Epidemiology of acute kidney injury: How big is the problem?

Eric A. J. Hoste, MD, PhD; Marie Schurgers, MD

Objective: **Acute kidney injury (AKI) is a complication that occurs frequently in hospitalized patients. In this article, we provide an overview of the literature on the epidemiology of AKI in hospitalized patients.**

Patients and Setting: **The overview is restricted to hospitalized patients, and most emphasis is put on intensive care unit patients.**

Measurements and Main Results: **The population incidence of less severe AKI and AKI treated with renal replacement therapy is approximately 2,000–3,000 and 200–300 per million population per year, respectively. These numbers are comparable with the estimates for severe sepsis and acute lung injury. Approximately 4–5% of general intensive care unit patients will be treated with renal replacement therapy, and up to two thirds of intensive care unit patients will develop AKI defined by the RIFLE classification. The incidence of AKI is increasing. Intensive care unit patients with AKI have a longer length of stay and therefore generate greater costs. In addition, AKI is associated with increased mortality, even after correction for covariates. Increasing RIFLE class is associated with increasing risk of in-hospital death. Patients with AKI who are treated with renal replacement therapy still have a mortality rate of 50–60%. Of surviving patients, 5–20% remain dialysis dependent at hospital discharge.**

Conclusion: **AKI has a high incidence, comparable with acute lung injury and severe sepsis, and is associated with higher hospital mortality. (Crit Care Med 2008; 36[Suppl.]:S146–S151)**

KEY WORDS: acute kidney injury; acute renal failure; renal replacement therapy; incidence; mortality; end-stage kidney disease; epidemiology; RIFLE classification; intensive care unit; length of stay

Acute renal failure (ARF) is long recognized as a severe and devastating disorder. It was during both World Wars in the 20th century that large numbers of patients—young wounded soldiers—developed ARF or *war nephritis*, as it was called then, as a consequence of shock, rhabdomyolysis, and sepsis. The first reports on this were published after World War I (1), but it was the publication by Bywaters and Beall (2) during World War II that provided a detailed description of the pathophysiological changes in patients with ARF. However, the term *acute renal failure* was first introduced by Homer W. Smith in the chapter "Acute renal failure related to traumatic injuries" in his textbook, *The Kidney–Structure and Function in Health and Disease* (1951). Since then, numerous reports have been published on the epidemiology of this disorder. Therefore, it is remarkable that it is only recently that there have been efforts to come to a uniform definition for ARF (3). The Acute Dialysis Quality Initiative (ADQI) reported in 2002 that >35 definitions were used in medical literature on ARF. These definitions cover a whole scope of severity of ARF, from less severe impairment of kidney function (e.g., a 25% increase in serum creatinine) to the need for treatment with renal replacement therapy (RRT). Even this last definition, treatment with RRT, is not as straightforward as it seems at first sight, as there are no uniformly agreed on indications for the initiation of RRT (4). A nice illustration of what effect different definitions of ARF may have on the epidemiology of this disease is illustrated by Chertow et al. (5) in their study of 9,210 patients who had two or more assessments of serum creatinine during their hospitalization period. These authors applied nine commonly used definitions of ARF; the most sensitive defined ARF by an absolute increase of serum creatinine of $\geq$0.3 mg/dL, and the most specific defined ARF by an absolute increase of serum creatinine of $\geq$2.0 mg/dL. The prevalence of ARF ranged from 1% to 44% of hospitalized patients (Fig. 1). Accordingly, the odds ratio for in-hospital death ranged from 4.1 to 16.4! In other words, studies on ARF using different definitions are comparing apples and oranges! This study also nicely illustrates that even less severe impairment of kidney function is associated with an important effect on hospital mortality. The Acute Dialysis Quality Initiative developed a consensus definition of acute kidney injury (AKI): the risk, injury, failure, loss, and end-stage renal disease classification (RIFLE) (6) (see also "Acute Kidney Injury" by Kellum in this issue of *Critical Care Medicine*). RIFLE defines three increasing grades of severity of AKI (risk, injury, failure) based on a relative increase of serum creatinine or a period of decreased urine output. Also, two outcome criteria (loss and end-stage renal disease) are defined as, respectively, 4 wks and 3 months of treatment with RRT. Since its publication, RIFLE has been adopted enthusiastically by researchers on AKI and is now increasingly used in medical literature (7, 8).

