The utility of computed tomography for recent-onset partial seizures in childhood

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Objectives. To determine the diagnostic yield of computed tomography (CT) of the head in children presenting for the first time with partial seizures in a region with a high prevalence of tuberculosis and neurocysticercosis.

Design. Prospective cohort study.

Setting. The secondary-level ambulatory service of Red Cross Children's Hospital, Cape Town.

Subjects. Children aged 6 months - 12 years with a first partial seizure.

Outcome measures. Abnormal CT findings; clinically unsuspected abnormal CT findings.

Results. Of 118 enrolled children, CT findings were available for 94 (80%). Sixteen (33%) of 49 children scheduled to return later for an initial CT scan failed to do so. Thirty-two scans (34%) were reported normal, 45 (48%) showed single or multiple granulomas, and 17 (18%) showed other findings. All 8 children with persistent specific CT findings were suspected of having the condition before CT scan. Of 68 cases with prospectively recorded clinically expected CT findings, normal scans were expected in 2 cases (3%) and occurred in 33 cases (49%).

Conclusions. Routine CT scan for children presenting with a first partial seizure in an area with a high prevalence of neurocysticercosis failed to identify findings other than neurocysticercosis that meaningfully altered clinical management. Assuming a 70% relative reduction of seizures with albendazole treatment for neurocysticercosis, routine CT scanning in the study population would require 11 scans and 5 courses of albendazole to prevent 1 child from having seizures, compared with no CT scans and 11 courses of albendazole with blanket use of albendazole.

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It is widely agreed that neuroimaging is not required for all children with seizures.[1-4] Suggested selective indications for neuroimaging include partial seizures because of a higher prevalence of abnormalities, including tumours, associated with such seizures.[1-4] An association of partial seizures with treatable lesions has been observed in adults,[5,6] but partial seizures are more common in children than in adults[5,7] and the clinical spectrum and aetiology of seizures in children are very different. It has been found that childhood partial seizures are more likely to involve abnormal neuroimaging.[8-10]

When neuroimaging is required, magnetic resonance imaging (MRI) is regarded as the investigation of choice in most circumstances in industrialised countries.[1-4,11] However access to MRI in low- and middle-income countries is extremely limited. Computed tomography (CT) is available in some settings, but availability remains limited.

Several studies[10,12,13] have examined the diagnostic yield of CT in children with a first partial seizure. Although 4% of children required further diagnostic workup in one study,[12] it is not reported whether this work-up was followed by therapeutically important decisions. In another study,[13] 14 (21%) of 66 children who had CT performed had abnormal findings. Two were of 'immediate therapeutic significance', but both findings were predictable from clinical history or examination. The third study[10] found abnormalities in 19 (18%) of 107 CT scans, but it was not reported whether these abnormalities had been suspected clinically. All three studies were retrospective or contained large retrospective elements. This is likely to have led to unrepresentative samples of children receiving scans and potential biases in the extraction of clinical data from clinical records, particularly in assessing changes in clinical management. The importance of partial seizures, or of specific clinical features in such seizures, as predictors of therapeutically important CT findings is therefore not clear.

These three studies were conducted in industrialised countries and have limited applicability to areas of the developing world with a high prevalence of parasitic brain cysts and tuberculosis (TB) and limited access to CT. Of a group of 23 neurologically normal Indian children with partial seizures (65% with first seizures), 35% had abnormal CT scans, but the patients were a selected group and not consecutive because of cost constraints.[15]

In Cape Town a strong impression was gained that in children over 2 years of age with a single partial seizure and no underlying neurological deficit, the overwhelming majority of therapeutically important CT abnormalities were those of neurocysticercosis or TB. The CT features of neurocysticercosis and TB are often difficult to differentiate, and our practice had been to exclude TB (using chest radiography and skin testing) and to manage the remaining patients for neurocysticercosis.

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At the time that the study was planned there was little convincing evidence to support the use of albendazole for neurocysticercosis. If there were no other clinically significant causes of the seizures in this group of children, it would then have been rational to exclude TB and manage all remaining patients conservatively, as if they had normal scans or neurocysticercosis, without performing CT. Such a policy would have had considerable beneficial resource implications, particularly for patients referred long distances for scans, and would free up limited CT facilities for more fruitful investigations.

Objective

To determine the diagnostic yield of head CT scans in children presenting for the first time with partial seizures in a region with a high prevalence of TB and neurocysticercosis.

Methods

Participants

Children aged 6 months - 12 years presenting for the first time with partial seizure to the secondary-level ambulatory service of Red Cross Children's Hospital, Cape Town, were prospectively enrolled from 12 October 1999 to 31 December 2002. Details of history and clinical examination, as listed in Table I, were recorded by the clinician caring for the child on a pro forma record sheet adapted to form part of the routine clinical record. In children whose CT findings were not already known the clinicians also recorded their expected CT findings. The investigators extracted the CT findings from the formal radiological report, and extracted details of actual clinical management and follow-up from the routine clinical notes.

CT findings were categorised as normal, granuloma (single or multiple, with or without calcification), incidental findings without clinical significance (reported as such or ignored by the clinicians), findings of uncertain significance, and specific findings other than granuloma.

Agreement between the clinicians' expected findings and the actual CT findings was adjusted for chance agreement using the kappa statistic. A planned multiple regression analysis to identify clinical predictors of specific scan findings was not performed because it was judged not to be clinically meaningful, given the small number and very heterogeneous nature of findings other than granuloma.

Ethical approval

The study was approved by the Research Ethics Committee of the University of Cape Town.

Results

One hundred and eighteen children were enrolled. CT scan findings were available for 94 (79.7%). The reasons for loss to follow-up of other participants are shown in Fig. 1, and were mainly due to missed appointments for the CT scan. The clinical characteristics of children for whom CT scans were performed are shown in Table I.

Of the 95 children who had CT scans, 32 (34%) were reported as normal, 45 (48%) showed single or multiple granulomas, and 17 (18%) showed other findings, while in 1 case no record of the findings was traceable. A breakdown of the findings is shown in Table II.

Table I. Characteristics of children with CT scan reports

	N	(%)
Age in months (median, IQ range)	94	64, 33 - 99
Gender (male	94	46 (49)
Complex seizure	85	68 (80)
Right-sided seizure	92	47 (51)
Duration of seizure in minutes (median, IQ range)	73	30, 10 - 60
Fever (reported by caregiver)	93	16 (17)
Preceding headache	87	17 (20)
Preceding vomiting	91	20 (22)
Tuberculosis contact	92	12 (13)
Developmental delay	91	5 (6)
Developmental regression	92	0
Recent change in behaviour or school performance	91	1 (1)
Papilloedema (when fundi seen)	42	0
Neck stiffness	91	5 (6)
Cranial nerve palsy	93	5 (5)
Hemiplegia	93	6 (6)
Cranial nerve palsy or hemiplegia	93	9 (10)

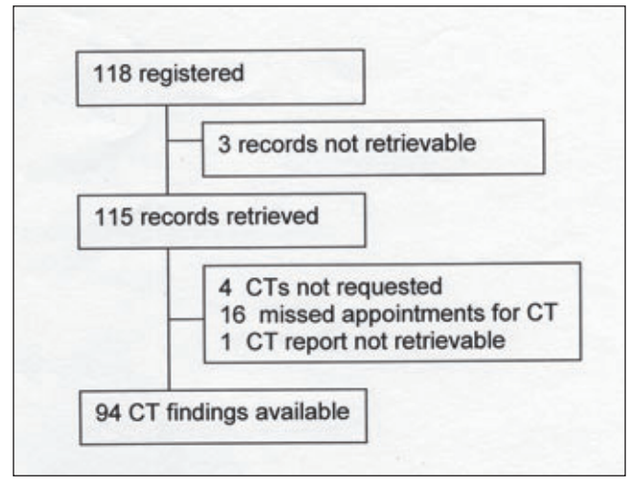

Fig. 1. Lost to follow-up.

Table II. Findings on CT scan

	N (%)	95%CI
Reported as normal	32 (34)	24 - 44%
Granuloma	45 (47)	
Single	26 (27)	37 - 58%
Single with calcification	3 (3)	
Multiple	4 (4)	
Multiple with calcification	11 (17)	
Calcification only	1 (1)	
Other	17 (18)	11 - 27%
Incidental findings reported as not clinically significant or ignored by clinicians*	5 (5)	
Findings of uncertain significance, discharged after follow-up*	4 (4)	
Specific	8 (8)	
No report†	1 (1)	
Total	95	

*Categorised as normal in subsequent analyses.
†Excluded from subsequent analyses.

There were findings of uncertain significance on 4 scans that resolved on follow-up. These were ill-defined lesions that disappeared or were judged insignificant after repeat CT scan. Of the 8 children with specific CT findings, all were suspected of having the condition before CT scan (Table III).

Of 68 cases where the clinician recorded the expected CT finding (normal, granuloma or other) and a CT report was available, expected findings agreed with CT findings in 31 cases (46%). Chance-adjusted agreement (kappa) was 16% (95% confidence interval (CI): -2 - 34%) (Table IV). A normal scan was expected in 2 cases (3%) and occurred in 33 cases (49%). 'Other' findings were expected in 17 cases (25%), and occurred in 5 cases (7%). Granuloma was expected in 49 cases (72%), and occurred in 30 cases (44%).

Of the 49 children scheduled to return at a later date for the initial CT scan, 16 (33%) failed to do so.

