Acute Renal Failure in the Same Hospital Ten Years Apart

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SUMMARY

A three month prospective study was carried out in 1994 (8/3/94 - 7/6/94) and late 2004/early 2005 (24/11/2004 - 15/2/2005) among patients with acute renal failure (ARF) (serum creatinine > 0.200 mmol/l). Incidence of ARF had increased from 0.48% (78/16,418) to 1.1% (211/18,697) of admissions between 1994 and 2004. Two thirds of patients were male. Mean age was 57.7 ± 20.1 years in 1994 and 55.6 ± 17.8 years in 2004. No difference was noted in causative factors, rate of oliguric ARF (about 10%) and mean peak urea and creatinine. The cause was pre-renal failure in 43.6% in 1994 and 53.5% in 2004. The second commonest cause was sepsis with 41% in 1994 and 37.9% in 2004. One in six patients needed dialysis and peritoneal dialysis was the main dialysis modality (69.2% and 74.3%). Mortality was 56.4% in 1994 and 44.5% in 2004. A quarter of deaths occurred within two days of admission due to severe underlying illness. Mortality among non-oliguric patients decreased from 52.9% in 1994 to 37.0% in 2004 (p=0.04); for patients from intensive care units it was 78.3% in 1994 and 68.5% in 2004.

KEY WORDS:
Acute renal failure, Dialysis, Mortality

INTRODUCTION

Mortality rates in patients with acute renal failure (ARF) have remained high despite advances in its management over the last four decades[1-4]. This may be caused by the changing demography of patients (e.g. age, co-morbid factors)[5]. Previous reports have described the demography of ARF in Malaysia[6-7]. However, there is no local data showing the trends in ARF over time. This study is based on a comparison of two prospective studies in Sultanah Aminah Hospital Johor Bahru (HSAJB) over a ten year period.

MATERIALS AND METHODS

A prospective study over a three month period was carried out in 1994 (8/3/94 - 7/6/94) and repeated in late 2004/early 2005 (24/11/2004 - 15/2/2005) among patients with ARF (serum creatinine > 0.200 mmol/l). Patients with obstructive uropathy, chronic renal failure, glomerulonephritis and those less than ten years old were excluded.

This was an observational study and the protocol was not submitted to the Ethics Committee for approval. Informed consent by study subjects was deemed unnecessary. The number of total admissions in HSAJB during the study periods was obtained from admission room records. Prior written approval had been obtained from the hospital director and respective heads of departments to include their patients in the study. The investigators were not involved in the management of the patients unless a formal referral had been made to the Nephrology unit. Daily computerised records of hospitalised patients in HSAJB with serum creatinine >0.200mmol/l were obtained from the Division of Biochemistry. All patients were reviewed within 48 hours. Those found to have ARF were included in the study. Patients were seen in their respective wards in the hospital and a review of the patients' case notes and observation charts were made. A cause of renal failure was attributed based on available clinical and laboratory data by the investigators. Statistical analysis was performed using chi square (X^2). Statistical significance was defined as p value < 0.05. Numbers were expressed as percentage and mean ± standard deviation (SD) where appropriate.

Oliguria was defined as daily urine volume of less than 400 ml/day. Patients with oliguria persisting for more than 48 hours were classified as having oliguric ARF. If the initial oliguria persisted for less than 48 hours and is followed by a urine volume exceeding 400 ml/day the patients were classified as having non-oliguric ARF. Pre-renal failure was identified by one or more of the following observations (1) weight loss accompanied by signs of volume depletion on physical examination (2) a decrease in blood pressure to less than 90/60mmHg (3) clinical evidence of congestive heart failure (4) improvement of renal function from correction of volume depletion/dehydration with restoration of renal blood flow and (5) the absence of other causes of ARF.

Sepsis was defined by positive blood cultures accompanied by hypotension or haemodynamic measurements consistent with sepsis on measurements of pulmonary artery pressure and peripheral resistance. Medications were implicated as the cause when the increase in creatinine level was temporally related to administration of the medication with one or more of the following criteria (1) clinical or laboratory evidence supporting acute tubular necrosis, interstitial nephritis or haemodynamic effect (2) absence of other pathogenetic mechanisms and (3) improvement with discontinuation of the agent. Radiographic contrast media were determined to be the cause when serum creatinine level increased within 48 hours of the procedure in which the patient was administered contrast.

