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Acute Kidney Injury in Children

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ABSTRACT

Acute renal failure is an important cause of morbidity and mortality in children. Since it has been variously defined in the past, leading to wide variations in the reported incidence and mortality of the condition, the Acute Kidney Injury Network (AKIN), an expert body comprising of nephrologists and intensivists worldwide, has replaced the term 'acute renal failure' by 'acute kidney injury (AKI)' and adopted a uniform definition and classification for the new terminology. The new AKIN classification is useful since early detection of AKI helps in commencement of several preventive and therapeutic strategies including avoidance of potentially nephrotoxic drugs, judicious usage of radio-contrast imaging studies, appropriate fluid management, correction of acid-base and electrolyte disturbances, and optimization of blood pressure control. It also allows rational comparison of studies that assess preventive and therapeutic AKI strategies, helps in generalization of data generated from single center studies, and allows patient stratification based on AKI severity. AKI has a wide differential diagnosis. History can help classify the pathophysiology of AKI as prerenal, intrinsic renal or postrenal failure, and may suggest a specific etiology. While sepsis, glomerulonephritis, hemolytic uremic syndrome, acute tubular necrosis and obstructive nephropathy predominate in developing countries, these have been replaced by hemato-oncologic complications and pulmonary failure as causes of AKI in the western world. This review summarizes the epidemiology, etiopathogenesis, evaluation and management of children with AKI. Current concepts regarding pharmacological interventions for early management of AKI and the long term outcome of pediatric AKI are also discussed.

Key words: Acute kidney injury; RIFLE classification; Renal replacement therapy

Acute renal failure (ARF) is a complex disorder that occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure. It is often under-recognized and is associated with severe consequences [1]. ARF has been the focus of extensive clinical and basic research efforts over the last decades. Yet its epidemiology is not well determined, with more than 30 definitions in use in the literature. The variety of definitions used in clinical studies had led to large variations in the reported incidence (ranging from 1% to 31%) and the associated mortality (ranging from 19% to 83%) [2]. Studies have described ARF based on serum creatinine changes, absolute levels of serum creatinine, changes in blood urea nitrogen or urine output, or the need for dialysis [3-7]. The lack of standardized definitions that can be applied across patient populations impeded rational comparison of studies that assessed preventive and therapeutic ARF strategies, limited generalization of data generated from single

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center studies, and prevented patient stratification based on ARF severity.

The AKIN definition and classification of acute kidney injury

There has been a gradual evolution of the concept of acute kidney injury (AKI) defined as 'an abrupt and sustained decrease in kidney function' . The term AKI has now replaced ARF. To make consensus-based recommendations and delineate key questions for future studies, the Acute Dialysis Quality Initiative (ADQI) workgroup identified a definition/classification system for AKI. They formulated the Risk, Injury, Failure, Loss, and End-stage kidney (known by the acronym RIFLE) classification for AKI which represented a new classification system issued from a process of formal evidence appraisal and expert opinion in order to standardize the definition of ARF [8]. Three grades of increasing severity of acute kidney injury – risk (class R), injury (class I) and failure (class F) – and two outcome classes (loss and end-stage kidney disease) were defined based on changes in either serum creatinine or urine output from the baseline condition (Figure 1). These criteria were proposed to be used across all age groups around the world.

The RIFLE classification has been further modified by the Acute Kidney Injury Network (AKIN) [9],comprising of nephrologists and intensivists worldwide, which proposed a uniform definition of AKI as '*an abrupt (within 48 hours) reduction in kidney function currently defined as a absolute increase in serum creatinine of either ≥ 0.3 mg/dl or a percentage increase of e"50% or a reduction in urine output (documented oliguria of < 0.5 ml/kg/hr for > 6 hours)'*.The group has also defined three grades of severity for AKI based on increase in serum creatinine over a 48 hour period and/or urine output. The outcome classes (loss and end-stage kidney disease) were eliminated in this classification (Table 1)

The new AKIN classification is useful since early detection of AKI helps in commencement of several preventive and therapeutic strategies including avoidance of potentially nephrotoxic drugs, judicious usage of radio-contrast imaging studies, appropriate fluid management, correction of acid-base and electrolyte disturbances, and optimization of blood pressure control. Even minor changes in serum creatinine are associated with increased in-patient mortality [3-5]. Because AKI is known to be associated with high mortality and treatment with renal replacement therapy (RRT) is costly, we must identify patients early and intervene to avoid RRT.

