otto von Bismarck, the German chancellor in 1880s⁶. However various cut-off points like 60, 65, 70, 75, 80 or even 85 years are used in medical literature for definitions of the elderly⁷. It should be noted that advanced age today is a subjective term rather than a precise point in one's life as chronological age does not always reflect physiological age. Thus variables like hair colour, skin elasticity etc may correlate with the chronological age; variables like lung capacity, visual acuity and hearing do not.

Acute kidney injury (AKI, formerly called acute renal failure) affects all ages. Until recently, a universally acceptable definition of AKI did not exist and therefore, its reported incidence varied from 3-30%. In recent years, Acute Dialysis Quality Initiative (ADQI) and Acute Kidney Injury Network (AKIN) have formulated pragmatic definitions of AKI (Risk, Injury, Failure, Loss and End-stage disease – RIFLE of ADQI and Stages 1,2 and 3 of AKIN)^{8,9}. Although its incidence in intensive care unit (ICU) patients can be as high as 20%, AKI occurs in about 0.7%-1% of hospitalised patients^{10,11}. Development of AKI in the critically ill is an independent factor associated with increased morbidity, ICU and hospital mortality¹².



Age related change in kidneys

Integrity of renal function has been suggested as one of the major predictors of longevity¹³. It is well recognised that there are changes in kidney morphology and function with increasing age^{14,15}. However, these changes can be difficult to isolate from changes that occur in diabetes, atherosclerosis and hypertension – the accompanying comorbidities often found in the elderly and whether or not significant changes in renal function in the elderly occur in absence of any disease is controversial¹⁵. Despite the controversies, there is compelling evidence that age does affect kidney structure and function independent of any coexisting comorbidities¹⁴. These changes are described briefly as follows:

- Changes in renal vasculature like intimal and medial hypertrophy and arteriosclerosis are seen at autopsy or renal biopsy even in absence of any notable comorbidities¹⁶. Fibrointimal hyperplasia is a common feature, is seen even in normal individuals without hypertension, is particularly evident in interlobular arteries and is almost universally present¹⁴. These changes are exaggerated in hypertension and diabetes^{14,15}. These vascular changes lead to various structural abnormalities such as interstitial fibrosis, cortical glomerulosclerosis, tubular atrophy, compensatory tubular hypertrophy and consequent medullary glomerular hyperfiltration^{14,15}. There also is formation of direct channels between afferent and efferent arterioles which maintains medullary blood flow but potentially bypassing the glomerulus causing ischaemia, but more importantly, reduction in renal function¹⁷.
- Kidney size starts to decrease after about 5th decade, much of this change is thought to be due to infarction, scarring and fibrosis rather than purely due to loss of glomeruli¹⁴. Tubular atrophy is accompanied by basement membrane thickening, flattening of tubular epithelium, dilatation of the tubular lumen and accumulation of hyaline material within the tubule¹⁴.
- Associated with interstitial fibrosis, there is a steady decline in renal tubular volume and length in the elderly, thus compromising function both in proximal and distal tubule¹⁵. There is, thus a decreased ability to reabsorb electrolytes and glucose in the proximal tubule and reduced capacity to concentrate or dilute urine in the distal tubule; these changes lead to a compromise in renal tubular feedback mechanism as well^{14,18}.
- Cellular changes in the renal cell include brush boarder abnormalities, DNA mutation accumulation, increased apoptotic cell death and various degrees of oxidative stress¹⁴.
- Gender and genetic influences are also recognised as contributing to changes in renal function associated with aging e.g., African-American heritage has been reported to confer increased susceptibility for hypertensive nephrosclerosis¹⁹.
- There is age related decrease in renal blood flow, both in actual terms as well as in relation to declining cardiac output. Available data also suggest that there are changes in renal autoregulation as well as altered responsiveness of renal vessels to number of vasoactive agents¹⁴. These changes may be consequent upon changes in nitric oxide and angiotensin II expression/responsiveness¹⁴.



