Acute Renal Failure: Causes and Prognosis

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There are many causes—more than fifty are given within this present chapter—that can trigger pathophysiological mechanisms leading to acute renal failure (ARF). This syndrome is characterized by a sudden decrease in kidney function, with a consequence of loss of the hemostatic equilibrium of the internal medium. The primary marker is an increase in the concentration of the nitrogenous components of blood. A second marker, oliguria, is seen in 50% to 70% of cases.

In general, the causes of ARF have a dynamic behavior as they change as a function of the economical and medical development of the community. Economic differences justify the different spectrum in the causes of ARF in developed and developing countries. The setting where ARF appears (community versus hospital), or the place where ARF is treated (intensive care units [ICU] versus other hospital areas) also show differences in the causes of ARF.

While functional outcome after ARF is usually good among the surviving patients, mortality rate is high: around 45% in general series and close to 70% in ICU series. Although it is unfortunate that these mortality rates have remained fairly constant over the past decades, it should be noted that today's patients are generally much older and display a generally much more severe condition than was true in the past. These age and severity factors, together with the more aggressive therapeutical possibilities presently available, could account for this apparent paradox.

As is true for any severe clinical condition, a prognostic estimation of ARF is of great utility for both the patients and their families, the medical specialists (for analysis of therapeutical maneuvers and options), and for society in general (demonstrating the monetary costs of treatment). This chapter also contains a brief review of the prognostic tools available for application to ARF.

CHAPTER

8

Causes of Acute Renal Failure

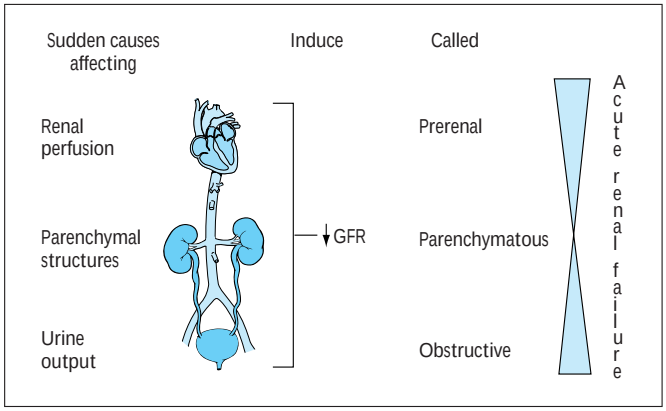


FIGURE 8-1

Characteristics of acute renal failure. Acute renal failure is a syndrome characterized by a sudden decrease of the glomerular filtration rate (GFR) and consequently an increase in blood nitrogen products (blood urea nitrogen and creatinine). It is associated with oliguria in about two thirds of cases. Depending on the localization or the nature of the renal insult, ARF is classified as prerenal, parenchymatous, or obstructive (postrenal).

CAUSES OF PRERENAL ACUTE RENAL FAILURE

- Decreased effective extracellular volume
- Renal losses: hemorrhage, vomiting, diarrhea, burns, diuretics
- Redistribution: hepatopathy, nephrotic syndrome, intestinal obstruction, pancreatitis, peritonitis, malnutrition
- Decreased cardiac output: cardiogenic shock, valvulopathy, myocarditis, myocardial infarction, arrhythmia, congestive heart failure, pulmonary emboli, cardiac tamponade
- Peripheral vasodilation: hypotension, sepsis, hypoxemia, anaphylactic shock, treatment with interleukin L2 or interferons, ovarian hyperstimulation syndrome
- Renal vasoconstriction: prostaglandin synthesis inhibition, α-adrenergics, sepsis, hepatorenal syndrome, hypercalcemia
- Efferent arteriole vasodilation: converting-enzyme inhibitors

FIGURE 8-2

Causes of prerenal acute renal failure (ARF). *Prerenal* ARF, also known as prerenal uremia, supervenes when glomerular filtration rate falls as a consequence of decreased effective renal blood supply. The condition is reversible if the underlying disease is resolved.

CAUSES OF PARENCHYMATOUS ACUTE RENAL FAILURE

- Acute tubular necrosis
  - Hemodynamic: cardiovascular surgery,* sepsis,* prerenal causes*
  - Toxic: antimicrobials,* iodide contrast agents,* anesthesics, immunosuppressive or antineoplastic agents,* Chinese herbs, Opiaceous, Extasis, mercurials, organic solvents, venoms, heavy metals, mannitol, radiation
  - Intratubular deposits: acute uric acid nephropathy, myeloma, severe hypercalcemia, primary oxalosis, sulfadiazine, fluoride anesthesics
  - Organic pigments (endogenous nephrotoxins):
    - Myoglobin rhabdomyolisis: muscle trauma; infections; dermatopolymyositis; metabolic alterations; hyperosmolar coma; diabetic ketoacidosis; severe hypokalemia; hyper- or hyponatremia; hypophosphatemia; severe hypothyroidism; malignant hyperthermia; toxins such as ethylene glycol, carbon monoxide, mercurial chloride, stings; drugs such as fibrates, statins, opioids and amphetamines; hereditary diseases such as muscular dystrophy, metabolopathies, McArdle disease and carnitine deficit
    - Hemoglobinuria: malaria; mechanical destruction of erythrocytes with extracorporeal circulation or metallic prosthesis, transfusion reactions, or other hemolysis; heat stroke; burns; glucose-6-phosphate dehydrogenase; nocturnal paroxystic hemoglobinuria; chemicals such as aniline, quinine, glycerol, benzene, phenol, hydralazine; insect venoms
- Acute tubulointerstitial nephritis (*see* Fig. 8-4)
- Vascular occlusion
  - Principal vessels: bilateral (unilateral in solitary functioning kidney) renal artery thrombosis or embolism, bilateral renal vein thrombosis
  - Small vessels: atheroembolic disease, thrombotic microangiopathy, hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura, postpartum acute renal failure, antiphospholipid syndrome, disseminated intravascular coagulation, scleroderma, malignant arterial hypertension, radiation nephritis, vasculitis
- Acute glomerulonephritis
  - Postinfectious: streptococcal or other pathogen associated with visceral abscess, endocarditis, or shunt
  - Henoch-Schonlein purpura
  - Essential mixed cryoglobulinemia
  - Systemic lupus erythematosus
  - ImmunoglobulinA nephropathy
  - Mesangiocapillary
  - With antiglomerular basement membrane antibodies with lung disease (Goodpasture is syndrome) or without it
  - Idiopathic, rapidly progressive, without immune deposits
- Cortical necrosis, abruptio placentae, septic abortion, disseminated intravascular coagulation

FIGURE 8-3

Causes of parenchymal acute renal failure (ARF). When the sudden decrease in glomerular filtration rate that characterizes ARF is secondary to intrinsic renal damage mainly affecting tubules, interstitium, glomeruli and/or vessels, we are facing a *parenchymatous ARF*. Multiple causes have been described, some of them constituting the most frequent ones are marked with an asterisk.

MOST FREQUENT CAUSES OF ACUTE TUBULOINTERSTITIAL NEPHRITIS

- Antimicrobials
  - Penicillin
  - Ampicillin
  - Rifampicin
  - Sulfonamides
- Analgesics, anti-inflammatories
  - Fenoprofen
  - Ibuprofen
  - Naproxen
  - Amidopyrine
  - Glafenine
- Other drugs
  - Cimetidine
  - Allopurinol
- Immunological
  - Systemic lupus erythematosus
  - Rejection
- Infections (at present quite rare)
- Neoplasia
  - Myeloma
  - Lymphoma
  - Acute leukemia
- Idiopathic
  - Isolated
  - Associated with uveitis

FIGURE 8-4

Most common causes of tubulointerstitial nephritis. During the last years, acute tubulointerstitial nephritis is increasing in importance as a cause of acute renal failure. For decades infections were the most important cause. At present, antimicrobials and other drugs are the most common causes.

CAUSES OF OBSTRUCTIVE ACUTE RENAL FAILURE

- Congenital anomalies
  - Ureterocele
  - Bladder diverticula
  - Posterior urethral valves
  - Neurogenic bladder
- Acquired uropathies
  - Benign prostatic hypertrophy
  - Urolithiasis
  - Papillary necrosis
  - Iatrogenic ureteral ligation
- Malignant diseases
  - Prostate
  - Bladder
  - Urethra
  - Cervix
  - Colon
  - Breast (metastasis)
- Retroperitoneal fibrosis
  - Idiopathic
  - Associated with aortic aneurysm
  - Trauma
  - Iatrogenic
  - Drug-induced
- Gynecologic non-neoplastic
  - Pregnancy-related
  - Uterine prolapse
  - Endometriosis
- Acute uric acid nephropathy
- Drugs
  - ε-Aminocaproic acid
  - Sulfonamides
- Infections
  - Schistosomiasis
  - Tuberculosis
  - Candidiasis
  - Aspergillosis
  - Actinomycosis
- Other
  - Accidental urethral catheter occlusion

FIGURE 8-5

Causes of obstructive acute renal failure. Obstruction at any level of the urinary tract frequently leads to acute renal failure. These are the most frequent causes.