INCIDENCE AND MORTALITY IN AKI

Recently, few studies have evaluated the incidence and outcome of AKI using RIFLE classification [10-15] (*Table 2*). The incidence of AKI (using RIFLE classification) in these studies ranged from 19% to 67%. This could be due to use of different populations. Moreover, various authors have classified patients into different RIFLE categories at different points. For example, Cruz et al [15] have classified the patients on ICU admission; Abosaif et al [12] on ICU admission, Kuinten et al [10] at peak creatinine levels and Hoste et al [13] at maximum RIFLE class attained. Mortality has been variously reported in various studies to be ranging from 8% to 38.3% in class R, 11.4% to 50% in Class I, and 26.3 % to 49.5% in class F. However, there is a paucity of studies evaluating the incidence and outcome of AKI using RIFLE /AKIN classification in children. Akcan-Arikan et al [16] have recently used modified RIFLE criteria in 150 critically ill pediatric patients to assess acute kidney injury incidence and course. Of these children, 11 required dialysis and 24 died. 82% of acute kidney injury occurred in this initial week. Within this group of 123 children, 60 reached Risk category, 32 reached Injury, and 31 reached Failure. Acute kidney injury during admission was an independent predictor of intensive care; hospital length of stay and an increased risk of death. In another retrospective descriptive study from the Netherlands [22], 103 children with respiratory failure requiring mechanical ventilation for more than 4 days were studied. Median age was 4.5 years (range 1 month-17

years). Sixty patients (58%) developed AKI by modified RIFLE criteria. Six patients received renal replacement therapy. Seventeen patients (17%) died. In yet another study from California, USA [23], 123 consecutive pediatric patients with a burn injury of 10% or more of total body surface area percentage admitted during a 2 year period were studied. The incidence of AKI was 45.5%. Patients with AKI tended to have higher mortality than those without AKI. In a recent retrospective analysis of prospectively collected clinical data in 3396 patients in a pediatric intensive care unit [24], 194 (5.7%) patients had some degree of acute kidney injury at the time of admission, and 339 (10%) patients had acute kidney injury develop during the pediatric intensive care unit course. Almost half of all patients with acute kidney injury had their maximum RIFLE score within 24 hrs of intensive care unit admission, and approximately 75% achieved their maximum RIFLE score by the seventh intensive care unit day. After regression analysis, any acute kidney injury on admission and any development of or worsening of acute kidney injury during the pediatric intensive care unit stay were independently associated with increased mortality, with the odds of mortality increasing with each grade increase in RIFLE score.

ETIOLOGY OF AKI IN CHILDREN

There are well defined susceptible populations representing very high risk for AKI where early detection of renal dysfunction might result in a favorable outcome. These comprise children with sepsis, shock and dehydration, which are still common in developing countries. The inciting insults can occasionally be subtle and the cause of renal failure remains unobvious. They are often reversible if identified and managed in time. Children admitted to intensive care units are at high risk for AKI due to extensive invasive procedures, mechanical ventilation, potentially nephrotoxic medications and co-morbid conditions such as sepsis. Children with chronic kidney disease are also predisposed to AKI.

The etiology of AKI varies in different parts of the world. While sepsis, glomerulonephritis, hemolytic uremic syndrome, acute tubular necrosis and obstructive nephropathy predominate in developing countries [25], these have been replaced by hemato-oncologic complications and pulmonary failure as causes of AKI in the western world[26].