Discussion

None of the children in this study had a meaningfully abnormal CT finding other than neurocysticercosis that was not clinically suspected before CT. Routine CT scanning did not meaningfully change the clinical management of 94 children aged 6 months - 12 years with a first presentation for partial seizure. From this sample the upper 95% confidence limit for such management change is 3.85%. That is, even at the highest CT yield that might plausibly be expected from this population, 26 CT scans would be needed to detect 1 clinically meaningful unsuspected abnormality other than neurocysticercosis.

Table III. Specific findings on CT scan, other than granuloma

	N	Clinical details
Atrophy	1	Developmental delay, attending special school
Tuberculous meningitis	3	Diagnosis clinically suspected in all 3 cases
Mass lesion	1	Final diagnosis tuberculous meningitis with tuberculoma. Diagnostic work-up for tuberculosis had been started before CT scan
Acute glomerulonephritis with hypertensive encephalopathy	1	Clinical diagnosis before CT scan
Fracture through ethmoid sinus	1	Fracture visible only on special CT views requested because of clinical suspicion
Benign hydrocephalus	1	Previous CT scan for macrocephaly
Total	8	

Table IV. Agreement between clinically expected and actual CT findings (*N*)

	CT findings			
Clinical expectation	Normal	Granuloma	Other	Total
Normal	2	0	0	2
Granuloma	21	26	2	49
Other	10	4	3	17
Total	33	30	5	68

There was poor agreement between clinicians' expectation and actual scan findings – only 16% after adjustment for chance agreement. The main areas of disagreement were the clinicians' overestimate of the probability of granulomata and other specific findings, and an underestimate of the probability of a normal scan, present in 49% of cases but expected in only 3%. The falsely high expectation of abnormal findings (regardless of their potential impact on clinical management) is a potential barrier to the successful implementation of guidelines for more rational use of CT scans in this context.

An incidental finding of concern in this study is the large proportion of patients lost to follow-up. One-third of children for whom outpatient CT appointments were made did not attend for the scan. If CT scans are performed, systems must be in place to ensure maximal follow-up. Routine CT scanning for partial seizure may in itself contribute to the drop-out rate by adding to pressure on existing services and extending waiting times for the procedure.

The strengths of this study include prospective enrolment that enabled more accurate collection of clinical data. The sample also included a meaningful spectrum of patients from a specified clinical setting. Retrospective folder review to measure subsequent management was unavoidable if clinical management was not to be interfered with. A weakness of the study is that children were enrolled and examined by a large number of clinicians involved in their routine care. This may have detrimentally affected the quality of clinical data and resulted in some missing data.

Although clinicians' expectations were a very poor predictor of CT findings, the CT findings had virtually no impact on diagnosis, except in the common case of granuloma. The impact of a CT finding of neurocycticercosis depends on the effectiveness of treatment for neurocysticercosis. If treatment is ineffective, the CT scan appears to have little impact on clinical management, and appears unnecessary in the absence of the clinical suspicion of a specific finding other than granuloma. If treatment with albendazole is effective, the blanket use of albendazole in all patients presenting with partial seizures may result in fewer harmful effects than incurred with routine CT scanning (e.g. radiation dose, use of scarce resources, anxiety due to inconsequential incidental findings). Assuming that a recent imprecise estimate of the effect of albendazole on reducing the number of children with seizures in the first 6 months is correct (odds ratio 0.30, 95% CI: 0.1 - 0.9),[14] i.e. that albendazole reduces the risk of subsequent seizures from 33% to 13%, routine CT scanning would require 11 scans and 5 courses of albendazole in our setting to prevent 1 additional child from having seizures, compared with no CT scans and 11 courses of albendazole with blanket use of albendazole.

On the basis of our findings, we are restricting the use of CT scanning in children over the age of 2 years who present to the hospital with a first focal seizure and no neurological history and no physical signs that cannot be explained by the seizure itself. Investigations are limited to a chest radiograph and tuberculin skin test. Management includes a single dose of albendazole for treatment of possible intestinal tapeworm.

The applicability of the findings of this study to other settings depends on the prevalence of the underlying pathologies. The findings appear to be broadly applicable to settings with a high prevalence of neurocysticercosis and tuberculous meningitis. Health system issues such as loss to follow-up may occur elsewhere, suggesting that local audit may be necessary.

In summary, routine CT scan for children presenting with a first partial seizure in an area with a high prevalence of neurocysticercosis failed to identify findings other than neurocysticercosis that meaningfully altered clinical management. If treatment of neurocysticercosis with albendazole is judged to be worthwhile, the benefits of routine screening to identify patients with granulomata would depend on the prevalence of neurocysticercosis, and the trade-off between the benefits of albendazole and the harmful effects of CT scans and/or albendazole.

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The impact of subspecialty services on health care delivery – a community health centre based study

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Objectives. The objective was to evaluate the role of a paediatric surgical consultant at a primary health care facility.

Design. Descriptive and prospective.

Setting. In the process of planning and implementation of the 2010 health plan of the Provincial Government of the Western Cape, a shift occurred in the delivery of health care to children from a provincially based hospital system to a municipally based primary health care system. To contribute towards enabling this process, the Department of Paediatric Surgery at Red Cross War Memorial Children's Hospital established a paediatric surgical day clinic at a local community health centre during 2001.

Subjects. Information was obtained from patient data sheets containing details of consultations at the sub-specialist surgical clinic at Michael Mapongwana Community Health Centre.

Results. Over a 58-month period 1 171 children were seen, of whom 655 were male and 427 female. Their ages ranged from 0 to 19 years, the largest group being under 1 year. Eighty per cent of patients were accompanied by their mothers. The correct diagnosis was established by the nurse practitioners in 71%. General paediatric surgical conditions predominated, followed by medical, dermatological, orthopaedic, trauma, otolaryngo-pharyngology, infectious diseases, ophthalmology, urology, neurosurgery, malignancy and maxillofacial conditions. The details are set out in the report. In total 597 patients were referred directly to an appropriate care facility and 574 patients could be managed entirely at the clinic level.

Conclusions. This study demonstrated the significant public health problem of paediatric surgical disease. It emphasised the preventative and cost-effective role of a surgical clinic at primary health care level. The clinic allowed for timely surgical intervention in 65% of surgical cases, thereby decreasing inappropriate tertiary referrals. We believe that bringing specialists into the community can only strengthen the 2010 health care plan.

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'Small steps and big leaps'[1]

The process of planning and implementation of the 2010 health plan of the Provincial Government of the Western Cape brought about changes in the delivery of health care to children. These changes emanated from a need for a more equitable, efficient, affordable and integrated health care system. To achieve these goals, a pragmatic evolution of care for a service delivery platform was adopted by the provincial and municipal health authorities. This approach resulted in the introduction of municipality-based health care centres.

A network of municipality primary health care clinics (PHCs) functions as the first level where patients gain entry into the health system. These centres are situated in the community. Within this new dispensation, nurse practitioners would primarily be responsible for managing childhood ailments. Should more advanced diagnosis or treatment be required, patients would be referred to community health centres (CHCs), or secondary level or tertiary health facilities. The referral system is depicted in Fig. 1.

While the Provincial Health Department had previously been directly responsible for providing health services, it now assumes the role of providing guidelines, co-ordination, funding, monitoring and supporting the PHCs, which have become the primary providers.

A quantum shift therefore occurred in the delivery of health care to children from a provincially based hospital system to a municipally based PHC system. To contribute towards enabling this process, the Department of Paediatric Surgery at Red Cross War Memorial Children's Hospital (a tertiary referral centre) decided to establish a paediatric surgical day clinic at a local community health centre during 2001. The health centre is 1 of 9 CHC facilities that provide health services to the local community with a drainage population of approximately 300 000 inhabitants.

This site was chosen because 11% of children with surgical conditions seen at the tertiary hospital originated from this community. The clinic was established after extensive negotiations with the health authorities and the local communities. A specialist paediatric surgeon conducted a weekly 3-hour clinic. Children were referred from five PHCs or seen *de novo*. A dedicated nurse was allocated to the clinic.

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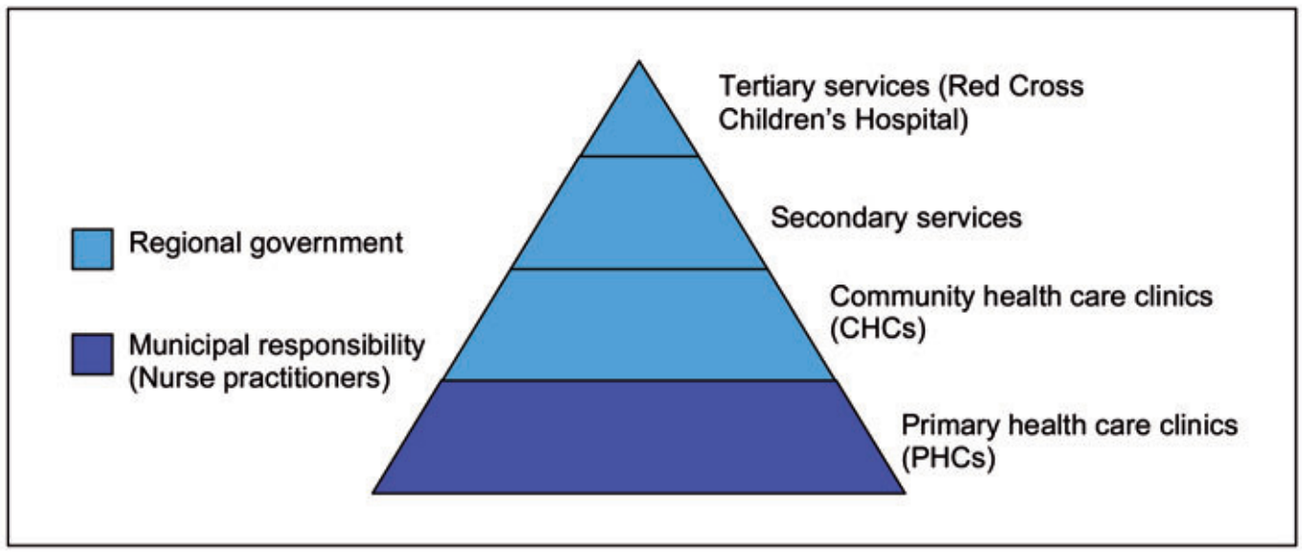

Fig. 1. Referral pattern for patients under the 2010 health care plan.