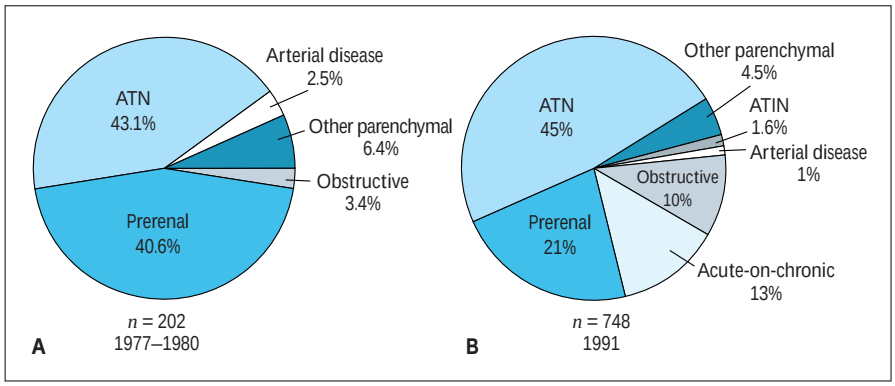


FIGURE 8-6

This figure shows a comparison of the percentages of the different types of acute renal failure (ARF) in a western European country in 1977–1980 and 1991: **A**, distribution in a typical Madrid hospital; **B**, the Madrid ARF Study [1]. There are two main differences: 1) the appearance of a new group in 1991, "acute on chronic ARF," in which only mild forms (serum creatinine concentrations between 1.5 and 3.0 mg/dL) were considered, for methodological reasons; 2) the decrease in prerenal ARF suggests improved medical care. This low rate of prerenal ARF has been observed by other workers in an intensive care setting [2]. The other types of ARF remain unchanged.

FINDINGS OF THE MADRID STUDY

Condition	Incidence (per million persons per year)	95% CI
Acute tubular necrosis	88	79–97
Prerenal acute renal failure	46	40–52
Acute on chronic renal failure	29	24–34
Obstructive acute renal failure	23	19–27
Glomerulonephritis (primary or secondary)	6.3	4.8–8.3
Acute tubulointerstitial nephritis	3.5	1.7–5.3
Vasculitis	3.5	1.7–5.3
Other vascular acute renal failure	2.1	0.8–3.4
Total	209	195–223

FIGURE 8-7

Incidences of different forms of acute renal failure (ARF) in the Madrid ARF Study [1]. Figures express cases per million persons per year with 95% confidence intervals (CI).

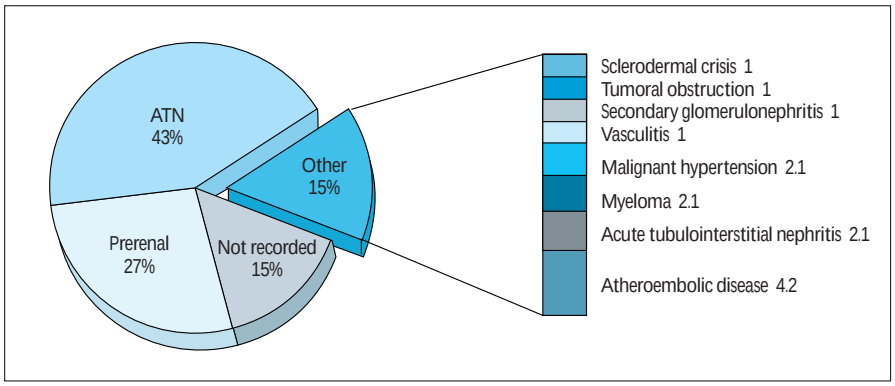


FIGURE 8-8
The most frequent causes of acute renal failure (ARF) in patients with preexisting chronic renal failure are acute tubular necrosis (ATN) and prerenal failure. The distribution of causes of ARF in these patients is similar to that observed in patients without previous kidney diseases. (*Data from* Liaño *et al.* [1])

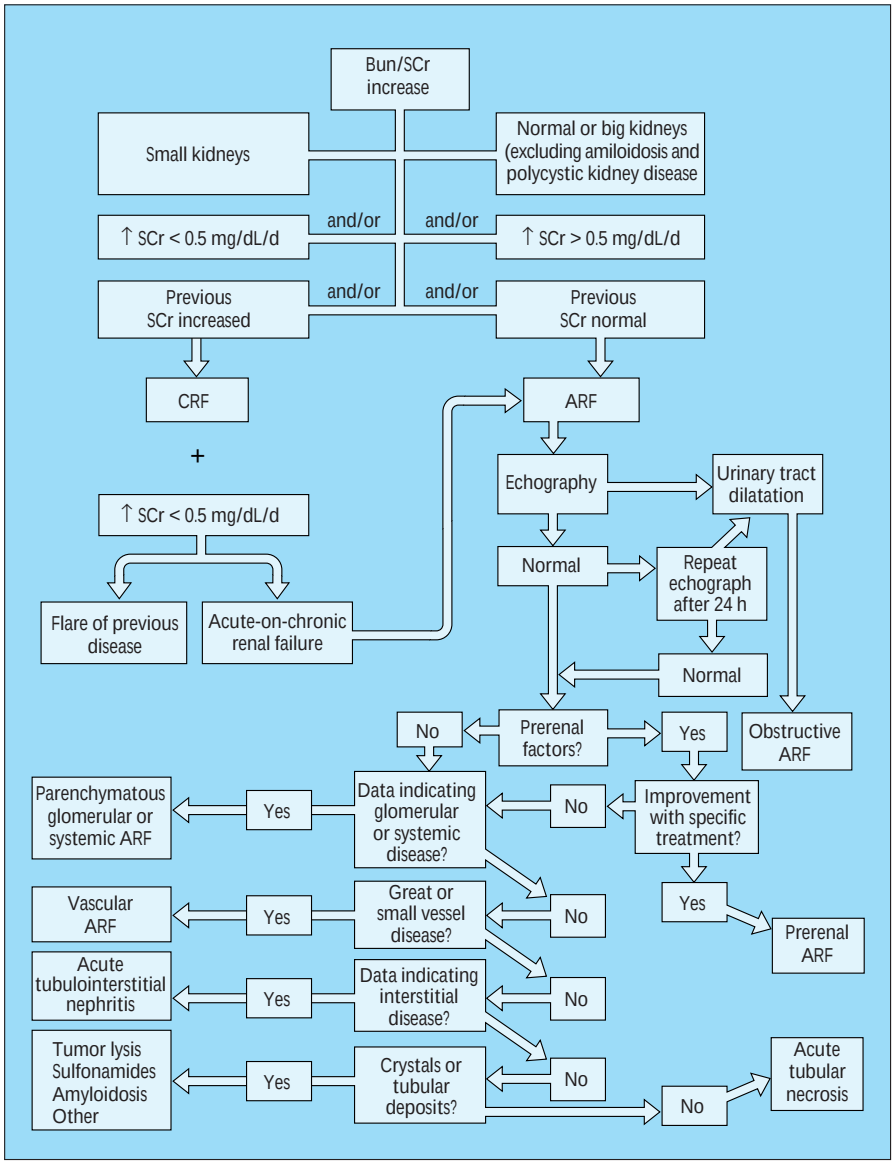


FIGURE 8-9
Discovering the cause of acute renal failure (ARF). This is a great challenge for clinicians. This algorithm could help to determine the cause of the increase in blood urea nitrogen (BUN) or serum creatinine (SCr) in a given patient.

BIOPSY RESULTS IN THE MADRID STUDY

Disease	Patients, n
Primary GN	12
Extracapillary	6
Acute proliferative	3
Endocapillary and extracapillary	2
Focal sclerosing	1
Secondary GN	6
Antiglomerular basement membrane	3
Acute postinfectious	2
Diffuse proliferative (systemic lupus erythematosus)	1*
Vasculitis	10
Necrotizing	5*
Wegener's granulomatosis	3
Not specified	2
Acute tubular necrosis	4*
Acute tubulointerstitial nephritis	4
Atheroembolic disease	2
Kidney myeloma	2*
Cortical necrosis	1
Malignant hypertension	1
ImmunoglobulinA GN + ATN	1
Hemolytic-uremic syndrome	1
Not recorded	2

* One patient with acute-on-chronic renal failure.

FIGURE 8-10

Biopsy results in the Madrid acute renal failure (ARF) study. Kidney biopsy has had fluctuating roles in the diagnostic work-up of ARF. After extrarenal causes of ARF are excluded, the most common cause is acute tubular necrosis (ATN). Patients with well-established clinical and laboratory features of ATN receive no benefit from renal biopsy. This histologic tool should be reserved for parenchymatous ARF cases when there is no improvement of renal function after 3 weeks' evolution of ARF. By that time, most cases of ATN have resolved, so other causes could be influencing the poor evolution. Biopsy is mandatory when a potentially treatable cause is suspected, such as vasculitis, systemic disease, or glomerulonephritis (GN) in adults. Some types of parenchymatous non-ATN ARF might have histologic confirmation; however kidney biopsy is not strictly necessary in cases with an adequate clinical diagnosis such as myeloma, uric acid nephropathy, or some types of acute tubulointerstitial nephritis . Other parenchymatous forms of ARF can be accurately diagnosed without a kidney biopsy. This is true of acute post-streptococcal GN and of hemolytic-uremic syndrome in children. Kidney biopsy was performed in only one of every 16 ARF cases in the Madrid ARF Study [1]. All patients with primary GN, 90% with vasculitis and 50% with secondary GN were diagnosed by biopsy at the time of ARF. As many as 15 patients were diagnosed as having acute tubulointerstitial nephritis, but only four (27%) were biopsied. Only four of 337 patients with ATN (1.2%) underwent biopsy. (*Data from* Liaño *et al.* [1].)

