

Treatment of acute renal failure due to myeloma kidney

ROBERT A. BEAR, MD, FRCP[C], FACP; EDWARD H. COLE, M SC, MD;
ARNOLD LANG, MD, FRCP[C]; MICHAEL JOHNSON, MD, FRCP[C]

Severe renal insufficiency is considered to indicate a poor prognosis in patients with multiple myeloma, their reported median survival being approximately 2 months. In five consecutive patients with severe renal failure secondary to acute myeloma kidney early aggressive therapy, including chemotherapy and peritoneal dialysis, led to a significant improvement in the renal function of four; the fifth patient received a cadaveric renal transplant after 1 year of peritoneal dialysis. After a median follow-up period of 12 months all the patients were alive and had improved renal function. This experience contrasts with that previously reported and suggests that aggressive management may improve the survival of patients with acute renal failure due to myeloma kidney.

On considère une insuffisance rénale comme étant l'indice d'un mauvais pronostic chez les patients souffrant de myélome multiple, alors que la survie médiane rapportée est d'environ 2 mois. Chez cinq patients consécutifs atteints d'insuffisance rénale grave secondaire à un myélome rénal aigu l'instauration d'un traitement agressif précoce, comprenant chimiothérapie et dialyse péritonéale, a produit chez quatre d'entre eux une amélioration significative de la fonction rénale; le cinquième patient a reçu une greffe de rein d'origine cadavérique après 1 an de dialyse péritonéale. Après une période d'observation médiane de 12 mois tous les patients étaient vivants et présentaient une fonction rénale améliorée. Cette expérience diffère de celle qui a déjà été signalée et indique qu'un traitement agressif peut améliorer la survie des patients souffrant d'une insuffisance rénale aiguë consécutive à une atteinte du myélome du rein.

Renal insufficiency occurs in approximately 50% of patients with multiple myeloma and is second only to infection as a cause of death.¹ Dawson and Ogston² found that of 42 patients with initial blood urea nitro-

gen (BUN) levels exceeding 60 mg/dl (21.4 mmol/l) only 12 survived beyond 3 months. In a Medical Research Council study in Great Britain 55 patients with initial BUN levels of 80 mg/dl (28.6 mmol/l) or greater had a median survival of only 2 months, compared with 20 months for those with initial levels of 41 to 79 mg/dl (14.6 to 28.2 mmol/l) and 33 months for those with initial levels of 40 mg/dl (14.3 mmol/l) or less.³ In DeFronzo and colleagues' series of 14 patients with multiple myeloma and renal failure, only 5 survived the initial period of acute renal failure, and 4 of them died within several months.⁴ These studies included patients with potentially reversible causes of renal failure, such as volume contraction and hypercalcemia, which suggests that the survival of patients with renal failure due to myeloma kidney is even worse.

In this report we describe the management and course of five consecutive patients with severe acute renal insufficiency secondary to myeloma kidney. Aggressive management, with short-term dialysis or renal transplantation if necessary, resulted in substantial improvement in kidney function and 100% patient survival over a median follow-up period of 12 months. This experience contrasts sharply with that previously described and thus suggests a role for aggressive treatment of acute renal failure in selected patients with underlying multiple myeloma.

Patients and findings (Table I)

The five patients ranged in age from 44 to 77 years; three were male. All had an increased count of atypical or immature plasma cells in the bone marrow. Four had typical λ -light-chain disease⁵ and one had IgG myeloma with λ light chains in the urine.

Case histories

Patient 1: This man presented at age 69 years with

From the department of medicine, division of nephrology, St. Michael's Hospital and the University of Toronto

Reprint requests to: Dr. Robert A. Bear, 55 Queen St. E, Ste. 405, Toronto, Ont. M5C 1R6

Table I—Data for five patients with acute renal failure due to myeloma kidney

Patient no.	Age at time of presentation, yr	Initial serum creatinine level, mg/dl (μ mol/l)	Duration of dialysis, mo	Serum creatinine level after therapy, mg/dl (μ mol/l)	Duration of follow-up, mo
1	69	10.2 (902) [†]	2	3.2 (283)	13
2*	58	19.0 (1680) [†]	6	3.6 (318)	9
3	76	8.5 (751)	0	4.9 (433)	9
4	44	21.0 (1856) [†]	12	1.2 (106) [‡]	38
5	77	10.8 (955) [†]	1	6.8 (601) [§]	12

*Gentamicin therapy was given before the onset of acute renal failure.