Only recently has it been recognized that even small changes in kidney function have important effects on outcome. One of the first studies, in the mid 1990s, that demonstrated this was published by Levy et al (9). They demonstrated that patients who developed contrast nephropathy after undergoing radiocontrast procedures had an adjusted odds ratio of 5.5 of dying. Contrast nephropathy was

From the Intensive Care Unit, Ghent University Hospital, Ghent, Belgium.

For information regarding this article, E-mail: eric.hoste@ugent.be

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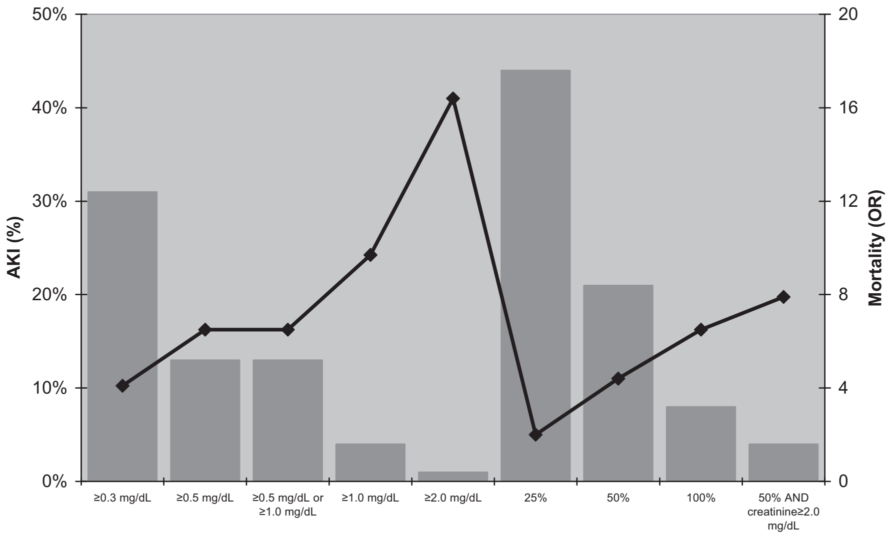

Figure 1. Different definitions of acute kidney injury (*AKI*) and effect on incidence and outcome (5). The same cohort is classified as AKI by nine different definitions, indicated on the *horizontal axis*: absolute increase of serum creatinine of, respectively, ≥0.3 mg/dL, ≥0.5 mg/dL, ≥0.5 mg/dL (when baseline serum creatinine of <2 mg/dL) or ≥1.0 mg/dL (when baseline serum creatinine ≥2.0 mg/dL and <5.0 mg/dL), 1.0 mg/dL, and 2.0 mg/dL, or relative increase of serum creatinine of 25%, 50%, 100%, or 50% to a minimum peak of 2.0 mg/dL. *OR*, odds ratio.

Table 1. Acute kidney injury (AKI) defined by the maximum RIFLE class in different cohorts[a]

First Author (Reference No.)	Cohort	Patients, n	AKI, %	Risk, %	Injury, %	Failure, %
Cruz (14)	ICU	2,164	10.8	2.1	3.8	4.9
Heringlake[b] (51)	CS-ICU	29,623	16	9	5	2
Uchino[b] (44)	Hospital	20,126	18	9.1	5.2	3.7
Kuitunen (43)	CS-ICU	813	19.1	10.8	3.4	4.9
Lopes (48)	BMT	140	33.5	13.5	10	14.3
Lopes[b] (46)	Burn	126	35.7	14.3	8.7	12.7
Ostermann[b] (52)	ICU	41,972	35.8	17.2	11	7.6
O'Riordan[b] (53)	Liver Tx	359	35.9	NA	10.9	25.1
Lopes[b] (47)	Sepsis	182	37.4	6.0	11.5	19.8
Lopes[b] (45)	HIV-ICU	97	47.4	12.4	9.6	25.8
Ahlstrom (54)	ICU	685	52.0	25.5	15.2	11.2
Guitard[b] (55)	Liver Tx	94	63.8	NA	41.5	22.3
Hoste (11)	ICU	5,383	67	12.4	26.5	28.1
Lin (56)	ICU-ECMO	46	78.2	15.2	39.1	23.9
Abosaif (57)	ICU-AKI	183	86.9	32.8	30.6	23.5
Bell[b] (15)	ICU-RRT	207	90.8	8.2	24.2	58.5
Maccariello (16)	ICU-RRT	214	100	25.0	27.0	48.0