Predisposing Factors for Acute Renal Failure

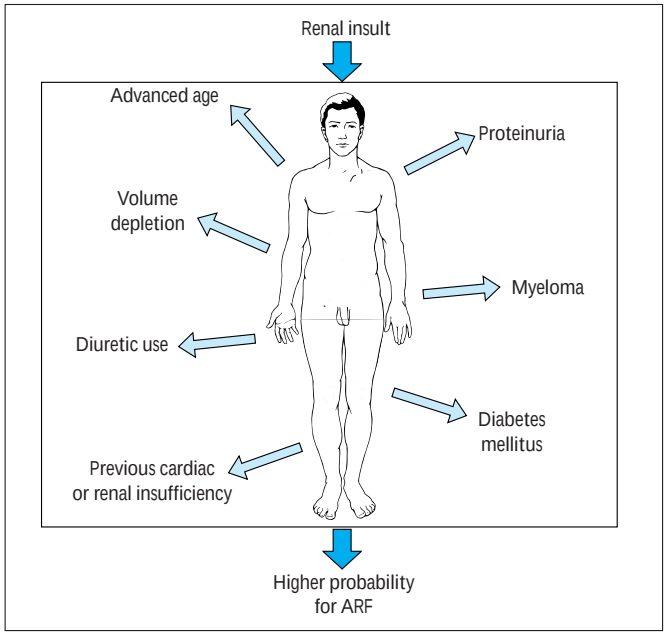


FIGURE 8-11

Factors that predispose to acute renal failure (ARF). Some of them act synergistically when they occur in the same patient. Advanced age and volume depletion are particularly important.

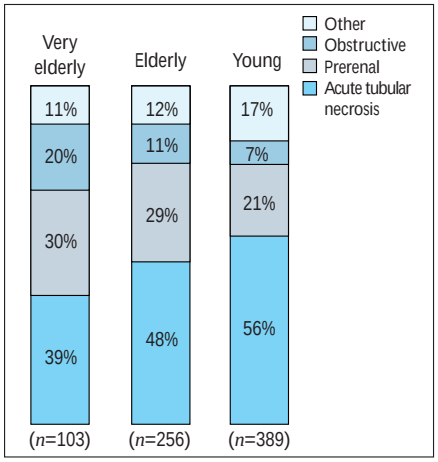


FIGURE 8-12

Causes of acute renal failure (ARF) relative to age. Although the cause of ARF is usually multifactorial, one can define the cause of each case as the most likely contributor to impairment of renal function. One interesting approach is to distribute the causes of ARF according to age. This figure shows the main causes of ARF, dividing a population diagnosed with ARF into the very elderly (at least 80 years), elderly (65 to 79), and young (younger than 65). Essentially, acute tubular necrosis (ATN) is less frequent (P=0.004) and obstructive ARF more frequent (P<0.001) in the very old than in the youngest patients. Prerenal diseases appear with similar frequency in the three age groups. (*Data from* Pascual *et al.* [3].)

Epidemiology of Acute Renal Failure

EPIDEMIOLOGY OF ACUTE RENAL FAILURE

Investigator, Year	Country (City)	Study Period (Study Length)	Study Population (millions)	Incidence (pmp/y)
Eliahou *et al.*, 1973 [4]	Israel	1965–1966 (2 yrs)	2.2	52
Abraham *et al.*, 1989 [5]	Kuwait	1984–1986 (2 yrs)	0.4	95
McGregor *et al.*, 1992 [6]	United Kingdom (Glasgow)	1986–1988 (2 yrs)	0.94	185
Sanchez *et al.*, 1992 [7]	Spain (Cuenca)	1988–1989 (2 yrs)	0.21	254
Feest *et al.*, 1993 [8]	United Kingdom (Bristol and Devon)	1986–1987 (2 yrs)	0.44	175
Madrid ARF Study Group, 1996 [1]	Spain (Madrid)	1991–1992 (9 mo)	4.23	209

FIGURE 8-13

Prospective studies. Prospective epidemiologic studies of acute renal failure (ARF) in large populations have not often been published . The first study reported by Eliahou and colleagues [4] was developed in Israel in the 1960s and included only Jewish patients. This summary of available data suggests a progressive increase in ARF incidence that at present seems to have stabilized around 200 cases per million population per year (pmp/y). No data about ARF incidence are available from undeveloped countries.

EPIDEMIOLOGY OF ACUTE RENAL FAILURE: NEED OF DIALYSIS

Investigator, Year	Country	Cases (pmp/y)
Lunding *et al.*, 1964 [9]	Scandinavia	28
Eliahou *et al.*, 1973 [4]	Israel	17*
Lachhein *et al.*, 1978 [10]	West Germany	30
Wing *et al.*, 1983 [11]	European Dialysis and Transplant Association	29
Wing *et al.*, 1983 [11]	Spain	59
Abraham *et al.*, 1989 [5]	Kuwait	31
Sanchez *et al.*, 1992 [7]	Spain	21†
McGregor *et al.*, 1992 [6]	United Kingdom	31
Gerrard *et al.*, 1992 [12]	United Kingdom	71
Feest *et al.*, 1993 [8]	United Kingdom	22†
Madrid ARF Study Group [1]	Spain	57

* Very restrictive criteria.
† Only secondary care facilities.

FIGURE 8-14

Number of patients needing dialysis for acute renal failure (ARF), expressed as cases per million population per year (pmp/y). This has been another way of assessing the incidence of the most severe cases of ARF. Local situations, mainly economics, have an effect on dialysis facilities for ARF management. In 1973 Israeli figures showed a lower rate of dialysis than other countries at the same time. The very limited access to dialysis in developing countries supports this hypothesis. At present, the need for dialysis in a given area depends on the level of health care offered there. In two different countries (*eg*, the United Kingdom and Spain) the need for dialysis for ARF was very much lower when only secondary care facilities were available. At this level of health care, both countries had the same rate of dialysis. The Spanish data of the EDTA-ERA Registry in 1982 gave a rate of dialysis for ARF of 59 pmp/y. This rate was similar to that found in the Madrid ARF Study 10 years later. These data suggest that, when a certain economical level is achieved, the need of ARF patients for dialysis tends to stabilize.

HISTORICAL PATTERNS OF ACUTE RENAL FAILURE

	Proportion of Cases, %				
	France 1973	India 1965–1974	France 1981–1986	India 1981–1986	South Africa 1986–1988
Surgical	46	11	30	30	8
Medical	30	67	70	61	77
Obstetric	24	22	2	9	15

FIGURE 8-15

Historical perspective of acute renal failure (ARF) patterns in France, India, and South Africa. In the 1960s and 1970s, obstetrical causes were a great problem in both France and India and overall incidences of ARF were similar. Surgical cases were almost negligible in India at that time, probably because of the relative unavailability of hospital facilities. During the 1980s surgical and medical causes were similar in both countries. In India, the increase in surgical cases may be explained by advances in health care, so that more surgical procedures could be done. The decrease in surgical cases in France, despite the fact that surgery had become very sophisticated, could be explained by better management of surgical patients.

(Legend continued on next page)

FIGURE 8-15 *(Continued)*

Changes in classification criteria—inclusion of a larger percentage of medical cases than a decade before—could be an alternative explanation. In addition, obstetric cases had almost disappeared in France in the 1980s, but they were still an important cause of ARF in India. In a South African study that excluded the white population the distribution of ARF causes was almost identical to that observed in India 20 years earlier. In conclusion, 1) the economic level of a country determines the spectrum of ARF causes observed; 2) when a developing country improves its economic situation, the spectrum moves toward that observed in developed countries; and 3) great differences can be detected in ARF causes among developing countries, depending on their individual economic power. (*Data from* Kleinknecht [13]; Chugh *et al.* [14]; Seedat *et al.* [15].)

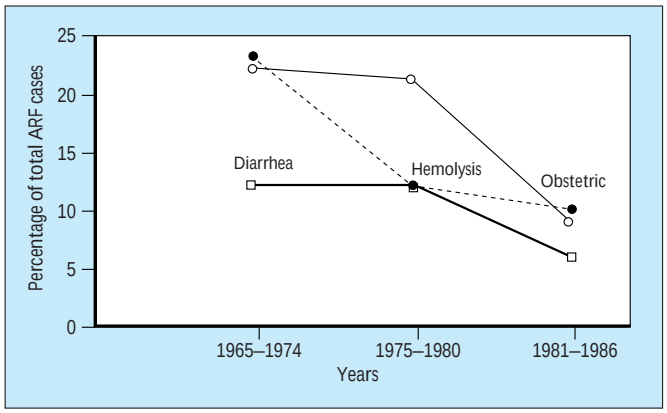


FIGURE 8-16

Changing trends in the causes of acute renal failure (ARF) in the Third-World countries. Trends can be identified from the analysis of medical and obstetric causes by the Chandigarh Study [14]. Chugh and colleagues showed how obstetric (septic abortion) and hemolytic (mainly herbicide toxicity) causes tended to decrease as economic power and availability of hospitalization improved with time. These causes of ARF, however, did not completely disappear. By contrast, diarrheal causes of ARF, such as cholera and other gastrointestinal diseases, remained constant. In conclusion, gastrointestinal causes of ARF will remain important in ARF until structural and sanitary measures (*eg*, water treatment) are implemented. Educational programs and changes in gynecological attention, focused on controlled medical abortion and contraceptive measures, should be promoted to eradicate other forms of ARF that constitute a plague in Third World countries.