[†]Peak level prior to peritoneal dialysis.

[‡]After 1 year of peritoneal dialysis a cadaveric kidney was successfully transplanted.

[§]The level subsequently rose, however, because of failure to adhere to the follow-up treatment regimen.

flank pain and general malaise. The serum creatinine level, initially 6.0 mg/dl (530 μ mol/l), rose to 10.2 mg/dl (902 μ mol/l) over 5 days. Urinalysis demonstrated 1+ proteinuria with occasional leukocytes and hyaline casts. The initial serum bicarbonate level was 21 mmol/l. Serum protein electrophoresis demonstrated a decrease in the levels of IgA and IgM and the presence of λ light chains. The amount of λ light chains excreted in the urine in 24 hours was 900 mg. The bone marrow contained 60% malignant plasma cells. There were lytic lesions of the cranial vault and the upper right humerus. The serum calcium level was normal, but the serum uric acid level was high, 11.6 mg/dl (0.69 mmol/l). A renal biopsy demonstrated the characteristic changes of myeloma kidney.

A 0.9% saline solution was given to expand the extracellular fluid volume and sodium bicarbonate was given to correct the metabolic acidosis and alkalize the urine. Peritoneal dialysis was begun. The multiple myeloma was treated with melphalan and prednisone at 6-week intervals. The patient's renal function progressively improved: the serum creatinine level fell to 3.2 mg/dl (283 μ mol/l) and peritoneal dialysis was stopped after 2 months.

Eleven months later the renal function remained stable, but bone marrow aspiration revealed a continued high content of plasma cells, the bony lytic lesions were unchanged, diffuse hypogammaglobulinemia persisted and λ light chains continued to be present in both serum and urine.

At the time this study ended, therapy was being undertaken with vincristine sulfate, bischloronitrosourea (BCNU), cyclophosphamide, melphalan and prednisone. Clinically the patient was perfectly well.

Patient 2: At age 58 years this man was excreting in the urine 10 to 16 g of λ light chains in 24 hours. The bone marrow findings were diagnostic of multiple myeloma. The levels of all the serum immunoglobulins were reduced, but initially no circulating light chains were demonstrated. A roentgenographic survey of the skeleton demonstrated multiple lytic lesions of the skull and compression fractures of the spine. The serum calcium and uric acid levels were normal.

Courses of vincristine, BCNU, cyclophosphamide, melphalan and prednisone were given every 6 weeks. A fever developed and gentamicin was given for 5 days; the serum levels of the drug were in the therapeutic range. Hypotension was not observed, but there was mild contraction of the extracellular fluid volume. Acute renal failure developed, the serum creatinine level rising from 1.2 to 19.0 mg/dl (106 to 1680 μ mol/l). Urinalysis demonstrated occasional leukocytes but no casts. The serum bicarbonate level was 18 mmol/l. Lambda light chains appeared in the serum.

Peritoneal dialysis was begun, a 0.9% saline solution given to expand the extracellular fluid volume and sodium bicarbonate given to correct the metabolic acidosis and alkalize the urine. Multiple myeloma therapy was continued.

The patient's renal function gradually improved; after 6 months the serum creatinine level was 3.6 mg/dl (318 μ mol/l) and dialysis was stopped. The

bone marrow was now normal. The amount of protein excreted in the urine in 24 hours fell to 270 mg, and λ light chains disappeared from both serum and urine. Nine months after the development of acute renal failure the patient remained clinically well.