Methodology

The objective of this descriptive and prospective study was to evaluate the role of a paediatric surgical consultant at a CHC. The goals were to review the demographics, disease profiles, referral patterns and the prevalence and magnitude of surgical conditions in order to better understand the surgical needs of the community. In addition, the quality of care provided by the municipal health services, the diagnostic and therapeutic roles that nurse practitioners play in this setting, the benefits and drawbacks of having a sub-specialty service at community level in a low-resourced and low-income environment and the outcome following consultation were also assessed.

Information was obtained from the patient data sheets for the surgical clinic at Michael Mapongwana Community Health Centre. The information reported reflects those patients attending the sub-specialist paediatric surgery clinic from March 2001 to December 2005. When the opportunity arose, the time at the clinic was used to educate medical students and community service doctors about childhood surgical conditions.

Results

Patient demographics

One thousand one hundred and seventy-one paediatric patients were assessed and managed over the 58-month period. Patient numbers generally increased as the clinic became well known, from 160 in 2001 to 345 in 2005. Ages ranged from 0 to 19 years, the largest group being under 1 year of age. There were 655 males and 427 females (Fig. 2). The gender of 89 patients was not documented.

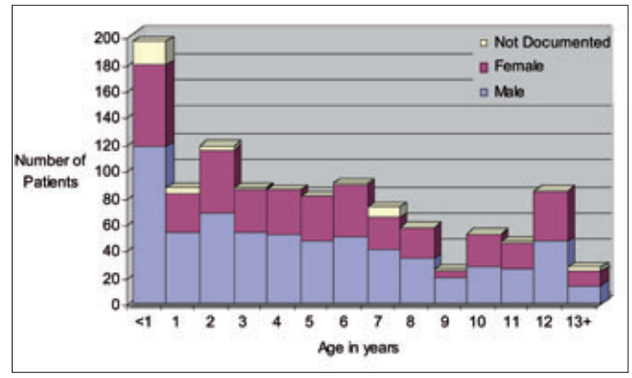

Fig. 2. Age and gender distribution of patients.

Accompanying person

The accompanying guardian was noted on 469 patient data sheets. Mothers accompanied the patients in 375 cases (80%), and fathers in 35 cases (7%). Six children presented with no escort.

Diagnostic accuracy of nurse practitioners' referral letters

A referral diagnosis made by the nurse practitioner from the referring municipal clinic was recorded in 357 cases. The correct diagnosis was established in 255 children (71%) and the diagnosis was incorrect in 102 (29%).

Medical sub-specialties

Fig. 3 represents an analysis by medical specialty of the total number of children seen at the clinic. As could be expected, general paediatric surgical conditions predominated, followed

by medical, dermatological, orthopaedic, trauma otolaryngo-pharyngology, infectious diseases, ophthalmology, urology, neurosurgery, malignancy and maxillofacial conditions.

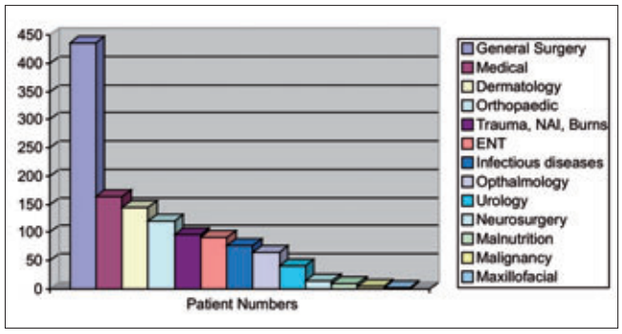

Fig. 3. Patient numbers in each specialty.

General surgery

Four hundred and thirty-one surgical patients were seen and a total of 451 diagnoses made. The prevalence and analysis of surgical disease profiles are depicted in Table I. Minor surgical conditions were more prevalent and most required elective surgical intervention. Acute appendicitis was diagnosed in 2 children, and 2 cases of malignancy, both advanced, were incorrectly diagnosed initially at PHC level. Four other children had lumps that were subsequently diagnosed as malignant. Management of surgical conditions involved 285 patients being referred to selected tertiary level facilities. In 104 children, management consisted of observation, advice and review. Antibiotics, analgesia and other medications were given to 36 children. The balance received dressings for burn wounds or septic wounds or had abscesses aspirated.

Medical conditions

A total of 140 medical patients were observed with a total of 164 diagnoses. Although there was a clinical suspicion of HIV infection in many patients, only 22 patients were tested and documented as HIV-positive. Developmental delay, respiratory diseases and HIV accounted for 71% of the diseases. Sixty-six patients were treated on site with medication and antibiotics. Fifty-one required referral. Further investigations and social grant applications were required in 25.

Table I. General surgical diagnoses

Diagnosis	Number
Inguino-scrotal pathology	157
Abscess/cellulitis/infection	92
Mass/cyst	53
Umbilical hernia/granuloma	34
Minor surgical conditions	28
Peri-anal conditions	21
Lymphadenopathy	17
Phimosis/paraphimosis/balanitis	14
Oesophageal atresia/stricture/dysphagia	9
Abdominal pain/constipation	9
Appendicitis	2
Malignancy – sarcoma/leukaemia/lipoma	6
Normal	9
Total	451

Dermatology

Dermatological conditions (in 144 children) were among the most common conditions encountered. These consisted of primary skin disorders and infections, and molluscum contagiosum in 93%. One hundred and six patients were managed at the clinic either by prescription of medication or local procedures and management, while 38 were referred to a dermatology department for diagnostic and therapeutic reasons.

Orthopaedics

During the 58 months 120 orthopaedic patients were seen and managed. Their diagnoses ranged from congenital skeletal abnormalities to fractures and bone and joint infections. These diagnoses accounted for 83.3% of orthopaedic conditions. Seventy-two patients required referral to a tertiary care institution, while 48 patients could be dealt with locally with splinting, prescription of medication and minor procedures.

Other conditions

Nine children were seen after a non-accidental injury (NAI); 2 of these had been assaulted and sustained fractures, while 7 had been sexually assaulted. These children were managed according to the NAI protocol of the Western Cape.

Other sub-specialty patients were also seen. Ninety-one patients had problems of an ENT nature, mostly otitis media, foreign bodies in the ear or nose, and parotitis (related to HIV). Ophthalmological cases numbered 65 – meibomian cysts, strabismus, visual impairment, conjunctivitis and molluscum contagiosum being the most common diagnoses. Infectious diseases were documented in 76 patients. These included the usual childhood viral infections of mumps, measles, chickenpox, and most commonly tuberculosis. Central nervous system conditions (hydrocephalus and post-traumatic headaches) were encountered in 13 patients.

Acute trauma was diagnosed in 45 patients. This included a spectrum of injuries such as lacerations, contusions and fractures. Nineteen were referred, the others being treated at the local level with dressings, splinting or sutures. Forty-two patients presented with a history of burns, either acute or with chronic contractures. Fourteen of these were referred to a burn unit, one as an emergency. The others were managed locally with satisfactory outcome.

Excluding undescended testes and phimosis, 41 patients with a problem of a urological nature were encountered. The

most common diagnoses were congenital mega-prepuce, hypospadias and incontinence. Because of the nature of these problems, 29 patients were referred.

Overall management

Table II reflects the management of the group as a whole. In total 597 (51%) were referred directly to an appropriate care facility and department and 574 (49%) could be managed at the clinic level. Management included prescription of medication, dressings, advice and reassurance, and application for social care grants.

The surgeon was involved in the resuscitation of 2 children during this period. One had inhaled paraffin and the other was in shock as a result of gastroenteritis. Emergency ambulance transfer was not immediately available and they were transported directly to the tertiary unit in the surgeon's car. One neonate at the adjoining midwife obstetric unit was certified dead at birth.

There were occasional adult consultations for trauma, abdominal pain, surgical infections, diabetes, TB, haemoptysis and vascular abnormalities. The statistics for these conditions were not included in the audit.

Table II. Management summary of total cases

Management	Number
Referred/admitted	597
Observed/followed up	142
Antibiotics/medications/analgesia	234
Advised/X-rays	145
Dressings	32
Social grant	12
Plaster of Paris	9
Total	1 171

Discussion

Primary health care is defined as provision of first contact care; it is aimed at providing continuity, co-ordination and comprehensiveness. For this service to function optimally, it has to be multidimensional and requires a pathway for referral for diagnostic and management options when required. This survey has highlighted many of these aspects.

As part of the 2010 health plan of the Western Cape, an impressive network of municipally based primary health care facilities was developed where nurse practitioners were primarily responsible for preventive and primary curative care. However, within this new dispensation the provision of basic paediatric surgical care at primary and secondary levels was deficient, hence the decision to establish a surgical platform at this level. This novel service was introduced as a complementary service to the existing municipality health clinics.