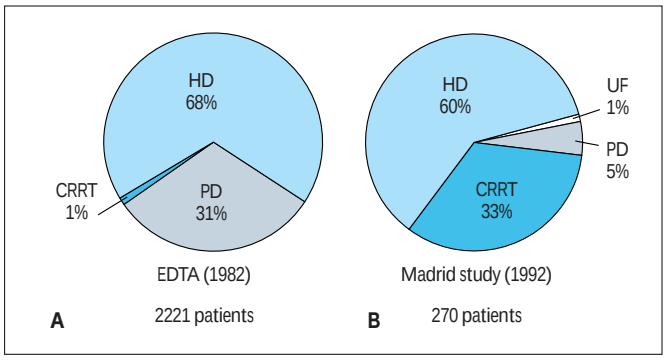


FIGURE 8-17

Evolution of dialysis techniques for acute renal failure (ARF) in Spain. **A**, The percentages of different modalities of dialysis performed in Spain in the early 1980s. **B**, The same information obtained a decade. At this latter time, 90% of conventional hemodialysis (HD) was performed using bicarbonate as a buffer. These rates are those of a developed country. In developing countries, dialysis should be performed according to the available facilities and each individual doctor's experience in the different techniques. PD—peritoneal dialysis; CRRT—continuous renal replacement technique; UF—isolated ultrafiltration. (**A**, *Data from* the EDTA-ERA Registry [11]; **B** *data from* the Madrid ARF Study [1].)

Hospital-Related Epidemiologic Data

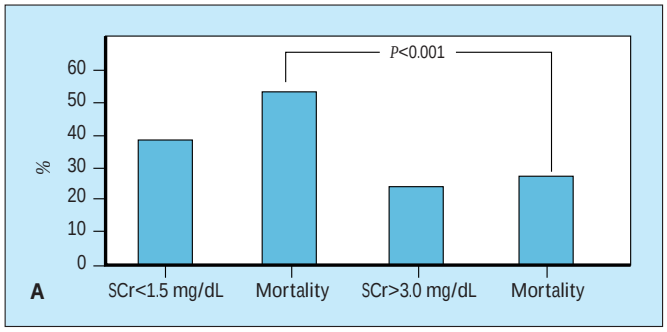


FIGURE 8-18

Serum creatinine (SCr) at hospital admission has diagnostic and prognostic implications for acute renal failure (ARF). **A**, Of the patients included in an ARF epidemiologic study 39% had a normal SCr concentration (less than 1.5 mg/dL) at hospital admission. It is worth noting that only 22% of the patients had clearly established ARF (SCr greater than 3 mg/dL) when admitted (no acute-on-chronic case was included). Mortality was significantly higher in patients with normal SCr at admission.

(Continued on next page)

ARF	Community-acquired (SCr at admission>3 mg/dL)	Hospital-acquired (SCr at admission<1.5 mg/dL)
ATN	41.8	58.2
Prerenal	47.5	52.5
Obstructive	77.3	22.7
Total	49.7	50.3

B

FIGURE 8-18 *(Continued)*

B, With the same two groups, acute tubular necrosis (ATN) predominated among the hospital-induced ARF group, whereas the obstructive form was the main cause of community-acquired ARF. In conclusion, the hospital could be considered an ARF generator, particularly of the most severe forms. Nonetheless, these iatrogenic ARF cases are usually "innocent," and are an unavoidable consequence of diagnostic and therapeutic maneuvers. (*Data from* Liaño *et al.* [1].)

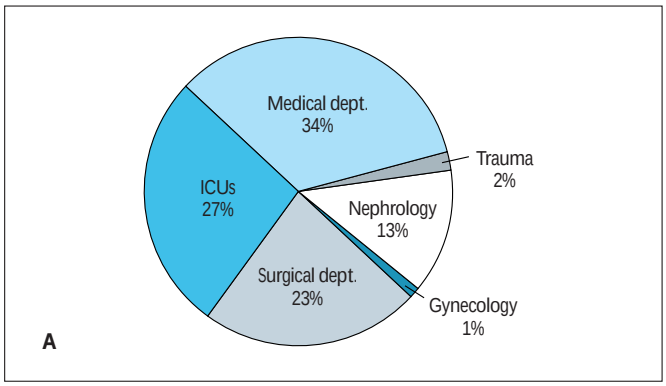


FIGURE 8-19

Acute renal failure: initial hospital location and mortality. **A**, Initial departmental location of ARF patients in a hospital in a Western country. The majority of the cases initially were seen in medical, surgical, and intensive care units (ICUs). The cases initially treated in nephrology departments were community acquired, whereas the ARF patients in the other settings generally acquired ARF in those settings. Obstetric-gynecologic ARF cases have almost disappeared. ARF of traumatic origin is also rare, for two reasons: 1) polytrauma patients are now treated in the ICU and 2) early and effective treatments applied today to trauma patients at the accident scene, and quick transfer to hospital, have decreased this cause of ARF. **B**, Mortality was greater for patients initially treated in the ICU and lower in the nephrology setting than rates observed in other departments. These figures were obtained from 748 ARF patients admitted to 13 different adult hospitals. (*Data from* Liaño *et al.* [1].)

EPIDEMIOLOGIC VARIABLES

Investigator, Year	Acute Renal Failure in Hospitalized Patients (per 1000 admissions)
Hou *et al.*, 1983*	49.0
Shusterman *et al.*, 1987*	19.0
Lauzurica *et al.*, 1989*	
First period	16.0
Second period	6.5
Abraham *et al.*, 1989	1.3
Madrid Study, 1992	1.5

* Case-control studies.

FIGURE 8-20

Epidemiologic variable. The incidence of hospital-acquired acute renal failure (ARF) depends on what epidemiologic method is used. In case-control studies the incidence varied between 49 and 19 per thousand. When the real occurrence was measured in large populations over longer intervals, the incidence of hospital-acquired ARF decreased to 1.5 per thousand admissions. (*Data from* [1,5,16,17,18].)

Prognosis

HISTORICAL PERSPECTIVE OF MEDICAL PROGNOSIS APPLIED IN ACUTE RENAL FAILURE

Criteria	Derivation	Applications	Advantages	Drawbacks
Classical	Doctor's experience	Individual prognosis	Easy	Doctor's inexperience Unmeasurable
Traditional	Univariate statistical analysis	Risk stratification	Easy	Only one determinant of prognosis is considered
Present	Multivariate statistical analysis Computing facilities	Risk stratification Individual prognosis?	Measurable Theoretically, "all" factors influencing outcome are considered	Complexity (variable, depending on model)
Future	Multivariate analysis Computing facilities	Risk stratification Individual prognosis Patient's quality of life evaluation Functional prediction	Measurable "All" factors considered	Ideally, none

FIGURE 8-21

Estimating prognosis. The criteria for estimating prognosis in acute renal failure can be classified into four periods. The *Classical* or heuristic way is similar to that used since the Hippocratic aphorisms. The *Traditional* one based on simple statistical procedures, is not useful for individual prognosis. The *Present* form is more or less complex, depending on what method is used, and it is possible, thanks to computing facilities and the development of multivariable analysis. Theoretically, few of these methods can give an individual prognosis [19]. They have not been used for triage. The next step will need a great deal of work to design and implement adequate tools to stratify risks and individual prognosis. In addition, the estimate of residual renal function and survivors' quality of life, mainly for older people, are future challenges.

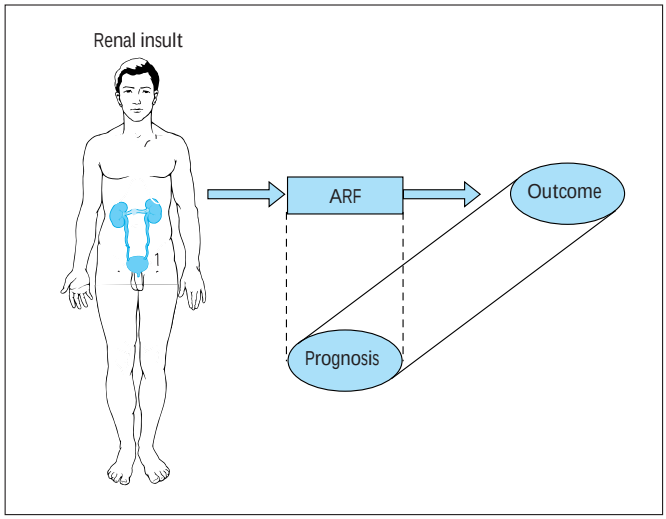


FIGURE 8-22

Ideally, prognosis should be established as the problem, the episode of acute renal failure (ARF), starts. Correct prognostic estimation gives the real outcome for a patient or group of patients as precisely as possible. In this ideal scenario, this fact is illustrated by giving the same surface area for the concepts of outcome and prognosis.