Patient 3: This 76-year-old woman was assessed by her family physician for general malaise. Her hemoglobin level was 14.1 g/dl and her serum creatinine level 1.3 mg/dl (115 μ mol/l). Three weeks later nausea and vomiting developed. Mild contraction of the extracellular fluid volume was observed, and the serum creatinine level was noted to be 8.5 mg/dl (751 μ mol/l). The serum bicarbonate level was 13 mmol/l. Urinalysis demonstrated occasional leukocytes as well as hyaline and hyaline-granular casts. The bone marrow contained 15% to 20% abnormal plasma cells. Serum protein electrophoresis revealed an increase in the λ -globulin level to 4.5 g/dl, with a spike in the IgG region. The amount of λ light chains excreted in the urine in 24 hours was 4.2 g; λ light chains were also observed in the serum. A roentgenographic survey of the skeleton showed no abnormalities. The serum calcium level was normal, but the serum uric acid level was 10.3 mg/dl (0.61 mmol/l).

A 0.9% saline solution was given to expand the extracellular fluid volume and sodium bicarbonate was given to correct the metabolic acidosis and alkalize the urine. A diagnosis of multiple myeloma (IgG type, with λ -light-chain proteinuria) was made, and melphalan and prednisone were administered every 6 weeks.

The patient's renal function gradually improved, with the serum creatinine level falling to 4.9 mg/dl (433 μ mol/l). The amount of λ light chains excreted in the urine was 2.4 g at that time. Nine months after the development of acute renal failure the patient remained clinically stable.

Patient 4: At age 44 years this man presented with a brief history of nausea, vomiting, a metallic taste in the mouth and generalized itching. The serum creatinine level was 21.0 mg/dl (1856 μ mol/l). The serum bicarbonate level was 15 mmol/l. Urinalysis revealed occasional leukocytes. The bone marrow contained 80% malignant plasma cells. Serum protein immunoelectrophoresis demonstrated a general decrease in the levels of all immunoglobulins. Lambda light chains were noted in both serum and urine. A roentgenographic survey of the skeleton showed no abnormalities. The serum calcium level was normal, but the serum uric acid level was 9.8 mg/dl (0.58 mmol/l). The kidneys were shown by nephrotomography to be of normal size. A renal biopsy, however, demonstrated the characteristic changes of myeloma kidney, and immunofluorescent studies revealed λ light chains within tubular casts.

A 0.9% saline solution was given to expand the extracellular fluid volume and sodium bicarbonate was given to correct the metabolic acidosis and alkalize the urine. Peritoneal dialysis was begun and the patient trained to perform it at home. The multiple myeloma was treated with melphalan and prednisone every 6 weeks. The bone marrow became normal and the λ

light chains disappeared from both serum and urine.

After 12 months of peritoneal dialysis the patient's renal function had not improved, so a cadaveric kidney was transplanted and immunosuppressive therapy given with cyclophosphamide and prednisone (maintenance doses 50 mg and 12.5 mg respectively per day). The multiple myeloma therapy was withdrawn.

At the time this study ended, the patient had been followed for 26 months after transplantation. His renal function was normal, as was his bone marrow, and there were no λ light chains in either serum or urine. A roentgenographic survey of the skeleton showed no abnormalities. Clinically the patient remained perfectly well.

Patient 5: This woman presented at age 77 years because of general malaise and anemia. The serum creatinine level was initially 5.0 mg/dl (442 μ mol/l), then rapidly rose to 10.8 mg/dl (955 μ mol/l). The serum bicarbonate level was 18 mmol/l. Urinalysis revealed occasional leukocytes and hyaline casts. The bone marrow findings were diagnostic of multiple myeloma. The serum immunoglobulin levels were generally low. Lambda light chains were present in both serum and urine. A roentgenographic survey of the skeleton demonstrated wedge compressions of the spine. The serum calcium level was normal, but the serum uric acid level was 10.9 mg/dl (0.65 mmol/l). A renal biopsy demonstrated the characteristic changes of myeloma kidney.