In a recent study from Turkey[27],causes of 100 pediatric patients with AKI were as follows: bone marrow transplantation in 27%, renal disease in 14%, dehydration in 10%, nephrotoxic medication in 8%, cardiac surgery related in 8%, and congenital anomalies in 2%. In a recently published study from a tertiary hospital in Kolkata, India, [28] glomerulonephritis and snake bite were found to be the two most important causes of acute kidney injury in the total 37 pediatric subjects studied, making up 70% of all cases. The acute mortality was 35% (n = 13), and it was significantly associated with peak creatinine and presence of multiple organ failure. The outcome at 6 months could be assessed for 92% (n = 22) of acute survivors and at 10 years for 67% (n = 16). The children that were traced showed in 32% (n = 7) at 6 months and 38% (n = 6) at 10 years, respectively, at least one of the four (abnormal creatinine, hypertension, hematuria and proteinuria) abnormal renal parameters. Nearly 25% (n = 6) of the survivors of an acute episode of renal failure had renal morbidity after 10 years, a percentage significant enough for these children to need long-term follow-up. In another study [29] involving 300 children with acute renal failure from Tehran, Iran, the three common causes of ARF were acute tubular necrosis (38%), acute glomerulonephritis (24%) and hemolytic uremic syndrome (24.1%). The overall mortality rate among patients was 24.7%.

EVALUATION OF THE CHILD WITH AKI

AKI has a wide differential diagnosis. History can help classify the pathophysiology

of AKI as prerenal, intrinsic renal or postrenal failure, and may suggest a specific etiology.

Prerenal failure

Ask about volume loss from diarrhea, vomiting, polyuria, or hemorrhage.

Ask symptoms related to hypovolemia, including thirst, decreased urine output, dizziness, and orthostatic hypotension.

History of orthopnea and paroxysmal nocturnal dyspnea may point towards congestive cardiac failure being the etiology.

Intrinsic renal failure

Patients can be divided into those with glomerular etiologies and those with tubular etiologies of ARF.

Glomerular diseases: Nephritic syndrome of hematuria, edema, and hypertension indicates a glomerular etiology of AKI. Ask about prior throat or skin infections.

Tubular diseases: Acute tubular necrosis should be suspected in any patient presenting after a period of hypotension secondary to cardiac arrest, hemorrhage, sepsis, drug overdose, or surgery.

A careful search for exposure to nephrotoxins should include a detailed list of all current medications and any recent exposure to radiologic contrast agents.

Prior history of dysentery especially in an infant may point towards hemolytic uremic syndrome, while crying during micturition may point towards urinary tract infection.

History of fever may point towards an etiology such as malaria or leptospirosis

Allergic interstitial nephritis should be suspected with fevers, rash, arthralgias, and exposure to certain medications including NSAIDs and antibiotics.

The presence of rash and arthritis may suggest Henoch Schonlein Purpura or lupus.

Postrenal failure

Posterior urethral valves should be suspected in any male infant with poor urinary stream

Flank pain and hematuria should raise a concern about renal calculi or papillary necrosis as the source of urinary obstruction.

Laboratory investigations should include blood urea, creatinine, sodium, potassium, complete blood counts including peripheral smear for any evidence of hemolysis, serum calcium, arterial blood gases, urinalysis for red blood cells, casts and albumin; renal ultrasonography and chest roentgenogram. Specific investigations should be guided by the history and examination findings.

MANAGEMENT

The basic principles of management are avoidance of life-threatening complications, maintenance of fluid and electrolyte balance, and nutritional support. It is of paramount importance to measure the daily weight, monitor the blood pressure and look for signs of fluid overload, pulmonary edema, pleural or pericardial effusion; and encephalopathy.

In a newborn with suspected posterior urethral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. Determination of the volume status is of utmost importance when initially evaluating a patient with AKI. If there is no pointer towards volume overload or cardiac failure, intravascular volume should be expanded by intravenous administration of isotonic saline, 20 mL/kg over 30 min. After volume resuscitation, hypovolemic patients generally void within 2 hr; failure to do so points toward the presence of intrinsic or postrenal AKI. Diuretic therapy should be administered only after the adequacy of the circulating blood volume has been established. Furosemide (2–4 mg/kg) may be administered as a single intravenous dose. If urine output does not improve, a continuous diuretic infusion may be given. If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction becomes

essential. Patients with a relatively normal intravascular volume should initially be restricted to 400 mL/m^2/24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, gastrointestinal tract) fluid losses should be replaced, volume for volume, with appropriate fluids. Fluid intake, urine output, body weight, and serum chemistries should be monitored on a daily basis.