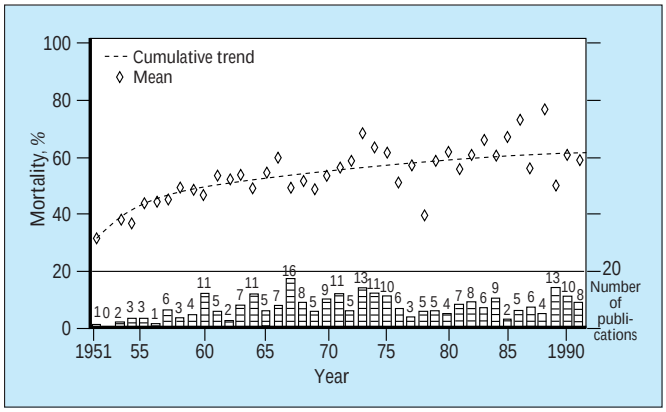


FIGURE 8-23

Mortality trends in acute renal failure (ARF). This figure shows the evolution of mortality during a 40-year period, starting in 1951. The graphic was elaborated after reviewing the outcome of 32,996 ARF patients reported in 258 published papers. As can be appreciated, mortality rate increases slowly but constantly during this follow-up, despite theoretically better availability of therapeutic armamentarium (mainly antibiotics and vasoactive drugs), deeper knowledge of dialysis techniques, and wider access to intensive care facilities. This improvement in supporting measures allows the physician to keep alive, for longer periods of time patients who otherwise would have died. A complementary explanation could be that the patients treated now are usually older, sicker, and more likely to be treated more aggressively. (*From* Kierdorf *et al.* [20]; with permission.)

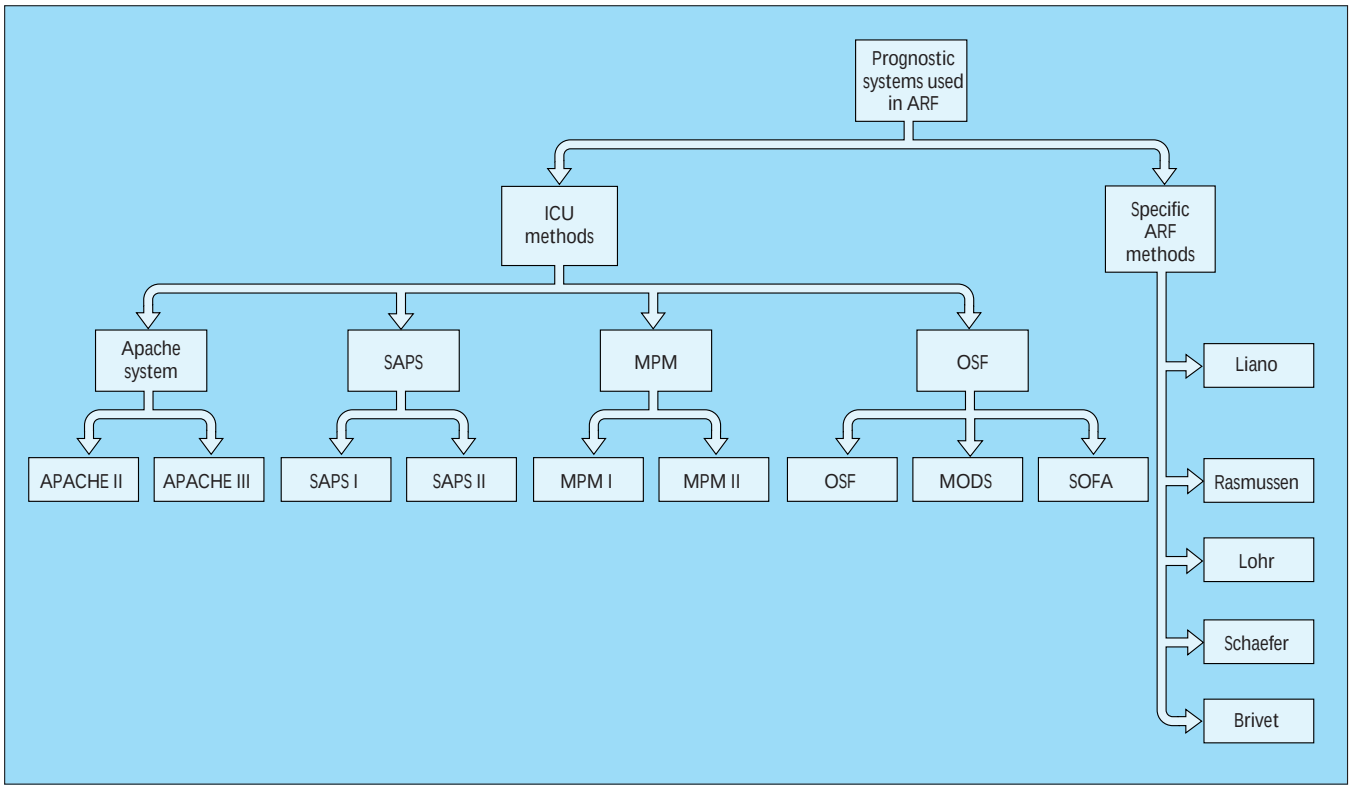


FIGURE 8-24

Ways of estimating prognosis in acute renal failure (ARF). This can be done using either general intensive care unit (ICU) score systems or methods developed specifically for ARF patients. ICU systems include Acute Physiological and Chronic Health Evaluation (APACHE) [21,22], Simplified Physiologic Score (SAPS)[23,24], Mortality Prediction Model (MPM) [25,26], and Organ System Failure scores (OSF) [27]. Multiple Organ Dysfunction Score (MODS) [28] and Sepsis-Related Organ Failure Assessment Score (SOFA) [29] are those that seem most suitable for this purpose. APACHE II used to be most used. Other systems (white boxes) have been used in ARF. On the other hand, at least 17 specific ARF prognostic methods have been developed [20,30]. The figure shows only those that have been used after their publication [31], plus one recently published system which is not yet in general use [2].

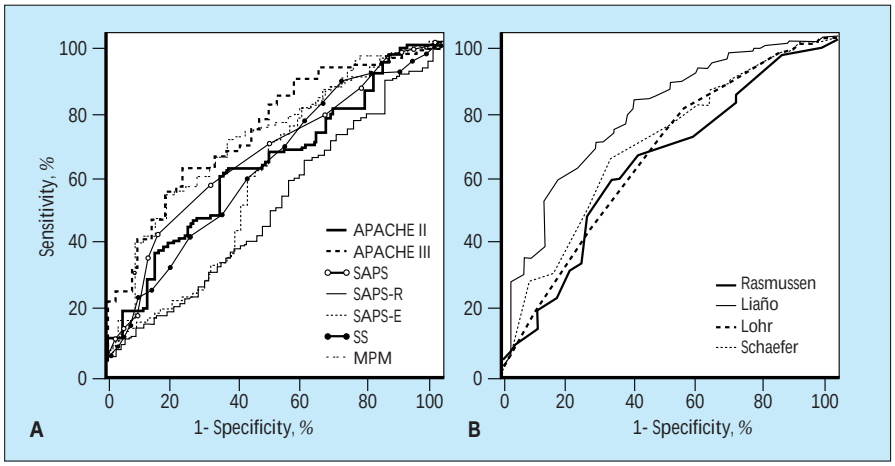


FIGURE 8-25

Comparison of prognostic methods for acute renal failure (ARF) by ROC curve analysis [31]. A method is better when its ROC-curve moves to the upper left square determined by the sensitivity and the reciprocal of the specificity. **A**, ROC curves of seven prognostic methods usually employed in the ICU setting. The best curve comes from the APACHE III method, which has an area under the ROC curve of 0.74 ± 0.04 (SE). **B**, Four ROC curves corresponding to prognostic methods specifically developed for ARF patients are depicted. The best curve in this panel comes from the Liaño method for ARF prognosis. Its area under the curve is 0.78 ± 0.03 (SE). APACHE—Acute Physiology and Chronic Health Evaluation, (II second version [21]; III third version [22]); SAPS—Simplified Acute Physiology Score [23]; SAPS-R—SAPS-reduced [33]; SAPS-E—SAPS-Extended [32]; SS—Sickness Score [33]; MPM—Mortality Prediction Model [25]; ROC curve—Receiving Operating Characteristic curve; SE—Standard Error. (*From* Douma [31]; with permission.)