ICU, intensive care unit; CS-ICU, cardiac surgery ICU; BMT, bone marrow transplant patients; Burn, burn unit patients; Liver Tx, liver transplant patients; NA, not assessed; HIV-ICU, patients with human immunodeficiency virus infection admitted to the ICU; ICU-ECMO, ICU patients treated with extracorporeal membrane oxygenation for acute renal failure; ICU-AKI, ICU patients with AKI; ICU-RRT, ICU patients treated with renal replacement therapy for AKI.

[a]The studies are ordered according to the incidence of AKI in the study cohort; [b]studies that assessed RIFLE status only on basis of creatinine criteria.

defined as a ≥25% increased level of serum creatinine to a minimum of 2 mg/dL. Since then, several others have demonstrated that small decreases of kidney function have an important effect on outcome in different cohorts (10, 11).

As the insight has grown that even less severe impairment of kidney function is associated with important effects on outcome, the term *acute kidney injury* has been introduced and widely adopted (12, 13).

Incidence of AKI and ARF

Incidence of AKI. The success of the introduction of a consensus definition, the RIFLE classification, is illustrated by the fact that in 2006, virtually all studies on AKI used the RIFLE classification system to define the disorder. In total, >100,000 patients have been assessed for AKI by use of the RIFLE criteria in 13 publications (Table 1). The rate of AKI naturally varies according to the cohort under study (8), from 10.8% to 100% (11, 14) (Table 1). Two studies classified AKI patients who were started on RRT (15, 16), in other words, a cohort with severe ARF according to the treating physicians and no longer at risk of AKI (RIFLE-risk) or with less severe AKI (RIFLE-injury). What is the clinical course of patients who meet the AKI diagnostic criteria? Most studies to date classified AKI patients according to the maximum RIFLE class. In a single-center study, we found that 55.6% of patients with RIFLE-risk progressed to RIFLE-injury or RIFLE-failure, and 36.8% of patients with RIFLE-injury progressed to RIFLE-failure (11). RIFLE-risk was therefore an adequate terminology, as more than half of these patients progressed to more severe AKI.

Incidence of ARF on International Classification of Diseases, Ninth Edition*, Coding.* Recently, three articles representing large multicenter administrative databases demonstrated that approximately 2% of hospitalized patients in the United States had a diagnosis of ARF according to the *International Classification of Diseases, Ninth Edition*, coding on the discharge records (17–19). The population incidence rose from 610 per million population (pmp) in 1988 to 2,888 pmp in 2002 (17). This administrative coding represents a very sensitive and less specific diagnostic criterion, and it may also be prone to different sorts of bias (20). With these restrictions in mind, the data from these large databases provide us with interesting data on the incidence and outcome of AKI and ARF during a 10-yr observation period. Interestingly, the incidence of ARF in hospitalized patients shows an increase of approximately 11% per year (18). Despite increasing comorbidity, the outcome has gradually improved (17, 18)—a finding confirmed in a study performed in Australia (21) and in a smaller single-center study in intensive care unit (ICU) patients (22).

Incidence of ARF Requiring RRT. There are many variables that may influence the use of RRT. The most important variation in incidence will probably be explained by variation in the baseline characteristics of the patient population.

