How should immunosuppressive therapy in transplant patients with chronic liver disease be handled?

Immunosuppressive therapy may enhance viral replication and exacerbate or accelerate the progression of chronic hepatitis B and C. A late reduction in the dosage of azathioprine seems not to cause any changes in the natural course of chronic hepatitis B, and therefore an early reduction in the dosage of the drug might be a possible approach for such patients. Corticosteroids seem to be particularly harmful, in that they favour viral replication. To avoid or minimize this risk the maintenance doses of prednisone should be kept as low as possible from the time of transplantation. As there is growing evidence that cyclosporin alone may lead to excellent graft survival, steroid-free immunosuppression might be tried for HBsAg-positive and/or HCV-positive patients. This is even more justified since HBsAg-positive and/or HCV-positive patients have a lower immunological reactivity. Unfortunately, however, no specific trial with such an immunosuppressive patients with viral infection has been done. Although immunosuppressive therapy should be kept as low as possible after transplantation, it cannot be ignored that rapid reduction of immunosuppressive therapy in patients with deteriorating liver function might accelerate liver damage in some cases. This paradoxical response is probably due to the fact that while immunosuppressive agents may protect from the autoimmune response to virus, in some cases an abrupt reduction or discontinuation of immunosuppressive therapy might lead to cytolysis and further destruction of the livers.

During immunosuppressive therapy, levels of serum HBV DNA may be a useful non-invasive method for monitoring both viral replication and progression of liver disease in patients with HBV. In some cases, however, one cannot manage patients properly without resorting to periodic liver biopsies in order to assess the activity and progression of liver damage. A decline in HBV DNA levels in patients with established CAH may reflect either reversal to CPH or the onset of cirrhosis [9].

Therapeutic approaches to eradication of viral replication are not available for patients with renal transplants. New antiviral agents such as adenine arabinoside 5'-monophosphate, prostaglandin E, and famiclovir are still under investigation. Although interferon α seems to be effective against chronic active hepatitis C, most investigators agree that this drug should be used with caution in kidney recipients in view of the observation that occurrence of relapses cannot be totally excluded and that there may well be graft rejection, especially in those patients with impaired graft function. It is paradoxical that for those who develop end-stage liver cirrhosis as a consequence of renal transplantation the only hope rests on transplantation of the liver.

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Delayed referral for dialysis

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Introduction

Age and non-renal comorbidity dominate survival in end-stage renal disease [1]. Modifiable factors include extracellular volume/blood pressure control [2], nutrition and solute clearance [3]. Experience of renal replacement therapy in elderly and 'complicated' patients, with inherently reduced survival, has sharpened awareness of morbidity and quality of life as complementary outcomes. Timely referral of patients with chronic renal failure to a nephrologist optimizes conservative management, including dialysis planning. Unfortunately many patients suffer a needlessly rough journey on the road to dialysis.
Definition and causes

Progression of chronic renal failure slows with optimal blood-pressure control, and by preventing or limiting superimposed insults. Active management of bone metabolism and acidosis are useful. Delayed referral is definable simply as 'when management could have been improved by earlier contact with renal services'. This is unavoidable if ESRD follows acute renal failure, CRF is advanced when detected, or patients reject help until symptoms are critical [4]. Avoidable delays in referral are influenced most by physicians in primary and secondary care. Reassuringly, socioeconomic indices have no impact on referral patterns or assessment for dialysis [4,5].

Non-nephrologists underestimate the benefits of RRT. Delayed referral stems from ignorance of the value of early referral, viewing nephrologists as 'diyers', or ambivalence concerning appropriateness of RRT for 'high risk' cases. With moderate CRF (creatinine > 300 µM) referral is more likely in 'low risk' patients (69%) than in 'medium risk' (58%) and 'high risk' (21%) cases [6]. With severe CRF (creatinine > 500 µM) referral occurred in 100%, 88% and 37% of these risk groups. Patients not referred died within 2 years from intercurrent illness or because dialysis was deemed inappropriate.

Timing of referrals which occur is dictated by perceived biochemical severity; proportions of low-, medium-, and high-risk patients are similar when stratified by serum creatinine at referral [7]. Half of the patients with advanced CRF (creatinine > 500 µM) require dialysis within 3 months; comorbidity is again influential. Serum creatinine underestimates severity of CRF as muscle mass falls, the natural history of renal diseases affecting high-risk patients is often shorter, and uraemia is tolerated poorly. Intervals between referral and dialysis (low risk 9 months, medium risk 4 months, high risk 3.5 months), and creatinine at dialysis (low risk 1104 µM, medium risk 998 µM, high risk 835 µM) emphasize this [7].

Effects

Delayed referral leaves patients beginning dialysis with biochemically more advanced uraemia [4,8], more severe acidosis and anaemia, poorer nutritional status as reflected in lean body mass and serum albumin [4,7], and inferior control of blood pressure and hyperparathyroidism [4]. The sequel is often emergency haemodialysis during a life-threatening uraemic complication. This affects 35–50% of patients [4,7], an unchanging proportion [9], from 5% for low-risk patients under nephrological follow-up for > 6 months up to > 90% for high-risk patients requiring dialysis within 1 month of referral.