Hyperkalemia (serum potassium level >6 mEq/L) may lead to cardiac arrhythmia and cardiac arrest. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. Measures to normalize body potassium stores should be initiated when the serum potassium value rises above 6.0 mEq/L. Exogenous sources of potassium (dietary, intravenous fluids) should be eliminated. Sodium polystyrene sulfonate resin (Kayexalate), 1 g/kg, should be given orally. Severe elevations in serum potassium (>7 mEq/L), especially if accompanied by ECG changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

Calcium gluconate 10% solution, 1.0 mL/kg IV, over 3–5 min

Sodium bicarbonate, 1–2 mEq/kg IV, over 5–10 min

Regular insulin, 0.1 U/kg, with glucose 50% solution, 1 mL/kg, over 1 hr

Persistent hyperkalemia should be managed by dialysis.

Hypocalcemia is primarily treated by lowering the serum phosphorus level. Calcium should not be given intravenously, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should be instructed to follow a low phosphorus diet, and phosphate binders (such as calcium carbonate) should be orally administered. Hyponatremia is most commonly a dilutional disturbance that must be corrected by fluid restriction. Symptomatic hyponatremia (seizures, lethargy) or serum sodium level <120 mEq/L should be managed with hypertonic (3%) saline. Mild metabolic acidosis is common in AKI but it rarely requires treatment. If acidosis is severe (arterial pH <7.15; serum bicarbonate <8 mEq/L) or contributes to hyperkalemia, acidosis should be corrected partially by the intravenous route, generally giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L).

Hypertension is common in AKI. Calcium channel blockers (amlodipine, 0.1–0.6 mg/kg/24 hr od) or â blockers (propranolol, 0.5–8 mg/kg/24 hr divided bid or tid; labetalol, 4–40 mg/kg/24 hr divided bid or tid) may be helpful in maintaining control of blood pressure. Children with severe symptomatic hypertension (hypertensive urgency/emergency) should be treated with continuous infusions of sodium nitroprusside (0.5–10 ìg/kg/min), labetalol (0.25–3.0 mg/kg/hr), or esmolol (150–300 ìg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

Nutrition is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be restricted moderately while maximizing caloric intake to prevent a catabolic state.

Indications for renal replacement therapy (dialysis) in patients with AKI

1. Fluid overload: Pulmonary edema, congestive cardiac failure, hypertension not controlled by fluid restriction

2. Uremic encephalopathy

3. Metabolic disturbances:

a) Severe metabolic acidosis (blood pH < 7.2) refractory to bicarbonate therapy

b) Hyperkalemia (serum potassium >6 mEq/L) not responding to medical therapy

c) Symptomatic hyponatremia (serum sodium <120 mEq/L)

4. Anuria > 48 hours

Role of Pharmacologic Interventions for Early Management of AKI

The efficacy of a number of pharmacologic interventions has been evaluated in the early management of AKI [31]. Renal-dose ("low dose") dopamine, once widely used, is ineffective in improving kidney function in AKI, with the possible exception of increasing diuresis on the first day of use. In addition, renal dose dopamine may even worsen kidney perfusion. Despite early promise in pilot studies of contrast nephropathy and sepsis-associated AKI , the selective dopamine A1 agonist, fenoldopam, did not improve or protect kidney function in larger studies of early AKI nor in contrast nephropathy. Low doses of atrial natriuretic peptide attenuate the rise in serum creatinine in postoperative ischemic renal failure. Larger doses, however, have not been effective in large randomized clinical trials of both nonoliguric and oliguric acute tubular necrosis.