In addition, there are no uniform criteria for initiation of RRT, so this may also "color" the epidemiologic data. Finally, there may be a discrepancy between the indication for RRT and the initiation of this treatment. It is well possible that factors, such as older age, hemodynamic instability, access to dialysis monitors, hemorrhage, and even financial constraints, may influence the decision to initiate RRT in some units or countries.

In a single-center study in hospitalized patients, the incidence of hospital-acquired ARF treated with RRT was 1.1% (23). In cardiac surgery patients, rates of RRT range between 0.3% and 1.4% (24, 25). Metnitz et al. (26) found that 4.9% of ICU patients from a large cohort of 17,126 patients admitted to 30 Austrian ICUs during a 2-yr study period were treated with RRT. Uchino et al. (27), with the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators, found that among a cohort of 29,269 ICU patients admitted to 54 ICUs in 23 countries, 4.2% of patients were treated with RRT for ARF.

Population Incidence of ARF Requiring RRT. Whereas the unit incidence allows comparison between different cohorts or units, the population incidence allows comparison between regions, countries, and also the incidence of the disorder over time (17, 28–36). Figure 2 nicely illustrates that there has been an increase in the incidence of ARF treated with RRT over time. This is also shown by the study by Hsu et al (29). These authors evaluated an adult cohort of beneficiaries of the healthcare delivery system Kaiser Permanente of Northern California during an 8-yr period, from 1996 to 2003, and found that the acute RRT use increased from 195 pmp/yr in the period 1996–1997 to 295 pmp/yr in the period 2002–2003. In addition, they demonstrated that the incidence is greater in men compared with women (356 vs. 240 pmp/yr in the period 2002–2003) and increases with age until the ninth decade (in the period 2002–2003, 103 pmp/yr for patients <50 yrs, 815 pmp/yr for patients 60–69 yrs, 1,232 pmp/yr for patients 70–79 yrs, and 625 pmp/yr for patients 80–89 yrs).

A nice illustration of the importance of case mix on the incidence of ARF treated by RRT can be found in the three studies performed in Scotland during more or less the same time period (31, 35, 36). The study by Ali et al. (35) covered a population of 523,000 in the Grampian region and found an incidence of 183 pmp/yr during a 6-month period in 2003. Metcalfe et al. (31) covered 1,112,200 people in the Grampian, Highland, and Tayside regions, and found an incidence of 203 pmp/yr, and Prescott et al. (36) covered 5,054,800 people in the whole of Scotland and found an incidence of 286 pmp/yr.

Incidence of AKI and ARF in Relation to the Incidence of Other Common Diseases in the ICU. How do the incidences of AKI and ARF relate to other common diseases in ICU patients? Sepsis and the more severe forms, severe sepsis and septic shock, are considered the most severe threat for ICU patients. Based on data from seven states in the United States in 1995, it was estimated that the incidence of severe sepsis was 3,000 pmp/yr, of whom 51% were treated in an ICU facility (37). Subsequent data from the United States reported an incidence of 2,404 cases of sepsis per million population in 2000 (38). In the United Kingdom, 27% of ICU admissions developed severe sepsis during the first 24 hrs of admission, which corresponded to a population incidence of 660 pmp in 2003 (39). In analogy with the data on AKI, there is an increasing incidence. In the United States, there was an annual increase of 8.7% in the period from 1979 to 2000 (38). In the United Kingdom, the proportion of patients with severe sepsis in the ICU rose from 23.5% in 1996 to 28.7% in 2004 (39). In summary, the population incidence of severe sepsis is roughly comparable with that of AKI.

Respiratory insufficiency as a consequence of acute lung injury, or the more severe entity, acute respiratory distress syndrome (ARDS), is another complication that frequently occurs in ICU patients. The incidence of these syndromes roughly parallels that of RRT. An estimate based on data from the U.S.-based ARDS Network found that 112–320 pmp develop acute lung injury (40). In summary, AKI parallels the incidence of severe sepsis, and ARF requiring RRT has a comparable incidence to acute lung injury!