ACUTE RENAL FAILURE: VARIABLES STUDIED WITH UNIVARIATE ANALYSIS

Age	Hypotension
Jaundice	Catabolism
Sepsis	Hemolysis
Burns	Hepatic disease
Trauma	Kind of surgery
NSAIDs	Hyperkalemia
BUN increments	Need for dialysis
Coma	Assisted respiration
Oliguria	Site of war injuries
Obstetric origin	Disseminated intravascular coagulopathy
Malignancies	Pancreatitis
Cardiovascular disease	Antibiotics
X-ray contrast agents	Timing of treatment
Acidosis	

FIGURE 8-26

Individual factors that have been associated with acute renal failure (ARF) outcome. Most of these innumerable variables have been related to an adverse outcome, whereas few (nephrotoxicity as a cause of ARF and early treatment) have been associated with more favorable prognosis. For a deep review of variables studied with univariate statistical analysis [34, 35]. NSAID—nonsteroidal anti-inflammatory drugs; BUN—blood urea nitrogen.

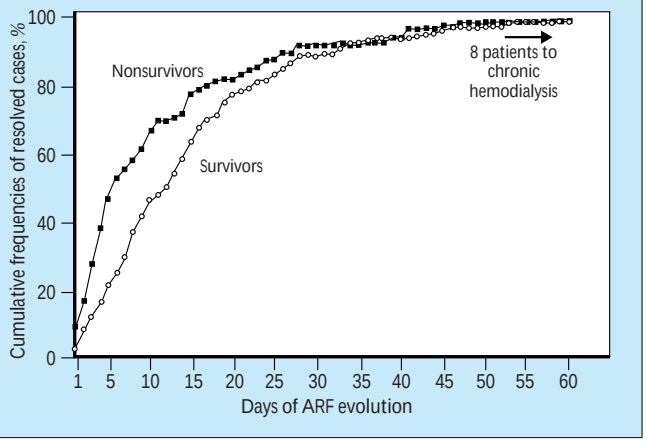


FIGURE 8-27

Duration and resolution of acute renal failure (ARF). Most of the episodes of ARF resolved in the first month of evolution. Mean duration of ARF was 14 days. Seventy-eight percent of the patients with ARF who died did so within 2 weeks after the renal insult. Similarly, 60% of survivors had recovered renal function at that time. After 30 days, 90% of the patients had had a final resolution of the ARF episode, one way or the other. Patients who finally lost renal function and needed to be included in a chronic periodic dialysis program usually had severe forms of glomerulonephritis, vasculitis, or systemic disease. (*From* Liaño *et al.* [1]; with permission.)

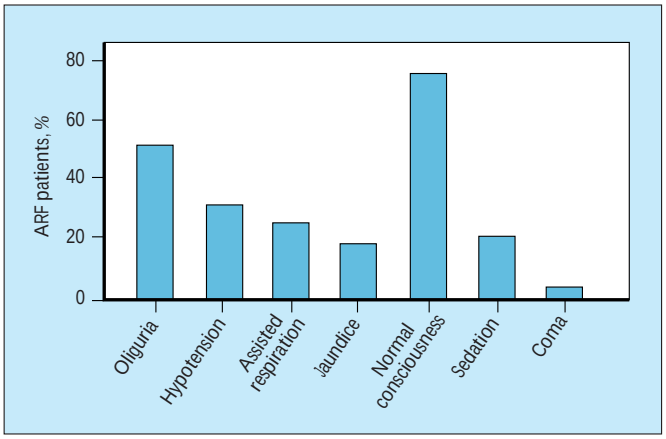


FIGURE 8-28

Precipitating condition of acute renal failure (ARF). The initial clinical condition observed in ARF patients is shown. *Oliguria*: urine output of less than 400 mL per day; *hypotension*: systolic blood pressure lower than 100 mm Hg for at least 10 hours per day independent of the use of vasoactive drugs; *jaundice*: serum bilirubin level higher than 2 mg/dL; *coma*: Glasgow coma score of 5 or less. The presence of these factors is associated with poorer outcome (*see* Fig. 8-29). (*Data from* Liaño *et al.* [1].)

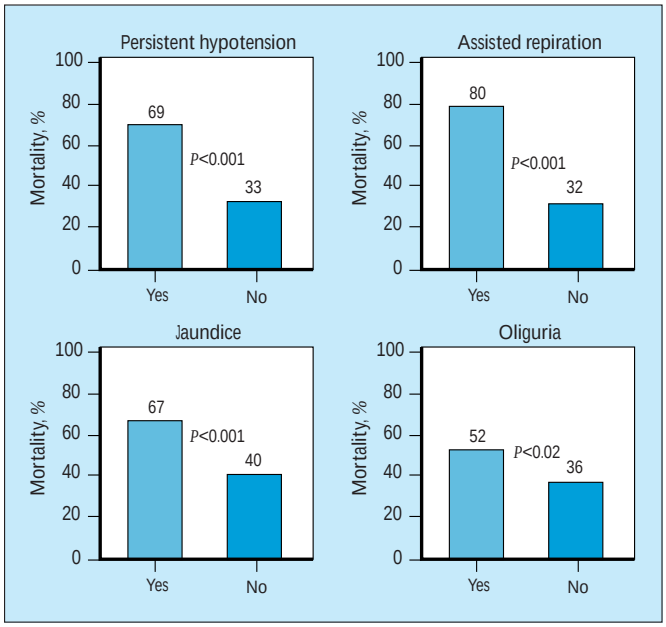


FIGURE 8-29

Mortality associated with the presence or absence of oliguria, persistent hypotension, assisted respiration and jaundice (as defined in Fig. 8-28). The presence of an unfavorable factor was significantly associated with higher mortality. (*Data from* Liaño *et al.* [1].)

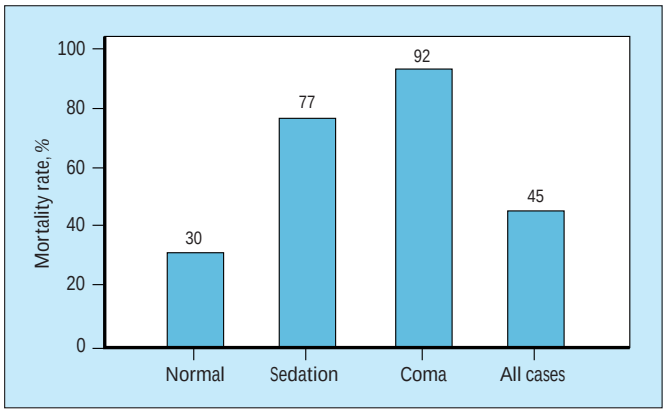


FIGURE 8-30

Consciousness level and mortality. Coma patients had a Glasgow coma score of 5 or lower. *Sedation* refers to the use of this kind of treatment, primarily in patients with assisted respiration. Both situations are associated with significantly higher mortality ($P<0.001$) than that observed in either patients with a normal consciousness level or the total population. (*Data from* Liaño *et al.* [1].)

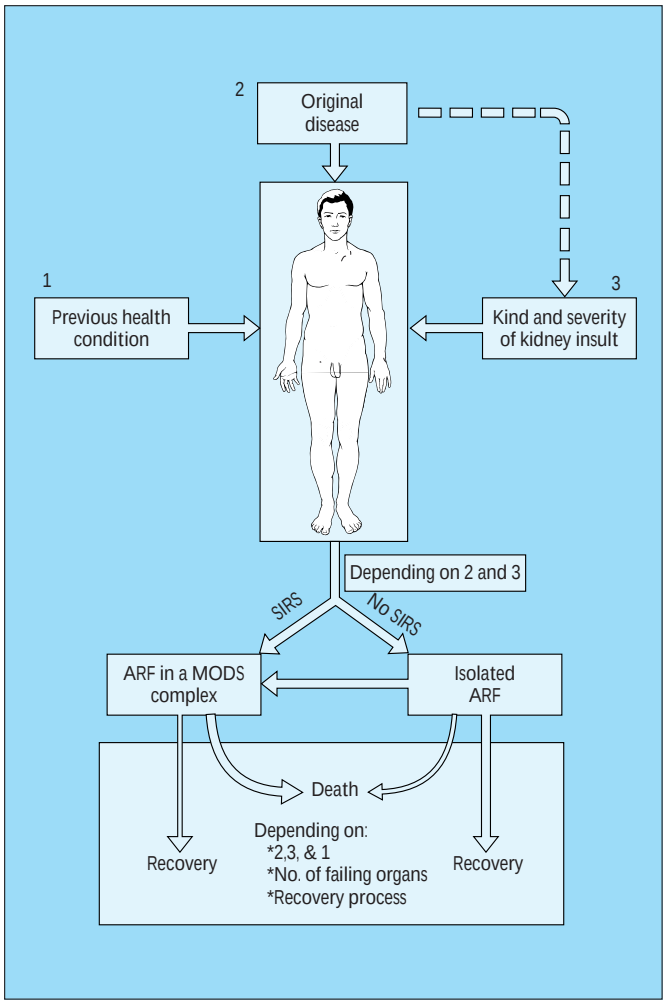


FIGURE 8-31

Outcome of acute renal failure (ARF). Two groups of factors play a role on ARF outcome. The first includes factors that affect the patient: 1) previous health condition; 2) initial disease—usually, the direct or indirect (*eg*, treatments) cause of kidney failure; 3) the kind and severity of kidney injury. While 1 is a conditioning element, 2 and 3 trigger the second group of factors: the response of the patient to the insult. If this response includes a systemic inflammatory response syndrome (SIRS) like that usually seen in intensive care patients (*eg*, sepsis, pancreatitis, burns), a multiple organ dysfunction syndrome (MODS) frequently appears and consequently outcome is associated with a higher fatality rate (*thick line*). On the contrary, if SIRS does not develop and isolated ARF predominates, death (*thin line, right*) is less frequent than survival (*thick line*).