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RESULTS

Over the three month period, the incidence of ARF had increased from 0.48% (78 patients with ARF out of 16,418 admissions) in 1994 to 1.1% (211 patients with ARF out of 18,697 admissions) in 2004 (p=0.00). There was no difference in sex, age and ethnicity between the 1994 and 2004 cohorts (Table I). Approximately two thirds of the patients were male. Forty-eight percent of ARF patients in 1994 were 60 years of age or more compared to 43.1% in 2004. Medical causes of ARF accounted for 69.2% in 1994 and 73.0% in 2004. The rest were from general surgery, urology, neurosurgery or orthopaedics. In 2004, there were two patients from the obstetric ward. One patient had ARF secondary to disseminated intravascular coagulopathy as a result of septic abortion. The other had post partum haemorrhage. The mean length of stay decreased from 13.7 $\pm$ 12.7 days in 1994 to 10.1 $\pm$ 10.2 days in 2004 (p=0.02). The number of referrals to the Nephrology unit had increased 5 fold from 16 in 1994 to 85 in 2004 (p=0.04).

There was no difference in the aetiology of ARF between 1994 and 2004 (Table II). Pre-renal causes were the commonest contributor 43.6% in 1994 and 53.5% in 2004. This was mainly due to dehydration. In 1994 dehydration was caused by infection (28.0%), malignancy (20.0%), acute gastroenteritis (16.0%), trauma (16.0%), central nervous system disorders (8.0%), poor oral intake (8.0%) and hyperglycaemia (4.0%). In 2004, poor oral intake contributed 37.3% followed by malignancy (19.3%), central nervous system disorders (15.7%), infection (12.1%), trauma (7.2%), hyperglycaemia (3.6%) and others (4.8%).

Pre-renal ARF from decrease cardiac output remains as important contributor. Acute coronary syndrome was the commonest cause. In 2004, congestive cardiac failure caused ARF in seven patients. Of these, three were from the cardiothoracic unit. All three had ARF post coronary artery bypass graft (CABG). One patient had mitral valve replacement in addition to CABG. All patients were more than 55 years of age and had non-oliguric ARF. None of the patients needed renal replacement therapy. One patient died from cardiogenic shock while the remaining two patients survived.

Other causes of ARF were sepsis and nephrotoxins. The common causes of sepsis in 1994 were pneumonia, soft tissue infection (carbuncle, cellulitis, necrotising fascitis, abscess), intraabdominal infection (liver abscess, acute cholangitis, perforated viscus) and urinary tract infection. In 2004 pneumonia and soft tissue infection were common. There was an increase in diabetic foot infections in 2004 compared to 1994 (12.5% versus 6.3% of patients with sepsis). Leptospirosis caused ARF in seven patients in 2004. In 1994, gentamicin was the main cause of drug induced ARF (50.0%) (Table III). In 2004 the most common agents causing ARF were angiotensin converting enzyme inhibitors (ACEI) and contrast media. Radiographic contrast media were responsible for four episodes of ARF in 2004. Three were from coronary artery angiography and one was from a computed tomography scan. In the miscellaneous group four patients in 1994 had hepatorenal syndrome. In 2004, four patients had hepatorenal syndrome and one had tumour lysis syndrome from chronic myeloid leukaemia.

One sixth of patients needed dialysis (Table IV). A higher percentage of patients in the oliguric group required dialysis (62.5% in 1994, 29.6% in 2004) compared to the non-oliguric group (11.4% in 1994, 14.7% in 2004). Mortality decreased from 56.4% in 1994 to 44.5% in 2004 but this was not statistically significant. Mortality rates were higher in the oliguric group (87.5% in 1994, 96.3% in 2004) compared to the non-oliguric group (52.9% in 1994, 37.0% in 2004). The mean peak blood urea and serum creatinine levels were higher in the oliguric group compared with the non-oliguric group in both cohorts of patients. Peritoneal dialysis was the main dialysis modality (69.2% in 1994 and 74.3% in 2004). Other modalities of treatment included intermittent haemodialysis and continuous venovenous haemodiafiltration. Survival rates in patients using various modalities of renal replacement therapy were inconsistent as the number of patients was small (Table IV).

Approximately a quarter of the deaths occurred within two days of admission due to severe underlying illness (22.7% in 1994 and 26.6% in 2004) (Table VI). Death rate in patients more than 60 years of age decreased from 65% in 1994 to 40.7% in 2004 (p=0.02) (Table VII). Mortality among non-oliguric patients decreased from 52.9% in 1994 to 37.0% in 2004 (p=0.04). The mortality rate in intensive care unit (ICU) and high dependency unit (HDU) patients was high, 78.3% in 1994 and 68.5% in 2004. In 1994 there was a single ICU in HSAJB with ten beds. By 2004 when the second study was done there were several additional HDUs functioning i.e. CCU (coronary care unit), cardiothoracic ICU, Medical HDU and neurosurgical HDU, performing the functions of the original ICU with a total of 32 beds.