Specific risk factors in the elderly for development of AKI

All of the above changes in the kidney structure described in the elderly contribute to increased susceptibility to dehydration and drug toxicity. There is also a decline in creatinine clearance (CC) and glomerular filtration rate (GFR) as well as nephron regeneration ability and all of these factors further increase the propensity of the elderly to develop AKI in response to minor insults that might otherwise be insignificant in younger populations.

The elderly also have coexisting diseases that increase their risk of developing AKI. Thus hypertension and, particularly important in Indian context, diabetes are two important risk factors in this regard. Other important conditions that contribute to increased risk of AKI in the elderly are presence of cardio-vascular disease (especially cardiac failure), chronic kidney dysfunction, urinary tract infections consequent upon obstruction (e.g. prostatic hyperplasia in men and uterine prolapse in women) and drug toxicity. Hospitalised elderly patients are prescribed a variety of drugs, many of them potentially or actually nephrotoxic (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs, NSAIDs etc), while they may already be on a plethora of medications before their hospital admission and drug interactions are a high probability²⁰. Risk of drug toxicity is also increased in the elderly because of changes in volume of distribution (reduced muscle mass), reduced drug metabolism, and reduced ability for drug excretion and imbalance in local vasoconstrictor/vasodilator mechanisms that favour renal vasoconstriction¹⁵. An important avoidable cause of renal drug toxicity is poor appreciation of and therefore dosage adjustment to occult decrease in GFR^{14,18}. NSAIDs are frequently (and often unnecessarily) prescribed in the elderly and these drugs constitute the leading cause of AKI in this population. Doctors should also exercise caution in prescribing loop diuretics in the elderly as they have reduced ability to concentrate urine, are thus vulnerable to dehydration becoming hypovolaemic; besides loop diuretics increase toxicity of drugs like aminoglycosides^{15,18}. In addition to these drugs, elderly patients have much more increased chances of undergoing radiological investigations involving contrast media.

Altered immunological function in the elderly also renders them susceptible to development of infections, sepsis and augmented inflammatory response to infections as well as to renal injury itself^{14,15}. Indeed, sepsis may often go unrecognised in the elderly because of their decreased ability to develop pyrexia, leukocytosis etc and this has serious implications in these patients as sepsis is an important cause of AKI¹⁵.

Elderly patients are also increasingly being subjected to major surgery, especially cardiac surgery which is one of the important contributing factors for development of AKI in these patients²¹; this risk is only exacerbated by preoperative radiological investigations involving contrast media. In fact any major surgery e.g. oesophageal surgery, vascular surgery are important contributing factors for AKI, especially in patients at risk (diabetes, hypertension, chronic kidney dysfunction etc). All phases of surgical journey can contribute to this problem, especially in patients at risk. These factors (and risks) are summarised as follows¹⁵:



- **Preoperative factors:** Pre-existing renal dysfunction, cardiac insufficiency (e.g. congestive failure, whether compensated or not), diabetes, sepsis, hypovolaemia, hepatic failure, crush injuries, multiple trauma, nephrotoxic drugs (e.g. antibiotics, radio-contrast media, loop diuretics etc).
- **Intraoperative Factors:** Intraoperative haemorrhage and insensible fluid loss (both causing hypovolaemia), inflammation, hypotension, increased abdominal pressure, renal ischaemia and embolism, obstruction to renal tract, low cardiac output and hypotension (due to anaesthetic techniques; e.g. combined general anaesthesia and epidural analgesia), exposure to nephrotoxins.
- **Postoperative causes:** Hypovolaemia (bleeding, insensible fluid loss, poor oral intake or intravenous replacement), abdominal compartment syndrome, poor cardiac output, hypotension, nephrotoxins, inflammation, sepsis, mechanical ventilation, urinary tract obstruction etc.

The list is not exhaustive and often multiple factors are simultaneously responsible.