Paediatric surgical disease is a significant public health problem. In an attempt to determine the surgical needs of children in Africa, it was estimated that 543/10 000 children, aged 0 - 14 years will require surgical care on an annual basis. Furthermore, a total of 46% of children presenting with surgical problems required surgical procedures, 68% of which were classified as minor. The estimated accumulated risk of developing surgical conditions was 85% by the age of 15 years.[2]

Traditionally surgery has been seen as an expensive, high-tech service and not considered part of a primary public health model. Primary health care policies, although excellent for child health in general terms, did not adequately address or reflect the surgical needs of children in the PHC system. (Powell D, Van der Merwe B, De War R. Survey of Child Health Services in the Western Cape Province, May 2003 – unpublished data available at the Institute of Child Health Library, Red Cross Hospital (printed copy as well as CD)).There is considerable uncertainty about a national and provincial plan for paediatric surgery, the lack of surgical facilities for children at primary health care level, the lack of anaesthetic facilities for children at a secondary level and the future role of specialists and sub-specialist paediatric surgical services at primary, secondary and tertiary level. The issue is not whether selected children can receive surgical care, but whether children have access to appropriate services.[3]

As primary care facilities developed, a progressively greater number of children were identified with surgical conditions and a concomitant need for an increase in primary surgical care or referral for diagnosis and treatment developed. The wide spectrum of diseases and conditions documented in this series is a reflection of the surgical needs of the community, and can also serve as a barometer of surgical needs in any stable regional community. Although this clinic was primarily established as a surgical service, 30% of the patients seen had diagnoses of a 'medical' nature. This possibly emphasises the need for such clinics to be established in other disciplines.

In our tertiary institution the outpatient load is disproportionately high for specialist attention. A large percentage of patients could be dealt with at non-specialist level, but are at present referred because of a lack of specialised services or knowledge of surgical conditions within community facilities. In this series 49% of patients were treated at the community level with no need for further referral. Had this clinic not been in operation, these patients would have been referred to already congested secondary and tertiary services. The proximity of a surgical specialist clinic to the primary health care clinics thus allows for easy referral of patients to the tertiary institution and lessens the financial burden on patients.

On the other hand, 51% of patients were referred directly to the appropriate surgical clinic or booked directly for surgical intervention, negating a preoperative outpatient visit. Patients thus receive streamlined service, with less waiting, fewer

points of contact within the system because of direct referral from a primary to a tertiary institution, less time off work and school, and reduced transport costs while the tertiary system is less flooded with outpatient visits.

A substantial number of children were seen with conditions necessitating early referral, including sick, dehydrated children and those with appendicitis, fractures, burns, diarrhoea and paraffin inhalation. Ambulance services were not always available as they were overburdened, hence the immediate transfer of 27 patients by means of private transport.

We were pleasantly surprised by the diagnostic and therapeutic skills of the PHC nurse practitioners. However, in 29% of cases their initial diagnosis or treatment programmes were incorrect. Inadequate history taking, inability to elicit and interpret clinical signs and symptoms and unfamiliarity with surgical conditions were contributing factors. The extended role of nurse practitioners in this area of primary care must be encouraged.[4] Surgeons must be involved with their training and supervision through the establishment of a continuing medical education programme, incorporating eight surgical sub-specialties.

The medical and pharmaceutical infrastructure within the CHC were adequate to meet the local demands. A knowledgeable clinic nurse is essential, not only for organising the clinic, but also for translation purposes, history taking, and explanation of the condition and outcome. The clinic also offers an ideal opportunity to engage in a holistic health care approach, i.e. immunisation, physical growth assessment, developmental needs and psychosocial issues in the family.

Mothers carry a heavy burden in caring for their children. Of the cases where details of the accompanying individual were recorded, 80% of the children were brought to the clinic by their mothers. They often have to take a whole day off work and pay large transport fares to get to a tertiary centre. Having a community-based clinic allows the mothers to go to work for the second half of the day, thus decreasing the time off work – vital in this impoverished community where no work often means no pay.

The PHC system for children will not function well without an efficient referral and communication system. Problems encountered were difficulties in contacting the appropriate referral centres, long waiting lists for tertiary clinics, seeking the father's consent for surgical procedures and significant financial constraints. Another restricting factor has been the lack of communication from the tertiary centre once a patient was referred. Over the duration of the study, the CHC only received 13 (2.3%) letters of acknowledgement and outcome from the tertiary services. We regard these replies as vital feedback to the primary nurse practitioners, to further their understanding and diagnostic ability.

The success of this clinic suggests that there is a role for sub-speciality services at PHC level. Clinics of this nature could be run on a weekly or monthly basis. The argument that sub-specialists are unable to conduct a general surgical or medical clinic at PHC level is not valid. This is substantiated by our findings. We believe that the presence of sub-specialists will make a definitive difference to both primary health care and tertiary care clinics.

Conclusions

This study demonstrated the significant public health problem of paediatric surgical diseases. It also emphasised the preventive and cost-effective role of a surgical clinic at primary health care level, which strengthens the 2010 health care plan.

A specialist consulting at a primary health centre allows more children to be seen at an appropriate level. This allowed for timely and cost-effective medical intervention in the majority of children, thereby decreasing inappropriate hospital admissions, outpatient visits and reducing the overall financial burden. Other benefits include opportunities for continuing medical education for medical students, community service doctors and nurses, and facilitation of social grant applications.

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The evolving management of Burkitt's lymphoma at Red Cross Children's Hospital

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Background. Treatment for Burkitt's lymphoma at Red Cross Children's Hospital has evolved from the use of aggressive surgery and less intensive chemotherapy to a conservative surgical approach with more intensive chemotherapy.

Methods. The study was a retrospective folder review of patients diagnosed with Burkitt's lymphoma at RCCH between 1984 and 2004.

Results. Ninety-two children were treated for Burkitt's lymphoma at RCCH between 1984 and 2004. There were 10 patients with group A or fully resected disease, 52 with group B or extensive localised disease, and 30 with dissemination to the bone marrow and/or central nervous system or group C disease. Protocol 1 (less intensive chemotherapy based on the COMP regimen) was used from 1984, with protocol 2 (more intensive chemotherapy based on the LMB regimen) introduced in 1988 for group C disease, 1991 for group B disease and 1996 for group A disease. Overall 5-year survival increased from 20% with protocol 1 to 66% with protocol 2 for group C disease, and from 76.5% with protocol 1 to 88.2% with protocol 2 for group B disease. There were more admissions for neutropenic fever in patients on protocol 2 and more episodes of mucositis, and these patients required more red cell and platelet transfusions. With a more conservative surgical approach, biopsy largely replaced attempts to partially resect the tumour at primary surgery, and there was a consequent decline in surgical complications.

Conclusions. Intensive chemotherapy with protocol 2 has resulted in improved survival for group C and group B patients, but with more morbidity. Protocol 1, which is less intensive with less morbidity, remains a viable strategy for group A and group B disease in resource-poor settings.

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Burkitt's lymphoma (BL) is the third most common solid tumour occurring in children in Africa, being exceeded only by brain tumours and Wilms' tumour. This is due to the high incidence of endemic BL (estimated at 40 - 100 per million per year in children under 15)[1] in the 'lymphoma belt', an area from 10° north to 10° south of the equator, which corresponds roughly with the malaria belt. The ability of the Epstein-Barr virus (EBV) to transform lymphocytes by inducing the translocations typically found in BL appears to be augmented by malarial parasitaemia. These translocations involve the c-Myc oncogene on chromosome 8 and one of the immunoglobulin heavy or light chain loci on chromosomes 2, 14 and 22.

The endemic form found in these areas is characterised by a jaw mass (58%), with or without abdominal disease (58%). Bone marrow involvement is rare (7%) but central nervous system involvement is more common (19%). The sporadic form found throughout the Western world typically presents as an abdominal mass (88%). Bone marrow involvement is more common than in the endemic form (21%) while jaw masses (14%) and central nervous system involvement (11%) are less common.[2] In South Africa most cases fall into the sporadic group.

This review examines the evolution in treatment for BL at Red Cross War Memorial Children's Hospital (RCCH) between 1984 and 2004. With the use of protocol 1 (P1) and aggressive surgery during the 1980s, excellent results were being achieved for patients with extensive localised disease. This was however at the cost of considerable surgical morbidity, and the outcomes of patients with bone marrow and central nervous system involvement remained dismal. A more intensive regimen, protocol 2 (P2), was introduced during the late 1980s, first for those with disseminated disease, and then for localised disease. At the same time a consensus was emerging internationally that with more intensive chemotherapy, debulking of large abdominal tumours was no longer necessary.[3] In addition, relook surgery to assess disease response after induction chemotherapy could be reserved for patients where residual disease was suspected.

We undertook this review of patients treated for BL at RCCH in order to establish whether our patients with disseminated disease have a superior survival with P2 and

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whether the outcome for extensive localised disease improved despite the increased toxicity associated with more intensive chemotherapy.

Methods

The study was a retrospective folder review of patients diagnosed with BL at RCCH between 1984 and 2004. Patients were identified from the Oncology Registry of the RCCH Haematology-Oncology Service. Data on each patient were collected from the hospital notes. Four HIV-positive patients presented with BL between 2003 and 2004. These patients were treated with antiretroviral therapy and an alternative protocol, and were excluded from this study.

The diagnosis of BL was made on histological examination. Upon diagnosis, staging for each patient involved bilateral bone marrow biopsy, and examination of the cerebrospinal fluid (CSF). Chest X-ray and ultrasound of the abdomen were mandatory, and CT scans of the head, chest or abdomen were obtained where indicated.