DISCUSSION

This was a prospective study repeated ten years apart describing the changing trends of ARF in HSAJB. Conceptually ARF is defined as the loss of renal function, with a decline in glomerular filtration rate over a period of hours or days. Clinically ARF is manifested by the retention of urea, creatinine and other metabolic waste products. There is no consensus on an operational definition. Variability in the definitions used in epidemiologic studies and clinical trials confound their interpretation and limit comparisons between studies. Mehta and Chertow showed that the spectrum of definitions in published studies of ARF was broad, ranging from severe (e.g. ARF requiring dialysis) to relatively modest observable increases in serum creatinine concentration[8]. A multidimensional definition of ARF was proposed during the Second Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)[9-10]. ARF was stratified based on the severity and duration of injury into stages of Risk, Injury, Failure, Loss and End-stage disease (RIFLE). In this study the criteria used allowed the study of patients with mild degrees of renal insufficiency rather than only patients requiring dialysis. There is evidence that relatively small increases in serum creatinine level are associated with large increases in mortality even after correction for co-morbid conditions[11].

There was a nearly three fold increase in the number of ARF episodes over the ten year study period. There was a modest increase in admissions to the hospital. There was an increase in pre-renal causes of ARF due to dehydration. Some of the

Table I: Demographics of patients with ARF, 1994 and 2004

	1994 (N = 75)*		2004 (N = 211)		p
Male (%)	47	(62.7)	138	(65.4)	NS
Mean age, years + SD	57.7 + 20.1		55.6 + 17.8		NS
Age distribution, years (%)					
11 – 20	2	(2.6)	5	(2.4)	
2 1- 40	17	(21.8)	38	(18.0)	
41 – 60	21	(26.9)	77	(36.5)	
61 - 80	28	(35.9)	83	(39.3)	
> 80	10	(12.8)	8	(3.8)	
Race (%)					NS
Malay	39	(50.0)	115	(54.5)	
Chinese	27	(34.6)	64	(30.4)	
Indian	9	(11.5)	23	(10.9)	
Indonesian	1	(1.3)	6	(2.8)	
Others	2	(2.6)	3	(1.4)	
Number (%)					NS
Medical	54	(69.2)	154	(73.0)	
Surgical	24	(30.8)	55	(26.0)	
Obstetrics	0	(0)	2	(1.0)	

* Seventy-five patients developed ARF 78 times
NS – not significant (p>0.05)

Table II: Causes of ARF

	1994 (N = 78)		2004 (N = 211)		p
	No	**(%)**	**No**	**(%)**	
Pre-renal					
Decreased cardiac output					NS
Acute coronary syndrome	7	(9.0)	23	(10.9)	
Congestive cardiac failure	0	(0)	7	(3.3)	
Decreased intravascular volume					
Dehydration	25	(32.1)	83	(39.3)	
Gastrointestinal bleed	2	(2.5)	0	(0)	
Sepsis					NS
Pneumonia	8	(10.3)	18	(8.5)	
Soft tissue infection/abscess	5	(6.4)	11	(5.2)	
Intra-abdominal infection	5	(6.4)	6	(2.8)	
Urinary tract infection	4	(5.1)	4	(1.9)	
Diabetic foot ulcer	2	(2.5)	10	(4.7)	
Leptospirosis	0	(0)	7	(3.3)	
Septic abortion	0	(0)	1	(0.5)	
Infective endocarditis	0	(0)	1	(0.5)	
Meningitis	0	(0)	2	(1.0)	
Unknown	8	(10.3)	20	(9.5)	
Nephrotoxins	8	(10.3)	13	(6.2)	NS
Miscellaneous	4	(5.1)	5	(2.4)	NS

Table III: Aetiology of toxin induced ARF

	1994 (N = 8)		2004 (N = 13)	
	No	**(%)**	**No**	**(%)**
Gentamicin	4	(50)	1	(7.7)
Paraquat	1	(12.5)	2	(15.4)
Anti-tuberculosis drugs	1	(12.5)	0	(0)
Cisplatin	1	(12.5)	0	(0)
ACEI*	0	(0)	3	(23.1)
NSAID**	0	(0)	1	(7.7)
Contrast media	0	(0)	4	(30.7)
Cyclosporin	0	(0)	1	(7.7)
Rhabdomyolysis	1	(12.5)	1	(7.7)

*ACEI - Angiotensin converting enzyme inhibitor
**NSAID - Non steroidal anti-inflammatrory drug