A 0.9% saline solution was given to expand the extracellular fluid volume and sodium bicarbonate was given to correct the metabolic acidosis and alkalize the urine. Peritoneal dialysis was given for 1 month. The multiple myeloma was treated with intermittent melphalan and prednisone. The serum creatinine level gradually improved, to 4.7 mg/dl (415 μ mol/l), and then stabilized at 6.8 mg/dl (601 μ mol/l). The patient had a number of medical problems unrelated to the myeloma and was erratic in adhering to the follow-up treatment regimen. Melphalan and prednisone were not administered regularly. Without specific therapy the serum creatinine level rose to 9 mg/dl (796 μ mol/l) by 12 months after the development of renal failure.

Renal biopsy findings

A renal biopsy was performed in three of the five patients and demonstrated the typical features of myeloma kidney. Dilated and atrophic tubules were noted in both cortex and medulla: many of these contained pale, eosinophilic "hard casts", and almost every cast was surrounded by a syncytium that appeared to be distinct from the tubular epithelium. The interstitium was mildly fibrotic and contained an inflammatory infiltrate of lymphocytes, mononuclear cells and occasional neutrophils. The glomeruli showed only mild diffuse mesangial widening, without hypercellularity.

Discussion

In each of the five cases we have described, the diagnosis of multiple myeloma was made on the basis of bone marrow findings and serum and urine protein

abnormalities. In three cases a renal biopsy demonstrated the characteristic changes of myeloma kidney. In the other two cases the clinical picture was compatible with myeloma kidney, and other causes of myeloma-related renal failure were not present. One of the two had received gentamicin at an appropriate dosage; however, the serum gentamicin levels were in the nontoxic range and the renal failure persisted for many months, a picture inconsistent with the results of gentamicin nephrotoxicity. In four of the five patients renal function improved significantly with supportive therapy and treatment of the multiple myeloma; the fifth patient received a cadaveric renal transplant after 1 year of peritoneal dialysis. After a median follow-up period of 12 months all the patients were well and had improved renal function.

Renal damage in patients with multiple myeloma is highly correlated with light-chain production and excretion, occurring most commonly in the 20% of patients who have light-chain disease, in 80% of whom light chains are found in both serum and urine. The renal disorders that may be induced by light chains range from various forms of renal tubular dysfunction⁶ to acute renal failure (myeloma kidney). Light chains are filtered at the glomerulus and then are reabsorbed and catabolized by renal tubular cells,⁷ where they may exert their toxic effect.⁸ It is unclear why light-chain proteinuria leads to renal problems in some patients and not others; variable duration and magnitude of light-chain proteinuria and differences in solubility and polymerization of specific light chains may be important factors. Contraction of the extracellular fluid volume or administration of radiologic contrast materials may enhance light-chain nephrotoxicity, although the mechanisms are uncertain. Polymerization of light chains occurs maximally at a pH of 4.8 to 6.0, so it may be increased within the renal tubule in metabolic acidosis.⁹

There have been occasional reports of patients with acute renal failure secondary to myeloma kidney whose renal function spontaneously improved.^{10,11} There are also a few reports of successful maintenance dialysis in such patients^{12,13} and of successful renal transplantation.¹⁴ In general, however, severe acute renal failure in patients with multiple myeloma is felt to indicate such a poor prognosis that patients are offered only supportive therapy. Our success with five consecutive patients, as detailed in this report, suggests that acute renal failure secondary to myeloma kidney may have a better prognosis than was previously suggested.

On the basis of our experience with this small group of patients we cannot state which factors are most important in reversing renal failure. Plasmapheresis has rapidly cleared the plasma of circulating light chains,¹⁵ but we did not use this technique in our patients. Peritoneal dialysis results in significant clearance of light chains,¹⁶ and the production of light chains is quickly reduced by chemotherapy for multiple myeloma; however, the resolution of renal failure in our patients did not appear to correlate with the disappearance of light chains from serum or urine. Previously alkalization of the urine was thought to

reduce the polymerization of light chains⁹ and tubular obstruction, but renal failure is now felt to be secondary to direct nephrotoxicity of light chains and not to obstruction. Clearly, more extensive studies of the optimum management of renal failure in patients with multiple myeloma are required.