Aetiology and epidemiology

A number of studies have attempted to categorise the aetiology of AKI in hospitalised patients; however, most studies were retrospective reviews of the hospital charts and only subjectively attributed a cause of AKI in patients without using properly predefined criteria¹⁵. One large study using predefined criteria specifically looked at the elderly hospitalised patients²². This prospective study, conducted in India, concluded that commonest aetiological factors in this patient population were drug toxicity, hypoperfusion, sepsis, surgery and contrast media associated with radiological investigations. These authors also concluded that aetiology of AKI was multifactorial in most clinical situations. Another larger prospective study, also using predefined criteria found that most common causes of AKI in hospitalised patients were poor renal perfusion (e.g. dehydration causing hypovolaemia, hypotension and congestive heart failure), drug related toxicity, radiological contrast media, postoperative AKI, urinary tract obstruction and hepatorenal syndrome²³. Abdominal compartment syndrome is another important, yet often unrecognised, aetiological factor.

In the past, because of lack of universally accepted definition of AKI, large variations have been reported in hospital acquired AKI. AKI in the community based studies has been reported to occur from 140 to 620 per million population²⁴. In a Scottish community based study²⁵, and applying RIFLE criteria to all creatinine measurements in 3 hospitals, the authors found that the incidence of AKI was higher than previously described (1,811 per million population). This study also found a higher than previously reported acute-on-chronic renal failure incidence at 336 per million population; the median age of patients developing acute-on-chronic renal failure being significantly higher than in AKI patients (80.5 years versus 76 years)²⁵. Nash et al²³ reported an overall incidence of AKI at 7.2% in hospitalised patients; these authors also reported that incidence increased as age advanced, being 3.7% in patients aged 15-39 years, 5.6% in 40-59 year olds, 8.6 in those aged 60-70



years and 10.6% in patients 80 years or older²³. Many other studies confirm these finding of increasing incidence of AKI in the elderly¹⁵.

Diagnosis of AKI in the elderly

Most clinicians rely on measurement of serum creatinine (SC) and/or decreased urine output (UO) to establish the diagnosis of kidney injury/failure. Although time honoured and prevalent in clinical practice for years, both parameters have serious limitations. There is usually a delay in SC increase after a renal insult; indeed it lags behind changes in GFR by several days²⁶, needs a steady metabolic state before it can be of diagnostic value (not generally a situation in AKI), and apart from ICU patients, it is not regularly measured in other hospitalised patients. Another serious drawback of relying on SC is that its blood level is dependent on muscle mass, an important consideration in the elderly because of their reduced muscle mass²⁶. SC levels also vary with state of hydration, diet and gender. Thus, for equivalent degree of renal dysfunction, SC tends to be lower in the elderly which often leads to a delayed recognition of AKI in these patients¹⁴. RIFLE criteria, by incorporating smaller increases in SC in their definition, offset this to some extent; however, delays in diagnosis can and still do occur¹⁵. There are problem with UO estimations as well; it is not reliably measured in ward patients, it depends upon patient's state of hydration and as the elderly have a reduced capacity for urine concentrate, an 'acceptable' UO may produce a false sense of security. Several biomarkers of kidney injury are being studied; in this respect, neutrophils gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interlukin-18 (IL-18) and cystatin C have been extensively studied. Cystatin C has been specifically investigated in the elderly and has been found to be a reliable predictor of death and cardiovascular events in these patients²⁷. However, a detailed description of various biomarkers is outside the scope of this paper; these tests are also not currently recommended for routine clinical use¹⁵.

Awareness, a high index of suspicion, evaluating and identifying risk factors are the only reliable markers of diagnosis of AKI in the elderly, complemented by laboratory investigations.