Several preliminary reports suggest beneficial effects of the adenosine antagonist, theophylline, in the management of contrast nephropathy and in some forms of nephrotoxic AKI, but adequately powered, controlled studies are lacking. Loop diuretics and osmotic diuretics have failed to successfully prevent AKI in humans despite their ability to decrease tubular oxygen demand and relieve intratubular obstruction in animal models of AKI. Diuretics do not have any significant effect on progression or outcome of AKI and could be harmful. Finally, N-acetylcysteine, has been investigated in multiple trials, primarily in the setting of contrast nephropathy. Despite several positive reports, the prophylactic efficacy of N-acetyl-cysteine for contrast nephropathy remains controversial, and in other settings of AKI it appears to be ineffective. Although bicarbonate and mannitol have lost favor in the early treatment of AKI in the setting of rhabdomyolysis, there may be an effect of bicarbonate administration to prevent or lessen contrast nephropathy.

Long term outcome of AKI

Few data exist regarding the long term outcome and sequelae of AKI, especially in children. In a study by Askenzi et al [17] the 3-5 years survival of children with AKI who survived to hospital discharge was 139/174(79.9%). Most deaths (68.5%) occurred within 12 m after initial hospitalisation. They followed up 29 children with ARF for 3-5 years for residual renal injury (in the form of microalbuminuria, decreased GFR, hypertension and hematuria). Fifty-nine percent of the subjects had at least one of these signs of renal injury.

In a recently published study from a tertiary hospital in Kolkata, India, [28] the acute mortality was 35% (n = 13), and it was significantly associated with peak creatinine and presence of multiple organ failure. The outcome at 6 months could be assessed for 92% (n = 22) of acute survivors and at 10 years for 67% (n = 16). The children that were traced showed in 32% (n = 7) at 6 months and 38% (n = 6) at 10 years, respectively, at least one of the four (abnormal creatinine, hypertension, hematuria and proteinuria) abnormal renal parameters.

Multiple factors have been described in literature as predictors of outcome in AKI. These include etiology of AKI and duration of symptoms before presentation (29). Sepsis and haemolytic uremic syndrome (HUS) with prolonged anuria have been associated with poor outcome. In rapidly progressive glomerulonephritis (RPGN), the outcome has been associated with prompt immunosuppressive therapy and severity of histopathological findings. On the other hand, acute tubular necrosis without complications has been associated usually with favourable outcome. Delay in seeking health care, presence of infections and/or presence of cardiovascular/ respiratory complications have been described as determinants of poor outcome. In a recent study on critically ill patients with AKI undergoing hemodialysis, presence of cardiovascular co-morbidities, metabolic acidosis and acute respiratory distress syndrome (ARDS) were found to be determinants of clinical outcome on multivariate logistic regression (30). In the light of the changing trends in the etiology of pediatric AKI, a clearer understanding of the long term outcomes of this condition would allow optimization of follow-up strategies.

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Figure 1: RIFLE Classification for acute kidney injury