Table IV: Outcome of patients with ARF

	1994 (N = 78)						2004 (N = 211)						p
	Oliguric		Non-oliguric		Total		Oliguric		Non-oliguric		Total		
	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	
Dialysis	5	(6.4)	8	(10.3)	13	(16.7)	8	(3.8)	27	(12.8)	35	(16.6)	NS
No dialysis	3	(3.8)	62	(79.5)	65	(83.3)	19	(9.0)	157	(74.4)	176	(83.4)	NS
Dead	7	(9.0)	37	(47.4)	44	(56.4)	26	(12.3)	68	(32.2)	94	(44.5)	NS
Alive	1	(1.3)	33	(42.3)	34	(43.6)	1	(0.5)	116	(55.0)	117	(55.5)	NS
Mean peak urea (mmol/l)	35.6 + 17.7		26.0 + 29.4				32.1 + 19.2		27.1 + 6.8				NS
Mean peak creatinine (mmol/l)	0.70 + 0.24		0.43 + 0.30				0.49 + 0.27		0.38 + 0.21				NS

Table V: Dialysis modality

	1994	Deaths		2004	Deaths	
	(N=13)	No	(%)	(N=35)	No	(%)
PD only	9	6	(66.7)	26	12	(46.2)
HD only	2	1	(50.0)	2	2	(100.0)
PD and HD only	1	0	(0)	1	1	(100.0)
CVVHDF only	1	1	(100.0)	1	1	(100.0)
PD and CVVHDF only	0	0	(0)	3	3	(100.0)
HD and CVVHDF only	0	0	(0)	1	0	(0)
PD, HD and CVVHDF	0	0	(0)	1	0	(0)

PD – Peritoneal dialysis, HD – Haemodialysis, CVVHDF – Continuous venovenous haemodiafiltration

Table VI: Deaths in the first two days of admission

1994	(N=10)	2004	(N=25)
Cause		Cause	
Septic shock	3	Cardiogenic shock with AMI	5
Cardiogenic shock with AMI	2	Leptospirosis	4
Gentamicin toxicity with DIVC	1	Carcinoma lung with dehydration	2
Primary peritonitis	1	Liver cirrhosis	2
Paraquat poisoning	1	Pneumonia	2
Ruptured AVM	1	Dengue shock syndrome	1
Severe AGE with PTB	1	Diabetic foot ulcer	1
		Dissecting aneurysm	1
		HIV infection, cellulitis	1
		Intestinal obstruction	1
		Intra-abdominal sepsis	1
		MVA with polytrauma	1
		Paraquat poisoning	1
		Retropharyngeal abscess	1
		Sepsis – unknown cause	1

AGE - Acute gastroenteritis
AMI - Acute myocardial infarction
AVM - Arteriovenous malformation
DIVC - Disseminated intravascular coagulopathy
HIV - Human immunodeficiency virus
MVA - Motor vehicle accident
PTB - Pulmonary tuberculosis

Table VII : Outcome

	1994 (N=78)						2004 (N=211)						p
	Survivors (N=34)		Non survivors (N=44)		Total (N=78)		Survivors (N=117)		Non survivors (N=94)		Total (N=211)		
	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	
Ward stay 2 days or less	0	(0)	10	(12.8)	10	(12.8)	8	(3.8)	25	(11.8)	33	(15.6)	NS
Ward stay more than 2 days	34	(43.6)	34	(43.6)	68	(87.2)	109	(51.7)	69	(32.7)	178	(84.4)	NS
Age 60 years or more	14	(18.0)	26	(33.3)	40	(51.3)	54	(25.6)	37	(17.5)	91	(43.1)	0.02
Age less than 60 years	20	(25.6)	18	(23.1)	38	(48.7)	63	(29.9)	57	(27.0)	120	(56.9)	NS
ICU	5	(6.4)	18	(23.1)	23	(29.5)	5	(2.4)	23	(10.9)	28	(13.3)	NS
HDU*	0	(0)	0	(0)	0	(0)	12	(5.7)	14	(6.6)	26	(12.3)	NS
No ICU/HDU stay	29	(37.2)	26	(33.3)	55	(70.5)	100	(47.4)	57	(27.0)	157	(74.4)	NS
Dialysis	4	(5.1)	9	(11.5)	13	(16.6)	16	(7.6)	19	(9.0)	35	(16.6)	NS
No dialysis	30	(38.5)	35	(44.9)	65	(83.4)	101	(47.9)	75	(35.5)	176	(83.4)	NS
Male	22	(28.2)	26	(33.3)	48	(61.5)	74	(35.1)	64	(30.3)	138	(65.4)	NS
Female	12	(15.4)	18	(23.1)	30	(38.5)	43	(20.4)	30	(14.2)	73	(34.6)	NS
Malay	13	(16.7)	26	(33.3)	39	(50.0)	63	(29.8)	52	(24.6)	115	(54.4)	0.04
Chinese	14	(18.0)	13	(16.7)	27	(34.6)	37	(17.5)	27	(12.8)	64	(30.3)	NS
Indian	5	(6.4)	4	(5.1)	9	(11.5)	13	(6.2)	10	(4.8)	23	(11.0)	NS
Others	2	(2.6)	1	(1.3)	3	(3.9)	4	(1.9)	5	(2.4)	9	(4.3)	NS
Medical	25	(32.1)	29	(37.2)	54	(69.3)	83	(39.3)	71	(33.7)	154	(73.0)	NS
Surgical	9	(11.5)	15	(19.2)	24	(30.7)	34	(16.1)	23	(10.9)	57	(27.0)	NS