Prevention of renal dysfunction in the elderly

Prevention of renal dysfunction is vitally important in all patients, especially in the elderly as this group of patients is highly prone to develop AKI after minor insults. The key to prevention of AKI in any clinical situation is - prevention of hypovolaemia and hypotension, avoidance of nephrotoxic drugs and radiological contrast media wherever possible, prompt treatment of sepsis (appropriate antibiotics, in appropriate doses, in appropriate time), prompt fixing of fractures and attention to nutrition etc²⁸. Dehydration must be recognised and treated aggressively; this includes attention to oral hydration in the elderly postoperative patients, who, under the influence of narcotic analgesics may suffer from nausea/vomiting and not maintain adequate oral intake. As elderly do not tolerate hypovolaemia well, diuretic therapy and laxatives should be used with caution in these patients. Nephrotoxic drugs should be avoided altogether; however where this is not possible, combination of potentially nephrotoxic drugs and drugs that cause hypovolaemia (e.g. diuretics) should be avoided. Radio-contrast media should be used only after due consideration and when specifically indicated, particular attention being paid to patient's hydration. There are few other strategies that prevent



contrast induced AKI except meticulous hydration; there being doubt about efficacy of sodium bicarbonate loading etc. If the use of contrast becomes necessary, smallest amounts of low or iso-osmolal, non-ionic contrast should be used. Immediate surgery after investigations involving radiological contrast media should be avoided if at all possible. Hypotension and hypovolaemia during surgery should be avoided and corrective measures taken should these occur (including adequate volume loading and use of inotropes/vasoactive drugs. Elderly patients are prone to infection with 'non-standard' signs of sepsis. Sepsis should be looked for and treated appropriately.

Management of AKI in the elderly

Preventative measures described above are key elements in managing AKI in patients, especially the elderly. In established AKI, there may still be room for aggressive resuscitation and further management of underlying condition (e.g. fracture stabilisation, antibiotic therapy for sepsis etc). Active management of comorbidities is an essential component of patient's overall management, if successful outcome is to be achieved²⁹. Conventional intermittent haemodialysis (IHD) is routinely used in the patients and is a well tested supportive modality. IHD is feasible in the elderly; however, this decision is not lightly taken. Rather, a multidisciplinary approach, involving the patient, relatives and other clinicians should carefully explore the management choices keeping in view the quality of life of a patient with a multiple comorbidities and AKI (or acute-on-chronic renal failure) as well as the reversibility or not of the condition. As the treatment is expensive and not universally available in countries like India³⁰, there should also be a realistic expectation among the parties involved, including the clinicians, and unnecessary treatment with dialysis should not be embarked upon in patients in whom futility is the only foreseeable outcome. The alternative of conservative therapy is not palliative therapy (although occasionally that may well be the best option), rather it involves active management of various clinical issues in the elderly²⁹ as many elderly do have many clinical issues.

Continuous forms of renal replacement therapy (CRRT) have not been extensively investigated in the elderly patients with AKI¹⁵. Older patients are more vulnerable to haemodynamic complications of IHD owing to their poor cardiovascular reserve, other comorbidities and increased autonomic dysfunction and thus may be more suited to CRRT. However, CRRT has its own limitations, most important being its continuous nature, thus restricting ambulation. A detailed description or various modalities of renal replacement therapies is not warranted here for the sake of brevity.

Concluding remarks

AKI imposes its own economic burden on the society; therefore its prevention is better than its management. Elderly patients are much more prone to develop AKI and consequently suffer increased further morbidity, prolonged hospital stay and increased mortality. Furthermore, dialysis dependent AKI increases societal costs and ties up resources that can effectively be employed elsewhere with much more benefit to the society. It is, therefore, incumbent on all physicians to recognise all patients at risk, especially the elderly, take steps to prevent AKI and effectively manage



other disease process that may lead to AKI. Finally, as nephrotoxicity is one of the leading causes of AKI in the elderly, clinicians will do well to look at their prescribing habits.

Conflict of interests

- The author has received honoraria from Gambro in the past.
- The author is a past member of National Working Party on Detection and Prevention of Acute Kidney Injury in the UK.

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