INDIVIDUAL SEVERITY INDEX

ISI=0.032 (age-decade) − 0.086 (male) − 0.109 (nephrotoxic) + 0.109 (oliguria) + 0.116 (hypotension) + 0.122 (jaundice) + 0.150 (coma) − 0.154 (consciousness) + 0.182 (assisted respiration) + 0.210

Case example

A 55-year-old man was seen because of oliguria following pancreatic surgery. At that moment he was hypotensive and connected to a respirator, and jaundice was evident. He was diagnosed with acute tubular necrosis. His ISI was calculated as follows:

ISI=0.032(6) − 0.086 + 0.109 + 0.116 + 0.122 + 0.182 + 0.210 = 0.845

FIGURE 8-32

Individual severity index (ISI). The ISI was published in its second version in 1993 [36]. The ISI estimates the probability of death. *Nephrotoxic* indicates an ARF of that origin; the other variables have been defined in preceding figures. The numbers preceding these keys denote the contribution of each one to the prognosis and are the factor for multiplying the clinical variables; 0.210 is the equation constant. Each clinical variable takes a value of 1 or 0, depending, respectively, on its presence or absence (with the exception of the age, which takes the value of the patient's decade). The parameters are recorded when the nephrologist sees the patient the first time. Calculation is easy: only a card with the equation values, a pen, and paper are necessary. A real example is given.

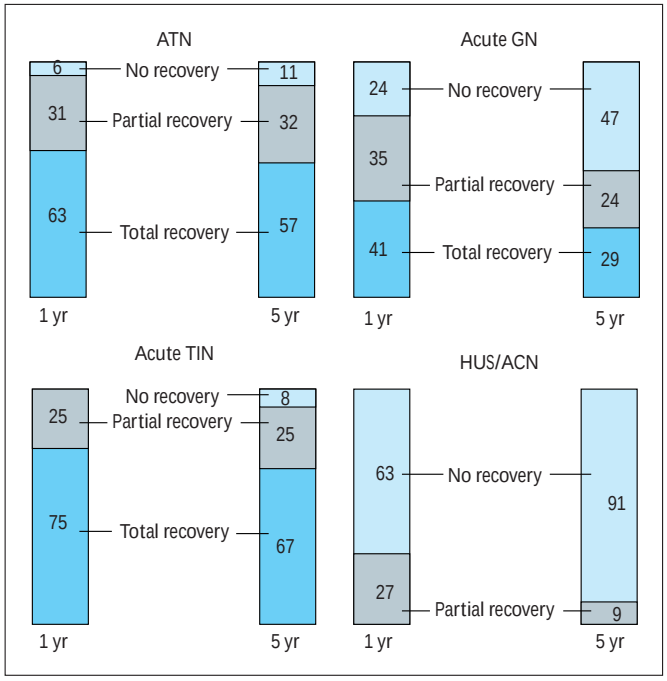


FIGURE 8-33

Outcome of acute renal failure (ARF). Long-term outcome of ARF has been studied only in some series of intrinsic or parenchymatous ARF. The figure shows the different long-term prognoses for intrinsic ARF of various causes. *Left*, The percentages of recovery rate of renal function 1 year after the acute episode of renal failure. *Right*, The situation of renal function 5 years after the ARF episode. Acute tubulointerstitial nephritis (TIN) carries the better prognosis: the vast majority of patients had recovered renal function after 1 and 5 years. Two thirds of the patients with acute tubule necrosis (ATN) recovered normal renal function, 31% showed partial recovery, and 6% experienced no functional recovery. Some patients with ATN lost renal function over the years. Patients with ARF due to glomerular lesions have a poorer prognosis; 24% at 1 year and 47% at 5 years show terminal renal failure. The poorest evolution is observed with severe forms of acute cortical necrosis or hemolytic-uremic syndrome. GN—glomerulonephritis; HUS—hemolytic-uremic syndrome; ACN—acute cortical necrosis. (*Data from* Bonomini *et al*. [37].)

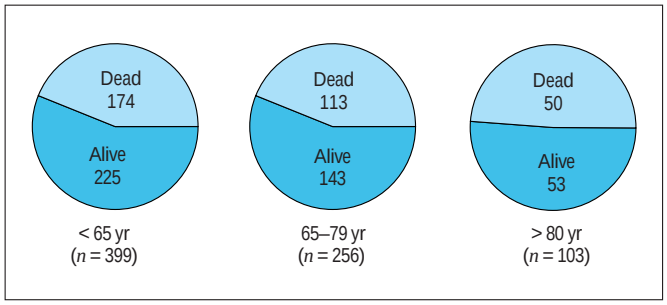


FIGURE 8-34

Age as a prognostic factor in acute renal failure (ARF). There is a tendency to treat elders with ARF less aggressively because of the presumed worse outcomes; however, prognosis may be similar to that found in the younger population. In the multicenter prospective longitudinal study in Madrid, relative risk for mortality in patients older than 80 years was not significantly different (1.09 as compared with 1 for the group younger than 65 years). Age probably is not a poor prognostic sign, and outcome seems to be within acceptable limits for elderly patients with ARF. Dialysis should not be withheld from patients purely because of their age.

VARIABLES ASSOCIATED WITH PROGNOSIS: MULTIVARIATE ANALYSIS (16 STUDIES)

Assisted respiration	11
Hypotension or inotropic support	10
Age	8
Cardiac failure/complications	6
Jaundice	6
Diuresis volume	5
Coma	5
Male sex	4
Sepsis	3
Chronic disease	3
Neoplastic disease	2
Other organ failures	2
Serum creatinine	2
Other conditions	12
Summary	
Clinical variables	20
Laboratory variables	6

FIGURE 8-35

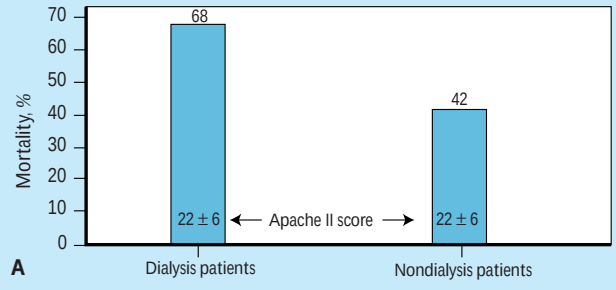
Outcome of acute renal failure (ARF). A great number of variables have been associated with outcome in ARF by multivariate analysis. This figure gives the frequency with which these variables appear in 16 ARF studies performed with multivariable analysis (all cited in [30]).

PROGNOSIS IN ACUTE RENAL FAILURE

	1960–1969	P	1980–1989
No.	119		124
Mortality (%)	51	NS	63
Mean age (y)	50.9	< 0.0001	63
Median APACHE II score	32	< 0.0001	35
Range	(22–45)		(25–49)

FIGURE 8-36

Prognosis in acute renal failure (ARF). This figure shows the utility of a prognostic system for evaluating the severity of ARF over time, using the experience of Turney [38]. He compared the age, mortality, and APACHE II score of ARF patients treated at one hospital between 1960 and 1969 and 1980 and 1989. In the latter period there were significant increases in both the severity of the illness as measured by APACHE II and age. Although there was a tendency to a higher mortality rate in the second period, this tendency was not great enough to be statistically significant.



A

Time	Nonsurvivors	Survivors
Admission in ICU	24	22
Before dialysis	22	22
24 h after dialysis	25	22
48 h after dialysis	24	22

B

FIGURE 8-37

APACHE score. The APACHE II score is not a good method for estimating prognosis in acute renal failure (ARF) patients. **A**, Data from Verde and coworkers show how mortality was higher in their ICU patients with ARF needing dialysis than in those without need of dialysis, despite the fact that the APACHE II score before dialysis was equal in both groups [39]. **B**, Similar data were observed by Schaefer's group [40], who found that the median APACHE II score was similar in both the surviving or nonsurviving ARF patients treated in an intensive care unit. Recently Brivet and associates have found that APACHE II score influences ARF prognosis when included as a factor in a more complex logistic equation [2]. Although not useful for prognostic estimations, APACHE II score has been used in ARF for risk stratification.

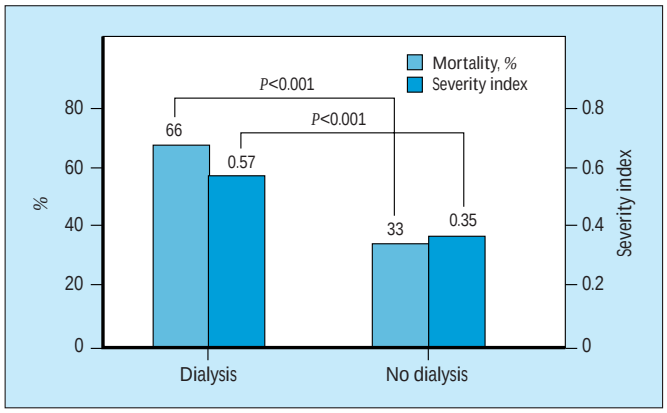


FIGURE 8-38

Analysis of the severity and mortality in acute renal failure (ARF) patients needing dialysis. This figure is an example of the uses of a severity index for analyzing the effect of treatment on the outcome of ARF. Looking at the mortality rate, it is clear that it is higher in patients who need dialysis than in those who do not. It could lead to the sophism that dialysis is not a good treatment; however, it is also clear that the severity index score for ARF was higher in patients who needed dialysis. Severity index is the mean of the individual severity index of each of the patients in each group [36]. (*Data from* Liaño *et al.* [1].)

