# Immunosuppressive therapy for renal transplantation in children and adolescents — is a NICE idea

Two years after its publication, Joanne Harding takes a look at the NICE technology appraisal on immunosuppressive therapy for renal transplantation in children and adolescents and assesses how well it has been implemented in local practice.

## Introduction

Renal transplant is the optimum treatment for patients with established renal failure (ERF; previously known as end-stage renal failure)[1] because, if successful, quality of life and longevity are greater than can be achieved with long-term dialysis.[2,3] Approximately 130 patients aged less than 18 years underwent renal transplantation in 2003/4 and almost all will require lifelong immunosuppressant therapy.[2]

In April 2006, the National Institute for Health and Clinical Excellence (NICE) published *Technology Appraisal 99, Immunosuppressive therapy for renal transplantation in children and adolescents.*[2,4] In the appraisal NICE set out with the explicit aim to 'explore the clinical and cost-effectiveness of immunosuppressive agents in children using non-RCT data, and to take account of the particular needs of children and adolescents in relation to minimising the adverse effects of immunosuppressive agents.' The appeal panel wanted the committee to look at all the available evidence and 'make judgments on what — overall — seems the best evidence'.[4]

There have been some criticisms of the paediatric NICE recommendations in that they have centred largely on a perceived reliance on expert opinion in the face of an inadequate evidence base, Also there have been controversial decisions to disregard paediatric data in favour of adult data in certain cases.[4]

This article aims to summarise the NICE recommendations, to explore the assumptions and decisions taken and to assess its implementation in local practice two years on.

## Overview of immunosuppression in renal transplant

The goal of immunosuppressive therapy is to avoid early acute organ rejection and to improve short-term and long-term kidney allograft survival. This is not easily achieved because over-suppression can expose the patient to an increased risk of complications, especially infection.[6] The choice of immunosuppressive regimen is based largely on the immunological risk of each patient. Immunological risk factors include prior renal transplants, suboptimal human leukocyte antigen matching, increased graft cold ischemia times and antibody sensitisation.

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## Side-effects of immunosuppressants in children and adolescents

Minimising long-term side-effects of immunosuppressants is especially important for children. These include increased risks of growth retardation, cardiovascular side-effects (such as hyperlipidaemia), post-transplant lymphoproliferative disorders (PTLD) and post-transplant diabetes mellitus (PTDM).

As with adults the potential for immunosuppressants to cause nephrotoxicity and to increase the risk of opportunistic infections, especially cytomegalovirus (CMV) infections, must be considered when choosing an immunosuppressant regimen for children.

Excellent one-year graft survival rates have been reported in the paediatric population — between 89–96% compared with 90% in low risk adults.[3] Five-year graft survival rates are best in patients aged less than 10 years (70–92%) and poorest in adolescents aged 11–17 years (65–79%).[7] It

**Table 1. Selected adverse-events of immunosuppressant medication**

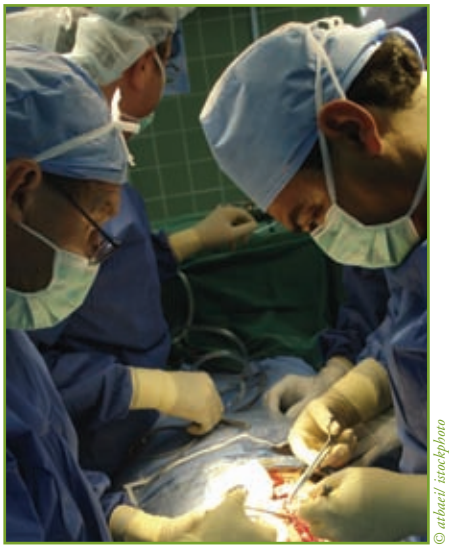
| | Very Common | Common | Uncommon |
|---|---|---|---|
| **Ciclosporin**[19] | Hyperlipidaemia, tremor, headache, hypertension, renal dysfunction | Electrolyte disturbances, GI disturbances, hypertrichosis, gingival hyperplasia, | Mood and sleep disturbances, oedema, weight increase |
| **Tacrolimus**[20] | Hyperglycaemia, diabetes mellitus, hyperkalaemia, insomnia, tremor, hypertension, renal impairment | Blood dyscrasias, fluid and electrolyte disturbances, hyperlipidaemia, mood disorders, CV disorders, GI problems, alopecia, increased sweating, acne | Coagulopathies, dysmenorrhoea and uterine bleeding |
| **Mycophenolate mofetil**[21] | Blood dyscrasias, sepsis, opportunistic infection, vomiting, abdominal pain, diarrhoea, nausea | Skin cancer, benign neoplasms, pancytopenia, leucocytosis, hyperlipidaemia, mood and sleeping disorders, tachycardia, GI disturbances, dermatological problems, renal impairment, cytomegalovirus, colitis | |
| **Sirolimus**[22] | Urinary tract infection, thrombocytopenia, anaemia, hyperlgycaemia, hypertriglyceridaemia, hypercholestrolaemia, lymphocoele, abdominal pain, diarrhoea, acne, arthralgia, peripheral oedema | Sepsis, infections (including CMV), skin cancer, blood dyscrasias, abnormal LFTs, tachycardia, DVT, respiratory disorders, epistaxis, stomatitis, osteonecrosis, proteinuria, oedema | Post-transplant lympho-proliferative disorders, pancytopenia, pericardial effusion, pulmonary embolism, pulmonary haemorrhage, pancreatitis, nephrotic syndrome |