In summary, aggressive treatment of both the renal insufficiency and the underlying multiple myeloma is indicated in selected patients with acute renal failure and myeloma kidney, for their renal function may improve significantly. If it does not quickly do so, long-term dialysis should be considered since the renal function may gradually improve.¹⁷ Finally, as demonstrated in one of our cases, renal transplantation can be a successful way of treating renal failure due to myeloma kidney.

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Phyllocontin q.12h.

PRESCRIBING INFORMATION

Actions: Aminophylline is the ethylenediamine salt of theophylline. The pharmacodynamics of Phyllocontin tablets are a function of theophylline blood levels.

Theophylline is a xanthine structurally related to theobromine and caffeine. As with other xanthine derivatives, the precise mechanism of action of theophylline has not been determined. Theophylline stimulates the central nervous system and skeletal muscles, stimulates cardiac muscle, relaxes certain smooth muscles including those of the bronchi, produces diuresis, and causes an increase in gastric secretion.

Phyllocontin tablets are sustained release tablets which produce peak blood levels of theophylline between 3 and 5 hours. Once the steady state level has been reached the therapeutic blood levels persist for 12 hours.

Indications: The symptomatic treatment of reversible bronchoconstriction associated with bronchial asthma, chronic obstructive pulmonary emphysema, chronic bronchitis and related bronchospastic disorders.

Contraindications: Phyllocontin tablets should not be administered to patients with hypersensitivity to xanthines or ethylenediamine, to patients with coronary artery disease where cardiac stimulation might prove harmful or to patients with peptic ulcer.

Warnings: Phyllocontin tablets, a sustained release preparation, are not recommended for conditions requiring immediate bronchodilation.

Use in Children: Children are very sensitive to xanthines; the margin of safety above therapeutic doses is small. Phyllocontin tablets are not presently recommended for children under 12 years of age.

Precautions: There is a marked variation in blood levels achieved in different patients given the same dose of theophylline. This may lead to serious side effects in some patients. This variability in blood levels is probably due to differences in the rate of metabolism. Therefore, it is advisable to individualize the dose regimen.

Ideally, all individuals should have serum theophylline levels measured and a theophylline half-life calculated which would enable doses and dosing regimens to be tailored to each patient to maintain a therapeutic level, to insure optimal clinical response and to avoid toxicity. The possibility of overdose must be considered in all patients and especially when large doses are used, because fatalities have been reported. Overdosage of theophylline may cause peripheral vascular collapse.

Special caution is necessary in patients with severe pulmonary or cardiovascular disease and in patients with hepatic dysfunction as metabolism of theophylline may be impaired in these patients leading to the possibility of toxic blood levels on a fixed dosage regimen.

Caution should be exercised when theophylline is used concurrently with sympathomimetic amines or other xanthines, as such use may increase the incidence and severity of adverse reactions. Phyllocontin should not be given within 12 hours of the ingestion of other xanthines. Theophylline may cause an elevation of urine catecholamines and plasma free fatty acids.

Adverse Reactions: The most common adverse reactions are gastric irritation, nausea, vomiting, epigastric pain, and tremor. These are usually early signs of toxicity, however, with high doses ventricular

arrhythmias or seizures may be the first signs to appear.

Adverse reactions include:

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea, anorexia, intestinal bleeding and reactivation of peptic ulcer.

Central Nervous System: headache, irritability, restlessness, insomnia, twitching, convulsions and reflex hyperexcitability.

Cardiovascular: palpitation, tachycardia, hypotension, circulatory failure, ventricular arrhythmias, extrasystoles and flushing.

Renal: albuminuria, diuresis and hematuria.

Others: hyperglycemia, tachypnea and inappropriate ADH syndrome.

Drug Interactions: Synergism with ephedrine has been documented and may occur with other sympathomimetic amines.

