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High risk factors in transplantation

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SUMMARY

A standardised system of assessing risk factors for renal transplant outcome and patient survival has been assessed.

INTRODUCTION

The growth of renal transplantation in the past decade and the increased amount of clinical experience in this area has allowed many transplant centres to broaden their criteria for patient selection. This has resulted in the acceptance of many patients, who were formerly considered as being 'non-ideal', into renal transplant programmes. While individual risk factors such as diabetes mellitus, cardiovascular disease, hypertension, age and race have been pointed out,[1-9] no standardised system has been employed to evaluate the contributions of the various risk factors to renal transplant outcome and patient survival.

At our centre, we have considered the combined effects of the multiple risk factors that are often simultaneously present in these patients prior to transplantation.[10] This has led to development of a scale for comparison of individual risk factors (Table I). Cumulative risk is then determined for each patient and transplant candidates are placed in an overall risk category. This allows for a more realistic pre-transplant evaluation. The present study compares the post-transplantation outcomes of two groups of high-risk renal allograft recipients at our centre receiving different immunosuppressive regimens.

PATIENT POPULATION AND IMMUNOSUPPRESSION

Group I of the study comprised 100 consecutive kidney transplants performed in 89 patients from September 1979 to November 1981. Follow-up of these patients was up to three years post-transplant. Eighty patients received primary renal transplants and 14 were transplanted with second renal allografts from cadaver donors. The remaining 6 patients received renal grafts from living related donors. Immunosuppression for patients in Group I consisted of azathioprine, prednisolone and antilymphoblast globulin (ALG). Rejection episodes were treated with ALG without increasing steroids.[11, 12]

The thirty patients in Group II were transplanted at our centre between December 1983 and August 1984. Twenty patients received primary kidney allografts, 6 patients received second renal transplants and 2 patients received a third renal graft from cadaver donors. Two patients were transplanted with kidneys from living related donors. Immunosuppression for these patients consisted of cyclosporin and prednisolone. Cyclosporin A was given pre-operatively at a dosage of 4 – 5 mg/kg (intravenously). No cyclosporin A was given during the

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TABLE I

Grading system for individual determinants contributing to cumulative risk to life of renal transplant recipients

Risk Factor	*R.R.I.**
Severe cardiac disease	0.50
Severe pulmonary disease	0.50
Disseminated collagen disease	0.50
Insulin dependent diabetes mellitus	0.40
Severe malnutrition ($\leq$50% ideal body weight)	0.40
Severe obesity ($\geq$60% ideal body weight)	0.40
Severe hypertension (diastolic pressure $\geq$110)	0.40
Oxalosis	0.40
Fabry's disease	0.40
Re-transplantation	0.40
Severe bladder disease (diversion required)	0.30
Drug addiction	0.30
Age $\geq$45 years	0.30
Liver disease	0.30
Peptic ulcer	0.30
Pancreatic disease	0.30
Controlled systemic infections	0.25
Major psychiatric disturbances	0.25
Diverticulosis	0.25
Amyloidosis	0.25
Rapid progressive glomerulonephritis	0.20
Pre-existing controlled malignancy	0.20
High level cytotoxic antibodies ($\geq$60%)	0.20
No blood transfusions	0.20
Persistent alcoholism	0.20
Membranoproliferative glomerulonephritis	0.20
Goodpasture's syndrome	0.20
Other recurrent glomerulonephritis	0.20
Focal glomerulosclerosis	0.10
Peptic ulcer disease	0.10
Heavy smoking	0.10
Endocrinopathy	0.10
Sickle cell anaemia	0.10
Hepatitis history	0.10
Poor antigen matching ($\leq$2 antigen match)	0.10

* Relative Risk Index.