is assumed that poor adherence is a major factor in declining graft survival rates in the adolescent group.[7] Therefore, the NICE appraisal committee set out to factor in the importance of cosmetic adverse-effects in adolescents (for example, ciclosporin-associated hypertrichosis and gingival hypertrophy) in it's analysis of the evidence. Unfortunately, the reporting of adverse events was routinely poor across all adult and paediatric papers reviewed for the NICE appraisal. As such, despite best intentions, the risks of individual side-effects could not be evaluated in economic models. Table 1 summarises the liklihood of various side-effects reported in adults for the four key immunosuppressants used in both adult and paediatric transplantation — ciclosporin, tacrolimus, mycophenolate mofetil and sirolimus.

## Economic evaluations

Cost-effectiveness was assessed using an adaptation of the Birmingham Sensitivity Analysis (BSA) decision model initially developed to model the NICE adult guidelines for the use of immunosuppressants in renal transplantation. For the paediatric guidance the model was to be adapted in three key ways:

1. Hazard ratios (HR) were intended to be paediatric-specific.



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2. 12-month biopsy-proven acute rejection (BPAR) levels were from paediatric randomised controlled trials (RCTs). If no paediatric RCTs were found then adult RCTs were used.
3. Drug doses and costs were adjusted to reflect licensed doses and weights.[3]

The yearly cost of support and renal replacement therapy used for the economic evaluations was £50–60K per annum (compared with £21,000 per year in adult patients). This disputed inflated cost was based on expert advice received from two UK paediatric centres and reflected costs from higher staff to patient ratios, specialist equipment and the need for additional support staff such as counsellors and play therapists.[5]

Ten-year patient and graft survival were calculated using surrogate markers at 12 months (either acute graft rejection rates or serum creatinine levels). Hazard ratios linked each surrogate marker with graft or patient survival. NICE opted to use a HR of 1.96 (linking acute graft rejection rates with graft survival) for the economic evaluations. This HR was derived from adult studies despite there being a paediatric study available where the HR was 1.41. This decision was based on concerns over the relevance of the study to the UK paediatric population (because only transplants from

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living, related donors were included). Critics have argued that paediatric data should have been used for paediatric guidelines.[3,5,8,9]

### *Monoclonal antibodies*

NICE recommend that basiliximab and daclizumab should be used for induction therapy in children; but only in combination with ciclosporin-based triple therapy (ciclosporin, azathioprine, steroid; CAS). NICE based this decision on the lack of benefit seen when basiliximab was added to a tacrolimus-based regimen (tacrolimus, azathioprine, steroid; TAS) in an unpublished, randomised paediatric study conducted over six months. This, controversially, makes the NICE paediatric immunosuppression guidelines more restrictive regarding basiliximab and daclizumab prescribing than is the case in adults.[5]

NICE also recommend using basiliximab and daclizumab in high-risk children, basing this decision on adult data because of a lack of paediatric evidence.[5]

Analysis of cost-effectiveness found the addition of basilixmab and daclizumab to CAS therapy in children was favourable (increasing quality-adjusted life years — or QALYs — and reducing costs). The addition of basiliximab to TAS treatment was also favourable.[3]

### *1. Basiliximab*

The committee identified one unpublished paediatric RCT in 197 patients where the addition of basiliximab to TAS therapy did not significantly improve six-month biopsy-proven acute rejection, graft loss or all-cause mortality.[3]

In a meta-analysis of four adult RCTs in 500 patients, treatment with CAS and basiliximab vs. CAS and placebo or no therapy significantly reduced short-term BPAR (22.4%, vs. 36.8%, RR=0.61, 95% CI: 0.46 to 0.80, number needed to treat, NNT=7). Graft loss, all-cause mortality and adverse events (including CMV infection, PTDM, PTLD and withdrawals because of adverse effects) were not significantly different between treatment groups.[3,6,10,11,12]