During the early years of the study, tumours were partially or completely resected where possible. More recently this was gradually superseded by biopsy (via laparotomy or laparoscopy) for all but small localised intra-abdominal tumours. Definitive surgery was performed in patients presenting with intraluminal complications such as intussusception. When the diagnosis could be made from the bone marrow, or cerebrospinal, pleural or ascitic fluid, surgical biopsy was not performed.

The patients were divided into groups according to the risk stratification devised by the French Paediatric Oncology Society[4] (Table I).

Two chemotherapy protocols were used, P1 based on the COMP arm of United States Children's Cancer Group protocol CCG-551,[5] and P2 based on the French Paediatric Oncology Society protocol LMB-89 (Fig. 1).[6] P2 was introduced for group C patients in 1988, for group B patients in 1991, and for group A patients in 1996.

All patients were treated with allopurinol, hyperhydration and urinary alkalinisation at the commencement of induction chemotherapy to prevent tumour lysis syndrome. Granulocyte colony stimulating factor at a dose of 5 µg/kg per day for 14 days was used in an attempt to shorten the period of neutropenia following intensive chemotherapy in P2.

Originally, second-look laparotomy was often performed as part of the review of advanced abdominal disease after induction chemotherapy. Later, it was reserved for cases where there was clinical or radiological suspicion of residual disease.

Relapse-free and overall survival were estimated by the method of Kaplan and Meier. Survival analysis was performed using Statistica 6.1 (Statsoft, Inc. 1984 - 2003).

Table I. Risk stratification for Burkitt's lymphoma (devised by the French Pediatric Oncology Society)

Group A	Complete surgical resection of stage I or abdominal stage II
Group B	All patients not eligible for group A or group C
Group C	Any tumour with CNS involvement Any tumour with more than 25% blasts in the bone marrow

Results

Ninety-two HIV-negative patients with BL were admitted to RCCH between January 1988 and December 2004. There were 64 males and 28 females, with a male/female ratio of 2.3:1. The patients ranged in age from 1.6 to 13.95 years, with a median age of 5.53 years. The two treatment cohorts had an almost identical demographic profile.

Seventy patients (76%) presented with symptoms related to abdominal disease, including pain, distension and vomiting. Nine patients presented with a jaw mass, and 6 with a neck mass. Four presented with generalised adenopathy and bone pain, and 3 with paresis due to paraspinal masses.

At diagnosis 77 (83.6%) were found to have abdominal disease. Fifty-nine had bowel involvement, including 10 with intussusception. Twenty patients had disease involving the liver and 10 had renal involvement. Thirteen patients had involvement of the uterus, ovary or bladder and 1 patient had involvement of the testes. Twenty-five patients had ascites. Nine patients (9.8%) had jaw masses and 12 patients had pleural effusions.

Fifteen patients (16.3%) had central nervous system involvement at diagnosis. Three had paraspinal masses, 4 had central nervous system masses with cranial nerve palsies, and 11 had blasts in the cerebrospinal fluid. Twenty-five patients (27.2%) had more than 25% blasts in the bone marrow. Ten of these patients also had central nervous system involvement.

In all, 30 patients (32.6%) had group C disease; 15 with leukaemia, 5 with central nervous system involvement and 10 with both. Ten patients (10.9%) had group A disease; 9 had fully resected localised abdominal lymphomas and 1 cervical adenopathy. The other 52 patients (56.5%), including 6 with less than 25% blasts in the bone marrow, had group B disease.

There were more group C patients in the P2 cohort (40% for P2 v. 17% for P1), and less group A patients (5% v. 23%), due to the staggered introduction of this protocol. Both cohorts had a similar percentage of group B patients (55% v. 60%).

All group A patients had complete resection. Thirteen (61.9%) of the abdominal group B and C patients treated with P1 but only 8 (15.7%) of those treated with P2 had partial resection. Second-look laparotomy was performed for 10

BURKITT LYMPHOMA PROTOCOL ONE

(based on the COMP arm of United States Children's Cancer Group protocol CCG-551)

INDUCTION	MAINTENANCE (monthly for 6 cycles)
Cyclophosphamide 1 200 mg/m^2 IV	Cyclophosphamide 1 000 mg/m^2 IV
Prednisone 60 mg/m^2 PO daily for 28 days	Prednisone 60 mg/m^2 PO daily for 5 days
Vincristine 2 mg/m^2 IV weekly x 4	Vincristine 1.5 mg/m^2 IV x 2
Methotrexate IT	Methotrexate IT
Methotrexate 300 mg/m^2 IV	Methotrexate 300 mg/m^2 IV

BURKITT LYMPHOMA PROTOCOL TWO

(based on the French Paediatric Oncology Society protocol LMB-89)

GROUP A	1.	Cyclophosphamide 250 mg/m^2 IV 12-hourly x 6 Vincristine 2 mg/m^2 IV x 2 Prednisone 60 mg/m^2 PO/day x 5 days Doxorubicin 30 mg/m^2 IV daily x 2	2 cycles
GROUP B	1.	Cyclophosphamide 300 mg/m^2 IV Vincristine 1 mg/m^2 IV Methotrexate + Hydrocortisone IT Prednisone 60 mg/m^2 PO daily for 7 days	1 - 2 cycles
	2.	Vincristine 2 mg/m^2 IV Methotrexate 3 g/m^2 IV over 3 hours Prednisone 60 mg/m^2 PO daily for 5 days Cyclophosphamide 250 mg/m^2 IV 12-hourly x 6 Doxorubicin 30 mg/m^2 IV daily x 2 Methotrexate + Hydrocortisone IT x 2	2 cycles
	3.	Methotrexate 3 g/m^2 IV over 3 hours Cytarabine 100 mg/m^2 IV daily x 5 Methotrexate/Cytarabine + Hydrocortisone IT x 2	2 cycles
	4.	Repeat 2 … but … Cyclophosphamide 500 mg/m^2 IV daily x 2 Methotrexate + Hydrocortisone IT x 1	1 cycle
GROUP C	1.	As for Group B … but … Methotrexate + Hydrocortisone + Cytarabine IT x 3	1 - 2 cycles
	2.	As for Group B … but … Methotrexate 8 g/m^2 IV over 4 hours Methotrexate + Hydrocortisone + Cytarabine IT x 3 Cyclophosphamide 500 mg/m^2 IV 12 hourly x 6 for 2nd cycle	2 cycles
	3.	Cytarabine 50 mg/m^2 IV x 5 Cytarabine 2000 mg/m^2 IV x 4 Etoposide 100 mg/m^2 IV x 5 Methotrexate + Hydrocortisone IT x 1 for CNS disease Methotrexate 8 g/m^2 IV and triple IT therapy between cycles for CNS disease	2 cycles
	4.	Repeat 2 … but … Cyclophosphamide 500 mg/m^2 IV daily x 2 Methotrexate + Hydrocortisone + Cytarabine IT x 1	1 cycle

Fig. 1. Protocols used for Burkitt's lymphoma at RCCH, 1984 - 2004.

(33.3%) patients treated with P1 – in all but 1 case as a routine procedure. Fourteen (22.5%) of those treated with P2 underwent relook laparotomy – all had a residual mass on clinical examination or imaging. In only 4 of these 24 cases was there histological evidence of lymphoma, and in all cases this was strongly suspected on clinical examination and imaging.

All group A patients on both protocols survived. The estimated 5-year overall survival for group B patients was 76.5% with P1, and 88.2% with P2 ($p = 0.35$) (Fig. 2). There were 5 deaths with P1, 4 from recurrent lymphoma and 1 in remission as a result of varicella encephalitis. Five of those treated with P2 died: 2 had recurrent lymphoma, 1 developed bowel infarction and peritonitis following surgery for tumour-related intestinal obstruction, and 2 deaths were treatment-related – 1 during induction with haemorrhagic oesophagitis, and 1 in remission with cerebral aspergillosis.

The estimated 5-year overall survival for group C patients was 20.0% with P1, and 66.0% with P2 ($p = 0.04$) (Fig. 3). All 4 deaths with P1 were the result of BL recurrence. Of those treated with P2, 6 died of recurrent disease, and 2 deaths were treatment-related. Both of these occurred during induction – 1 as a result of Gram-negative septicaemia and 1 due to mucormycosis.

Twenty-eight patients (30.4%) developed tumour lysis syndrome requiring some form of medical intervention. Three of these patients were treated with P1 and none required dialysis, whereas 25 were treated with P2 and 12 of them required either peritoneal or haemodialysis. All patients requiring dialysis had high tumour burdens with extensive abdominal disease (2), leukaemia (7) or large pleural effusions (3).

Twelve of the 49 abdominal group B and C patients who had laparotomy with biopsy or partial resection had surgical complications. These included adhesive small-bowel obstruction (6), anastomotic leaks or perforations (6), volvulus (1) and jejunal obstruction (1). Of the 13 in the P1 cohort who had partial resection, 5 patients (38.5%) experienced complications – mainly anastomotic leaks. Two of the 8 patients (25%) in the P2 cohort who underwent partial resection suffered adhesive small-bowel obstruction.

There were 26 episodes of neutropenic fever with P1 (0.9 episodes per patient) compared with 192 in the group treated with P2 (3.1 episodes per patient). There were also more positive blood cultures in the P2 cohort (0.94 per patient) compared with the P1 cohort (0.27 per patient). Transfusion requirements were higher for the P2 cohort. These patients required 4.1 red cell transfusions and 4.0 platelet transfusions per patient compared with 1.4 and 0.6 respectively for those treated with P1. Severe mucositis was more frequent with P2 (1.9 episodes per patient) compared with P1 (0.3 episodes per patient).