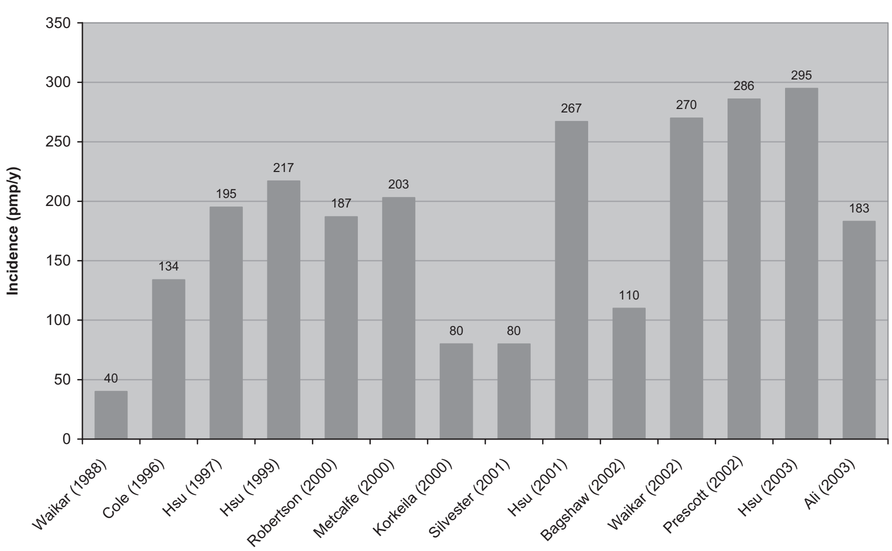

Figure 2. Population incidence of acute kidney injury treated with renal replacement therapy. The *bars* are named after the first author and the year the population incidence was evaluated. *pmp/y*, per million population per year.

Effect of AKI and ARF on Outcome

Length of Stay. Increased length of stay may give an indication of the severity of illness and may also serve as a marker for economic outcome and costs associated with a certain disease. However, length of stay can only be a surrogate marker, as it is heavily subject to bias. Increasing RIFLE class is associated with increasing length of hospital stay (11, 21). In Pittsburgh, patients without AKI had a median length of hospital stay of 6 days, compared with 8 days for RIFLE-risk, 10 days for RIFLE-injury, and 16 days for RIFLE-failure (11). Also, in a multicenter Austrian ICU study, length of ICU stay of AKI patients treated with RRT was, on average, 10 days longer compared with other ICU patients (median of 13 days vs. 3 days) (26). Although these data suggest a relationship between length of stay and occurrence and severity of AKI, other factors, such as other organ dysfunctions and hospital discharge policies, may influence these data. Therefore, a harder end point, such as mortality, may give more valuable information on the effect of AKI.

Mortality. It is well established in diverse cohorts that need for RRT is an independent risk factor for in-hospital mortality (41, 42). However, even contrast nephropathy (9), or AKI (11, 43–48), is associated with increased mortality, even after correction for comorbidities (Table 2). Increasing RIFLE class is associated with increasing mortality in almost all studies (Fig. 3). The two exceptions to this finding are studies on cohorts of AKI patients receiving RRT.

Ympa et al. (49) found that mortality of AKI patients treated with RRT remains more or less constant, according to studies published in the medical literature. However, these findings are heavily biased by the fact that the baseline characteristics of hospitalized patients have changed over the years. Patients treated more recently are more severely ill, older, and have more underlying diseases. When we corrected for severity of illness, age, and other organ dysfunctions, we showed that in our unit in Ghent, the outcomes after RRT improved during a 10-yr period (22). Similarly, several others showed, in large multicenter databases, that patients are now more severely ill than 10–15 yrs before and that the mortality of patients treated with RRT has improved (17, 18, 21). Mortality of ICU patients treated with RRT depends heavily on associated organ dysfunctions and comorbidity, but for a general ICU population, mortality is approximately 50–60% (26, 27).