Quantifying morbidity retrospectively is difficult; duration of hospitalization is a crude global surrogate measure, but acknowledges the value of minimizing dependence on the hospital unit. After adjusting for correlations between time from referral to dialysis, increasing age, and comorbidity, emergency treatment lengths inpatient stay 2–10-fold over elective management [4,5]. Hospitalization also increases when 'elective' dialysis starts less than after 3 months from referral [5]. Final dialysis modality does not affect morbidity.

Emergency haemodialysis absorbs excess human and material resources. Complications of temporary vascular access may prejudice permanent access sites. CAPD training, when appropriate, must be deferred until physical and mental functions improve; some suitable patients never gain confidence in their ability to treat themselves independently, further pressurizing haemodialysis facilities. Anxiety and uncertainty common to all patients are exacerbated. Younger patients risk losing employment and income, and costs to society of lost productivity and social benefits rise, as do emotional and economic strains on relatives and carers. Readmission rates for medium- and high-risk patients who were referred late are higher [5]. Multivariate modelling excludes referral pattern as an independent survival predictor, but long-term rehabilitation is undoubtedly irreversibly impaired for some patients, and survival shortened. High-risk patients first referred during a uraemic crisis are particularly disadvantaged by losing the opportunity for informed discussion of the benefits of chronic RRT. An optimistic 'trial of dialysis' may become a 'trial by dialysis', ending with treatment withdrawal or protracted dying [8].

Crude estimates illustrate the financial costs of delayed referral. The additional cost of each patient requiring emergency dialysis in France in 1992 was ~200,000 FFr (~£30,000) [4]; excess hospitalization increases bed occupancy for dialysis training by 40% [5]. CRF patients begin dialysis later in the UK than in Europe (creatinine clearance 0–5 ml/min; UK 95%, France 40%). Avoidable costs of emergency haemodialysis, whether reflecting delayed referral or delays created by restricted facilities, ironically increase when nephrology services suffer explicit budgetary constraints.

Can outcomes be improved?

The benefits of a 'dialysis induction programme' [10] support day-to-day experience illustrating that early referral is desirable. Data linking delayed referral and increased morbidity are multinational and, coming from populations served by single renal units, unbiased.

How should earlier referral of patients with CRF be encouraged? Briefly, the implications of the problem must be communicated to non-nephrological colleagues, both in hospital and in family practice, and to bodies responsible for planning and funding renal services. Details will vary according to circumstance, but several points need emphasis: (i) management of CRF is a dynamic process, not simply biochemical monitoring; (ii) variability in progression rates according to diagnosis, age, and comorbidity; (iii) limitations
of serum creatinine and usefulness of creatinine clearance in assessing severity; (iv) age is not a criterion for selection for RRT; (v) the absolute need to assess 'high risk' patients before uraemia has developed; and (vi) the value of integrated follow-up involving primary care, general physicians, and nephrologists. Management guidelines and clinical audit have several roles. Specialists in geriatric medicine and urology deserve special attention because of the number and characteristics of patients with CRF under their care.

One weakness of dialysis registries is only recording patients receiving dialysis. The annual incidence of ESRD is ~80 p.p.m., but the incidence of 'moderate' renal impairment (creatinine >300 μM) in patients <80 years is at least 240 p.p.m. [6]. Most predialysis mortality affects patients not referred to renal services. Aggressive management of cardiovascular diseases, notably myocardial and cerebral reperfusion, and control of hypertension, may reduce the toll of competing risks, but predicting who will reach ESRD is unreliable, and non-referral denies the benefits of nephrological advice, whether or not dialysis is ever required. Ideally all patients with significant CRF (creatinine >300 μM) would see a nephrologist at least once. However, this would create considerable workload problems, with continual nephrological follow-up being inappropriate for many patients, reiterating the principal point that progress depends on doctors managing these patients being aware of the value of early discussion with a nephrologist, even informally, to identify reversible factors, to delineate goals for conservative treatment, and to consider the benefits of dialysis if progression to ESRD should occur, acknowledging that only conservative treatment will be appropriate for some patients.

Future problems and conclusion

Pressure to offer effective technological innovations to ageing populations equitably and efficiently within the constraints of competing demands is straining all health services. Rather than wave the shroud of 'meeting total need', renal physicians should see improved evaluation of outcomes as integral to confirming clinical effectiveness and technical (economic) efficiency. Better referral patterns will reduce morbidity and increase efficiency (reduced cost per case); more patients may reach ESRD, and dialysis will certainly often start earlier. Increasing dialysis stocks, and total costs of renal services, may outstrip existing estimates. Long-term planning is essential if resources are to fulfil future demands.

Delayed referral of patients with chronic renal impairment carries heavy medical and economic costs. The phenomenon is synergistic with the effects of age and comorbidity. More time in the clinic optimizing conservative management and planning elective dialysis should replace avoidable emergency dialysis, reducing morbidity and costs for patients and services. Wide discussion of appropriate referral pathways with colleagues and funding agencies is essential to promote an evidence-based approach to management of progressive renal failure.

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