first 24 hours after transplantation, an oral dose of 4–5 mg/kg was administered on post-operative days 1–3, and 6–8 mg/kg on days 4–5. The serum cyclosporin A levels were determined on days 4 and 5, and the dose was then adjusted to maintain serum levels between 100 and 200 mg/ml. After two months the dose was fixed at 4–5 mg/kg daily regardless of serum levels. Prednisolone 1 mg/kg was given immediately prior to transplant. No prednisolone was given during the first 24 hours post-operatively. Patients received prednisolone at a

dosage of 1 mg/kg on day 2, 0.75 mg/kg on days 3–5, 0.5 mg/kg on days 5–7, and were maintained at this level until discharge. Within two weeks post-transplantation, prednisolone was tapered to 20 mg daily and decreased to 5–7.5 mg daily within 3 months after transplant. Some patients were later completely removed from prednisolone. Rejection was treated with methyl-prednisolone sodium succinate, 250 mg administered intravenously every 8–12 hours for 3 days. Occasionally, antilymphocytic globulin was used to treat rejection when no response to methylprednisolone was obtained.

ANALYSIS OF RISK

Each patient in Groups I and II was evaluated to determine his or her cumulative risk prior to transplantation. Each individual risk factor was weighted as in Table I and a final risk index was calculated by adding these together. Patients with a risk index $< .6$ were considered to be good risk candidates for transplantation. Risk indices $.6 \leq x \leq .9$ were considered to be at high risk. The very high risk category included cumulative indices in the $.9 < x \leq 1.1$ range. Extremely high risk was indicated by indices > 1.1.

RESULTS

Table II compared the 6 months actuarial patient survival for each risk category in each of the groups. Survival was observed to decrease as the cumulative risk to life increased in the antilymphocytic globulin treated group. Only one death from sepsis occurred in an extremely high risk recipient in the cyclosporin A group. When age was a risk factor, other risk factors were also frequently associated, such as severe cardiac disease, hypertension, obesity or malnutrition.

TABLE II

Effect of risk on patient survival in antilymphocytic globulin or cyclosporin A immunosuppressed patients

Risk Category	*Six Month Actuarial Patient Survival*				
	Group I (antilymphocytic globulin)		*Group II (cyclosporin A)*		*p**
	N	*%*	*N*	*%*	
Good risk	37	100	10	100	NS
High risk	27	88.5	7	100	$p<0.1$
Very high risk	15	78.1	9	100	$p<0.01$
Extremely high risk	21	71.0	4	75	NS

*Statistical comparison using Chi-square method.

DISCUSSION

Many authors have considered the effects of individual risk factors, present before transplantation, on the post-operative outcome. These determinants include age,[2, 13-16] preformed cytotoxic antibodies,[5] re-transplantation,[5] blood transfusion,[5, 6, 15] Fabry's disease,[17, 18] race,[7, 9, 15] malignant hypertension,[7]

glomerulonephritis,[7, 16] HLA-A, -B matching[14] and diabetes mellitus.[14] The preliminary analysis of risk factors in our transplant population has included these determinants as well as others in an effort to evaluate the cumulative effects of risk factors in renal transplantation.[10] This initial assessment categorised risk factors and assigned relative risk indices to each. When we applied this system to our transplant population, we found that, even though we did not employ a complex statistical analysis, our system was valid for grouping patients into risk categories as part of their pre-transplant evaluation. A relationship was observed between antilymphocytic globulin immunosuppressed patients in good, high, very high, or extremely high risk categories, and prognosis after transplantation.

It is apparent that a well developed system for determining the risk to life as part of the pre-transplant evaluation would be useful for decision-making both before and after transplantation. Accurate determinations of this risk could be used to individualise immunosuppressive therapy and would assist decisions regarding pursuit of re-transplantation after a graft has been lost to rejection. The results obtained from application of our risk categorisation system to cyclosporin A treated renal transplant recipients was affected by an overall reduction in patient mortality as compared with the previous antilymphocytic globulin treated group. Although our patient populations are small in both groups, this improvement in survival may be due to the steroid-sparing effect of cyclosporin A administration. Major risk factors such as cardiac disease and hypertension will cause fatal complications late in the course of the transplants, which will further influence survival.

We encourage other centres to utilise our system for risk categorisation or to modify it to accommodate the risk factors which may be additionally present in their patient population. In this way, risk categorisation may become an integral part of the pre-transplant patient evaluation and can be used to predict outcome after renal transplantation.

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