Among group B patients treated with P2, 88% required at least one red cell transfusion and 62% at least one platelet transfusion. Ninety-one per cent of patients suffered an episode of febrile neutropenia, and 97% suffered severe mucositis. Frequency of episodes

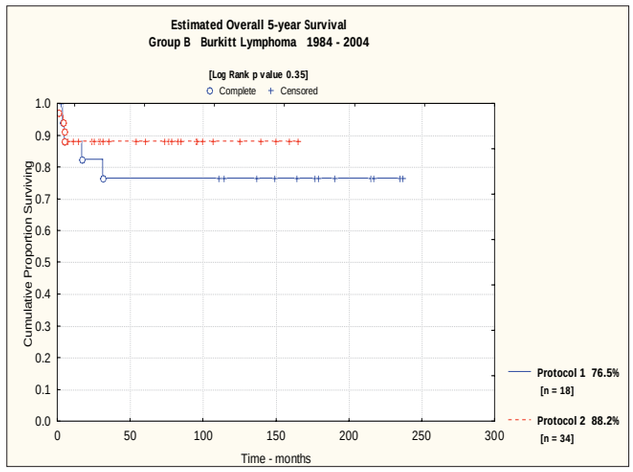

Fig. 2. Estimated overall 5-year survival for group B Burkitt's lymphoma, 1984 - 2004.

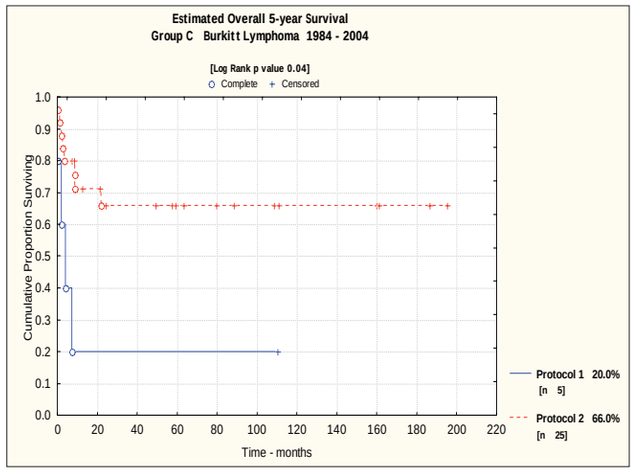

Fig. 3. Estimated overall 5-year survival for group C Burkitt's lymphoma, 1984 - 2004.

of neutropenic fever and severe mucositis, as well as red cell and platelet requirements, were particularly high for group C patients treated with P2.

Discussion

BL was first described by Dennis Burkitt in Uganda in 1958 as a 'sarcoma involving the jaw in African children'.[7] He observed its dramatic response to chemotherapy, demonstrating a number of long-term remissions with one or two doses of cyclophosphamide.[8] Further evaluation showed that this endemic variant was clinically related, and histologically identical, to the abdominal form[9] that constitutes the sporadic variant. Initially treatment consisted of surgical cytoreduction where possible and chemotherapy.[10]

The subsequent evolution of BL treatment has seen the use of increasingly intensive chemotherapy and a reduction in the role of surgery. Early work demonstrated increased survival where complete resection could be achieved,[11] and advocated an aggressive surgical approach to BL.[12] As the efficacy of chemotherapy regimens improved, it became obvious that aggressive attempts at surgical cytoreduction delayed the administration of chemotherapy, and were associated with an increase in complications requiring surgical intervention.[13,14] Debulking surgery to reduce tumour bulk no longer appears to be necessary. Surgery is now only required for diagnostic purposes, or in the event of surgical complications of the lymphoma such as intestinal obstruction.

While regimens such as COMP,[15] on which P1 was based, proved very effective for patients with localised disease, cure for those with dissemination to the bone marrow or central nervous system remained elusive. Successive studies by groups in France[16,17] and the USA[18] showed that high cure rates could be obtained with more intensive chemotherapy. The French reported a 5-year overall survival of 100% for group A, 94% for group B and 85% for group C.[6]

Our patients fitted the profile of the sporadic type of BL. Abdominal disease predominated (83.6%) with few jaw masses (9.8%), and bone marrow involvement (27.2%) was more common than central nervous system involvement (16.3%). As in all other series males predominated but the median age (5.53 years) is younger than that reported in the French study (8 years). This is presumably the result of almost universal exposure to EBV at a young age. The high rate of dissemination to the bone marrow and/or central nervous system (32.6%) illustrates the ongoing problem of late diagnosis of childhood malignancy in South Africa. There were only 21.9% group C patients in the French study.[6]

The introduction of P2 improved the estimated 5-year overall survival for group C patients from 20.0% for those treated with P1 to 66.0% for those treated with P2 ($p = 0.04$). There is a trend for improved survival among group B patients with an increase in the estimated 5-year overall survival from 76.5% with P1 to 88.2% with P2 ($p = 0.35$). The group B results are comparable to the 94% reported by the French, but the group C results are still disappointing compared with the 85% reported in the French study.[6]

Side-effects of chemotherapy have increased with the introduction of P2. Group B and C patients had more episodes of neutropenic fever and severe mucositis, and higher blood product requirements. There were 4 treatment-related deaths with P2 – 2 in group B and 2 in group C – and there was a high rate of tumour lysis requiring dialysis.

Our patients appear to have experienced more side-effects than those treated in the French study. Treatment-related mortality was higher among both our group B patients (5.9% v. 0.8%) and our group C patients (8% v. 4.1%). Our group B patients required more red cell transfusions (88% v. 58%) and platelet transfusions (62% v. 17%), and suffered more episodes

of febrile neutropenia (91% v. 82%) and severe mucositis (97% v. 38%).[6]

Partial tumour resection among group B and C patients declined from 61.9% with P1 to 15.7% with P2. At the same time the surgical complication rate following complete or partial resection declined from 38.5% with P1 (more than half of them anastomotic leaks) to 25% with P2 (both adhesive small-bowel obstruction). Second-look laparotomy rates also decreased from 33.3% on P1 to 22.5% on P2. Laparoscopy has been increasingly used for diagnosis in place of laparotomy, with the aim of minimising adhesions and consequent bowel obstructions.

In conclusion, the introduction of more intensive chemotherapy for the treatment of BL at RCCH has resulted in a marked increase in survival for patients with disseminated disease. Survival has improved more modestly for extensive localised disease, but this has been accompanied by increased morbidity, which appears to exceed that reported in the French study. A more conservative surgical approach to BL has decreased the surgical complication rate.

In our unit patients with extensive localised disease treated with P1 attained a 76.5% estimated 5-year overall survival. This compares favourably to the 62% failure-free survival reported in the original USA study,[4] and the 77.4% event-free survival reported in Lebanon for locally advanced disease.[19] Only one death in our P1 cohort was treatment-related, and toxicity was mainly limited to neutropenic fever and anaemia requiring red cell transfusion.

While regimens similar to P2 (also based on the French LMB protocol) are used in other South African centres,[20] less intensive regimens such as P1 are still used in the developing world. These regimens with their low side-effect profile and minimal transfusion requirements are ideal for African centres with limited resources, and are recommended for children with group B BL in these settings.

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Overview of a paediatric renal transplant programme

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Introduction. Renal transplantation is the therapy of choice for children with end-stage renal failure. There are many challenges associated with a paediatric programme in a developing country where organs are limited.

Methods. A retrospective review was undertaken of 149 paediatric renal transplants performed between 1968 and 2006 with specific emphasis on transplants performed in the last 10 years. Survival of patients and grafts was analysed and specific problems related to drugs and infections were reviewed.

Results. On review of the total programme, 60% of the transplants have been performed in the last 10 years, with satisfactory overall patient and graft survival for the first 8 years post transplant. At this point, transfer to adult units with non-compliance becomes a significant problem.

Rejection is less of a problem than previously but infection is now a bigger issue – specifically tuberculosis (TB), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections with related complications. A wide variety of drugs are available for tailoring immunosuppression to minimise side-effects.

Conclusion. It is possible to have a successful paediatric transplant programme in a developing country. However, to improve long-term outcomes certain issues need to be addressed, including reduction of nephrotoxic drugs and cardiovascular risk factors and providing successful adolescent to adult unit transition.

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Renal transplantation has undoubtedly become the therapy of choice for children with end-stage renal failure,[1] allowing them to return to a fairly normal way of life at home and to return to school. However paediatric renal transplant programmes have many challenges especially in a developing country. Optimising renal allograft survival is important because of limited resources to treat irreversible renal failure.[2,3] Paediatric numbers remain low compared with adult programmes and contribute approximately 2% of any national dialysis programme.[4]

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Patients and methods

A retrospective folder review was done of all patients < 16 years old who received renal transplants at Red Cross War Memorial Children's and Groote Schuur Hospitals' combined Transplant Unit from August 1968 to April 2006. The first paediatric transplant was performed in August 1968 and to date 149 renal transplants have been performed in 132 patients. Eighty-nine (60%) transplants have been performed in the last 10 years (1995 - 2005). The number of paediatric renal transplants per year is shown in Fig. 1.

Fourteen children received 2 grafts, 2 children 3 grafts and 1 child 4 grafts (2 at another centre). Gender distribution was 67 males and 65 females, who ranged in weight from 8 kg to 63 kg. Thirty-five (24%) received grafts from living related donors

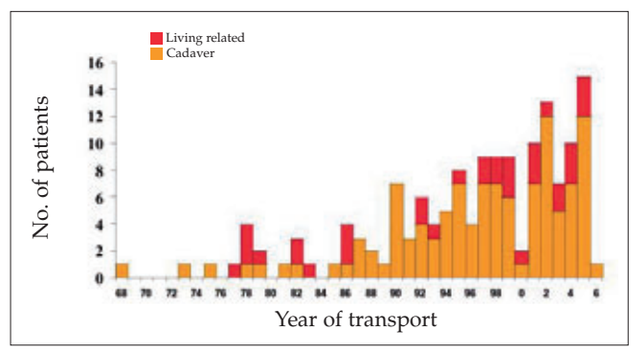

Fig. 1. Number of paediatric renal transplants by year.

and 114 (76%) were cadaveric transplants. Age at the time of transplant is shown in Fig. 2.