Three non-randomised paediatric studies were identified where basiliximab was compared with no therapy in patients receiving CAS therapy.[13,14,15] Unfortunately all three studies must be interpreted cautiously because of poor reporting and/or study design. Swiatecka-Urban and colleagues[15] had divergent baseline patient characteristics (gender, ethnicity, live vs. cadaveric donors) and (as with Duzova and colleagues)[14] did not report outcomes for age subgroups (range 7–21 years) whereas Pape and coworkers[13] reported minimal demographics at baseline and no withdrawal data. None of these studies showed a significant reduction in BPAR at 12 months with the addition of basiliximab although Duzova's group[14] did show a significant reduction at six months (0 vs. 26.1%, $p < 0.05$; RR=0.10; 95% CI: 0.01 to 1.70, NNT=4).

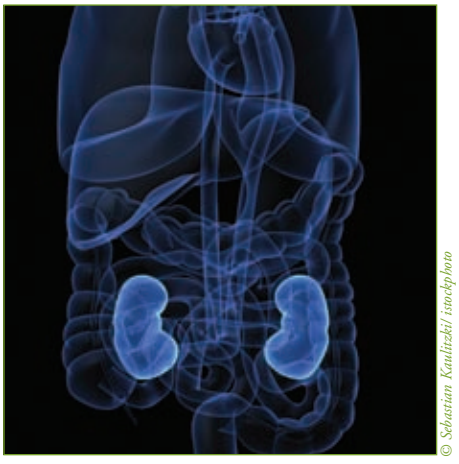
### *2. Daclizumab*

There were no paediatric randomised or non-randomised trials comparing daclizumab with no therapy or placebo in transplant patients. One adult RCT was identified in which the addition of daclizumab to CAS reduced BPAR at 6 months (22.2% vs. 35.1%, RR=0.63; 95% CI: 0.42 to 0.94, NNT=8). There was no BPAR reporting at 12 months. There were no significant differences in graft loss, all-cause mortality, or tolerability at 6, 12 or 36 months.[16,17,18]

### *Calcineurin inhibitors*

NICE recommend tacrolimus as an alternative to ciclosporin and suggest that the initial choice should be based on the relative importance of side-effect profiles for the individual patient. The more common side-effects of ciclosporin include hypertrichosis and gingival hypertrophy whereas tacrolimus-associated adverse events include hyperglycaemia, PTDM, tremor, GI disturbances, alopecia and acne (Table 1). Both ciclosporin and tacrolimus are nephrotoxic.[19,20]

One published paediatric RCT comparing tacrolimus with ciclosporin in 204 patients (aged less than 18 years) demonstrated that a TAS regimen reduced six-month BPAR and improved graft function assessed by glomerular filtration rate (GFR). By 12 months there was no significant difference in BPAR and this lack of difference was observed for the remainder of the study. Graft loss was similar in both groups at 6 and 12 months, but a significant reduction in graft loss was



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observed in the TAS group at two years and this was sustained at four years (11% vs. 22%, RR=0.49, p=0.0035) showing improved long-term graft survival. GFR rates in the TAS group also remained significantly increased at four years (71.5 vs. 53.0, p=0.0001) posing the question of whether GFR might be a better surrogate marker for long-term graft survival than the rate of acute rejection. There were no significant differences in tolerability between the two treatment groups (including PTDM and PTLD). However, there were significantly more withdrawals from adverse events in the ciclosporin group (15

vs. 10%, RR 0.64, 95% CI 0.30-1.38, number needed to harm, NNH=19).[8,23]

In a meta-analysis of nine adult RCTs (n=1664) improvement in BPAR was shown at 12 months with TAS vs. CAS (25.1% vs. 40.1%, respectively) although graft loss and all-cause mortality were similar in both groups. There was poor methodological reporting of these trials. The incidence of adverse events was not significantly different with the exception of PTDM, which was higher in TAS-treated patients compared with CAS (6.1 vs. 2.6%, RR=2.38, 95% CI: 1.32 to 4.31, NNH=29) and hyperlipidaemia, which was lower with tacrolimus (4.2 vs. 8.8%, RR=0.47, 95% CI: 0.24 to 0.93, NNH=22). Drug switching because of adverse events was significantly lower with tacrolimus compared with ciclosporin (1.1 vs. 11.1%, RR=0.10, 95% CI: 0.04 to 0.27, NNT=10).[3,5]