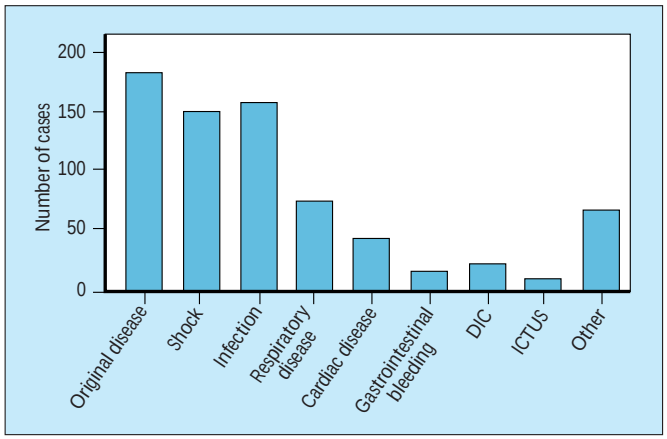


FIGURE 8-39

Causes of death. The causes of death from acute renal failure (ARF) were analyzed in 337 patients in the Madrid ARF Study [1]. In this work all the potential causes of death were recorded; thus, more than one cause could be present in a given patient. In fact, each dead patient averaged two causes, suggesting multifactorial origin. This could be the expression of a high presence of multiple organ dysfunction syndrome (MODS) among the nonsurviving patients. The main cause of death was the original disease, which was present in 55% of nonsurviving patients. Infection and shock were the next most common causes of death, usually concurrent in septic patients. It is worth noting that, if we exclude from the mortality analysis patients who died as a result of the original disease, the corrected mortality due to the ARF episode itself and its complications, drops to 27%. GI—gastrointestinal; DIC—disseminated intravascular coagulation.

References

1. Liaño F, Pascual J the Madrid ARF Study Group: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 1996, 50:811–818.
2. Brivet FG, Kleinknecht DJ, Loirat P, *et al.*: Acute renal failure in intensive care units—causes, outcome and prognostic factors of hospital mortality: A prospective, multicenter study. *Crit Care Med* 1995, 24:192–197.
3. Pascual J, Liaño F, the Madrid ARF Study Group: Causes and prognosis of acute renal failure in the very old. *J Am Geriatr Soc* 1998, 46:1–5.
4. Eliahou HE, Modan B, Leslau V, *et al.*: Acute renal failure in the community: An epidemiological study. Acute Renal Failure Conference, Proceedings. New York 1973.
5. Abraham G, Gupta RK, Senthilselvan A, *et al.*: Cause and prognosis of acute renal failure in Kuwait: A 2-year prospective study. *J Trop Med Hyg* 1989, 92:325–329.
6. McGregor E, Brown I, Campbell H, *et al.*: Acute renal failure. A prospective study on incidence and outcome (Abstract). XXIX Congress of EDTA-ERA, Paris, 1992, p 54.
7. Sanchez Rodrìguez L, MartÌn Escobar E, Lozano L, *et al.*: Aspectos epidemiolûgicos del fracaso renal agudo en el ·rea sanitaria de Cuenca. *Nefrologìa* 1992, 12(Suppl 4):87–91.
8. Feest TG, Round A, Hamad S: Incidence of severe acute renal failure in adults: Results of a community based study. *Br Med J* 1993, 306:481–483.
9. Lunding M, Steiness I, Thaysen JH: Acute renal failure due to tubular necrosis. Immediate prognosis and complications. *Acta Med Scand* 1964, 176:103–119.
10. Lachhein L, Kielstein R, Sauer K, *et al.*: Evaluation of 433 cases of acute renal failure. *Proc EDTA* 1978, 14:628–629.
11. Wing AJ, Broyer M, Brunner FP, *et al.*: Combined report on regular dialysis and transplantation in Europe XIII-1982. *Proc EDTA* 1983, 20:5–78.
12. Gerrard JM, Catto GRD, Jones MC: Acute renal failure: An iceberg revisited (Abstract). *Nephrol Dial Transplant* 1992, 7:458.
13. Kleinknecht D: Epidemiology of acute renal failure in France today. In *Acute Renal Failure in the Intensive Therapy Unit*. Edited by Bihari D, Neild G. London:Springer-Verlag; 1990:13–21.
14. Chugh S, Sakhuja V, Malhotra HS, Pereira BJG: Changing trends in acute renal failure in Third-World countries—Chandigarh study. *Q J Med* 1989, 272:1117–1123.
15. Seedat YK, Nathoo BC: Acute renal failure in blacks and Indians in South Africa—Comparison after 10 years. *Nephron* 1993, 64:198–201.
16. Hou SH, Bushinsky DA, Wish JB, *et al.*: Hospital-acquired renal insufficiency: A prospective study. *Am J Med* 1983, 74:243–248.
17. Shusterman N, Strom BL, Murray TG, *et al.*: Risk factors and outcome of hospital-acquired acute renal failure. *Am J Med* 1987, 83:65–71.

18. Lauzurica R, Caralps A: Insuficiencia renal aguda producida en el hospital: Estudio prospectivo y prevenciûn de la misma. *Med ClÌn (Barc)* 1989, 92:331–334.
19. Liaño F, Solez K, Kleinknecht D: Scoring the patient with ARF. In *Critical Care Nephrology*. Edited by Ronco C, Bellomo R. Dordrecht:Kluwer Academic; 1998; Section 23.1: 1535–1545.
20. Kierdorf H, Sieberth HG: Continuous treatment modalities in acute renal failure. *Nephrol Dial Transplant* 1995; 10:2001–2008.
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: A severity of disease classification system. *Crit Care Med* 1985, 13:818–829.
22. Knaus WA, Wagner DP, Draper EA, *et al*.: The APACHE III prognostic system: Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991, 100:1619–1636.
23. Le Gall JR, Loirat P, Alperovitch A, *et al*.: A simplified acute physiology score for ICU patients. *Crit Care Med* 1984, 12:975–977.
24. Le Gall, Lemeshow S, Saulnier F: A new Simplified Acute Phisiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993, 270:2957–2963.
25. Lemeshow S, Teres D, Pastides H, *et al*.: A method for predicting survival and mortality of ICU patients using objectively derived weights. *Crit Care Med* 1985, 13:519–525.
26. Lemeshow S, Teres D, Klar J, *et al*.: Mortality probability models (MPM II) based on an international cohort of intensive care unit patients. *JAMA* 1993, 270:2478–2486.
27. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: Prognosis in acute organ-system failure. *Ann Surg* 1985, 202:685–693.
28. Marshall JC, Cook DJ, Christou NV, *et al*.: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995, 23:1638–1652.
29. Vincent JL, Moreno R, Takala J, *et al*.: The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996, 22:707–710.
30. Liaño F, Pascual J: Acute renal failure, critical illness and the artificial kidney: Can we predict outcome? *Blood Purif* 1997, 15:346–353.
31. Douma CE, Redekop WK, Van der Meulen JHP, *et al*.: Predicting mortality in intensive care patients with acute renal failure treated with dialysis. *J Am Soc Nephrol* 1997, 8:111–117.
32. Viviand X, Gouvernet J, Granthil C, Francois G: Simplification of the SAPS by selecting independent variables. *Intensive Care Med* 1991, 17:164–168.
33. Bion JF, Aitchison TC, Edlin SA, Ledingham IM: Sickness scoring and response to treatment as predictors of outcome from critical illness. *Intensive Care Med* 1988, 14:167–172.
34. Chew SL, Lins RL, Daelemans R, De Broe ME: Outcome in acute renal failure. *Nephrol Dial Transplant* 1993, 8:101–107.
35. Liaño F: Severity of acute renal failure: The need of measurement. *Nephrol Dial Transplant* 1994, 9(Suppl. 4):229–238.
36. Liaño F, Gallego A, Pascual J, *et al*.: Prognosis of acute tubular necrosis: An extended prospectively contrasted study. *Nephron* 1993, 63:21–23.
37. Bonomini V, Stefoni S, Vangelista A: Long-term patient and renal prognosis in acute renal failure. *Nephron* 1984, 36:169–172.
38. Turney JH: Why is mortality persistently high in acute renal failure? *Lancet* 1990, 335:971.
39. Verde E, Ruiz F, Vozmediano MC, *et al*.: Valor predictivo del APACHE II en el fracaso renal agudo de las unidades de cuidados intensivos (Abstract). *Nefrologìa* 1996, 16(Suppl. 19):32.
40. Schaefer JH, Jochimsen F, Keller F, *et al*.: Outcome prediction of acute renal failure in medical intensive care. *Intensive Care Med* 1991, 17:19–24.