Theophylline may cause increased excretion of lithium carbonate.

Theophylline antagonizes the effects of propranolol.

Theophylline potentiates the diuretic effects of thiazide diuretics and the cardiac effects of digitalis glycosides.

Xanthines have been shown to be nephrotoxic with borne in mind when other potentially nephrotoxic drugs are administered concurrently.

Acidifying agents, by increasing urinary excretion of weak bases like the xanthines, inhibit theophylline action.

Alkalinizing agents, by decreasing urinary excretion of weak bases like the xanthines, potentiate theophylline action.

The methylxanthines increase blood levels of prothrombin and fibrinogen, shorten the prothrombin time and thus antagonize the effects of coumarin anticoagulants.

Combined use of several xanthines may cause excessive CNS stimulation.

Toxic reactions as a result of significant elevations of serum theophylline levels have been observed in patients after initiation of treatment with erythromycin preparations. Particular attention should therefore be directed towards monitoring the serum theophylline levels in such patients.

Xanthines may antagonize the antihyperuricemic action of allopurinol.

Xanthines antagonize the uricosuric action of probenecid, sulfipyrazone and pyrazolone derivatives.

Symptoms and Treatment of Overdosage

Symptomatology: Insomnia, restlessness, mild excitement or irritability, and rapid pulse are the early symptoms, which may progress to mild delirium.

Sensory disturbances such as tinnitus or flashes of light are common. Anorexia, nausea and vomiting are frequently early observations of theophylline overdosage.

Fever, diuresis, dehydration and extreme thirst may be seen. Severe poisoning results in bloody, syrup-like "coffee-ground" vomitus, tremors, tonic extensor spasm interrupted by clonic convulsions, extrasystoles, quickened respiration, stupor and finally coma. Cardiovascular disorders and respiratory collapse, leading to shock, cyanosis and death follow gross overdosages.

Treatment:

A. If potential oral overdose is established and seizure has not

occurred:

- 1) Induce vomiting.
- 2) Administer a cathartic (this is particularly important when a sustained release preparation has been taken).
- 3) Administer activated charcoal.

B. If patient is having a seizure:

- 1) Establish an airway.
- 2) Administer oxygen.
- 3) Treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to 10 mg.
- 4) Monitor vital signs, maintain blood pressure and provide adequate hydration.

C. Post-Seizure Coma:

- 1) Maintain airway and oxygenation.
- 2) If a result of oral medication, follow the above recommendations to prevent absorption of drug. Intubation and lavage will have to be performed instead of inducing emesis, and the cathartic and charcoal will need to be introduced via a large bore gastric lavage tube.
- 3) Continue to provide full supportive care and adequate hydration while waiting for the drug to be metabolized. In general, the drug is metabolized sufficiently rapidly so as not to warrant consideration of dialysis.

Dosage and Administration: Adults: The recommended initial adult dose is one or one and a half tablets (225-337.5 mg of Phyllocontin, equivalent to 182.2-273.3 mg anhydrous theophylline) q.12h. The tablets should not be chewed or crushed. Dosage adjustments should be based on the patient's clinical response and/or serum theophylline levels, with increases of one half tablet per dose at three or four day intervals. Individual requirements vary considerably and the physician should be prepared to adjust the patient's dose accordingly. Within any 24 hour period a maximum of five Phyllocontin tablets should not be exceeded.

Because of large inter-subject variability, monitoring of serum theophylline concentrations is very important especially during dosage adjustment. (See Precautions). The optimum serum theophylline concentration is in the range of 8-20 mcg/mL, depending on the severity of the condition. The incidence of adverse effects increases at levels in excess of 15 mcg/mL. In cases where it is not possible to monitor serum theophylline, patients should be closely observed for signs of toxicity.

Availability: Phyllocontin tablets are supplied in bottles of 100 and 500. Each scored, off-white, flat-faced, round tablet engraved "P" on one side, contains 225 mg of aminophylline USP (equivalent to 182.25 mg anhydrous theophylline) in a sustained release base.

PHY-4



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