Four combined liver-kidney transplants were performed, 3 for primary hyperoxaluria and 1 for polycystic kidney disease with hepatic fibrosis. These patients have currently survived between 2 and 6 years post transplant and all have adequate graft function. Causes of renal failure are shown in Table I. HLA matching is not ideal and often 5 or more mismatches are present.

Our first-line immunosuppression remains cyclosporin, azathioprine and prednisone, but we do have the ability to tailor immunosuppression to suit individual patients. Other drugs used include tacrolimus (Prograf/FK), mycophenolate mofetil (MMF) and sirolimus (Rapamycin). We use steroids and wean to 2.5 mg on alternate days (or 0.05 mg/kg/day) as the lowest dose – no complete steroid withdrawal or steroid avoidance is practised.

Induction agents (basiliximab, daclizumab) in the form of interleukin (IL) 2 receptor blockers have been used and, for cost containment, we have used daclizumab for smaller children (9 cases) and basiliximab for bigger children (7 cases).

Acute rejection has been biopsy proven and then treated with 'pulsed' intravenous methylprednisolone in dosing of 10 mg/kg/dose for 3 - 4 doses followed by increased oral steroids.

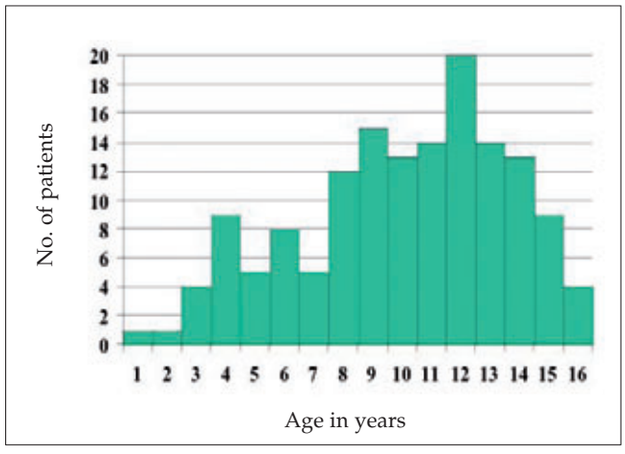

Fig. 2. Age at time of transplant.

Table I. Causes of renal failure in 149 transplanted children

Primary disease	Frequency (%)
Glomerulonephritis	19
Renal dysplasia	18
Posterior urethral valves	16
Reflux nephropathy	12
Systemic lupus erythematosis	9
Polycystic kidney disease	7
Glomerulosclerosis	7
Other	12

Complications resulting in graft loss have included rejection (1 graft lost due to hyperacute rejection) and surgical problems (2 cases of vascular thrombosis), with infections remaining the biggest problem.

Tuberculosis (TB) is endemic in our region (638 cases/100 000 population) and often presents late. During transplant workup, every patient is screened for TB (history of contact or previous TB, skin testing, gastric washings for bacilli and chest X-ray) and prophylaxis is not routinely used. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections also remain a major issue. Identification of CMV and EBV status of both donor and recipient is performed and where necessary 2 weeks of intravenous ganciclovir prophylaxis is administered.

Vaccinations that have been added to our routine immunisations schedule (polio, haemophilus b, diphtheria, pertussis, tetanus, hepatitis B) include hepatitis A and varicella zoster. Adequate immunisation prior to transplant is important with continued surveillance of non-live vaccines on a regular basis post transplantation.

Adolescent issues include our current adolescent cut-off age of 13 years after which the patients are transferred to an adult renal service in large referral hospital. This part of the programme produces most of the compliance issues with recent action implemented including preceding psychosocial input and transition at older age (Fig. 3).

Statistics. Kaplan Meier plots were used for calculating patient and graft survival.

Results

Survival figures

In the last 10 years we have performed 89 paediatric renal transplants; 68 patients are being followed up locally. Notably we are following up 38 patients who are 'over age' according to our cut-off of 13 years (see Fig. 3).

Graft survival for the overall programme is 72% at 1 year and 55% at 5 years. For the period 1995 - 2005 graft survival is

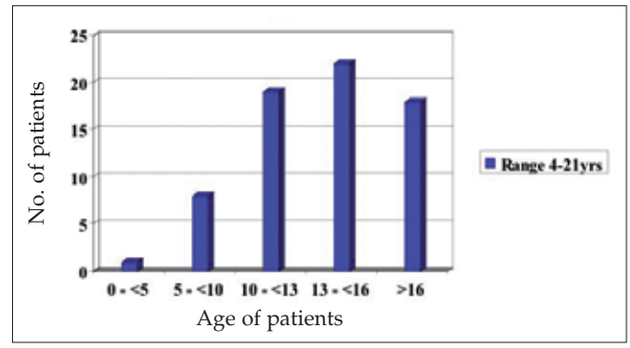

Fig. 3. Age of renal transplant patients followed up at RHX.

91% at 1 year and 80% at 5 years, but then starts dropping off at 7 years to 72% (Figs 4 and 5). Patient survival during this period is 96% at 1 year and 88% at 5 years.

This compares favourably with paediatric figures elsewhere; patients transplanted from 1993 to 1995 in the UK[5] have a 1-year graft survival of 79% and a 5-year survival of 68%, and North American[6] 5-year graft survival was 73% for cadaveric and 81% for living-donor recipients over the same time period.

Mortality in the group transplanted in the last 10 years (1995 - 2005) was 8/89 (9%). Causes of death include sepsis in 3 cases (2 of CMV and 1 of Gram-negative sepsis), recurrence of primary disease in 2 (focal segmental glomerulosclerosis), non-compliance with chronic rejection in 3 and hepatitis B infection in 1.

Surgical complications were few and included vascular thrombosis leading to graft loss in 2/89 cases (2.3%), ureteric leak in 1 case (successfully repaired), and 3 cases of vesicoureteric reflux (VUR) with recurrent urinary tract infections (requiring re-implantation of ureter).

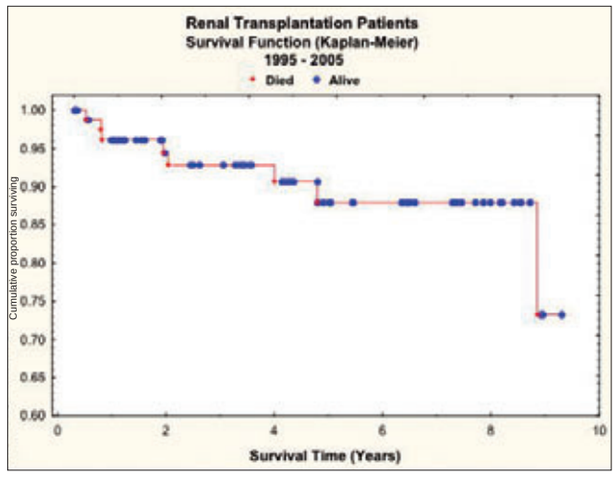

Fig. 4. Patient survival, 1995 - 2005.

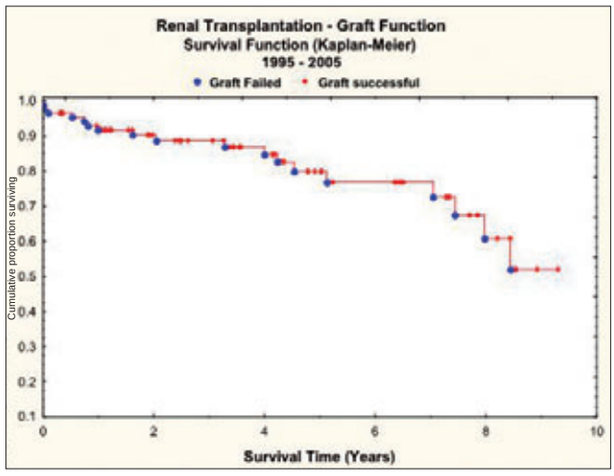

Fig. 5. Graft survival, 1995 - 2005.

In the light of our small donor pool[3] the HLA matching of our cadaver transplants in our paediatric patients was poor, with 60/89 (68%) of our patients having 5 or more mismatches out of 6.

Immunosuppression

Drugs used by our patients include azathioprine (40%), tacrolimus (25%), cyclosporin (24%), MMF (6%) and Rapamycin (5%). We have used similar proportions of both cyclosporin (49%) and tacrolimus (51%). Cyclosporin is significantly cheaper than tacrolimus and for cost-effectiveness this has been our first-line agent. In our paediatric patients on cyclosporin, cosmetic side-effects including hirsutism and gum hypertrophy have been significant problems. This together with rejection episodes has resulted in conversion to tacrolimus in individual cases.

Tacrolimus was implicated in diabetes mellitus in 8/131(6%) paediatric transplants (5 renal and 3 liver) currently being followed-up by our unit. Mean age at transplant was 10 years 4 months and mean age at diagnosis 11 years. Patients who developed diabetes had common risk factors: high body mass index, previously high dosage of steroids and high mean trough tacrolimus level of 10.4 ng/ml. There was also an increased incidence in our black patients – 4/8 (50%) patients who developed diabetes were black despite this group being only 28/89 (31%) of our total programme.