End-Stage Kidney Disease. Although the vast majority of surviving patients requiring RRT for ARF recover renal function by hospital discharge, a proportion of surviving patients develop end-stage kidney disease and need chronic RRT. In the large multicenter BEST Kidney trial, 13% of patients still required RRT at hospital discharge (27). Similar findings were reported in Sweden: 8.3% of patients on continuous RRT and 16.5% of patients on intermittent RRT developed end-stage kidney disease (50). In Canada, 22% of surviving patients developed end-stage kidney disease (34). Finally, patients who already have chronic kidney disease are at much greater risk of developing end-stage kidney disease. In the large Scottish database, 13% of patients with normal baseline kidney function developed end-stage kidney disease, compared with 53% in patients who at baseline already had chronic kidney insufficiency (36).

Table 2. Association of maximum RIFLE class and mortality: An overview of full articles that report on the risk of in-hospital death, corrected for other comorbidities in multivariate analysis

First Author (Reference No.)	Patients, n	RIFLE Class	OR or HR	*p*
Hoste (11)	5,383	Risk	1	.896
		Injury	1.4	.037
		Failure	2.7	<.001
Kuitunen (43)	813	AKI	2.6	<.001
Uchino (44)	20,126	Risk	2.5	<.001
		Injury	5.4	<.001
		Failure	10.1	<.001
Cruz (14)	234	Risk	1 (ref)	
		Injury	2.2	.108
		Failure	4.9	.013

OR, odds ratio; HR, hazard ratio; ref, reference value; AKI, acute kidney injury.

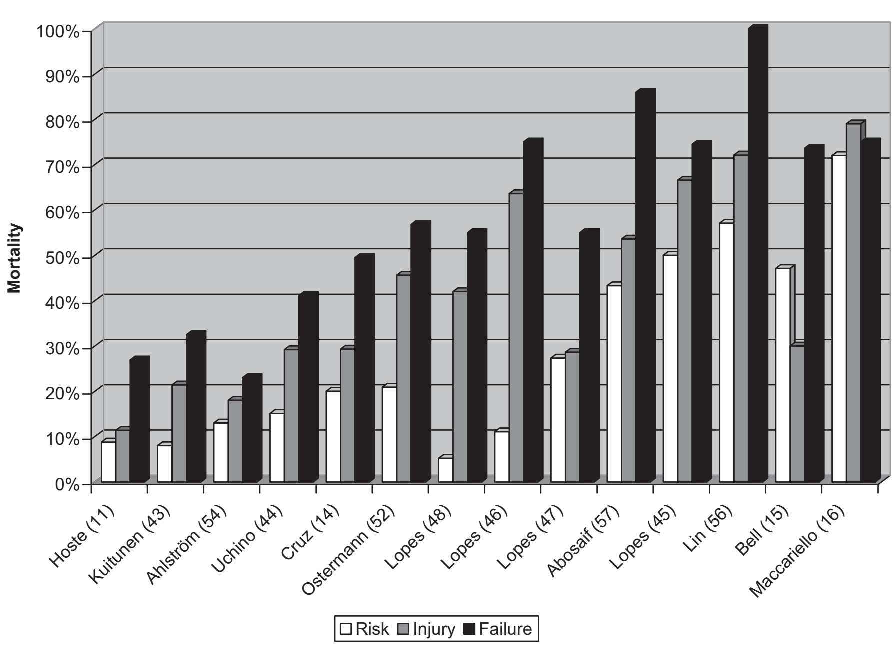

Figure 3. Mortality, according to RIFLE class, in different studies.

Conclusions

AKI is indeed a very big problem. Lack of uniformity of the definition of ARF has hampered comparisons and evaluation of the epidemiology over time. However, the RIFLE consensus classification for AKI has permitted a much clearer picture of the epidemiology.

AKI occurs in up to two thirds of ICU patients. The population incidence of AKI is approximately 2,000 to 3,000 pmp/yr. In a general ICU, 4–5% of patients are treated with RRT for ARF. This corresponds to a population incidence of ±300 pmp, which parallels the incidence of acute lung injury. The incidence of AKI and rate of RRT is rising. Patients with AKI have worse outcomes compared with patients without AKI. There is an increased length of stay, which represents an important economic outcome, and an independent effect on mortality. Increasing severity of AKI is associated with increasing odds of in-hospital death. Treatment with RRT has an associated mortality of 50–60%.

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