Cost analysis modeling for tacrolimus resulted in an incremental cost-effectiveness ratio (ICER) of £34,000 per QALY compared with CAS. The ICER calculation was highly sensitive to the HR of graft loss from acute rejection and dialysis costs, both of which were controversial. The ICER was also extremely sensitive to safety data, which was not able to be incorporated in the economic modeling because of poor reporting in the evaluated studies. The incorporation of safety data is likely to make the cost per QALY lower than £34,000.[3,5]

### *Mycophenolate mofetil*

NICE have recommended that mycophenolate mofetil (MMF) should only be used in children with:

1. proven intolerance to calcineurin-inhibitors — especially those with nephrotoxicity that could lead to chronic graft dysfunction
2. a very high risk of nephrotoxicity
3. children participating in RCTs investigating the use of MMF in a steroid-sparing or avoiding design.[5]

Critics have accused NICE of downplaying the significance of MMF in reducing or completely avoiding the use of corticosteroids in this patient group.[4]

The evidence appraised by NICE included four paediatric non-randomised comparative studies and seven adult RCTs evaluating ciclosporin, mycophenolate mofetil and a steroid (CMS) with azathioprine therapy. Compared with azathioprine, CMS significantly reduced graft loss at six months (2% vs. 17%), 12 months (2% vs. 17%) and three years (2% vs. 20%) in a paediatric study. BPAR rates were significantly lower with CMS at six months when compared with azathioprine (15 vs. 26%, RR=0.39, 95% CI: 0.19 to 0.79, NNT=10). Only one study reported results for graft function and the authors found no significant difference between CMS and azathioprine at 12 months.[3]

A meta-analysis of the adult studies showed reduced 12-month BPAR rates with CMS compared with azathioprine (18.5% vs. 31.6%, RR=0.60, 95% CI: 0.47 to 0.76, NNT=8). However, there was no significant difference in short or long term graft loss or all cause mortality. Although the rate of patient withdrawal because of adverse effects was not significantly different, patients in the MMF group showed increased levels of CMV infection.

Economic evaluations estimated an ICER of around £60,000 per QALY for MMF compared with azathioprine. The manufacturers calculated a much lower ICER of £17,000 per QALY, however, their model used much higher acute rejection rates (non-biopsy confirmed) based on a single paediatric study whereas NICE used the meta-analysis of adult patients.[3,5]

### *Mycophenolate sodium*

Mycophenolate mofetil is a prodrug of the active component mycophenolate sodium (MPS), an enteric-coated salt form of mycophenolic acid. MPS is not currently licensed for use in children and adolescents. Beacause of the paucity of evidence NICE do not recommend the use of MPS as part of an immunosuppressive regimen in children or adolescents who have received a renal transplant.[5]

A review of NICE guidance highlights the need for further RCTs to assess the use of immunosuppressants in paediatric renal transplant patients — particularly those reporting on adverse effects.

### *Sirolimus*

Sirolimus is a non-calcineurin-inhibiting immunosuppressant that is currently not licensed in children and adolescents. Only one paediatric RCT was identified that assessed the addition of sirolimus to CAS. There were no significant differences reported between groups for graft function or adverse events. The authors did not report on BPAR, graft loss or all-cause mortality.

Twelve-month BPAR rates were significantly reduced in the pooled results of two adult RCTs comparing sirolimus with azathioprine regimens (19 vs. 28%, RR=0.60, 95% CI: 0.45 to 0.80, NNT=10). However, the sirolimus group also showed increased serum creatinine levels (indicating reduced graft function) and increased hyperlipidaemia compared with controls. There were no other significant differences seen between groups.[3]

In the NICE guidance, sirolimus is only recommended for children or adolescents with a proven calcineurin-inhibitor-intolerance that requires complete calcineurin withdrawal.[5] Cost-effectiveness analysis was not performed for either MPS or sirolimus.

## Conclusion

In summary, the 2006 NICE guidance on the use of immunosuppressants for renal transplantation of children and adolescents was a nice idea, but one that was very difficult to execute given the lack of RCTs in children and the poor reporting quality.

Controversies with the NICE guidance generally surround areas where, in the absence of any robust paediatric data, the

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committee have based their recommendations on adult RCTs or expert opinion. However, this is still better than using one's own custom and practice to guide clinical decision-making so the NICE guidance is to be welcomed.

A review of this guidance highlights the need for further RCTs to assess the use of immunosuppressants in paediatric renal transplant patients — particularly those reporting on adverse effects. ✣


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Declaration of competing interests
The author declares that she has no competing interests.

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