ICU - Intensive care unit *Includes CCU - Coronary care unit, Medical HDU and Neurosurgical HDU - High dependency unit

extra patients may have resulted from increased awareness as most patients in 2004 had a renal profile done on admission; this may not have been the case in 1994 for patients who were not ill. The creation of HDUs meant that more patients with increasing severity were being treated in HSAJB. There was a two and a half fold increase in patients who needed dialysis and a five fold increase in Nephrology referrals for ARF over the last ten years; the threshold and indications for dialysis has remained the same over the last decade.

There were seven cases of leptospirosis in 2004 but none in 1994 and five cases of dengue fever causing in ARF (attributed to dehydration) in 2004 but none in 1994. The study in 2004 was conducted from November to February which coincided with the monsoon season; in 1994 the study was done in the dry season from March to June. There are changing patterns of emerging diseases like dengue[12] which impinge on the practice of nephrology over time. There were an increased number of diabetic foot ulcers causing ARF in 2004 which is probably the result of the increasing number of type 2 diabetics in the country[13].

Gentamicin associated nephrotoxicity has markedly reduced. There is a greater awareness of the potential nephrotoxic effects of aminoglycosides; less nephrotoxic antibiotics are being used in the treatment of gram negative infections. There is an increasing number of contrast media and ACEI induced ARF. Measures should be taken to reduce the risk of contrast induced nephropathy i.e. choosing an alternative investigation modality in high risk patients, hydration with normal saline, the use of nonionic contrast media, reducing the amount of contrast used and the use of N-acetylcysteine[14-17].

The overall mortality rate of ARF was similar in 1994 and 2004, although there was a trend towards a reduction in mortality. Studies of ARF note the failure to demonstrate an improvement in survival rates despite an improvement of supportive care[1-4]. These studies tend to show increasing age of patients, more co-morbid illnesses and introduction of more surgical procedures or drugs as possible causes of non improvement of ARF mortality rates[18-19]. However, these changes were not seen in our cohort. Even though patient mix in our cohort appears similar, risk stratification were not performed in our patients using risk stratification systems e.g. Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II and Mortality Probability Model II score. In addition, we used relative changes in serum creatinine levels as surrogates for changes in kidney function as in many other previous studies[8]. However, the performance and impact of serum creatinine level alone as a marker of severity of kidney dysfunction on mortality has not been assessed. We were also unable to incorporate the recently proposed RIFLE criteria because they were published after completion of our study. All these factors could have resulted in a less accurate evaluation of our patients. The number of patients treated with intermittent haemodialysis and continuous renal replacement therapy was also small. It is unclear if mortality would have been improved with the increase use of these treatment modalities.

The morbidity and mortality associated with ARF dictate that we should redouble our efforts to prevent it. Early resuscitation of patients with pre-renal ARF, aggressive treatment of sepsis, avoidance of nephrotoxins and closer observation in high risk patients could be a strategy. Several other issues need to be resolved: the dialysis modality of choice, the optimal dose of dialysis, the timing of renal replacement therapy and membrane biocompatibility. Randomised controlled trials did not show any benefit of continuous renal replacement therapy (CRRT) versus intermittent haemodialysis (IHD)[20-21]. Evidence from studies suggests that the delivered dose of dialysis may significantly affect outcome from ARF requiring dialysis[22-26]. Despite two meta-analyses being published, conclusions regarding the impact of membrane biocompatibility on outcomes are equivocal[27-28]. The knowledge and experience of the physician, the availability of infrastructure to support the therapy and patients' characteristics need to be taken into consideration when managing ARF.

CONCLUSION

In Sultanah Aminah Hospital Johor Bahru the incidence and severity of ARF is increasing. Mortality remains high despite better understanding of pathogenesis and management.

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