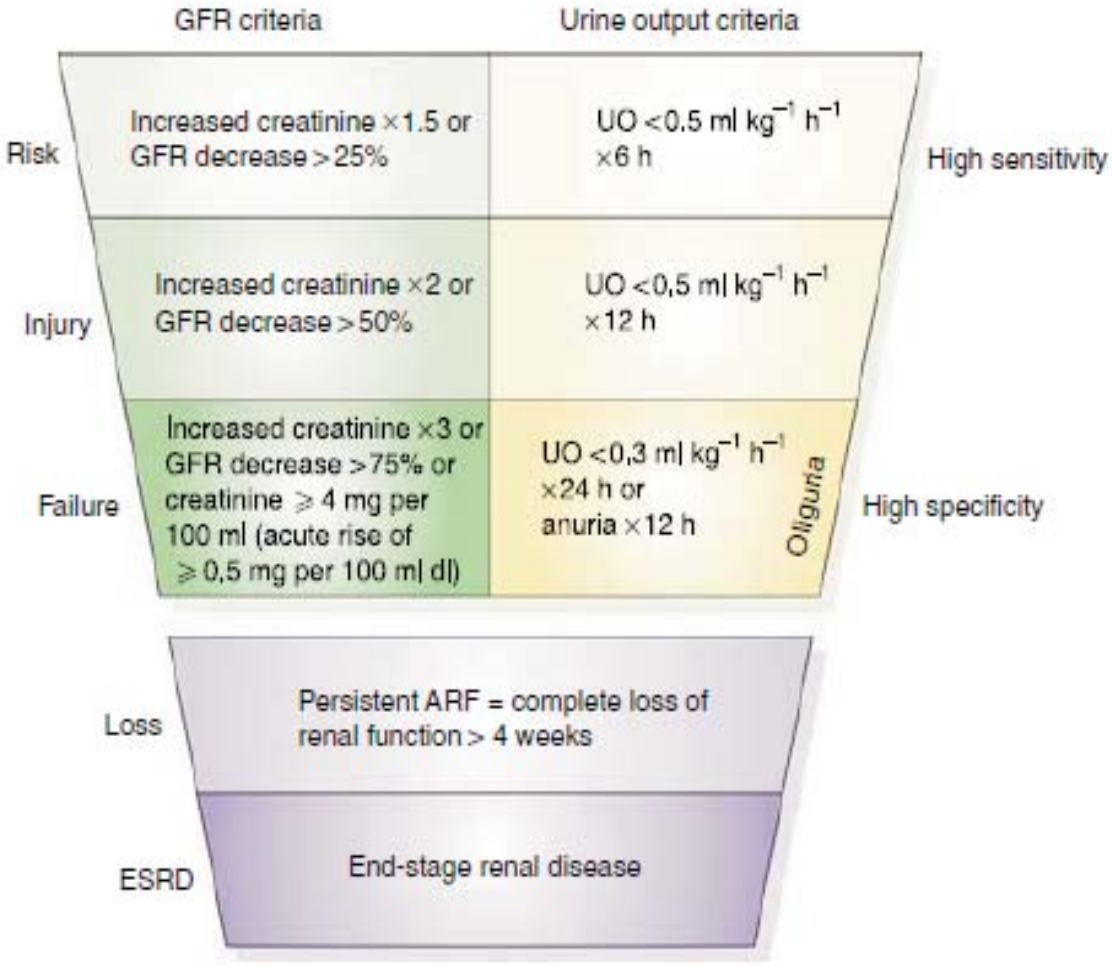

TABLE 1: Classification/staging system for acute kidney injury (AKIN)

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 1.5- to 2-fold from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 2- to 3-fold from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	Increase in serum creatinine to more than 3-fold from baseline or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours

Table 2: Recent studies on AKI using RIFLE classification

	Kuitunen (10)	Bell (11)	Abosaif (12)	Hoste (13)	Uchino (14)	Cruz (15)	Akcan-Arikan (16)	Plotz (22)
Country	Finland	Sweden	UK	USA	Japan	Italy	USA	Netherlan-ds
Study design	Single center	Retrospectiv-e single center	Retrospective single center	Retrospect-ive single centre	Retrospective single center	Prospective multicenter	Prospectiv-e single center	retrospecti ve cohort study
Study populati on	Cardiac surgery	ICU patients needing CRRT	ICU patients; serum creatinine >1.7 mg/ dl at admission	ICU admission-s	Hospitalized patients,14.6% of whom required intensive care	ICU admissions	Pediatric ICU admission-s	Pediatric ICU admission-s
Subjects	813	8152	N.S.	5383	20,126	2164	150	103
AKI incidenc e%	19.2	2.5	N.A.	67.2	18	10.8	82	58
R	56.4	9.0	32.8	18.5	9.1	19.2	48.8	24.1
I	17.9	26.6	30.6	39.7	5.2	35.0	26	18.2
F	25.6	64.4	23.5	41.8	3.7	45.7	25.2	57.7
RRT(% patients with AKI)	16.0	N.A. *	38.8	6.0	NS	30.3	6.9	5.8
Mortalit y %								17%
R	8.0	23.5	38.3	8.8	HR=2.54**	20.0	4.1	NS
I	21.4	22.0	50.0	11.4	HR=5.41**	29.3	NS#	
F	32.5	57.9	74.4	26.3	HR=10.12**	49.5	NS#	