MMF is increasingly being used as a calcineurin-sparing agent but diarrhoea has been a significant problem especially in adolescent patients. If tolerated, we have reduced our cyclosporin to achieve trough levels less than 50 ng/ml and tacrolimus to less than 5 ng/ml. In 3 cases we have successfully stopped calcineurin drugs and have maintained their grafts on MMF and low-dose alternate-day steroids only.

Rapamycin has also been used as a calcineurin-sparing agent but we have seen many of the side-effects described including high cholesterol (50%), interstitial pneumonitis (2 cases), severe bone-marrow suppression with thrombocytopenia and bleeding tendency (1 case) and proteinuria (2 cases). We have not had problems of delayed wound healing, as we have not used this agent in the early post-transplant period.

IL2 receptor blockers have been increasingly used as induction agents, especially in view of our poor HLA matching. This resulted in an acute rejection rate of only 3/16 (18.8%) compared with historic controls of 16/23 (70%). There has therefore been a significantly overall shorter stay in hospital with the potential to use lower doses of steroids. Long-term graft survival still remains to be seen. When comparing the drugs used, no rejection was noted in 4/7 cases on basiliximab and 9/9 cases on daclizumab, suggesting that daclizumab in our setting appears to have a better outcome, but this needs larger studies.

Infectious complications

TB represents a significant problem. During the period 1996 - 2004, the incidence of TB was 7/72 (9.7%) in our transplant patients. Presentation was 10 months to 8 years post transplant with symptoms of fever and cough in all and weight loss in most. No patients were on prophylaxis. With the exception of one renal case, the rest all had pulmonary TB with pericardial involvement in 2 cases. Immunosuppression at the time of diagnosis consisted of cyclosporin, azathioprine and prednisone. Diagnosis was made on finding acid-fast bacilli using a combination of sputum, nasogastric aspirate and bronchial lavage. In one case, a fine-needle aspirate of the lung produced the acid-fast bacilli. All the cases were typically mycobacterium TB and fully sensitive to rifampicin and INH. Three cases had had an increased dose of steroids in the preceding 3 months. An increased cyclosporin dose (up to 5 times) was required once starting the rifampicin. All cases were successfully treated with no loss of patient or graft.

Fatal CMV infection was seen in a 13-year-old girl with renal dysplasia and Fanconi's anaemia who received a CMV-mismatched organ (donor CMV positive: recipient CMV negative) in February 2001. Prophylactic intravenous ganciclovir was given for 2 weeks, but unfortunately she developed a pneumonia requiring ventilation 11 months later and died of CMV pneumonia.

EBV-driven post-transplant lymphoproliferative disorder (PTLD) was seen in 1 renal transplant who presented with a nodal mass in his inguinal region. Immunosuppression was reduced and ganciclovir and rituximab (anti-CD 20 agent) were given together with chemotherapy. Therapy remains successful together with preserved renal function.

Other serious infections in this group of patients have included disseminated varicella with transverse myelitis, *Pneumocystis jiroveci* pneumonia and cat scratch disease (*Bartonella henselae*). All were treated successfully and retained their grafts.

Vaccinations

Audit of vaccination status in a group of 32 cases with age range 93 - 225 months (mean 148 months) reviewed post transplant found protective immunity to hepatitis A (53% patients), hepatitis B (19% patients) and varicella (72% patients).

Adolescent transplant transition

We have had difficulty with transition of adolescents to adult units in the last 10 years with 5 adolescents having lost their grafts and 2 dying within 1 year of transfer despite adequate renal function at time of transfer. We have good 1- and 5-year graft and patient survival but our long-term outcome in the adolescent age group is significantly worse than in younger transplant recipients, as is reported universally.

Discussion

Paediatric transplantation poses numerous challenges, not only the conventional problems of acute rejection and infection, but also technically creative surgery to accommodate the significant size range (our group ranged from 8 kg to 63 kg) of paediatric patients. There may be further challenges in a developing country including difficult social circumstances, poor HLA matching (68% of our patients had 5 or more mismatches) as well as a limited number of donors exacerbated by the high incidence of HIV infection. In order to try and increase our donor pool, we may need to expand the current pool of living related donors (24%) beyond just the parents and potentially also consider non-heart-beating donors.

Whereas previously acute rejection was our biggest concern, this has now become easier to manage, by using the newer immunosuppressant agents including induction with IL2 receptor blockers. Our acute rejection rate has reduced to 18.8% using 2 initial doses of IL2 receptor blockers (both basiliximab and daclizumab used in 2-dosing regimen). Despite the initial cost of this form of therapy, these agents have allowed us to use an overall cheaper immunosuppressive protocol (such as cyclosporin and azathioprine) in our setting where cost containment is important.

However, the consequences of increased immunosuppression and reduced rejection are increased infection; this is highlighted by problems such as CMV infection or EBV-driven PTLD. This is particularly a problem in the young patient with no previous CMV or EBV exposure who receives a donor organ-recipient mismatch. The advent of qualitative and, more recently, quantitative polymerase chain reaction (PRC) testing will have a significant impact on both monitoring and management of these viruses. Intravenous ganciclovir is costly and inconvenient and hopefully prophylaxis will be made easier with the introduction of the oral valganciclovir form. As yet no vaccines are available for these two viruses.

TB is endemic in our region – our rate of TB in paediatric transplant patients was 9.7% – and together with HIV infection, raises issues of drug resistance, choice and duration of prophylactic agents.[6] Our patients developed TB 10 months to 8 years post transplant and it would thus be futile using prophylaxis for TB in the first 6 months only. Drug interactions between anti-TB drugs and immunosuppressants are also a concern.

On review of the vaccination status in a small group of our patients, hepatitis B levels were low post transplant with *Varicella* rates best overall. Paediatric studies have shown loss of antibodies to vaccinations within 6 months post-transplant.[7] Awareness of adequate vaccination pre-transplant, specifically live-attenuated vaccines, with regular post-transplant monitoring, is important in reducing complications from these infections.

In an established paediatric programme, with 1- and 5-year results which are satisfactory by international paediatric standards, despite all the problems of a developing country, emphasis on long-term graft and patient survival becomes an important focus. In view of this, we have tried to limit nephrotoxicity often caused by calcineurin inhibitors by using renal-sparing immunosuppressants. MMF has been useful in reducing dosing or even ceasing calcineurin inhibitors completely in those with chronic allograft nephropathy[8] and we have managed to use MMF and steroids as dual therapy only, with stable renal function so far in 3 of our patients.

Sirolimus has also been well described as a renal-sparing agent,[9] but we have seen a significant number of drug-related side-effects including interstitial pneumonitis and thrombocytopenia with purpura. In 2 cases we have noticed unexplained new-onset proteinuria, which has been described by a few centres as a concern.

In those patients on calcineurin inhibitors, cyclosporin has been responsible for significant cosmetic effects (hirsuitism and gum hypertrophy). These patients have usually been changed to tacrolimus therapy but this has also had problems of diabetes in 6% of our renal transplant in which 50% were black paediatric patients (relatively higher incidence than that of the total programme which consists of 31% black patients).

Children's growth in paediatric transplantation has received much attention recently and this is particularly important at a centre where growth hormone is not easily available. Steroids as immunosuppression have attracted negative press recently. In response to this, there have been three main approaches: (*i*) steroid elimination or avoidance in the first place[12] with use of heavier immunosuppression such as a prolonged course of daclizumab; (*ii*) steroid withdrawal in those who had steroids at time of transplant;[13] or (*iii*) steroid preservation at low dosing. We use the last approach using low-dose (0.05 mg/kg/day) alternate-day steroids. A recent review by Marks and Trompeter[14] also encouraged steroid preservation to prevent exchanging acute rejection for infection including EBV/PTLD. They suggest that steroids remain superior to many other immunosuppressive drugs in terms of cost and past experience, suggesting that it may be more sensible to remove calcineurin inhibition.

Long-term outcomes are greatly affected by adolescent issues and this is clearly seen by our results at 1 and 5 years compared with the group more than 7 years post transplant (Figs 4 and 5). This is notoriously the most difficult group of patients to follow up, a problem for colleagues in both paediatric and adult units alike, and we have this in common with the rest of the world.[15] This is particularly problematic where resources are limited, with adolescent issues similar to those in developed countries, but different economic constraints resulting in patients not being offered repeat dialysis or transplant.

In response to our poor long-term graft survival in adolescence, we have set up a combined transplant clinic with our adult and paediatric team based at the adult unit. This includes social support in the form of psychiatrists, nurses and social workers.

Challenges in the transition period include overcoming the fear of an unknown hospital, adjusting to a different patient/doctor ratio and increased independence in terms of their own health care. The move is preceded by psychological input in the form of workshops and one-to-one interviews prior to transfer to the adult unit.

We also delay the transfer to at least 16 years of age and often even older until patients are mature enough to do the transition with their independence established. Preparation of our younger adolescents, involving them in their own renal function results and medication adjustments, is also important with a positive goal of seeing transition to an adult unit as a successful 'graduation' process. A 'champion' on the adult service is required – be that a nurse or a doctor – so that the patients feel comfortable at the time of transfer by identifying a familiar face involved with them throughout the transition period.

Other factors affecting long-term outcome also depend on decreasing cardiovascular risk factors by reduction of steroid dosing, careful attention to body mass index to prevent obesity and inclusion of statins where necessary.

Despite all the challenges of a developing country, a successful paediatric transplant programme is possible, provided one is aware of all the pitfalls including infection, nephrotoxic drugs and adolescent transition.

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